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DEVELOPMENT OF COLON SPECIFIC MICROSPHERES FOR THE TREATMENT OF FAMILIAL ADENOMATOUS POLYPOSIS

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INTRODUCTION

Celecoxib, is a COX-2 specific NSAID, is currently indicated for the treatment of osteoarthritis, rheumatoid arthritis, acute pain and Familial Adenomatous Polyposis (FAP). It has been reported to have chemopreventive and therapeutic potential in the management of cancers such as oral cancer, superficial bladder cancer, breast cancer, prostate cancer, colon cancer, etc. Familial Adenomatous Polyposis (FAP) is a genetic disorder with autosomal dominant transmission, caused by mutations of the Adenomatous Polyposis Coli (APC) gene and is reported to be 100% precancerosis of colon cancer. Colon cancer has been reported to be the second leading cause of cancer, and is therefore a major public health problem. In view of the reported role of celecoxib in management of FAP and thus chemoprevention of colon cancer, a need was felt to develop a colon specific delivery system which could contribute to enhance the performance of the drug and thereby increase patient compliance.

The present study was undertaken with an objective to develop a delivery system for delivery of celecoxib that could prevent the release of drug at gastric and small intestinal pH and release most of the drug load at colonic pH, by the single continuous process of spray drying.

EXPERIMENTAL METHODS

Preparation of microspheres:

The polymers were first dispersed in isopropyl alcohol by stirring with a high speed agitator, followed by the addition of 1% w/v plasticizer, i.e. dibutyl phthalate. Drug was then added and stirring continued for 15 min. Then acetone was added to make the solution and stirring continued for 1 hour. Finally, talc 1% w/v was dispersed into the solution. The solution thus obtained was spray dried under following spray dryer operational conditions and the product was retrieved. Spray dryer settings were: inlet air temperature 65 to 70°C; Blower setting : 7; Pump setting : 1(5 ml/min.); Atomization air pressure : 2 to 4 kg/cm^2.

Drug content determination in the spray dried product:

10 mg of the product was weighed and dissolved in a mixture of pH 7.4 phosphate buffer: acetonitrile (65:35). The solution was subsequently filtered, analyzed by taking absorbance at 250 nm . Particle size was analyzed by Malvern Mastersizer. (Courtesy: Ranbaxy Research Laboratories Ltd., Gurgaon). DSC endotherms of the microspheres were obtained by scanning samples placed in aluminum pans from 50°C to 300°C at a heating rate of 20°C/min., using a Perkin Elmer DS calorimeter. The spray dried product was tabletted by direct compression on a 16 station rotary Clit compression press .

RESULT AND DISCUSSION

Since, the objective of the present study was to achieve colonic delivery of celecoxib, the drug delivery system was required to be capable of preventing the release of drug in stomach i.e., at gastric pH, release not more than 10% of drug in small intestine and release the drug completely in colon. Thus, the combination of Eudragit L 100 and Eudragit S 100 was optimized on the basis of content of celecoxib in the spray dried product and the ability of the system to prevent release of drug in 0.1 N HCl and pH 6.8 phosphate buffer. All the formulations successfully prevented the release of celecoxib in 0.1N HCl. The percentage of drug released in pH 6.8 phosphate buffer at the end of 3 hrs from formulations eudragit L:S (0:1), L:S(1:0), L:S(1:3), L:S(1:1), and L:S (3:1) were 5.73%,6.6%, 10.78%, 19.12%, and 23.83%, respectively. Thus, the formulation eudragit L:S (13) that had a polymer combination of Eudragit L 100: Eudragit S 100 in the ratio of 1:3, was found to give most suitable release profile of drug Varying the concentration of DBP from 0.5% to 2.0% w/v did not have any significant effect on the release profile of celecoxib.

CONCLUSION

The objective of the present study was to achieve colonic delivery of celecoxib. A microsphere formulation with a combination of eudragit L & S was developed that was found to perform well in *invitro* release studies.

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FORMULATION AND *INVITRO* EVALUATION OF CONVENTIONAL AND STERICALLY STABILISED LIPOSOMES CONTAINING METHOTREXATE

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INTRODUCTION AND METHODS

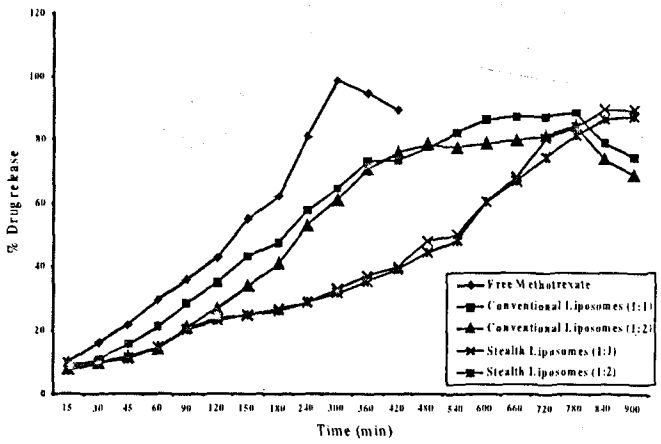
Four batches of methotrexate liposomes of conventional and stealth type were prepared by lipid film hydration technique using rotary flash evaporator. The formulated liposomes were subjected to scanning electron microscope (SEM) for characterizing size and shape of liposomes. Prepared liposomes reveal that they are spherical, small, unilamellar vesicles. The size range of conventional liposomes were from 69-85nm and for stealth liposomes it ranges from 57-68nm. The particle size in the formulation differs due to variation in the cholesterol and phosphatidyl choline composition..

Dialysis method was used to separate unentrapped drug from the entrapped drug. Increase in the lipid concentration increases the size and percent drug entrapment. The percentage drug entrapment of conventional liposomes were found to be 42.71% (1:1), 45.62% (1:2) and for stealth liposomes it was found to be 44.93% (1:1), 50.91% (1:2).

The *in vitro* release of conventional and stealth methotrexate liposomes were studied by simple diffusion cell apparatus using sigma dialysis membrane. For conventional liposomes the percentage release was found to be 84.41%, whereas for stealth liposomes it was found to be 80.83% within a period of 780min.

RESULTS

These results showed that the drug is released slowly over a prolonged period of time from stealth liposomal formulation when compared with free Methotrexate and conventional liposomes.



In vitro release of conventional and stealth liposomes

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LIPOSOMAL SYSTEM OF 5-FLUOROURACIL: OPTIMIZATION OF ENTRAPMENT EFFICIENCY AND SIZE DISTRIBUTION USING 2^2 FACTORIAL DESIGN.

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INTRODUCTION

5-Fluorouracil (5FU), a pyrimidine analogue is used in cancer treatment. Due to hydrophilic nature of 5FU, its incorporation into liposomes is a challenging task. Influence of processing and formulation factors on properties of pentoxifylline liposomes has been evaluated by use of optimization technique [1]. The present study deals with incorporation of 5FU in liposomes, characterization and optimization using 2^2 factorial design.

EXPERIMENTAL

Liposomal dispersions of 5FU were prepared by reverse phase evaporation method [2]. A 2^2 complete factorial designs were made use of to assess influence of various factors. Molar concentration of cholesterol and shaking time were selected as independent variables, while Entrapment Efficiency (EE) and particle size distribution were selected as dependant variables. Molar concentration of cholesterol was varied between 11 and 16 and shaking time was varied between 2 to 8 hours. Factorial designs were constructed at ratio of saturated to unsaturated lipid either 8:3 or 1:1 whereas potential variables such as concentration of 5FU, total concentration of hydration medium and quantity of glass beads were kept constant. A mathematical model containing only significant factors affecting each response was predicted by multiple linear regression and ANOVA using statistical software. Optimized liposomal dispersions were characterized using Differential Scanning Calorimetry (DSC) and Transmission Electron Microscopy (TEM). Dispersions were evaluated for retention of drug at different storage temperature over a period of three months.

RESULTS AND DISCUSSION

Maximum EE (48.71 ± 1.39%) was shown by formulation that contained phospholipid : cholesterol in a ratio of 11:16 where saturated to unsaturated lipids were in 1:1 proportion. With 2 hours of shaking, increase in cholesterol showed positive effect on EE and its interaction with shaking time was also significant. Also high level of cholesterol along with an increasing shaking time leads to decrease in EE. Increase in shaking time probably causes 5FU to leak from liposomal vesicles.

The particle size data of liposomes prepared with lipid-cholesterol ratio 1:1 showed bimodal distribution whereas liposomes with lipid-cholesterol ratio 11:16 showed unimodal size distribution. The laser diffraction method always gave higher value of mean particle size than that obtained with transmission electron microscopy. This may be due to aggregation of lipid vesicles, as aggregates are considered as one particle in laser diffraction studies.

DSC indicated good interaction of lipids and cholesterol and presence of the entrapped 5FU in the liposomal aqueous compartment without interaction with lipid bilayers. Optimized liposomal dispersions did not show significant leakage for a period of three months.

CONCLUSION

Factorial designs provide an understanding of formulation and processing factors influencing liposomal properties. Multiple linear regression were found to have excellent correlation and good validity of model for entrapment efficiency.

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DRUG RELEASE CHARACTERIZATION OF NATURAL GUAR GUM MATRICES

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INTRODUCTION

Non-Ionic hydrophilic carrier materials are widely used for sustained drug delivery system.[1] When hydrophilic matrix tablet is suspended in dissolution media, the water or biological fluid diffuses into the tablet. This results into polymer chain relaxation with volume expansion (swelling).[2] The drug diffuses out of such device. Numerous studies have been reported to investigate the drug release kinetics for HPMC based matrix tablets. Yet to our knowledge there has been no or fewer work done on to the study the release of drugs from the matrix tablets based on natural gums.

OBJECTIVE

The objective of the study was to examine the guar gum matrix swelling and erosion and to characterize the release of drugs from it in terms of diffusion and erosion contribution. Two model drugs, Metformin HCl and Tetracycline HCl, representing drugs of different solubilities were used for this study.

EXPERIMENTAL WORK

The drug:polymer ratio was maintained as 1:1 for soluble drug and 1:0.3 for insoluble drug. Metformin HCl matrix tablet contained 500 mg of active and Tetracycline 250 mg of active. No other exciepients were added except 5 mg Magnesium Stearate as lubricant. The tablet of Metformin HCl were prepared by direct wet granulation technique, where as Tetracycline HCl tablets by dry granulation. The mixture of drug and gum were compressed to representative tablet weight (1 g for Metformin HCl, and 500 mg Tetracycline HCl) using single punch tablet machine having punch size of 13 mm and compression pressure of 3500 kg/cm^2.

The release experiments were performed in USPXXIII dissolution apparatus II as a function of time. Distilled water (900 ml) 37 ± 0.5°C was used as dissolution medium with the paddle rotation speed of 75 rpm. Metformin HCl, was continuously monitored at 233 nm, and Tetracycline HCl at 358 nm, on UV Spectrophotometer (Shimadzu-1601) Release kinetics were determined by Higuchi, Korsmeyer and Peppas equation and were related to release mechanism.

In second series of experiment to study contribution of diffusion and erosion to release mechanism method used by Bettani et al was used. The tablets were locked between two glass slides and introduced into the vessel of dissolution apparatus and tested in the same condition as previous to measure swelling front, diffusion front and erosion front.

Percent erosion study and percent swelling was carried out according to method described by Reynolds et al. The tablets were submerged into the dissolution medium to designated time point (1 to 6 hrs). The individual hydrated tablets were weighed after weighing the hydrated tablets were dried at 105°C for 24hrs. The equilibrated tablet weight was taken.

RESULTS AND CONCLUSION

Drug release mechanism from guar gum matrices followed Korsmeyer equation for Metformin HCl and Higuchi equation for Tetracycline HCl. It was seen that to the release mechanism, contribution of diffusion is more as compared to erosion. Compared to Metformin HCl % erosion was less for Tetracycline HCl tablets however the % swelling became constant from 2 hrs for Tetracycline HCl tablet but linear increase was observed with Metformin HCl tablet.

It was thus concluded that the drug release from guar gum matrices was controlled by the interaction between water, gum and drug. At high drug loading (Tetracycline HCl) gel layer thickness is less and thus % erosion is more as compared to low drug loading (Metformin HCl) the % erosion is less. Thus drug concentration, thickness of gel layer and drug solubility governs the drug flux.

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DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM FOR CELECOXIB

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OBJECTIVES

The main objective of the study was to formulate single unit floating capsules of celecoxib using available hydrocolloids to increase the gastric residence time of the celecoxib in GI tract

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time would be a valuable asset for dosage forms. Floating drug delivery systems can remain in the gastric region for several hours. As this system comes in contact with the gastric fluids, it attains a density less than that of the gastric fluids and this property enables it to float and therefore significantly prolong the gastric residence time of drugs. Celecoxib, class II drug according to BCS classification has a poor aqueous solubility and is reported to have a bioavailability of 22-40% when given orally in a capsule dosage form. Paulson et al. reported that a lower dose and a longer GI residence time would promote the absorption of celecoxib and hence will improve bioavailability [1]. Based on this study an attempt was made to design floating drug delivery system which would improve the bioavailability of celecoxib by enhancing the GI residence time.

EXPERIMENTAL METHODS

Single unit capsules containing celecoxib were formulated with the help of different low density floating polymers so that the capsules would remain in stomach for a prolonged period of time improving the bioavailability. Different grades of the floating polymer Poly Ethylene Oxide (PEO) (grades-WSR 1105, WSR 301, WSR 303, WSR 60 K, and WSR N80), HPMC (K4 M, A4 M, K100 LV), sodium alginate and Eudragits (RL 100, S) were selected. Different ratios of the above said polymers were physically blended with 100 mg of celecoxib and filled in hard gelatin capsules (size 0). The buoyancy studies were carried out by placing the capsules in 900 ml of citrate buffer pH 3 (simulating the pH of gastric contents of stomach in fed state) in USP paddle type apparatus at 50 rpm [2]. The time between the introduction of the capsule in the dissolution medium and the time for which the capsules remained buoyant was observed and was taken as the floating time. The polymer that showed the best floating behavior was taken for *in vitro* release studies in USP paddle type dissolution test apparatus at 50 rpm using 900 ml of citrate buffer pH 3 (containing 1 % sodium lauryl sulphate). 5 ml of sample was withdrawn at regular intervals and replaced with the buffer to maintain sink conditions. The samples were evaluated spectrophotometricaly at 257 nm.

RESULTS AND DISCUSSIONS

It was observed that PEO WSR 60K and PEO WSR 303, HPMC K4 M and Eudragit RL100 containing formulations showed the best floating behavior i.e. they were found floating for 12 hrs.on the above mentioned dissolution medium while the formulation containing Eudragit RL100 floated for 8 hrs. *In vitro* release studies were carried out for 8 hrs. Formulation containing PEO WSR 60K gave 48.05% drug release while PEO WSR 303 containing formulations showed only 19 % drug release in 12 hrs. Formulation containing HPMC and sodium alginate gave 57.4% drug release while formulation containing PEO WSR 60K and Eudragit RL100 gave the best in vitro drug release of 78.97% in 8hrs. Hence on the basis of buoyancy behavior and *in vitro* release studies it can be concluded that formulation containing PEO WSR 60K and Eudragit RL100 was the optimized formulation and can be taken up for further studies.

CONCLUSIONS

The polymer PEO WSR 60K and Eudragit RL100 were found to have good buoyancy, hence suitable for floating drug delivery.

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EVALUATION OF GUM-DAMAR AND DAMAR-BATU AS SUSTAINED RELEASE MATRIX FORMING MATERIALS

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INTRODUCTION

Gum-Damar (GD) and Damar-Batu (DB) are the natural resins obtained from different species of *Dipterocapaarceae* trees of Indonesian origin. They have excellent film forming ability. They are mainly used as emulsifiers and stabilizers for the production of colour, paints, inks and aromatic emulsions in food and cosmetic industries. Their natural origin and above wide applications project better biocompatibility.

OBJECTIVE

The objective of the present work was to investigate GD and DB as a sustained release matrix forming materials for drug delivery applications using diclofenac sodium as a model drug.

EXPERIMENTAL

Preparation and evaluation of GD and DB matrix tablets:

GD and DB matrix tablets were prepared by wet granulation technique using microcrystaline cellulose (MCC) and dicalciam phosphate (DCP) as diluents and diclofenac sodium as a model drug. Different tablets employing 10%, 20% and 30% w/v concentrations of gums (in chloroform) were produced keeping tablet wt. (250mg) and diameter (9mm) constant. Prepared tablets were evaluated for weight variation, friability, hardness. Drug content uniformity and in vitro drug release profiles. To study the exact mechanism of drug release the data was compared with Zero-order, First-order and Higuchi square root models.

RESULTS AND DISCUSSION

GD and DB matrix tablets showed hardness values in the range of 5 to 5.5 Kg/cm^2. Wt variation, hardness, drug content and friability values were found to be within I.P. limits. 10%, 20% and 30% w/v GD tablets with MCC showed 97%, 99% and 89% drug release at the end of 4th, 10th, and 12th hour respectively. 10%, 20% and 30% w/v DB tablets with MCC showed 95%, 97% and 96% drug release at the end of 6th, 8th and 10th hour respectively. In both the cases, increase in gum concentration showed significant decrease in drug release rate and tablets with MCC showed slight higher drug release rates as compared to DCP tablets. Further dissolution data adequately fits the Higuchi square root model indicating diffusion as the primary mechanism for the drug release.

CONCLUSION

Results of the present research thus proposed GD and DB as a novel sustained release matrix forming materials for the drug delivery applications.

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EVALUATION OF GUM COPAL AS A MICROENCAPSULTING MATERIAL

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INTRODUCTION

Significant focus is directed towards evaluation of natural materials for pharmaceutical and biomedical applications. These materials are readily available and expected to be relatively inexpensive, biodegradable and ecofriendly.

Gum Copal is a natural resinous material from *Bursera bipinnata* , family Burseraceae. It is used as pigment binder in varnishes, diety food, meat preservative, remedy for stomach pain and dysentery.

OBJECTIVE

The objective of the present work was to investigate Gum Copal for its microencapsulating property using Diclofenac sodium as a model drug.

EXPERIMENTAL

Preparation and evaluation of microcapsules:

Microcapsules were prepared by modified solvent evaporation technique. The drug–gum solution in dichloromethane: isopropyl alcohol (1:1) was sprayed in a continuous stirring hot dispersion media (liquid paraffin) with 0.5 mm orifice nozzle spray gun. Microcapsules formed were collected by filtration under vacuum and dried after washing with petroleum ether (60-80) at room temperature. The effect of various gum–drug ratios (1:1,1:2,1:3,1:4and 1:5) on evaluatory parameters were studied. The optimum temperature and atomizing pressure for microencapsulation process were found to be 60° C and 40 psi, respectively. Microcapsules were evaluated for encapsulation efficiency, particle size (optical microscopy), surface topography (scanning electron microscopy), in vitro drug release and drug release kinetics by zero order, first order and Higuchi square root model.

RESULTS AND DISCUSSION

Highest encapsulation efficiency was observed with 1:1 gum-drug ratio but the release was retarded beyond 12 hours (65%). The drug release was above 90% at 12th hour from the microcapsules with gum-drug ratio 1:5. The drug release was retarded with increase in gum concentration. Decrease in gum concentration decreased the particle size of microcapsules, which can be explained by the gum concentration in the droplet reaching the hot dispersion media.. Microcapsules obtained were smooth and spherical as observed under scanning electron microscopy. Higuchi square root model adequately fits the release profiles of microcapsules with all gum-drug ratios studied, suggesting the drug diffusion through pores.

CONCLUSION

Modified solvent evaporation technique is suitable for preparing drug loaded microcapsules of gum copal. The results of the investigation encourages gum copal as a potential sustained release microencapsulating material.

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NOVEL APPROACH FOR RAPID DISSOLVING NABUMETONE

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OBJECTIVE

To improve dissolution rate of nabumetone tablets.

INTRODUCTION

Hydrophobic drugs have poor solubility, which result in their poor bioavailability. Nabumetone a hydrophobic prodrug has poor solubility and delayed onset of action since it is practically insoluble in water. Nabumetone is a selective COX-2 inhibitor (NSAID) and is used in the treatment of osteoaarthritis and rheumatoid arthritis. Nabumetone is absorbed in duodenum and undergoes extensive metabolism in liver to the major and only active metabolite 6-MNA (6-methoxy naphthyl acetic acid).

The work presented here deals with the preparation, optimization and evaluation of different batches of nabumetone tablets with different combinations of superdisintegrants.

EXPERIMENTAL METHODS

1. Selection of excipients: Different batches of tablets without drug were prepared by wet granulation method and evaluated for granule yield, particle size distribution, Carr's index, hardness of granules, tensile strength of tablets and disintegration time.

2. Preparation and evaluation of nabumetone tablets with single superdisintegrant: Different batches of nabumetone tablets using suitable diluent, binder, surfactant were prepared with single superdisintegrants by wet granulation method and evaluated for their physical and mechanical properties. In-vitro dissolution studies were performed using Electrolab USP Dissolution apparatus no.21, using 2% SLS in 900ml water, rotated at 50rpm for 45mins. Nabumetone released was measured by Jasco UV-VIS Spectrophotometer at 331nm.

3. Preparation and evaluation of nabumetone tablets with double superdisintegrant combination: Different batches of nabumetone tablets with double superdisintegrant combination were prepared by wet granulation method using suitable excipients and evaluated for their physical and mechanical properties. Further in-vitro dissolution studies were performed.

4. Preparation and evaluation of nabumetone tablets with triple superdisintegrant combination: Different batches of nabumetone tablets with triple superdisintegrant combination were prepared by wet granulation method using suitable excipients and evaluated for their physical and mechanical properties. Further in-vitro dissolution studies were performed.

RESULTS

Nabumetone tablets with single superdisintegrant showed >65% release in 45mins. Nabumetone tablets with double superdisintegrant combination showed >75% release in 45mins. Nabumetone tablets with triple superdisintegrant combination showed >95% release in 45mins.

DISCUSSION

Superdisintegrants improve solubility and dissolution rate of nabumetone (a hydrophobic prodrug). Here dissolution rate of nabumetone tablets with triple superdisintegrants combination > dissolution rate of nabumetone tablets with double superdisintegrants combination > dissolution rate of nabumetone tablets with single superdisintegrants. This marked difference in dissolution rate by using different combinations of superdisintegrants is probably due to synergistic effect since the three super disintegrants act by different mechanisms. However activity of super disintegrant combination in improving solubility of hydrophobic drug of molecular level is yet to be studied.

CONCLUSION

It was possible to improve the dissolution rate of nabumetone tablets.

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SODIUM ALGINATE-GELATIN COMPLEX COACERVATION: MICROENCAPSULATION OF NITROFURANTOIN AND STUDY OF IN-VITRO DISSOLUTION.

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OBJECTIVE

The present study was planned with the objective to develop nitrofurantoin microcapsules by sodium alginate-gelatin complex coacervation and to investigate in-vitro release profile of the same.

INTRODUCTION

In recent years, microcapsules have received considerable attention because of number of advantages that are offered in the field of pharmaceuticals. One of the applications of this technology is alteration of drug release profile with optimized effects.

Nitrofurantoin (NTF) is an antibacterial agent employed in treatment of urinary tract infections, a common disorder at all ages and in both sexes, which may be chronic or acute. It has short biological half-life and its use is limited by gastric irritation. Adminstration of NTF as microcrystals is reported to have lower incidence of side effects due to reduced contact of crystalline NTF with GI mucosa but showed variable bioavailability. Microencapsulation of NTF by complex coacervation is expected to provide longer action and reduce incidence of side effects.

EXPERIMENTAL METHODS

Coacervation was achieved by addition of 0.1N HCL to a suspension of NTF in solution of predetermined concentrations of colloids, namely sodium alginate (SA) and gelatin (G). After completion of coacervation the mixture was cooled while maintaining agitation followed by hardening with formaldehyde. Microcapsules were washed, filtered and were treated with IPA for dehydration. Experiments were performed in replicates with colloid (G: SA) ratio 2:1, 4:1, 10:1 and core: coat ratio of 1:2,1:1 and 2:1.The dried microcapsules were evaluated for NTF content and in-vitro release profile in USP dissolution tester type II, using phosphate buffer pH 7.2 and stirring at 50 rpm.

RESULTS

The encapsulation efficiency of microcapsules and loading of NTF in microcapsules of varying colloid ratio and core: coat ratio, was found to be in the range of 50-90%. The in-vitro release profiles of NTF microcrystals and NTF microcapsules prepared by varying colloid ratio and core: coat ratios were compared. The release profile of NTF microcapsules prepared with colloid ratio 4:1, core: coat ratio 2:1, filled capsule size 3, is shown in fig.1.

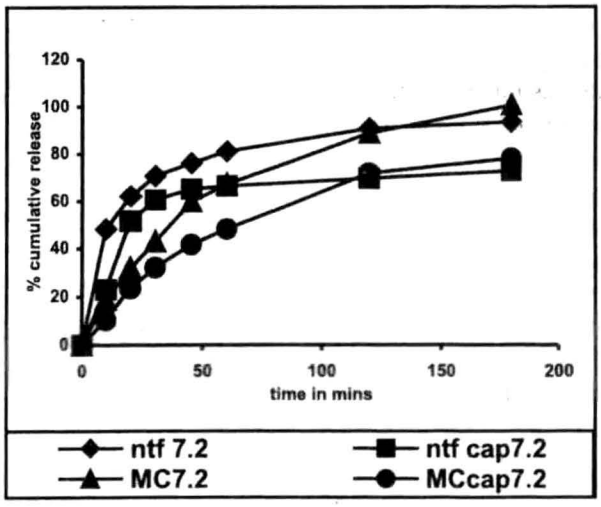

Fig.1: Dissolution ntf microcapsules in 7.2 buffer.

DISCUSSION

Results of percent loading and encapsulation efficiency indicate that the technique of encapsulation was effective and reproducible. In-vitro drug release from microcapsules was retarded in first 2 hours in phosphate buffer pH 7.2 for all colloid ratios and core: coat ratios. The short duration of retardation of drug release is attributed to solubility of coat in alkaline condition. When release profiles of microcapsules prepared at varying colloid ratios were compared it was observed that colloid ratio 4:1 gave more sustaining release than 10:1 and 2:1 Dissolution rate of microcapsules was further decreased (fig.1) when the microcapsules were filled in capsules. Microcapsules due to close proximity to each other inside the capsule formed a gel, as it was observed, although capsule shell was dissolved in buffer, which resulted in decreased release.

CONCLUSION

NTF microencapsulation by complex coacervation is an efficient technique providing satisfactory % loading and %encapsulation efficiency. Filling of microcapsules in hard gelatin capsules resulted in retardation of drug release.

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GASTRORETENTIVE SYSTEMS FOR CINNARIZINE

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OBJECTIVE

The present study was planned with the objective to design controlled release system of Cinnarizine, which would improve patient compliance by reducing frequency of administration.

INTRODUCTION

Controlled release drug delivery systems are designed to achieve prolonged therapeutic effect by continuously releasing the medication over extended period of time after administration of a single dose. Gastroretentive systems are important for drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in alkaline pH, gastric retention is expected to increase solubility before they are emptied, resulting in improved bioavailability. Many weakly basic drug molecules, exhibit pH dependent solubility in physiological ranges. They have good solubility at acidic pH but in the intestinal environment of higher pH these drugs show limited solubility.

Designing a system, which will have longer residence in stomach where the drug has good solubility, can provide controlled release of such drug. Cinnarizine, a piperazine derivative, is a weak base having plasma half life of 3-6 hours. Cinnarizine is, used in treatment of nausea, vertigo caused by Meniers disease, with oral dose of 30mg 3 times daily. This information suggests feasibility of designing gastroretentive controlled release delivery system for Cinnarizine with improved patient compliance.

EXPERIMENTAL METHODS

The tablets containing Cinnarizine were compressed by slugging method using hydroxy propyl methyl cellulose (K4MCR) as swelling and rate retarding agent, sodium glycine carbonate (SGC) as basic effervescent ingredient and citro glycine as acidic effervescent ingredient. The tablets containing sodium bicarbonate and citric acid were also prepared by direct compression and used for comparison. Non-effervescent floating tablets containing cellulose based excipients and polysaccharide were also prepared.

RESULTS AND DISCUSSIONS

Gastroretentive tablets with effervescent ingredients had good physical integrity and complied with drug content. The release of drug was observed in Simulated Gastric Fluid having pH 1.2 using USP I Dissolution Test Apparatus (Basket type). Tablets remained buoyant for 12 hours without disintegration and released the drug between 85-100% over 12 hours -24 hours. Floating tablets should finally erode,

dissolve or disintegrate and should not remain in stomach after the drug is released. Tablets containing sodium bicarbonate remained swollen at the end of 12 hours but the tablets containing SGC were reduced in size. It was observed that those containing SGC and those containing sodium bicarbonate showed similar release pattern.

Optimized formulation was also evaluated for its stability after storing the formulation at various accelerated storage conditions. No significant change was observed in release profile after 3 months of storage period.

CONCLUSIONS

Gastroretentive systems were developed for Cinnarizine, having optimum floating time and drug release profile with new effervescent ingredients.

ACKNOWLEDGEMENT

Yasham Ltd for providing the gift sample of sodium glycine carbonate and citro glycine.

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pH – INDEPENDENT CONTROLLED RELEASE ORAL FORMULATION OF WEAKLY BASIC DRUG – PHARMACOKINETIC EVALUATION AND IVIVC

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OBJECTIVE

The present study was planned with the objective to conduct pharmacokinetic evaluation of pH-independent controlled release oral dosage form in healthy human volunteers and to establish a *in vitro – in vivo* correlation (IVIVC).

INTRODUCTION

Weakly basic drugs with pH dependent solubility, show good solubility in acidic pH, where as its solubility drastically reduces at higher or alkaline pH. This may hinder the dissolution of the drug within the dosage form upon entry of gastrointestinal (GI) fluids and then subsequent diffusion of the dissolved drug out of the delivery device and hence its bioavailability. The present work involved development of pH-independent controlled release oral tablets of weak base (WB) with selective serotonic receptor antagonist.

EXPERIMENTAL METHODS

Matrix tablets of WB were prepared using hydrophilic polymer, and acidic agent by direct compression. *In vitro* dissolution study of the optimized formulation was carried out in different dissolution media such as 0.1N HCl, phosphate buffer pH 7.4, gradient pH method by double and triple buffer, full volume change. 500 ml of dissolution media was agitated at 50 rpm in paddle type, tablet dissolution tester and the medium was maintained at 37±0.5°C till the end of the study. The samples were analysed spectrophotometrically. Biobatch for pharmacokinetic evaluation in healthy human volunteers was prepared and analysed for *in vitro* release.

The protocol of pharmacokinetic study was approved by IEC of the Bombay College of Pharmacy and study was conducted in strict adherence with ICH-GCP and Helsinki Declaration. The study was single dose, open label and completely randomized cross over design. Six healthy human volunteers were included with their prior consent agreement, three of which were given conventional tablets (Con-Form) of WB and remaining volunteers were given the controlled release formulation (CR-Form) during the first run. The set of formulations given to the volunteers was completely reversed during the cross over after a washout period of 7 days. The drug in the plasma samples was extracted by liquid-liquid extraction procedure and analyzed by RP-HPLC. The data generated from the analysis was subjected to model-independent pharmacokinetic parameter evaluation. The plasma profile generated from the controlled release formulation was then subjected to level-A[1] IVIVC.

RESULTS AND DISCUSSION

The release of WB from optimized formulation was found to be pH-independent in 0.1N HCl, pH 7.4 and in gradient pH double and triple buffer change method.

Plasma levels of WB absorbed from the CR-form were seen up to 24 hours, whereas those from Con-form were seen up to 12 hours post-single dose administration. This indicated that WB was released for prolonged period of time. AUC (area under the curve) values for WB absorbed *in vivo* from CR-Form were same as that from Con-Form containing similar dose of WB. This indicated that the overall bioavailability of WB from CR-Form was same as that from Con-Form confirming to the release of WB from CR-Form. Furthermore the C_{max} of the CR-Form was less than the C_{max} of the Con-Form, while the t_{max} of the CR-Form was longer than corresponding t_{max} of Con-Form, indicating prolonged release of WB from CR-Form during its sojourn in gastrointestinal tract. Results confirmed that the release of WB from CR-Form was in a controlled and pH-independent manner. Level-A IVIVC was applied to the fraction of drug release *in vitro* from CR-Form and the fraction of drug absorbed from the formulation *in vivo*. A good correlation was observed in between the release profile and fraction of drug absorbed thus indicating good IVIVC.

CONCLUSION

The release of WB from optimized formulation exhibited pH-independent controlled release *in vitro*. Pharmacokinetic evaluation of the formulation in healthy human volunteers showed similar bioavailability in comparison to that obtained from a conventional formulation of WB. The level-A IVIVC was found to give good correlation indicating usefulness of dissolution testing methodology, which can be used in future to mimic *in vivo* evaluation in human volunteers.

ACKNOWLEDGEMENT

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IMPROVED DELIVERY OF ROFECOXIB BY COMPLEXATION WITH CYCLODEXTRINS

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INTRODUCTION

Rofecoxib is a non-steroidal anti-inflammatory (NSAID) drug prescribed for the long-term treatment of musculo-skeletal complaints. This drug is practically is insoluble in water (aqueous solubility = 4.6 mcg/ml)[1] and as such its oral absorption is dissolution rate limited. The major drawback to NSAID drug use is the preponderance of gastrointestinal (GI) side effects, which can reduce patient compliance and discourage physician from prescribing them. There is therefore, a need for a delivery system for NSAIDs with improved GI tolerability while retaining its efficacy. Cyclodextrins especially β-cyclodextrin (β-CD) and hydroxypropyl â-cyclodextrin (HPβ-CD) are widely used in the Pharmaceutical field owing to their high aqueous solubility and ability to stabilize insoluble drug molecules [2-4].

The present study is an attempt to prepare inclusion complexes of rofecoxib with HPβ-CD and Dimethylβ-CD to improve the aqueous solubility of the drug thus enhancing its dissolution rate, thereby showing a faster onset of action.

EXPERIMENTAL METHODS

The complexes were prepared by kneading (KN) and spray-drying method (SD) and stoichiometry of complexation was established by phase solubility studies. The aqueous solubility of the drug was determined practically by magnetically stirring excess of drug in water. Physico-chemical studies on the complex was done by DSC, XRD, SEM and FT-IR. Assay of the prepared complexes were carried out to in order to establish the drug content. Dissolution of the complexed powder was carried out for two hours along with pure drug for comparison in pH 1.2 and 7.4.

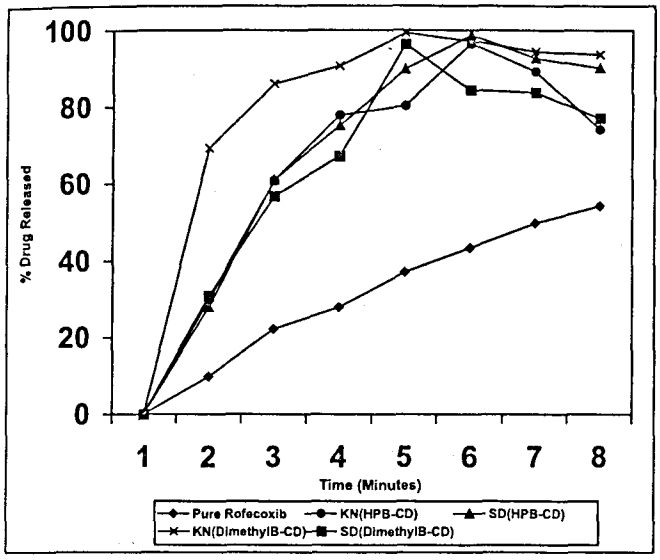

Fig. 1: Dissolution rate profile in pH 1.2.

RESULTS AND DISCUSSION

The phase solubility diagram indicated the formation of 1:1 complex between rofecoxib and HPβ-CD/ Dimethylβ-CD. The physico-chemical characterization indicated maximum complex formation in rofecoxib-HPβ-CD complexes. The aqueous solubility of rofecoxib HPβ-CD/ Dimethylβ-CD complex was more than the pure drug i.e., rofecoxib both in pH 1.2 and pH 7.4, indicating that a considerable portion of rofecoxib will be present in the non ionized form in the acidic gastric juice of the stomach. In the in-vitro release equivalence better release profile was shown with rofecoxib-Dimethylβ-CD kneaded dispersion as compared to rofecoxib-HPβ-CD (KN and SD) complex (1:1) and pure drug both in pH1.2 and pH 7.4. Release rate constants were calculated for first order and zero order kinetics and Lower coefficient of variation was observed in first order release kinetics.

CONCLUSIONS

An inclusion complex of rofecoxib with HPβ-CD and Dimethylβ-CD complex was prepared usefully by kneading and spray drying method, in a molar ratio of 1:1 with improved aqueous solubility and faster onset of action.

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STUDIES ON ISONIAZID RELEASE FROM CARBOPOL MATRICES

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OBJECTIVES

To design controlled release (C.R.) matrix tablets of isoniazid (INH) using carbopol 934-P at different proportions and to evaluate physical properties and in-vitro release characteristics.

INTRODUCTION

INH is one of the major first line drugs for tuberculosis treatment (1). It undergoes appreciable presystemic (first pass) metabolism resulting in inadequate plasma concentrations in rapid acetylators (2-3). This, along with the incidence of toxic effects, prompted the development of C.R. formulations of INH. Best results were claimed with the formulations containing 37% ordinary INH & 63% matrix component (3). It has also been found that the absorption of matrix formulations of isoniazid throughout the entire tract is as complete as ordinary INH (4).

EXPERIMENTAL METHODS

C.R. matrix tablets were formulated using different proportions of carbopol 934-P by direct compression method. Tablets were evaluated for physical characteristics. In vitro release studies were carried out in 7.4 phosphate buffer (PB). Release studies also done in 0.1 N HCl to analyze the effect

of pH on release. Release kinetics was analyzed by Peppas model, $Mt/M_\infty = Kt^n$ (5).

RESULTS & DISCUSSION

Drug content was analyzed as per Indian Pharmacopoeia (IP) 1996. Tablets passed the weight variation and friability tests. Hardness was kept at 6-7 kg/cm^2 for each batch of the tablets.

The drug release was extended from 6 to 20 h as polymer ratio was increased from 10 to 60% (Fig. 1). The release rate decreased as the polymer proportion increased. This might be due to increased gel layer thickness and diffusion path length as polymer ratio was increased. Initial release was higher at all polymer ratios probably because the quick dissolution of the surface drug before the formation of gel layer and polymer reached its disentanglement concentration. The initial higher release was good as it avoids the incorporation of separate loading dose of free drug (2-4). The nature of release was found to be first order. Release profiles also followed Higuchi's square root kinetics diffusion. The 'n' values (from Peppas equation) ranged from 0.61- 0.73 indicating that the release mechanism was anomalous non-Fickian diffusion. Such mechanism of release was due to combined effect of inherent diffusion (Fickian), as the drug was having good solubility, and polymer relaxation/ swelling at alkaline pH.

Drug release rate was higher in 0.1 N HCl than in 7.4 pH PB (as shown in Fig 2 for 40% polymer formulation). This was due to nonswelling nature of the carbopol (an acidic polymer) in 0.1 N HCl that lead to increased micropores and regions of low microviscosity resulting in the increased drug release. But, at 7.4 pH the ionization of carboxylic acid groups of the polymer resulted in the swelling and hence closing of the micropores. The release mechanism was found to be Fickian diffusion (n = 0.42) as swelling/ polymer relaxation contribution was negligible.

CONCLUSIONS

INH C.R. tablets formulated using carbopol 934-P by direct compression technique were found to be of good quality. Increase in the polymer ratio resulted in the decrease in the release. Release rate was higher in 0.1 N Hcl than in 7.4 pH Po4 and release mechanism shifted to Fickian (0.1 N HCL) from non-Fickian diffusion (7.4 Po4). These formulations could serve as better alternatives to conventional tablets to overcome toxic side effects and to optimize drug blood levels especially in case of fast/ rapid INH acetylators.

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FORMULATION AND COMPRESSION OF PELLETS: EFFECTS OF EXCIPIENTS AND PRESSURE ON DRUG RELEASE

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INTRODUCTION

Lutein is a good antioxidant useful in many ocular and cardiac diseases, but it has stability problems during formulation process such as sensitive to heat, moisture and light. The objective of present work was to formulate lutein into flexible coated pellets , then into tablet dosage form to over come its instability and evaluation of excipients the compression force.

EXPERIMENTAL WORK

Preparation of pellets:

Lutein and PVPK-30 (10-20%) were selected as drug and granulating agent respectively. HPMC (5-15%), methacrylate copolymer type3 (3-10%), ethylcellulose (5-10%). Pellets were prepared by both extrusion –spheronization and powder layering technique by using PVPK-30 as granulating agent. Then pellets were immediately coated by various

polymers to form flexible pellets in order to with stand the compression force

Stability studies:

Stability studies were carried out on the pellets at 25°C± 2°C, 60%RH and accelerated stability studies at 45°C± 2°C,75%RH.

Compaction studies:

Compaction studies were done on instrumented Jaguar rotary press fitted with one set of 12 mm standard concave tools. The press was setted at 20 rpm and 7Kg/cm² compaction force. Microcrystalline PH302, direct compressible lactose –21(DCL-21), direct compressible dicalcium phosphate, dicalcium phosphate hydrate and sodium starch glycolate were used as excipients for the compaction trials excipients were added on weight basis. The mixture blended in an Y-shaped blender for 3minutes at 35rpm.magnesium stearate was used as the lubricant at 0.5%by weight level. It was passed through #60mesh sieve added to the pellet mixture or blended for 3minutes.Tablets of 500mg containing 120mg of 5%coated pellets were manufactured from these blends and evaluated for drug release.

Tablet preparation:

Tablets were prepared by both direct compression and wet granulation methods. Microcrystalline cellulosePH302, DCL-21, direct compressible dicalcium phosphate, Sodium starch glycolate, magnesium stearate were used as excipients for direct compression .In wet granulation microcrystalline cellulose, DCP powder and lactose were used individually and granulated with pvpk-30 and dried passed through#24/#03.

The dried granules were blended with the remaining excipients and directly compressed into tablets by using 12mm, round, standard concave tooling.

Dissolution studies:

Dissolution were performed at 37± 0.5 °C in USP dissolution apparatus type II set at 100 rpm using 900ml 0.1NHCl as the dissolution medium.120mg of 5% coated pellets were introduced in the dissolution vessels and samples were collected at different time points.

Tablets were evaluated for weight, thickness, hardness, friability and assay.

Scanning electron microscopic studies were carried out to check the leakage of drug from the pellets.

RESULTS

Scanning electron microscopic studies showed the films to be well deposited on the pellets with very little defects.7Kg/cm² was used for all trials because it was the minimum force that could produce a compact when using microcrystalline cellulose as the excipient. DCP, DCL-21 did not form a compact at this force. MCC PH302 provided compacts that disintegrated and regenerated the coated pellets within less than 30secas opposed to 7-10minutes for other excipients

Scanning electron microscopic studies indicated that there was no leakage of drug from the pellets. The drug content in tablets was found 90-95%by HPLC method. The release of the drug from the pellets followed apparent zero order kinetics

CONCLUSION

Lutein pellets into tablet formulation was successfully prepared by using 5%HPMC as coating agent to withstand the compression force of 7kg/cm²

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FORMULATION AND EVALUATION OF FLOATING HOLLOW MICROSPHERES OF LANSOPRAZOLE

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INTRODUCTION

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time. An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, a prominent site for the absorption of many drugs, will lead to lower bioavailability.

Lansoprazole is a proton-pump inhibitor having short plasma half life and clearance. It has stability problems during formulation process such as sensitive to heat, moisture and light. The objective of present work was to formulate the floating microspheres to overcome its instability and evaluation of the characteristics.

EXPERIMENTAL

Preparation of floating microspheres:

Drug to carrier ratio were taken in different ratios by selecting carriers as Hydroxy propyl methyl cellulose(1-3%), Methyl Cellulose(1-3%) and Chitosan (1-3%). This technique was developed by solvent -diffussion method.PVA(1%) was used as cross linking agent.

Stability studies:

The prepared microspheres were placed in screw capped glass containers and stored at ambient humidity conditions, at room temperatures (27±2°C) at 60% RH, oven temperature (42±2°C) at 75% RH and in refrigerator (5-8°C) at 85% RH for a period of 45 days. The samples were assayed for drug content at regular intervals of two weeks.

EVALUATION

Dissolution studies:

Dissolution studies were performed at 37±1°C in USP dissolution apparatus type II set at 100 rpm using 900ml of 0.1N HCL as the dissolution medium . 100mg of microspheres were introduce into the dissolution vessels and samples are collected at different time points.

Floating characters were observed in 0.1N HCL for 24 hours and scanning electron microscopic studies were carried out to check the hollow nature and surface morphology of the microspheres.

Particle size analysis were carried out with the help of optical microscope.

RESULTS

Scanning electron microscopic studies showed the hollow nature of the spheres and also good surface morphology of the microspheres. Out of all the three polymers chitosan (3%) showed the good floating ability and incorporation efficiency.

Compatibility studies were carried out with HPLC method, there was no interaction found in the formulations.

CONCLUSION

Lansoprazole microspheres were formulated successfully by using chitosan 3% as carrier

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EVALUATION OF AN INDIGENOUS GUM FOR THE HYDROPHILIC LAYER IN TRI-LAYERED SR TABLETS

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INTRODUCTION

It is well known that sustained release dosage formulation may offer one or more advantages over immediate release formulation of the same drug. Incorporation of drug into an inert wax matrix is known as means of SR medicament because it offers low manufacturing cost, improved moisture resistance, good physico-chemical stability and reduction of unpleasant taste. According to Fick's first law of diffusion, the release of a drug from a monolithic matrix is inherently non-linear. Over the years, many innovative approaches have been proposed to smoothen the drug release. One of such technique relies on the use of multi-layered matrix tablets to provide zero-order controlled release. Multi-layered tablet is drug delivery device which comprises a matrix core containing the active solute and one or more barrier (modulating layers) incorporated during the tabletting process. *Sterculia foetida*, an indigenous tree, has been well documented for the utility of its various parts, gummy exudate of this tree has not been reported to be exploited as release rate retard excipient.

OBJECTIVE

The objective of this work was to design and evaluate tri-layered matrix tablets containing a highly soluble drug embedded in hydrophobic matrix middle layer and sterculia foetida gum, as hydrophilic barrier layer press coated to the faces of tablet core to aim at constant rate release.

EXPERIMENTAL METHODS

Materials:

1. Metoprolol tartarate (Drug)
2. Mixture of Carnubawax & beeswax (C & B)
3. Sterculia foetida gum (SFG) powder (#120)
4. Lactose
5. Micro Crystalline Cellulose (MCC)
6. Dicalcium phosphate.

Preparation of middle layer matrix tablet:

Drug and lactose were blended and slowly added to molten wax (C & B, 95:5) and mix of thoroughly. This mixture was allowed to congeal and the mass at room temperature passed through set wise of sieves in order to obtain the granule size varying from 400-1200mm. A separate study was carried out to determine the wax composition & its concentration used for this preparation. The prepared granules were compressed with varying punches and hardness in order to produce tablets with different aspect ratios.

Preparation of tri-layered tablet:

Sterculia foetida gum powder and MCC in different ratios were used as hydrophilic layers. After blending the hydrophilic mixture with granulating liquid (mixture of IPA & water), passed through suitable sieve combination to produce the granules varying from 400-1200mm.. Three layered tablets were prepared by placing the granules/partially compressed layers sequentially i.e. hydrophilic-hydrophobic-hydrophilic and compressed into tablets. The amount of barrier layer used were varied from 100-250 mg. A separate study was carried out in order to determine the composition of granulating liquid and suitable fillers from lactose, dicalcium phosphate and MCC. The tri-layered tablets were subjected to *invitro* studies employing USP apparatus 2, 50rpm, 37°C, distilled water. Further more, the optimized products were exposed to enhanced temperature and humidity conditions for accelerated stability evaluation.

RESULTS AND DISCUSSION

Carnubawax (C) is a natural excipient useful in sustaining the release in this situation. To increase the drug retarding capacity of carnubax, beeswax (B) was added. Among the different composition 95:05 (C:B) was optimized because of picking and sticking problems introduced by higher concentration of beeswax 40% wax concentration was optimized to achieve 100% drug release in 6 hours. The granulating liquid (water : IPA) was optimized in the ratio of 25:75 to produce granules of adequate strengthen. The optimum size of granule was found to be around 800mm. since

in the higher (1200mm.) size granules, erosion rate was not constant and lower (400mm.) size granules had no sufficient compression binding properties. The composition of barrier layer was optimized in to ratio of 6:4 MCC:SFG. The layer thickness was optimized at 150 mg to produce the required release profile. Accelerated stability studies indicated that the products maintained their qualities well within the acceptable limits.

CONCLUSION

The experiments & results obtained indicated successful construction of three-layered SR tablets using sterculia foetida gum as hydrophilic barrier layers.

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FORMULATION OF LITHIUM CARBONATE SR TABLETS WITH OPTIMIZED BIPHASIC RELEASE

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INTRODUCTION

Patients of manic depressive illness (MDI) go through the conditions of fluctuating mood ranging from excessive elation to severe depression. Lithium carbonate is well known in the treatment of acute mania and as long term mood stabilizer. In lithium therapy, it is important not only to attains the effective plasma concentration early in the beginning of oral regimen but also maintain for the period which is obviously extended. Majority of the plain and modified release tablets, available in the market, lack in logistic drug release profile for most beneficial plasma level achievement. In the present work SR matrix tablets were developed to achieve the desirable plasma level. Out of the many release retard polymers reported, waxes are considered preferable for their reliable SR matrix forming capability as well as being natural, safe and economical.

OBJECTIVE

Objective of the present work was to design and evaluate SR matrix tablets of Lithium carbonate using carnauba wax. It was the further objective of the present work to optimize the formulation in a way to improve the *invitro* release to lead to superior bioavailability.

EXPERIMENTAL METHODOLOGY

Lithium carbonate (therapeutic), Carnauba wax (retard polymer), Beeswax (plasticizer), Lactose (Channeling agent & release modifier) & Magnesium stearate (lubricant) were the main materials used. Carnauba wax who plasticized with the help of 4, 5 & 6% of been wax. The tablets represented 350 mg of the drug, 4-12% wax and 10-30% lactose. Tablets were prepared both via the method of direct compression (d.c.) and granulation. For d.c., all ingredients of #80 size were dry mixed and compressed using rotary press. For granulation, the blended ingredients were added to molten wax and passed through suitable screen at room temperature. Lactose was made available either as intragranular or extragranular. Granules were compressed into circular flat tablets using rotary press. For optimization EVOP method was used. Tablets were evaluated mainly for *invitro* release and *invivo* status. For the former USP dissolution method recommended for Lithium carbonate SR solids was employed and release profiles were constructed. For the *invivo* work human volunteers were employed. The biofluid estimated for the drug post oral administration as per well set ethical protocol was done via urine. Among many urinary profiles plotted, the "excretion rate vs time" was used to estimate the bioavailablility credibility of the dosages.

RESULTS

Carnauba wax containing 4% Bees wax produce the best technological and release results. By both d.c. and granulation process 5.5% wax concentration in tablets lead

to extension of release to the desired 10 hrs. When *invitro* & *invivo* profiles were compared it was noted that formulations with biphasic release, such that about 30% release by the end of 2 hrs and remaining 70% in next 8 hrs gave the desirable result. Most striking aspect noted was that though the optimized formula had the biphasic release i.e. first 2 hrs 15% per/hr and next 8 hrs 9% /hr release, the *invivo* picture indicated a smooth plasma gain in this duration. The rising part of the *invivo* graph was noted to be almost linear as confirmed by R. When some of the SR tablets of market leaders were tested they were found to be having monophasic near zero order of diffusion type release and showed presence of lag during the first 2hrs of *invivo*.

DISCUSSION

By incorporating Bess wax to carnauba wax its nature could be suitably modified. Presence of lactose in the tablet provided suitable channeling and release modification. The distinct physico chemical nature of the drug coupled with the unique nature of the formulation helped to ensure the needed biphasic release. This was due to higher rate release for about 2 hrs due to quick solubilisation of lactose encouraging channeling. For this performance about 20% lactose was better present as extragranular. After 2 hrs the release rate slowed to near zero order due to suitable rearrangement and erosion of wax network as time elapsed. The absence of burst effect and indication of smooth rise in plasma concentration hinted towards a poorer absorption rate in stomach. The net result was the occurrence of the most desirable *invivo* profile i.e. smooth rise about 8 hrs followed by domination of elimination. This would also aid in a suitable multidose SR regimen.

CONCLUSION

Proper balance of the two phases of release ensured superior *invivo* picture. It was made possible reliably by using a simple technology and suitable formation and production methods. Thus, the work was successful in recommending a simple technique for the production of lithium carbonate tablets for a better management of MDI patients.

PREPARATION AND EVALUATION OF RESIDRONATE SODIUM-GELUCIRE® 43/01 FLOATING GRANULES PREPARED BY MELT GRANULATION

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INTRODUCTION

Bisphosphonates such as alendronate, residronate, etidronate and teludronate are commonly prescribed drugs for treatment of osteoporosis and paget's disease. Despite their benefits bisphosphonates suffer from very poor oral bioavailability due to its highly hydrophilic nature. Residronate sodium (RDS) is best absorbed from the upper GI tract. Only gastric retention with controlled release allows the drug to the upper GI tract parts of the intestine should allow an improvement in bioavailability. Gelucire 43/01 (GEL), a mixture of triglycerides is hydrophobic and almost does not allow drug release in single unit matrix. In the present study this limitation has been exploited to design multi-unit floating systems of a highly hydrophilic drug Residronate sodium.

EXPERIMENTAL

RDS-GEL granules were prepared by melt granulation technique in the range of 1:1 to 1:3. Similarly RDS:GEL:EC (Elthylcellulose) and RDS:GEL:EU (Eudragit NE 30D) granules were prepared in the ratio of 1:1.5:0.5. The granules were evaluated for *in vivo, in vitro* floating ability, drug content and *in vitro* release. Ageing effect on the granules was studied using Hot Stage Polarizing Microscopy (HSPM), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) and *in vitro* drug release.

RESULT AND DISCUSSION

Drug content of the granules was 98-102%. Granules showed good *in vivo, in vitro* floating ability. The SEM photograph of the granules has shown presence of lipid on the surface. The SEM surface of aged sample showed significant changes, which may be due to phase transformation.

Drug release profiles in 0.1 N HCl showed that as amount of lipid increases the release rate decreases). DSC thermograms showed that energy require to melt the aged sample is more and melting temperature of aged sample is shifted to slightly higher side .HSPM microphotographs showed presence of some unmelted portion even at 45°C in aged sample This may be attributed to crystallization of glycerides during aging.

CONCLUSIONS

In the present study attempt has been made to design multiunit floating gelucire systems to overcome the side effects of Residronate sodium and the limitation of single unit systems. Designing of multiunit gelucire formulation requires less amount of gelucire as compared to single unit gelucire formulation. Ageing study shows phase transformation of gelucire, which is responsible for increase in drug release. Further attempts are required to stabilize Gelucire 43/01 against phase transformation.

ACKNOWLEDGEMENT

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EFFECT OF HLB OF GLYCERYL MONOSTERATE ON THE PROPERTIES OF GELUCIRE® 50/13 MATRICES DURING AGEING

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INTRODUCTION

GelucireÒ are a family of vehicles derived from mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These are available with a range of properties depending on their HLB (1-18) and melting point (33°-65°C) range. The gelucire containing only PEG ester (GelucireÒ 55/18) are generally used in preparation of fast release formulations and which contains only glycerides or mixture of glyceride and PEG esters (GelucireÒ 54/02, 50/13, 43/01) are used in preparation of sustained release formulations. But it is well established that glyceride based products may exhibit aging effect, where by a range of physical properties (melting point, softening time and hardness) and *in vitro* release may change on storage of a matrices. Objectives of the present study was to study the effect of the HLB of glyceryl monosterate (GMS) on the properties of gelucire matrices using Venlafaxine hydrochloride (VEN) as a model drug.

EXPERIMENTAL

Weighed amounts of bases (gelucire 50/13 and GMS HLB = 1.5/ 3/ 7/ 10) were heated into a glass beaker at 65°C. Venlafaxine Hydrochloride was added into molten base with stirring at 65°C and allowed to stand for 20 min to obtain homogenous mixture. The molten base was filled into the Licaps capsules size 0. Matrices were stored at 40°C up to one month for ageing and were evaluated for *in vitro* release, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC) and Tensile strength.

RESULTS AND DISCUSSIONS

Significant changes in the dissolution profiles of VEN were observed during ageing in distilled water. It may be due to conversion of triglycerides to more stable polymorphic forms. It has also been observed that addition of GMS decreases the release rates as compared to plain gelucire matrices and the release rates were found to increase with the increase in HLB of GMS. The release rates were found to decrease with increase in the amount of GMS. During ageing the release rates were found to be decrease with the increase in HLB of GMS. Surface roughness was observed in the SEM microphotographs of plain gelucire matrices and matrices containing GMS HLB =10 but no surface roughness were observed in case of matrices containing GMS

HLB = 1.5. Development of surface roughness can be correlated to increase in release rate. Addition of the GMS having lower HLB value stabilized the gelucire transformation but GMS having higher HLB value failed to stabilize the gelucire transformation during ageing. Tensile strength was found to decrease with increase in the amount and HLB of GMS. During ageing the tensile strength were found to decrease continuously but in case of matrices containing lower HLB GMS, the % of decrease is smaller as compared to matrices containing higher HLB GMS. It can be correlated to increase in release rate during ageing. DSC has also confirmed phase transformations in gelucire during ageing. It can be observed from the DSC thermograms that lower m. p. triglycerides were developed during aging in plain gelucire matrices. Similarly in matrices having higher HLB GMS lower m. p. triglycerides developed as compared to matrices having lower HLB GMS. HSPM also confirmed the phase transformation and increase in crystallinity during ageing.

CONCLUSION

By relating physical changes to dissolution increase in rate, it was possible to design a formulation and process to promote complete phase separation during manufacturing process and storage. It was also observed that addition of lower HLB GMS in the gelucire not only provide more sustaining action but also minimizes the phase transformation in the gelucire.

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EFFECT OF FORMULATION VARIABLES ON PREPARATION AND EVALUATION OF GELLED SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS) OF KETOPROFEN

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INTRODUCTION

Around 40 % NCEs introduced in market are lipophilic and hence are potential candidates for problems associated with dissolution rate limited absorption. Many investigators have investigated SEDDS for lipophilic drugs. SEDDS comprises medium chain triglycerides (MCT) and non-ionic surfactants, which emulsify spontaneously to produce fine oil-in-water emulsions. This process essentially involves formation of liquid crystals (LC), which significantly affect the formation of droplet and subsequent partitioning of drug. Few attempts are reported to formulate semisolid or solid SEDDS. We have attempted to formulate SEDDS with moderately lipophilic drug, ketoprofen (log P 0.98), which has limited solubility in both MCT and water. We have used Captex 200 (diglycerides), Tween 80 (surfactant) and Capmul (cosurfactant), along with silicon dioxide (Aerosil) as a gelling agent.

EXPERIMENTAL

Selection of oil, an important requisite, was done by preliminary studies. Mixtures of Captex and Tween 80 (4:3 parts, by volume) were prepared and ketoprofen (1g/7.0 ml of mixture) was dissolved in it. To study the effect of variables, different batches were prepared using 3^2 factorial design, each batch containing 100 mg ketoprofen and varying amounts of Capmul and Aerosil as two independent variables. All the batches were observed for isotropicity and then evaluated for time required for emulsification, turbidimetry, viscosity, droplet size analysis and in vitro diffusion. The results obtained were subjected to multiple regression analysis using Unistat® (Megalon, USA) software. The data was fitted in equation (1). $Y = b_0 + b_1 X_1 + b_2 X_2 + b_{11} X_1 X_1 + b_{22} X_2 X_2 + b_{12} X_1 X_2$ ... (1)

The results of multiple regression analysis for all the

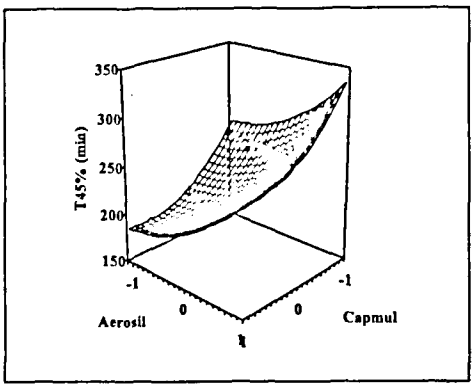

Fig. 1: Effect of variables on $T_{45\%}$.

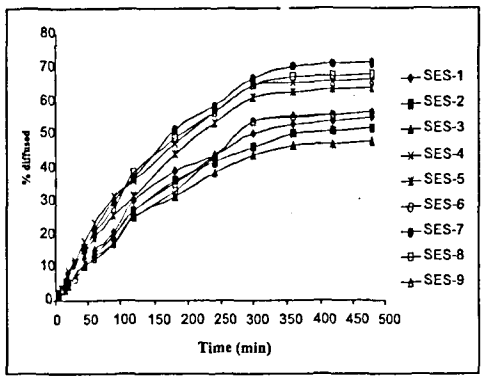

Fig. 2: In vitro diffusion profiles of SEDDS.

TABLE 1: SUMMARY OF REGRESSION RESULTS FOR THE MEASURED RESPONSES

Parameters	Coefficients							
	β_0	β_1	β_2	β_{11}	β_{22}	β_{12}	r^2	*P*
Time required for emulsification (sec)	36.667	-10.0	-	-	-	-	0.706	0.001
Turbidimetry (NTU)	149.56	-100.8	-	-	-	-	0.821	0.001
Avg. droplet size(nm)	143.95	-	45.65	-	-	-	0.465	0.004
$T_{45\%}$ (min)	216.88	-37.25	36.19	24.83	18.7	-	0.934	0.000

parameters studied are summarized in Table 1. The response surface plots were generated using PCP Disso v 3.0 software.

RESULT AND DISCUSSION

The present study is an attempt to formulate gelled SEDDS for moderately lipophilic drug, ketoprofen, unlike reported earlier. Selection of oil, which accommodates unit sustained release dose in minimum volume, was a critical aspect. Viscosity of LC was found to be higher as compared to undiluted systems and also was dependent on amount of Aerosil. Undiluted systems and LC obey power law and are shear thickening. Average droplet size was found to be directly proportional to viscosity of LC, which affects the angle of curvature during droplet formation. In vitro drug diffusion from LC was higher for the systems containing higher amounts of Capmul.

CONCLUSIONS

SEDDS comprising Captex 200, Tween 80 and Capmul MCM possess good potential to incorporate moderately lipophilic drug, ketoprofen. Gelling of SEDDS with a view of further processing into semi-solid, solid, sustained release formulations showed that Aerosil increases LC phase viscosity, which in turn causes increase in average droplet size, while Capmul was found to increase drug diffusion from LC phases.

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PREPARATION AND EVALUATION OF MUCOADHESIVE SUSPENSION OF ROXITHROMYCIN FOR THE TREATMENT OF CRYPTOSPOIRIDIOSIS IN AIDS PATIENTS

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OBJECTIVES

1) To improve the aqueous solubility of poorly soluble Roxithromycin by size reduction using Ultra Turrex and Ultrasonicator.

2) To study the effect of formulation and processing variables on particle size reduction.

3) To increase the residence time of drug in adverse diarrheal condition in G. I. T. by preparing mucoadhesive suspension using bioadhesive polymer.

INTRODUCTION

Roxithromycin is a macrolide antibiotic mainly used for the treatment of cryptosporidiosis in AIDS patient, Roxithromycin is a poorly water-soluble drug with oral bioavailability of only 50%. Thus a mucoadhesive suspension of Roxithromycin was developed to overcome the limitations of drug i.e. poor oral bioavailability and low residence time of the drug in GI tract in adverse pathophysiological condition of cryptosporidiosis.

EXPERIMENTAL METHOD

Particle size reduction of Roxithromycin was carried using Ultra Turrex and Ultrasonicator techniques. The process variables include speed, time and cycles of Ultra Turrex and ultrasonicator amplitude. The formulation variables include concentration of Pluronic F-68 and Soya lecithin.

The mucoadhesive suspension was formulated using bioadhesive polymer Carbopol 971 P. The resultant suspension was evaluated for particle size analysis, saturation solubility, specific surface area, in-vitro release study, Crystallographic investigation (DSC and XRPD), percentage of mucoadhesion and gamma scintigraphy.

RESULTS AND DISCUSSION

The processing and formulation variables were optimized to obtain desired particle size. The effect of variables on various parameters were as follows:

Particle size reduction: As speed of Ultra turrex was increased from 11000 to 16000 rpm and processing time increased from 5 to 15 min particle size decreased. The smallest particle size achieved was 9.35μm. Increase in amplitude of ultra sonication from 20 to 60 also led to particle size reduction.

Batch with optimum concentration of Soya lecithin (150mg) gave lowest particle size than batch without Soya lecithin.

Saturation solubility: Increase in speed, time and number of cycles of homogenization led to increase in specific surface area which in turn increased saturation solubility from 5.45 µg/ml to 37.87 µg/ml.

In vitro release: Processed suspension showed 99% release within 15 mins compared to 120 and 220 min for marketed suspension and unprocessed drug suspension respectively.

Crystallographic changes: Absence of peaks in XRPD and changes in integrated and normalized energy in DSC of processed drug indicated changes in the crystallinity of the drug.

Percentage bioadhesion: Carbopol 971 P was found to be suitable mucoadhesive polymer for Roxithromycin suspension. At 0.25 % of gel concentration and 3:2 suspension: gel ratio maximum bioadhesion 98.23% was obtained. An increase in gel concentration from 0.1 to 0.25%, percentage bioadhesion also increased.Gamma scintigraphy indicated that the preparation remains adhere to stomach for about 6 hours which increased residence time of formulation in diarrheal conditions of cryptosporidiosis.

CONCLUSION

From the present study of Roxithromycin Mucoadhesive Suspension, it can be concluded that increase in speed, time, number of cycles of homogenization and increase in amplitude of sonication particle size was observed to be decreased. XRPD and DSC study revealed that crystallinity decreased with reduction in particle size. Gel content is a

determining factor in mucoadhesion, greater the gel content better is the mucoadhesion

Mucoadhesive suspension is suitable formulation for Roxithromycin particularly useful in the treatment of cryptosporidiosis in AIDS patient.

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STUDIES ON MICROENCAPSULATION OF METFORMIN HCl USING ETHYL CELLULOSE

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OBJECTIVE

Aim of this study was to develop a microspherical dosage form for a highly water-soluble drug Metformin HCl using a water insoluble non-biodegradable polymer, ethyl cellulose.

INTRODUCTION

Metformin HCl, an antihyperglycemic agent that improves glucose tolerance in-patients with type II diabetes. Oil-in-oil emulsion solvent evaporation technique was found to be efficient for increasing encapsulation efficiency of the highly water-soluble drug and was adopted for preparation of microspheres of Metformin HCl where as ethyl cellulose. Factors affecting microencapsulation, yield, release and surface morphology were studied.

EXPERIMENTAL

Microspheres were prepared by o/o emulsion solvent evaporation technique. 10-25% w/v ethyl cellulose solutions were prepared in acetone. Solutions with D: P ratio of 1:1, 1:2, 1:3 and 1:4 were prepared and dispersed in 100 ml continuous phase consisting of light and heavy liquid paraffin (1:1) and span 80 (1% v/v) as surfactant. The solution was stirred at 500 rpm for 2.5 h. The temperature was increased gradually from 10 to 30 °C with an increment of 5 °C and was maintained at 30 °C till the end of cycle. The microspheres were filtered and washed with sufficient quantity of petroleum ether. Product obtained was evaluated for morphology, percent yield, drug content (loading/encapsulation efficiency) release, particle size, etc.

RESULTS AND DISCUSSION

The formulation variables were optimized to prepare the desirable microspheres having optimum loading and % yield using o/o solvent evaporation technique. The morphology of microspheres was studied by optical and scanning electron microscopy (SEM). As the D: P ratio was increased from 1:1 to 1:4,the microsphere surface become smooth. A 10% w/v polymeric solution concentration gave uniform free flowing microspheres. The particle size range of 50 to 250 mm. Increase in particle size and percent yield was observed with increase in polymer solution concentration. Percent yield was found to be more than 90%. Encapsulation efficiency in the range of 83-99 % was obtained with increasing D: P ratio from 1:1 to 1:4. Both the initial drug loading and polymer solution concentration significantly affect the release of Metformin HCl from microspheres. Release was extended as the D: P ratio increased from 1:1 to 1:4. Microspheres size was found inversely proportional to drug release rate. Drug release from microspheres followed predominantly the Peppas model. The release was extended upto 8 hrs. Burst release 30 % was observed with D: P ratio of 1:1 and was controlled with increase in polymer concentration.

CONCLUSION

It was noteworthy that the o/o emulsion solvent evaporation technique, usually used for microencapsulation of water-soluble compounds in to hydrophobic polymer was also efficient for preparing Metformin HCl microspheres. D: P ratio and polymer solution concentration affects the microencapsulation, %yield, release and morphology of

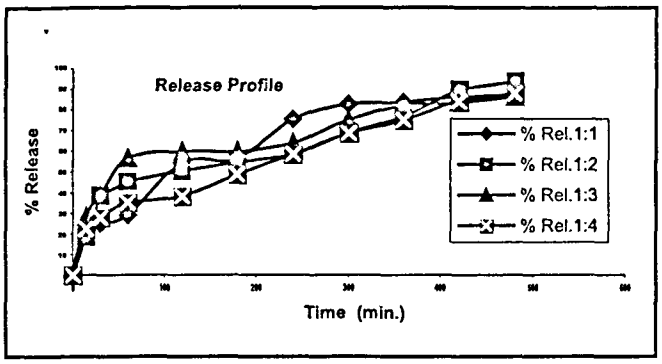

Fig. 1: Graph of drug release from. Microspheres in distilled water.

microspheres. Thus, it can be concluded that a multi particulate dosage form of Metformin HCl can be developed through an intelligent choice of polymer and optimizing the encapsulation technique.

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DESIGN AND EVALUATION OF A MULTIPARTICULATE SYSTEM OF KETOPROFEN FOR SITE-SPECIFIC RELEASE TO THE COLON

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INTRODUCTION

Chronotherapeutics refers to a clinical practise of synchronizing drug delivery in a manner consistent with the circadian rhythm to produce maximum health benefits and minimum harm[1]. A colon specific drug delivery system is a controlled onset system, which can be used to approximate the chronobiology of certain diseases such as rheumatoid arthritis, the symptoms of which were found to be most intense when awaking from a nighttime sleep[2]. Methods utilizing pH sensitive polymers such as Eudragit S-100 would be a simple and practical means of site-specific release to the colon. A multiparticulate system was designed considering several advantages it presents in comparison to single units forms such as higher colonic retention time, more predictable gastric emptying and less local irratation. Ketoprofen a non-steroidal anti-inflammatory drug, prescribed for long-term treatment of rheumatoid arthritis was used as a drug candidate.

EXPERIMENTAL METHODS

Preparation of drug loaded cellulose acetate cores: Cellulose acetate cores of ketoprofen were prepared by solvent evaporation technique in a oily phase. The mixture of the drug and cellulose acetate in different ratios such as 1:1, 2:1, and 4:1 were dissolved in acetone. The resulting solution was emulsified into an external phase of liquid paraffin containing 1% span-80 to produce a stable o/o emulsion using a three bladed propeller stirrer.

Microencapsulation of drug-loaded cellulose acetate cores:

Cellulose acetate cores of ketoprofen were encapsulated with eudragit S-100 by the same method. Drug-loaded cores were suspended in a ethanolic solution of eudragit S-100 and emulsified into an external phase of liquid paraffin containing 1% span-80 using three bladed propeller stirrer.

Evaluation of the eudragit microcapsules:

The morphology and surface topography of the microcapsules were studied using SEM The projected mean diameter and size distribution was determined by optical microscopy. DSC thermograms and PXRD patterns were recorded to characterize the solubility and physical state of the drug in the cellulose acetate polymeric matrix. In order to check the integrity of the drug in the microcapsules, FTIR.Spectra of the drug and the microcapsules were obtained and compared. Dissolution tests were performed fol-

lowing pH progression method for a period of 16 h simulating the gastro intestinal tract condition.

RESULTS AND DISCUSSION

SEM revealed that the eudragit microcapsules were uniform, spherical, and free flowing exhibiting a smooth and dense surface topography without any pores. The microcapsules varied in size between 700 to 1600 m and the size distribution as determined by optical microscopy was log-normal. The theoretical drug content of the different batches of microcapsules was found to be uniform and ranged from 6.40 to 9.67% w/w. The dissolution profiles of eudragit microcapsules. The dissolution studies indicated the fact that the microcapsules exhibited both pH sensitive and controlled release properties. The studies indicated that limited amount of drug was released from the microcapsules below pH 7 during the first five hours, following which the cellulose acetate cores effectively controlled the release for a period of 11 h. The drug release from the microcapsules depended on the drug: cellulose acetate ratio and was characterized by first order release kinetics. The DSC thermograms and the PXRD patterns indicated that the drug was dissolved in the cellulose acetate polymeric matrix, which could explain its controlled *in vitro* release from the microcapsules. IR Spectra of ketoprofen and the microcapsules indicated no chemical interaction between the drug and the excipients used.

CONCLUSIONS

The obtained results collectively indicated that a multiparticulate system consisting of drug loaded cellulose acetate core encapsulated into a pH sensitive polymer could be successfully designed using double microencapsulation technique for site-specific release to the colon. A bedtime administration of such dosage form may prove valuable to patients with diseases like rheumatoid arthritis that are affected by circadian rhythm.

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FORMULATION, DEVELOPMENT OF CONTROLLED RELEASE FORMULATION OF NITROGLYCERIN USING POLYMER COMBINATION

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OBJECTIVE

Aim of the present study is to develop a stable dosage form of nitroglycerin intended to give a controlled release when taken orally. To control the migration of drug from the dosage from. A multiparticulate system is proposed to be used for the variety of reasons and the benefits of the system as a modified release dosage forms.

INTRODUCTION

Nitroglycerin is an inherently potent drug for the pathophysiological condition of angina pectoris. Nitroglycerin if not masked also leads to a burning sensation in mouth and a throbbing headache[1]. All this conditions are major hurdle for patient compliance and for the dosage form.One of the major concerns of nitroglycerin in any of the dosage form is the migration of the drug from the dosage form.

EXPERIMENTAL

Formulation of controlled release pellets:

Nitroglycerin pellets were prepared by using powder layering technique. Nitroglycerin adsorbed on lactose powder was directly loaded on the non-pariel seeds using a coating pan. These drug-loaded pellets were then coated with different acrylic and non-acrylic polymeric solutions prepared

in organic solvents. In case of polymer blend two different polymer solutions was made and then homogenized in a mixer. HPLC method was employed for the assay procedure. Water, methanol, accetonitrile and Triethylamine was used as a solvent system. Standard plot was plotted for further calculation.

Dissolution Studies:

USP apparatus 2 (paddle), rpm: 100,medium: 500 ml 7.2pH 0.05M Potassium dihydrogen Phosphate buffer for 8 hours, temperature: 37.5±0.5°C

RESULTS

Assay of all the batches of coated pellets was carried and the drug content as compared to the drug loaded pellets was decreasing during processing due to volatilization. Moisture content of all the batches of nitroglycerin was less then 4 %. After the dissolution studies it was notable that all the batches coated with acrylic polymers were giving good release profile where as pellets coated with non acrylic polymers were releaseing the drug fast. The pellets coated with combination of Eudragit® RS and Eudragit® NE were giving a good release profile and sustained release effects was found to be for 10hrs. Pellets coated with 7.5 % of polymer to the pellet weight was found to be giving best results.

Stability studies was performed on the optimized pellets after feeling them in the capsule. Study was performed for 120 days as different temperatures. Shelf life was predicated by the following data using Arhenius plot. The shelf life was found to be 611.76 days. SEM photographs of the pellets were taken on different magnification. Photomicrographs on 150, 500 and 1000 X magnification shows uniformity of coating on the pellets, which might be the reason for controlled release of the drug through the pellets.

Differential Scanning Calorimetry studies were carried out by subjecting the plane polymer, drug powder, and the combination of the of the drug and the polymer, to the elevated temperature to study there enthalpy changes. A slight change was observed in the second endothermic peak which is not there in the plane drug thermogram. This change in the second peak suggest a weak physical interaction between the polymer and the drug.

DISCUSSION

Pellets coated with acrylic polymers Eudragit® RS and Eudragit® NE both gave a good release profile of Nitroglycerin pellets, but in both these batches the consistency of the release profile was not found and the reason being the migration of the drug to the surface. After 120 days of the study the percentage loss of the drug was around 6-15%. The shelf life was found to be 611 days. Dissolution study was again performed on the batches subjected elevated temperature and there was no much difference in the release profile. This once again confirms that the polymer combination controls the migration of the drug even at elevated temperature. DSC Studies shows the third thermogram of the polymer-drug combination, a slight change was observed in the second endothermic peak which is not there in the plane drug thermogram. This change in the second peak suggest a weak physical interaction between the polymer and the drug, which could be one factor responsible for the decrease in the migration of the drug. The interaction shown in the DSC does not always means chemical incompatibility.

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PREPARATION AND CHARACTERIZATION OF SPHERES-IN-OIL-IN WATER (S/O/W) SYSTEM BEARING METHOTREXATE

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OBJECTIVE

The objective of the present work was to study effect of gelatinization of internal aqueous phasde on the stability of multiple emulsion system and drug release profile.

INTRODUCTION

the potential of multiemulsions for controlled and prolonged release of drug has been reported by various authors(1,2 In the present study an attempt was made to impart further stabilization to the multiple emulsion by gelatinizing internal aqueous phase. A resulting system is termed as sphere-in-oil-in water(s/o/w) multiple emulsion system.

EXPERIMENTAL

An improved version of the two steps emulsification procedure was employed for preparing multiple emulsions (w/o/w)(Formulation code-Fw/o/w). Following same method s/o/w multiple emulsion was prepared by using an optimum concentration of gelatin(20%w/v) in an internal aqueous phase. Internal phase and oil phase(Sesame oil+Span80) were emulsified by ultrasonication at 70-80°C followed by rapid cooling at about 0°C. The s/o/w emulsion was prepared by subsequent emulsification of primary s/o emulsion with an equal part of water containing 1 %w/v Tween80 as the secondary emulsifier using sonication(Formulation code-Fs/o/w). emulsions were characterized for their various in-vitro attributes namely globule size Percent entrapment (By a dialysis method), Percent phase separation and release of the drug By dialysis method) as shown in the table.

RESULTS AND DISCUSSIONS

Mean diameter of multiple oil droplet of formulation Fw/o/w and Fs/o/w was found to be 6.4±0.5 and 6.5±0.8mm respectively while size for the internal aqueous droplets were found to be 2.2±0.5 and 1.6±0.4 mm respectively. After storage for two weeks, no significant change in globule size in Fs/o/w was observed(8mm), while Fw/o/w showed a significant change in size (12.5mm). Fs/o/w exhibited flocculation of the gelled globules but did not show coalescence nor any increase in particle diameter. Percent entrapment studies revealed that Fw/o/w had lower entrapment initially (74.0±1%), while further decreased on storage for two weeks (40.0±2%). While Fs/o/w could entrap the drug at higher level effectively(89.0±3%) and drug content did not vary significantly after two weeks storage at room temperature(75.5±3%). The % phase separation for Fw/o/w was recorded to be 30 while it was noted to be 7.5 for Fs/o/w after storage for two weeks at room temperature. The improved stability of Fs/o/w may be attributed to the stabilized inner aqueous phase. This system consists gelled globules of gelatin and these globules could be considered to resemble a quassi-solid, which demonstrates resistance against coalescence. The in-vitro release of drug was higher in Fw/o/w(54±2% in 12 hrs), which after storage was found significantly higher(90±2%). This may be due to transformation from small globules to bigger globules owing to coalescence. Significantly low cumulative drug release(37±4% in 12 hrs.)was observed ion freshly prepared Fs/o/w emulsion, which was not significantly increased even after storage for two weeks(41.5±2% in 12 hrs) this may be due to steric hindrance more strong efficient diffusion barrier and absence of too much coalescence in Fs/o/w.

Formulation	Avg. Dia. mm		% phase Separation	
	Fresh	Stored	Fresh	Stored
Fw/o/w	6.4± 0..5	12.5	0	30
Fs/o/w	6.5± 0.8	8.0	0	7.5

Formulation	% Entrapment		%Drug release in 12 hrs.	
	Fresh	Stored	Fresh	Stored
Fw/o/w	74± 1	40±2	54±2	90±2
Fs/o/w	89± 3	75.5±3	37±4	41.5±2

CONCLUSION

Gelatinization of inner aqueous phase could be successfully used for stabilization of multiple emulsion system and superiority of the s/o/w emulsion as a controlled drug delivery system.

ACKNOWLEDGEMENT

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DEVELOPMENT OF MULTIPLE EMULSIONS FOR IMPROVED DELIVERY OF ANTICANCER DRUGS

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OBJECTIVES

The present study aimed to develop stable multiple emulsion (W/O/W) systems of two anticancer agents, viz., Methotrexate (MTX) and Doxorubicin (DOX) to achieve prolonged release with improved efficacy.

INTRODUCTION

Novel emulsions like lipid emulsions, microemulsions and multiple emulsions have gained particular interest as carriers, especially for lipophilic drugs. Multiple emulsions are the emulsion systems in which the dispersed phase contains smaller droplets that have the same composition as the external phase. They have been termed "Liquid membrane systems", as the thin film separating the liquid phases is like a semipermeable membrane, through which solute must diffuse in order to traverse from one phase to another. Multiple emulsions systems are reported to possess intrinsic lymphotrophic characteristics, and hence have been envisaged for the delivery of therapeutic agents for treatment of cancer metastases and bacterial infections involving the lymphatic system.

EXPERIMENTAL

The w/o/w multiple emulsions of MTX and DOX were formulated by using double emulsification method. Various parameters were optimized to obtain stable multiple emulsions: type of oil, ratio of W:O for primary emulsion, concentration of primary emulsifier (Span 80), selection of secondary emulsifier and its concentration (Tween 80, Pluronic F87 and Pluronic F88), ratio of w/o: W for secondary emulsification, viscosity enhancers (gelatin, albumin CMC and HPMC).

The prepared multiple emulsions were characterized to assess colour, odour, visual appearance, physical stability (creaming, separation and redispersibility), viscosity by Brookefield viscometer, Globule Size by Coulter N4 plus and pH. Selected formulations were considered for incorporation of the model drugs (MTX and DOX). These formulations were evaluated for drug content by UV spectroscopy, in-vitro drug release in pH 7.4 buffered saline. Toxicity of the formulations in Swiss albino mice. In-vitro cytotoxic efficacy of selected formulations was evaluated on *Allium cepa* root meristems and expressed as mitotic index.

RESULTS AND DISCUSSION

The liquid multiple emulsions prepared were stable with average globule size of 2-3mm and 90-95% entrapment. The drug release was prolonged for upto 72 hrs. The formulations were found to be safe as indicated in acute toxicity studies in mice and RBC hemolysis test. Mitotic index of drug solutions and the formulations as calculated from in vitro cytotoxic efficacy studies revealed the prolonged action from the multiple emulsion formulations.

CONCLUSION

It can be concluded that stable emulsions can be used to achieve prolong release of cytotoxic drugs like MTX and DOX. These formulations were safe and efficacious.

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FORMULATION OF FLOATING DRUG DELIVERY SYSTEM USING ION EXCHANGE RESIN

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INTRODUCTION

Ion exchange resins (IERs) are water insoluble, cross-linked polymers containing salt forming groups in repeating positions on the polymer chain. A substantial amount of work has been published concerning the use of IERs for taste masking of active ingredient, tablet disintegration, drug stabilization and sustained release applications. But application of IERs in floating drug delivery systems is limited. Atyabi *et al* (1996) has described a novel gastric retentive system containing IERs based on bicarbonates, which may not be applicable for drugs susceptible to alkaline pH. The objective of this study was to design floating system using Tulsion 344®, a strong acid cation exchange resin which contains polystyrene co-polymer matrix structure with sulphonic acid functional group. Chlorpheniramine maleate (CPM) was chosen as a model cationic drug. The following variables affecting the drug release and floating ability from matrix tablet containing drug without resin, drug-resin complex or physical mixture of drug and resin were investigated: the particle size of resin (< 80μm, 80-150μm and 150 -250μm), amount of resin (1:1.5, 1:2,1:3), type of polymer (HPMC K4M and K15M).

EXPERIMENTAL

Activation of resin was carried out by treatment with 5 N HCl followed by washing with deionised water. Drug-resin complex was formed by batch method where by the resin particles were added to aqueous drug solution and agitated for 24 hours. Drug-resin particles were separated by centrifugation, washed with deionised water to remove unbound drug and dried in dessicator. The active ingredients (drug, drug-resin complex, or drug and resin) and HPMC K4 M and K15M (1:1) were blended uniformly. Tablets were prepared by compressing the powder blend manually on hydraulic press. The dissolution profile and floating ability was studied by USP 24 type II method in 0.1N HCl. Other parameters used for characterization of drug-resin complexes were based on PXRD, DSC, and IR studies.

RESULT AND DISCUSSION

The optimum ratio for the system to float within 15 minutes was observed in the range of 1:1.5 to 1:3 drug to IER ratio. The drug was released fastest from resin-free HPMC tablets but did not show floating. In contrast the release of drug from HPMC tablet containing drug-resin complexes was significantly slower. The drug was not released in deionised water since there were no counterions in the medium to replace drug ions from the ion exchange resin within gelled matrix. Interestingly the similar sustained release pattern along with floating could be obtained by just using physical mixture of drug and IERs rather than preformed drug-resin complex. Upon contact with dissolution medium a gelled layer formed rapidly around solid tablet core and the complex between drug and resin formed in-situ within the gelled regions. The in-situ method was advantageous with regard to simplifying manufacturing process when compared to the use of preformed complexes. The amount of drug binding increased with decreasing particle size of resin thereby retarding the drug release. PXRD, DSC and IR studies also justified the formation of drug-resin complex.

CONCLUSION

In conclusion, the addition IERs to HPMC-matrices showed floating within 15 minutes and significantly modified the release of CPM. A complex between the drug and resin formed in-situ within the gelled matrix and retarded the drug release. The drug release could be varied with the particle size of resin and the drug: resin ratio.

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DEVELOPEMENT OF SUSTAINED RELEASE MATRIX TABLETS OF CAPTOPRIL USING CARRAGEENANS

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INTRODUCTION AND OBJECTIVE

Polymers are widely used to control drug release from tablets. Generally, synthetic or modified natural gums are used for this purpose. Until recently, there were only a few natural gums that could be used to sustain drug release because there was problem with standardization. The raw material showed different compositions depending on harvesting [1]. Carrageenans are natural polysaccharides extracted from seaweed. Today, these seaweeds can be cultivated; therefore, the raw material is much more homogeneous. Till now, Carrageenans were mainly used as gelling and thickening agents. Recently the Carrageenans were thoroughly evaluated for the tabletting properties and it has been found that they are good candidates for preparation of matrix tablets, which could be used for sustained release of the drug [2,3]. Our aim was to prepare a solid oral dosage form with carrageenan as a matrix former. Three Carrageenans two *k*-Carrageenans (Gelcarin® GP-812 NF and GP-911 NF) and one *i*-carrageenan (Gelcarin® GP-379) were evaluated for there potential use as a release retarding agents.

EXPERIMENTAL

Determination of swelling of Carrageenans:

The swelling of three Carrageenans, was measured in a 10 ml cylinder.

Determination of flow properties of Carrageenans

The flow properties of all Carrageenans were investigated by the Carr's method [4].

Tablet preparation

The tablets were made using model drug Captopril and using different concentration of Carrageenans (40, 50, 60, 70 %) with and without added cation. The tablets were made using 9mm S/C punch on a single rotary tabletting machine.

Evaluation of tablets

The tablets were evaluated for their hardness, thickness and friability.

In vitro drug release:

Drug release was analysed using paddle method according to USP 24 in 0.1N HCl (900 ml, 37°C±1°C, 100 rpm) for 12 hours. After proper dilution with 0.1N HCl, the samples were analysed spectrophotometrically at 206 nm

RESULT AND DISCUSSION

The results indicate that all three Carrageenans swell immediately. No carrageenan was found "excellent" in terms of flow, but they were free flowing and could be used in the pharmaceuticals. The tablets made were of good quality.

Their hardness, thickness was good enough and friability was within limits. The drug release behavior shows that *i*-carrageenan was very good candidate for matrix tablets as it sustained the drug release for upto 10 Hrs.

CONCLUSION

The drug release behavior for the tablets made with carrageenans were contradictory to other reports [2,3] where *k*-carrageenan was found a good sustained release polymer after addition of cations. In our case *i*-carrageenan was the best. Addition of cations did not change the in vitro release pattern significantly.

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FORMULATION OF FAST DISSOLVING TABLETS OF VALDECOXIB

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INTRODUCTION AND OBJECTIVE

Valdecoxib 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide, a novel highly selective COX-2 inhibitor is used for a variety of acute and chronic inflammatory diseases.[1] However, low aqueous solubility (< 10 μg/ml) and poor dissolution of this molecule, delays its rate of absorption and finally the onset of action. Solid dispersion has been successfully utilized as dissolution enhancement technique for wide variety of poorly water-soluble drugs. These binary systems could be employed to formulate Fast dissolving dosage forms to provide faster onset of action.

The present study aims at enhancement of dissolution profile of valdecoxib using Polyvinyl pyrrolidone (PVP) as carrier and finally, formulation of a fast dissolving dosage form. Furthermore, the study attempts at deducing the possible mechanism of dissolution rate improvement

EXPERIMENTAL

Phase solubility analysis:

Excess amounts of drug were added to 10 ml of polymer solutions in distilled water (0.05-0.25% w/v) in 25 ml stoppered conical flasks and shaken at 25 ± 0.5° C. At equilibrium, aliquots were withdrawn, filtered (0.45mm pore size) and spectrophotometrically assayed for drug content at 244 nm (Shimadzu-UV 160A Spectrophotometer).

Solid dispersions of valdecoxib and PVP K-30 were prepared by kneading method in 1:1 and 1:2 weight ratios. Fourier transform IR spectra of Valdecoxib, PVP and PVP-Valdecoxib solid dispersions were recorded on Jasco FTIR 5300 spectrophotometer. The scanning range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1} A Perkin Elmer DSC model 7 was used for recording DSC thermograms of Valdecoxib and its solid dispersions. Samples (2-8 mg) heated in open aluminium cells at a rate of 10°C/min between 30 and 300°C temperature range under a nitrogen flow of 40 ml/min.

Powder X-ray diffraction patterns were recorded on a Jeol JDX-8030 powder X-ray diffractometer using Ni-filtered, CuKa radiation, a voltage of 40 kV and a current of 25 mA. The scanning rate employed was 1° min^{-1} over the 10-30° 2q range.

Dissolution studies were carried out using USP-24 paddle method revolving at 50 rpm. Solid dispersion containing 5 mg of drug was subjected to dissolution using 900-mL distilled water. Aliquots withdrawn at predetermined period were analysed spectrophotometrically at 244 nm.

Formulation of Fast dissolving tablets:

Tablets containing solid dispersion were prepared using 16-station single rotary tabletting machine (GMC, India). Tablets were subjected to dissolution test and compared with marketed tablets of valdecoxib.

RESULTS AND DISCUSSIONS

The increment in the aqueous solubility of valdecoxib is in the rank order of PVP K-30>HPMC>Poloxamer-188>PVA. PVP was found to increase the water solubility of valdecoxib by 4 times and therefore PVP was selected for preparation of solid dispersion and further studies.

The characteristic peaks of the drug are present in the IR spectra of solid dispersions indicating there is no significant interaction between drug and carrier in the solid dispersion. X-ray diffractogram and DSC thermal curve suggested that there is no strong interaction at molecular level and drug is dispersed in carrier in its native crystalline form.

The binary systems with PVP K-30 exhibited faster dissolution rates than valdecoxib alone. The significant enhancement of the dissolution rate that occurred with kneaded products may be attributed to improved wetting of drug by reducing interfacial tension, particle size reduction and presence of drug in highly dispersed state in crust of polymer.

Comparison of formulated tablets and marketed tablets in terms of dissolution efficiency clearly indicates that tablets containing solid dispersion perform better.

CONCLUSION

The results from studies shows that dissolution rate of Valdecoxib can be enhanced to a great extent. Though solid state studies revealed absence of any well defined chemical/physicochemical interaction between the components of drug-carrier solid dispersion system, Presence of drug in its crystalline state will ensure higher stability of system in long time. Moreover, kneading method is the industrially acceptable and there is avoidance to exposure of hazardous organic solvent, as may be the case with commonly reported methods, coprecipitation and coevaporation. Hence valdecoxib-PVP binary systems could be considered for formulation of fast-dissolving dosage forms of valdecoxib.

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GASTRORETENTIVE DRUG DELIVERY SYSTEM

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OBJECTIVES

To improve oral bioavailability of Verapamil hydrochloride by designing a controlled release gastroretentive dosage form.

INTRODUCTION

Verapamil hydrochloride is a calcium channel blocker, widely prescribed in management of essential hypertension. It is available as conventional tablet with dose ranging 40 mg – 180 mg to be administered 2-3 times a day. Also available as 120 mg – 240 mg once a day dosage form. Verapamil hydrochloride has maximum solubility at gastric pH (360 mg/ml) than at intestinal pH 6.8 (54 mg/ml).

Present work focuses on development of once a day controlled release oral tablets with gastroretentive properties containing 120mg of verapamil hydrochloride. This would enhance absorption of verapamil hydrochloride, improving its bioavailability and favorable pharmacokinetics in comparison to conventional tablets currently in use.

EXPERIMENTAL

Gastroretentive floating tablets were formulated using following criteria viz

A small 'collapsed' configuration which enables convenient oral intake.

Expanded form that is achieved in stomach and thus preventing passage through pyloric sphincter (more than 2 cm-2.5 cm)

Finally reduced form, which would evacuate from stomach after releasing the drug.

Caplets of dimension 7mm X 17mm were prepared by dry blending of verapamil hydrochloride (120mg), swellable polymers (hydrophilic cellulose derivatives), gas generating agent along with suitable diluents. The ratio of drug: polymer was optimized from 1:1.5 to 1:2 and also amount of bicarbonate source was optimized from 25 mg to 100 mg using factorial design. Marketed SR tablets of Verapamil hydrochloride was evaluated for *in-vitro* drug release profile.

Tablets were evaluated for dimensions, weight variation, hardness, drug content, *in-vitro* drug release, swelling characteristics, floating time and floating lag time. *In-vitro* drug release studies were carried out in 900 ml of pH 1.2 buffer using USP XXIII pharmacopoeial convention dissolution method for extended release dosage forms. The optimized formulation was subjected to stability studies as per ICH guidelines.

RESULTS AND DISCUSSION

The developed formulation showed uniform extended release of more than 90% in 12 hrs. The release followed Higuchi kinetics; diffusion through gel barrier being the primary mechanism for drug release. Tablets disintegrated at lower polymer concentration whereas release was retarded for a longer period of time at higher polymer concentration. The drug content was found to be within limits and tablets remained buoyant for more than 12 hrs.

CONCLUSION

A floating dosage form of Verapamil hydrochloride was formulated. This type of dosage form can improve therapeutic efficacy of acid soluble drug, Verapamil hydrochloride. The optimum quantity of swellable polymer and gas generating agent was required to impart buoyancy to the system and desirable dimension after swelling to prevent its gastric emptying through pylorus.

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INDION 414: A POTENTIAL SUPERDISINTEGRANT

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OBJECTIVE

Ion exchange resins are cross-linked polymers containing salt forming groups in repeating positions on the polymer chains. Their swelling property makes them ideal candidate as superdisintegrants. The aim of the present investigation was to evaluate the efficacy of Ion exchange resin (Indion 414) as superdisintegrant in fast disintegrating dosage forms and also comparison of its activity with conventional superdisintegrants.

INTRODUCTION

The scope of ion exchange resins in pharmaceutical use is wide and inexhaustible. The conventional superdisintegrants used in formulation of fast disintegrating dosage forms [1,2] are expensive thus adding to the cost of final product. Ion exchange resins, being swellable, could be explored in formulating these dosage forms. Indion 414 is off- white, odorless and free flowing powder having good compressibility. It is compatible with actives and excipients and no combination with other superdisintegrants required. Indion 414 is cost effective and proved to be safe for oral use. Drugs from various classes like antibiotics, antiasthmatics, antispasmodics and antihistaminics were selected. They were formulated into fast disintegrating dosage forms using Indion 414 as superdisintegrant.

EXPERIMENTAL

U.V spectroscopy, Colorimetry, HPLC methods of analysis were developed for analysis of the drugs.

Antibiotics like Roxithromycin, Ofloxacin and antispasmodic Dicyclomine HCl were taste masked using cross linked polymers and incorporated into mouth dissolve tablets using granulation technique.

Mouth dissolve tablets of antiasthmatic Montelukast Sodium were formulated using direct compression technique.

Melt in mouth pellets of Chlorpheniramine maleate and Pseudoephedrine hydrochloride were formulated using Extrusion Spheronization technique.

In all the above formulations, Indion 414 was added a superdisintegrant. Also formulations containing conventional superdisintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone were prepared for comparative purposes.

Formulation were evaluated for physical properties, organoleptic properties, assay and drug release. *In-vitro* dispersion time was measured by dropping the tablet in the beaker containing 6 ml water. *In-vivo* dispersion time was noted after administration to human volunteers.

RESULTS AND DISCUSSION

Mouth dissolve tablets of the drugs could be successfully formulated. Various concentrations of Indion 414 were employed to arrive at an optimum disintegration time. The disintegration time of the tablets was 15-25 seconds with a resin concentration of 2-5%. The tablets containing Indion 414, Croscarmellose sodium, Sodium starch glycolate appeared smooth with a good mouthfeel. Tablets containing crospovidone had a pitted appearance. Indion 414 was found to be effective in both direct compression and wet granulation techniques. Also, Indion 414 could be successfully incorporated in melt in mouth Chlorpheniramine maleate and Pseudoephedrine hydrochloride pellets. The rapid wicking action of Indion 414 aided in softening of pellets. Conventional superdisintegrants failed to soften the pellets. The formulations exhibited optimum physicochemical properties.

CONCLUSION

Ion exchange resins can act as very good superdisintegrants thus replacing the expensive ones.

No combination of superdisintegrants is required. Their use can be extended to many other fast disintegrating dosage forms and can help in developing a cost effective formulation.

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CONSUMER FRIENDLY MUCOLYTIC FORMULATIONS

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OBJECTIVE

Convenience of administration and patient compliance are gaining significant importance in the design of novel drug delivery systems. Recently, more stress is laid on the development of organoleptically elegant drug delivery systems for pediatrics. The present investigation was focused to formulate patient friendly, taste masked formulations viz. melt tablets and jelly of Ambroxol hydrochloride for pediatrics.

INTRODUCTION

Melt tablets are dosage forms that dissolve or disintegrate quickly in the oral cavity, resulting in solution or suspension and have pleasant taste. Jellies are a class of gels in which the structural coherent matrix contains a high proportion of liquid usually water. Ambroxol hydrochloride is a mucolytic used to reduce sputum viscosity to facilitate expectoration in chronic asthma and bronchitis.

EXPERIMENTAL

A simple HPLC method for the assay of Ambroxol hydrochloride was developed and validated. Also, UV spectrophotometric method for routine analysis was developed and validated.

Jelly – The jelly base was prepared using polyacrylic acid resin, natural polysaccharides etc as gelling agents. Sugar and artificial sweeteners were added to improve the palatability of the formulation. Further, Ambroxol hydrochloride was incorporated in the jelly base. The formulation was flavored and color was added for aesthetic appeal.

Melt tablets – Ambroxol hydrochloride was mixed in geometric proportions with sweeteners, superdisintegrants, flavors and diluents. The resulting mix was screened through 40# and was further mixed with lubricants. The blend was then compressed on Cadmach single tablet press machine equipped with 10 mm standard concave punches. Taste masking was achieved by various sweeteners, flavors and several combinations of both.

Jelly was evaluated for quality control parameters like appearance, pH, taste, rheology, assay, *in-vitro* drug release. Also, Melt tablets were evaluated for physical properties, organoleptic properties, assay, *in-vitro* dispersion time, *in-vivo* dispersion time and *in-vitro* drug release.

RESULTS AND DISCUSSION

Ambroxol hydrochloride exhibited ëmax (UV spectroscopy) at 307 nm and the linearity range was found to be 20-100 mg/ml. Ambroxol hydrochloride was detected by HPLC at a flow rate of 0.8 ml/min. The mobile phase employed was 0.01M phosphate buffer:Acetonitrile. The linearity range was found to be 1-10 mg/ml.

In case of jelly, the concentration of polyacrylic acid resin and sweeteners was optimized to offer a clear product of optimum viscosity so as to remain in contact with respiratory mucosa. In case of melt tablets, various concentrations of superdisintegrants were tried to arrive at an optimum disintegration time. Also the quantity of flavors and sweeteners were optimized.

The formulated jelly and melt tablets tasted non-bitter with a good mouth feel. The melt tablets disintegrated within 30 seconds. Both the formulations showed more than 80% of drug release within 30 minutes. Viscosity data indicated that the jelly had a thixotropic behavior, offering ease of administration. Both the formulations exhibited optimum physicochemical properties.

CONCLUSION

Palatable melt tablets of Ambroxol hydrochloride for pediatrics were formulated with in-vivo disintegration time

of 30 seconds. Taste masked jelly with optimum physicochemical properties were formulated. This novel approach to the treatment of cough would appeal to the pediatrics.

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FORMULATION AND BIOPHARMACEUTIC EVALUATION OF SELF-MICROEMULSIFYING DELIVERY SYSTEMS OF NIMODIPINE

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OBJECTIVE

The objective of the present instigation was to enhance solubility, in turn vitro release and ultimately oral bioavailability of NIM using Self-Microemulsifying Drug Delivery Systems.

INTRODUCTION

Self-Microemulsifying Drug Delivery Systems (SMEDDS) are mixtures of oil and surfactant(s) which form fine oil-in-water emulsions when introduced into aqueous phase under conditions of gentle agitation. SMEDDS represent a possible alternative to the more traditional oral formulations for lipophilic compounds. The delivery system is expected to self-emulsify rapidly in aqueous contents of stomach, presenting the drug in solution in the form of small oil-droplets. These fine oil-droplets empty their contents into GI tract. SMEDDS offer an improvement in both rate and extent of absorption and thereby reproducibility of plasma profiles. In present investigation, SMEDDS have been developed for Nimodipine (NIM) - a dihydropyridine class calcium channel blocker prescribed for prevention and treatment of ischaemic neurological deficit following subarchnoid haemorrhage. NIM has oral bioavailability 10%. The low oral bioavailability is attributed to its poor water solubility leading to dissolution rate dependant absorption.

EXPERIMENTAL

All the materials used in the formulating SMEDDS were GRAS listed. Gelucires were used as oily phase, surfactants used were caprylocapryol macrogolglyceride, diethylene glycol monoethyl ether, Polyglyceryl oleate FCC.

An UV-Spectrophotometric method was developed for in vitro drug release study. A validated stability indicating HPLC method was developed to monitor stability of SMEDDS during shelf life as per ICH guidelines. The drug plasma concentrations were quantified by HPLC method. A sensitive plasma extraction method was developed and validated.

The GRAS listed components for the development of SMEDDS were selected depending on NIM solubility in oils, surfactants and cosurfactants.

The developed SMEDDS were evaluated by:

1) Pseudoternary Phase diagrams: Using cross polarizer.
2) *Self-microemulsification efficiency:* By visual inspection.
3) Particle size analysis: using Photon Correlation Spectroscopy.
4) In vitro release: using USP Apparatus I, Medium: Distilled water (900 ml),

   Speed: 100 rpm, 37°±1C.
5) Stability studies: The stability studies were carried out as per ICH guidelines.
6) In vivo studies: A cross over study was designed in healthy rabbits divided in four groups: Oral solution

(Ethanolic solution of NIM), NIM SMEDDS, oily solution, micellar solution and drug powder. Dose: 5 mg/kg.

RESULTS AND DISCUSSION

Pseudoternary Phase diagrams helped to screen a small number of formulations from a large pool of formulation in the area of microemulsion existence. The Km (Surfactant/cosurfactant) ratio was optimized by comparing area of microemulsion existence at various stages. Depending on self-microemulsification efficiency and particle size measurements (<300 nm), ratio of oil to surfactant was optimized. The optimized NIM SMEDDS showed > 90% in vitro release in 10 minutes. The in vivo studies in rabbits showed enhanced relative oral bioavailability from NIM SMEDDS. The relative oral bioavailability compared to oral solution was found in order: SMEDDS>Micellar solution>oily solution>drug powder. Fine oil droplets would be expected to empty rapidly from stomach, distribute throughout the GI tract and provide larger surface area for drug partitioning.

CONCLUSION

For the class II drugs in BCS undergoing dissolution rate limited absorption, significant improvement in reproducibility and bioavailability may be realized with self-microemulsifying formulations as observed in nimodipine.

ACKNOWLEDGEMENT

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TASTE MASKED AZITHROMYCIN DOSAGE FORMS

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OBJECTIVE

The aim of the present investigation was to develop and evaluate taste masked Oral Suspension and Dispersible Tablets of Azithromycin dihydrate.

INTRODUCTION

Azithromycin dihydrate, a macrolide antibiotic commonly prescribed for pediatric infections of the respiratory tract and middle ear is extremely bitter in taste which hampers patient acceptability. One of the major challenges in research today lies in the development of palatable and patient compliant dosage forms. The thrust of the present study involved the formulation of non-bitter Oral Suspension and Dispersible Tablets of Azithromycin dihydrate using cross linked polymer as a complexing agent. The importance of study increases manifold as the drug is going off patent in the year 2005, increasing competition for generic products.

EXPERIMENTAL

Analytical Method Development:

Azithromycin dihydrate was analyzed by Colorimetry, using Folin-Ciocalteau reagent in presence of 20% sodium carbonate at 751 nm.

Taste masking of Azithromycin dihydrate:

Azithromycin dihydrate was complexed with cross linked polymer in different ratios. The quantity of polymer required to completely mask the bitter taste of the drug was optimized.

Formulation Development:

1. Oral Suspension: The taste masked complex of Azithromycin dihydrate and the polymer was incorporated into a prototype suspension base.
2. Dispersible Tablets: Dispersible tablets of taste masked Azithromycin-polymer complex were formulated by direct compression technique using excipients like superdisintegrants (Ac-di-sol), sweetners and lubricants.

Evaluation of Formulations:

The Oral suspension was evaluated for characteristics like appearance, taste, pH, particle size distribution, rheological behavior, drug content, and *in vitro* drug release.

The Dispersible tablets were evaluated for taste, appearance, dimensions, drug content, dispersion time, fineness of dispersion and *in vitro* drug release.

Also, subjective evaluation of both the optimized formulations was carried out on a panel of 10 healthy human volunteers.

RESULTS AND DISCUSSION

Analytical Method Development:

The linearity range of standard curve of Azithromycin in 0.1 HCl was 10-60 mg/ml with a slope of 0.01± 0003.

Taste masking of Azithromycin:

Complete taste masking of Azithromycin dihydrate was achieved in 1:3 ratio of drug and polymer.

Formulation Development and Evaluation:

1. Oral Suspension: Azithromycin dihydrate could be incorporated into a palatable and non bitter suspension. Viscosity data indicated that the suspension had a thixotropic behavior, offering ease of administration. The particle size studies revealed that the suspension was of polydispersed nature.

2. Dispersible tablets: The taste of the developed tablets was perceived non bitter with good mouthfeel as compared to the marketed dispersible tablets of Azithromycin.The dispersion time of developed dispersible tablets was found to be 45-50 seconds.

The drug content of the formulations was found to be within limits and released more than 80% of Azithromycin in 30 minutes. Both the formulations were well accepted by all 10 volunteers.

CONCLUSION

Azithromycin dihydrate could be successfully taste masked using the technique of complexation.The taste masked drug polymer complex could be effectively incorporated into patient compliant oral suspension as well as dispersible tablets having optimum physicochemical properties.

ACKNOWLEDGEMENTS

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SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF VALDECOXIB

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OBJECTIVE

The objective of the investigation is to develop self microemulsifying drug delivery system of a poorly water soluble NSAID; Valdecoxib.

INTRODUCTION

SMEDDS are isotropic mixtures of oil, surfactants and co-surfactants which when introduced into the body rapidly disperse to form droplets of approximately the same size range as those observed in micro emulsion systems. Once dispersed such systems would be expected to behave in vivo much the same way as oil-in-water microemulsion and these fine droplets empty their contents in to the gastrointestinal tract. The SMEDDS can serve as a very good approach of delivering poorly water soluble drug so as to increase its rate and extent of absorption and ultimately to increase the oral bioavailability of the drug. In the present experiment Valdecoxib has been chosen as a poorly water soluble drug (10μg/ml) and SMEDDS of Valdecoxib has been developed. Valdecoxib, a potent NSAID, a Cyclooxygenase-2 (COX-2) inhibitor is used as an oral analgesic and anti-inflammatory drug. Valdecoxib is indicated in the treatment of primary dysmenorrhoea and for symptomatic relief in osteoarthritis and rheumatoid arthritis. It has an elimination half life of 8.11 hrs and Tmax of 2.25 hrs justifying the selection of SMEDDS.

EXPERIMENTAL

All the materials used in formulating SMEDDS were GRAS approved.

Oil phase: Medium chain triglycerides & mono and di glycerides of Caprylic/ Capric acid.

Surfactants: Caprylocaproyl Macrogolglycerides, Polyoxyl castor oil, Purified diethylene glycol mono ethyl ether, Gelucires.

Formulation:

Various oils, surfactants and co-surfactants were screened for the development of SMEDDS based on saturation solubility studies of drug in their respective components and pseudoternary phase diagrams.

Evaluation of SMEDDS:

The developed system was evaluated for:

Ability to self microemulsify by visual inspection.

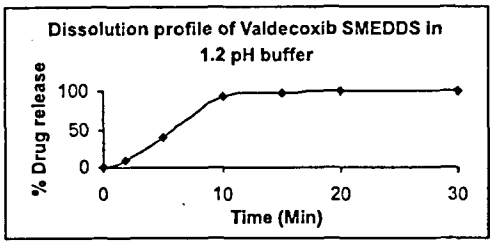
Particle Size Analysis using Photon Correlation Spectroscopy.

In vitro release studies using USP Apparatus I and II, Medium: 1.2 pH buffer solution (900ml), Speed: 50 and 100 rpm at 37±1°C.

Stability studies: The stability studies were carried out as per ICH Guidelines.

RESULT AND DISCUSSION

UV Spectrophotometric method was developed for in vitro drug release study. Various formulations were screened from a large pool of formulations in the area of microemulsion by plotting pseudoternary phase diagrams. The ratio of



Gelucire/Surfactant (0.25, 0.5, 1.0, 1.5 and 2.0) was further optimized and depending on the self microemulsification efficiency, ratio of oil to surfactant ratio was optimized. The system was found to be transparent, having optimum viscosity and surface tension to be filled in size "0" hard gelatin capsule. The in vitro dissolution studies showed more than 85% release in 10 minutes.

CONCLUSION

SMEEDS of Valdecoxib as a fast release capsule dosage form has been successfully developed to provide the drug in solubilised form to enhance absorption of the drug through gastro- intestinal tract.

ACKNOWLEDGEMENT

The authors are thankful to Glenmark for the gift sample of Valdecoxib, ACG for hard gelatin capsule, Colorcon Asia Pvt. Ltd. for providing Gattefosse excipients and BASF for surfactants.

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SMETS®: A NOVEL FAST RELEASE DOSAGE FORM

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OBJECTIVE

To develop SMETs® of loratadine to enhance its solubility.

INTRODUCTION

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra and inter subject variability and lack of dose proportionality. One of the techniques reported to enhance the bioavailability of such drugs is use of lipid based drug delivery systems. Bioavailability of active moiety can be improved by utilizing anhydrous microemulsion and formulating the system as a Self Microemulsifying Tablets. The present study reports utilization of Self Micro-emulsifying Drug Delivery Systems (SMEDDS) to formulate a convenient and robust and stable dosage form referred to as SMETs® of Loratadine. Loratadine, structurally related to antihistamine azatadine and Cyproheptadine, is used in the treatment of seasonal rhinitis chronic idiopathic urticaria. It has longer elimination half life and its bioavailability fluctuates with fed condition. Justifying its rationale for selection as a model drug for SMETs®

MATERIAL AND METHOD

Loratadine was procured from Cadila Pharmaceuticals Ltd. Ahmedabad, Peceol, Labrafil M 1944 CS, Maisine, Labrafac CC, Labrafil M 2125 CS, Gelucire 44/14, Labrasol, Transcutol P and Caproyl – 90 were procured from Gattefosse France through Colorcon India ltd. Cremophore EL was gifted by BASF, Tagot TO was gifted by Gotaschmidt Germany, Aerosil was obtained from Ajanta Pharma, Mumbai, Avicel PH 101, Primojel and Pearlitol SD 200 were obtained from Signet Chemical Corporation, Celactose was procured from Anshul agencies, Carbopol 934 P was gifted by Noveon Asia Pacific, flavors (powdered) were gifted by Bush Boake Allen India Ltd and Magnesium stearate was obtained as generous gift from Yash Pharma mumbai. Other chemicals and solvents were of AR/ GR grade procured as commercial sample and used as they were received.

For SMEDDS the excipients screened for solubility of drug included Sunflower oil, Peceol, Labrafil M 1944 CS, Maisine, Labrafac CC, Labrafil M 2125 CS, Cremophore EL, Tagot TO, Caproyl 90, Labrasol, Transcutol P and Gelucire 44 / 14. Screening was based on miscibility and compatibility of oil:surfactant mixture as well as globule size of the resulting SMEDDS.

SMEDDS of Loratadine were prepared by utilizing Caproyl 90 as oil phase and Labrasol, Transcutol P and Gelucire 14/44 as the surfactant system. The composition was selected using ternary phase diagram. The SMEDDS were adsorbed on to inert excipients and the resulting dry adsorbate was passed through 60 # sieve, mixed with other auxiliary tablet excipients. The dry mixture was evaluated for flow properties, compressibility and tablets were compressed using 12 mm circular flat beveled punches.

The resulting tablets were evaluated for various parameters including appearance, shape, hardness, disintegration time, friability, variation, drug content and release profile.

RESULT AND DISCUSSION

1. Selection of type and quantity of oil, surfactant and co-surfactant are critical with respect to drug (API). For Loratadine Caproyl 90 was selected as oil phase and Labrasol-Transcutol P-Gelucire surfactant system was finalized.

2. Selection of adsorbent and quantity should be monitored or else results in leaching of oil from tablet. It also leads to structurally weak tablets.

3. The resulting SMETs® (average weight 517±15.25 mg and drug content 101.09 % ± 1.69 with 12.3 2 ± 0.029 mm in diameter) disintegrate in 40-50 sec. with hardness of 4-5 kg/cm^2, which is sufficient to maintain tablet integrity during packing and shipping.

4. The resulting SMETs® release more than 97% of the drug with in 5 minutes in 1.2 pH buffer.

5. The SMETs® were found to be stable physically and chemically for 3 months at room temperature, 60% RH/ 30° C, 75% RH/ 40°C.

CONCLUSION

The case study undertaken demonstrates successful use of SMETs® as fast release dosage forms which may present advantages associated with lipid based drug delivery systems. (Apparently improvement in both rate and extent of absorption).

ACKNOWLEDGEMENT

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CUBIC LIQUID CRYSTALLINE PHASE FOR THE ORAL DELIVERY OF ENZYMES

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INTRODUCTION

Liquid crystalline system has been recently used as a reservoir from which drug releases by diffusion through the water channels of matrix. Glyceryl monooleate (GMO or monoolein) is popular amphiphilic compound, when placed in aqueous environment, it swells and forms several lyotropic liquid crystalline structures, which include lamellar phase, the cubic phase and the transferosomes. A globular protein has same size as the dimensions of water channels in the bicontinuous cubic phases. These characteristics of cubic phase thus make it potentially useful excipient for peptide drug delivery. Serratopeptidase (52kDa), when consumed in unprotected form, the enzyme is destroyed by the acid in the stomach. The cubic phase reduces diffusion coefficient of water and incorporated peptide and thus due to reduction in translational mobility of peptide and water, it may protect an incorporated protein from degradation. Recently our group has demonstrated application of GMO in floating drug delivery system. Magnesium trisilicate(MTS) was included in matrix with the objective that it would prevent floating of GMO matrix and provide a basic microenvironment required for stability of enzyme. Gelucire 43/01 a hydrophobic polyglycolyzed glycerides was incorporated to delay and prolong release.

EXPERIMENTAL

Glycerol monooleate was taken in a beaker and melted at 55°C on water bath, to which MTS or GelucireÒ 43/01 and serratopeptidase was added with stirrer. The molten mass was poured in fabricated cylindrical moulds and frozen at −15° C. The matrices was equilibrated at room temperature for 6 hrs before evaluation. The movement of matix to intestine was confirmed by Gamma Scintigraphy, proteolytic activity was assayed using casein as a substrate, the degree of swelling is determined by Roy and Rohera method and in-vitro drug release testing was done in triplicate using USPXXIV typeII dissolution testing apparatus.

RESULTS AND DISCUSSIONS

The matrix system did not float and remain intact during dissolution. Similarly scintigraphic study confirmed its passage to intestine in two hrs. treatment of the matrix for two hrs in 0.1N HCl has shown that the incorporation of MTS provided protection to the enzyme resulting in higher activity. In plain GMO matrix activity retained was only 15%, whereas in case of MTS alone or combination of MTS and GelucireÒ 43/01activity was found to be >100%. Retention and increase in activity is due to divalent cation is reported. MTS reduces the water uptake by GMO matrix as its concentration increased thereby reducing the release of serratopeptidase. Incorporation of MTS into lipid bilayer reduces the volume of water uptake in the two aqueous channels and causes resistance to the movement of macromolecule from the bilayer structure to the aqueous channels, in so doing it limits release of drug by diffusion. Its alkaline nature provides the basic microenvironment and protects serratopeptidase from acidic environment, alter the environment for enzyme stability. Therefore incorporationof MTS has improved enzyme stability in three ways –

i) Effect of divalent cation, ii) reduction in HCl uptake and iii) providing basic microenvironment. Apart from MTS, GelucireÒ 43/01 has further reduced water uptake and prolonged drug release.

CONCLUSION

this work demonstrated that cubic liquid crystalline phases of glyceryl monooleate are suitable for delivery of enzymes. Further incorporation of excipients with magne-

sium trisilicate and GelucireÒ 43/01 could help to delay the release and protect the peptide drug from degradation.

ACKNOWLEDGEMENTS

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PANCREATIN MICROSPHERES IN COMBINATION WITH GASTRIC ACID INHIBITORS AND *IN VIVO* ASSESSMENT USING A CHRONIC PANCREATITIS ANIMAL MODEL FOR SITE-SPECIFIC DELIVERY

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INTRODUCTION

Exogenously administered pancreatin enzymes from animal sources have been extensively used to remedy the digestive disorders caused by pancreatin enzyme deficiency[1]. Multiparticulate microsphere delivery systems using enteric polymers would circumvent the gastric inactivation; provide optimal mixing with food contents and target release in duodenum. Combination of pancreatin microspheres with gastric acid inhibitors like omeprazole, a proton pump inhibitor, and famotidine, H_2 antagonist would optimize the intraduodenal pH by diminishing free acid and provide a proper environment for the activity of the pancreatin enzymes.

OBJECTIVES

- To prepare and evaluate multiparticulate delivery systems of pancreatin enzymes by microencapsulation and to protect their degradation in acid environment using enteric polymer.
- To study the effect of gastric acid neutralization by proton-pump inhibitors and H_2 antagonists on the enzyme replacement therapy.
- Develop a suitable animal model with pancreatin insufficiency & further elucidate the in-vivo efficacy of the developed formulations.

EXPERIMENTAL

Pancreatin microspheres (ECPM) were prepared by emulsification phase separation-solvent evaporation technique with HPMCP as enteric polymer at varying core-coat ratios. A 2^2 factorial design was used to optimize process variables. Selected formulations were assessed for enzyme content – lipase, amylase and protease, encapsulation efficiency, DSC & SEM studies. Dissolution profile at varying pH buffers was determined to simulate duodenal conditions which vary extensively in patients with chronic pancreatitis. Combination formulations with omeprazole & famotidine were prepared and subjected to evaluation of physicochemical characteristics.

The chronic pancreatitis model was induced by sustained alcohol intoxication and high-fat liquid diet in albino rats. Induction of chronic pancreatitis was monitored by measuring changes in serum pancreatic amylase, serum triglycerides & serum bilirubin levels. Fecal fat content was determined by gravimetric analysis at weekly intervals to check for development of steatorrhoea[2]. Rats induced with alcoholic chronic pancreatitis were treated with ECPM and role of omeprazole and famotidine in neutralizing acid secretions was evaluated.

RESULTS & DISCUSSIONS

ECPM with core-coat ratio of 2:1 provided sufficient gastric resistance. DSC studies indicated no interaction between the polymer and encapsulated enzymes. SEM studies indicated that the microspheres were spherical in shape and had a uniform deposition of polymer on the enzyme surface. ECPM released enzyme contents within 5mins. in

alkaline conditions dispersing throughout the dissolution media as compared to the marketed tablets which took almost 30mins. to disintegrate. In buffers below pH 6.0, the release was affected by creating an alkaline microenvironment with 0.5% sodium bicarbonate. Alcohol in concentrations 5.68gm/kg body weight/day and olive oil 1mL/day induced chronic pancreatitis within 5 weeks. With the progression of pancreatic injury, fecal fat levels were significantly elevated, indicating development of steatorrhoea. In groups treated with combination formulations of omeprazole and famotidine, fecal fat content was significantly lower compared to ECPM monotherapy at the end of 4 weeks (fig 1).

CONCLUSION

Encapsulating pancreatin enzymes within enteric polymers offered protection and gastric resistance. The enzymes were released rapidly in the alkaline pH. Development of animal model provided useful information regarding mechanisms of alcoholic chronic pancreatitis. Pancreatin in combination with H_2 antagonist- famotidine & proton pump inhibitor- omeprazole helped to combat the acidic conditions in stomach and resulted in better enzyme replacement therapy in animal model.

ACKNOWLEDGEMENTS

Signet Chemical Corporation, Mumbai for financial support.

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SUSTAINED RELEASE NANOPARTICLES: NOVEL DRUG DELIVERY SYSTEM FOR GLICLAZIDE

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INTRODUCTION

The major hurdles with delivery of gliclazide, a second-generation oral hypoglycemic agent are poor aqueous solubility, delayed absorption (2-8 hrs) coupled with its short half-life (1.5- 4 hrs) and low bioavailability (60-80%)[1]. Nanoparticles are 'unique' colloidal drug delivery system with dual features, which can enhance solubility and dissolution rate of poorly water-soluble drug thereby improving bioavailability while providing controlled drug delivery[2].

The present study deals with the development of sustained release nanoparticles of gliclazide to overcome the bioavailability problems of gliclazide while providing an effective, patient compliant alternative to conventional drug delivery.

OBJECTIVE

The objective of present study includes:

Preparation of the drug loaded Eudragit nanoparticles (ENP).

Optimization of ENP for high drug loading, encapsulation efficiency and decreased particle size.

In- vitro and in- vivo evaluation of the ENP as a controlled release carrier for gliclazide

EXPERIMENTAL

Analytical method development of gliclazide:

a) Simple UV-Spectrophotometric method was developed for routine analysis of gliclazide.

b) Stability indicating HPLC method was also developed.

Preparation of nanoparticles:

Eudragit L 100 nanoparticles (ELNP): Eudragit L 100 nanoparticles were prepared by controlled precipitation method and solvent evaporation method.

Eudragit RSPO nanoparticles (ERNP): Eudragit RSPO nanoparticles were prepared using solvent evaporation method.

***In- vitro* evaluation of nanoparticles:**

Encapsulation efficiency: Encapsulation efficiency of nanoparticles (NP) was evaluated for monitoring drug loss during nanoparticles preparation. NPs were also evaluated for

- Drug content
- Particle size analysis Coulter N4- Plus (Beckman submicron sizer)
- Drug-release study

Nanoparticles were also characterized by IR Spectra and DSC studies.

***In- vivo* evaluation of nanoparticles:**

Selected nanoparticulate formulations of ELNP and ERNP were evaluated for decrease in blood glucose level (BGL) in albino wistar rats by using following models:

Streptozotocin- Induced Diabetic Rat Model.

Glucose Loaded Diabetic Rat Model

RESULT AND DISCUSSION

Eudragit nanoparticles were optimized for drug loading, encapsulation efficiency and particle size. ELNP and ERNP revealed sustained release in dissolution medium of various pH. In streptozotocin –induced diabetic rat model, both ELNP and ERNP revealed significant sustained decrease in blood glucose level as compared to plain gliclazide. In Glucose loaded diabetic model, ELNP and ERNP treated rats (normal as well as diabetic) showed significant sustained tolerance to orally administered glucose as compared to plain gliclazide treated animals.

CONCLUSION

Sustained release Eudragit (L100 and RSPO) nanoparticles of gliclazide were successfully formulated with optimum drug loading, encapsulation efficiency and particle size. In- vivo studies in glucose loaded model and diabetic rat model showed sustained activity of ENP as compared to gliclazide treated animals. Hence, the developed oral Eudragit nanoparticles of gliclazide would be novel effective approach to conventional gliclazide tablets.

ACKNOWLEDGEMENT

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NOVEL DIVISIBLE MATRIX SYSTEM FOR ORAL CONTROLLED DRUG DELIVERY

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INTRODUCTION

Diltiazem hydrochloride, a potent calcium channel blocker, is widely used for the treatment of angina pectoris and hypertension. Its high aqueous solubility, short elimination half-life (3-5hr), and use in chronic diseases make it a suitable candidate for sustained release formulations [1]. It is available as immediate release and sustained release capsules and tablets. The doses vary form 60 - 240 mg for sustained release dosing.

Scored tablets provide dose flexibility for increasing and decreasing dosage schedules, ease of swallowing for big sized tablets and may reduce the cost, both for the producing industry as well as for the pharmacy and the patient. However many patients are confronted with scored tablets that are broken unequally and with difficulty; often leading to loss of mass on breaking, reducing compliance and reliance on the drug. Moreover the separation of conventional divisible tablet exposes a substantial amount of new surface area, these tablets are unsuitable for multiple dosing of oral sustained release preparations, as the increased surface area would alter the drug release rate.

OBJECTIVE

The objective of the present study were dual:

a) Design of an innovative punch design for divisible tablets with -

   i) Ease of breaking.

   ii) Minimal increase in surface area.

b) Controlled release tablets with pH independent drug release.

EXPERIMENTAL METHODS

A UV spectrometry method was developed for the estimation of Diltiazem hydrochloride at

λ_{max} 235 nm. A dose of 180 mg was selected for the development of the once - a - day, divisible, oral controlled release drug delivery system. Tablets were prepared by wet granulation technique using a blend of polymers and different release modulating agents to obtain an optimum formulation. The tablets were compressed on a single stroke Cadmach tablet press using an innovative caplet punch designed in our research lab. The tablet hardness was kept at 4-5 kg/cm^2. The tablets were evaluated for various parameters viz. hardness, appearance, weight variation, dimensions, friability, drug content uniformity and uniformity of mass on sub dividing into segments. In-vitro dissolution tests was carried out on half, two half together and full tablet (n=3) using pH change method i.e. 0.1N HCl / pH 1.2 (0 - 2 hrs.), pH 4.5 phosphate buffer (2 - 4 hrs.) and pH 7.4 phosphate buffer (4 - 24 hrs.). The effect of pH on drug release was also studied.

RESULTS AND DISCUSSION

The tablets passed the tests for weight variation and friability as laid down in the Pharmacopoeia. The low RSD (< 2%) for both half and full tablets were indicative of excellent content uniformity. The tablets passed the test for uniformity of mass on sub dividing into segments (not more than 1%) [2].

The in vitro dissolution studies indicated a similarity [f2 test] in the release rate of the drug from the half, two half together and the full tablet and that they all follow the Higuchi kinetics. Also the similarity [f2 test] in the drug release profiles at various pH (pH 1.2, pH 4.5 and pH 7.4) suggested a pH independent drug release.

CONCLUSION

The use of the novel tablet design and a simple matrix system readily amenable to scale up; provides a simple, patient friendly, reliable and cost effective means for precise fractional dosing of many sustained release medicaments.

ACKNOWLEDGEMENTS

Natco Pharma, Hyderabad, India - for the gift sample of Diltiazem hydrochloride.

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ERODIBLE OSMATS FOR POORLY SOLUBLE DRUG

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INTRODUCTION

Osmotic drug delivery system utilizes osmosis as the major driving force for drug release. Adequate water solubility of the drug is prerequisite for osmotic drug delivery systems. This was a major factor limiting the use of such systems for poorly soluble drugs. However, various approaches have been designed to modify the basic system to combat this limitation. These mainly include increase in water flux through the use of high permeability polyurethane membranes ,Zer-os tablet technology, osmagent coated with elastic semi permeable membrane[1], microporous coats, permselective and asymmetric membrane coating etc.

OBJECTIVE

The objective of the present investigation is the design of a novel osmotic drug delivery system by the judicious use of erosional and osmotic phenomenon for improved control of release kinetics for poorly soluble drug Roxithromycin[2], a macrolide antibiotic, was selected as a model drug.

EXPERIMENTAL

A simple, precise and specific colorimetric method has been developed for analysis of Roxithromycin involving condensation reaction (colour formation) between hydrolysis product of Roxithromycin and p-dimethylaminobenzaldehyde in acetic acid environment. The yellowish orange chromogen formed was estimated at 484nm.

Osmats containing 300mg Roxthromycin was prepared by conventional direct compression technique. Osmats were evaluated for following parameters namely physical appearance, dimensions, hardness, friability, drug content and in-vitro drug release. Effect of formulation variables viz. type of polymer (Carbopol 71G, Eudragit, HPMC K100, Kollidone SR), concentration of polymer, conc. of osmagent, pH modulating agent on release rate were studied. Gravimetric erosion studies were also performed on selected formulations. Influence of dissolution medium osmotic pressure and agitation on drug release was also investigated.

RESULTS & DISCUSSION

Maximum retardation was observed with Carbopol 71 G as polymer. Desired release was obtained with formulation containing Kollidone SR. Increase in osmagent concentration showed significant increase in the release rates. An increase in osmotic pressure of the dissolution medium (NaCl solutions) resulted in significant reduction in drug release from osmats. Moreover, agitation independent drug release was observed from the osmats. This steep dependency of the release rate on osmotic pressure of medium & agitation independent drug release suggested that osmosis is a major driving force for drug release. Gravimetric erosion studies showed some contribution of erosion of matrix tablet towards drug release Thus, initially drug release from osmats occurs via osmotic process until the outer polymer layer reaches its critical disentanglement concentration and the additional release component due to erosion was manifested.

CONCLUSION

Osmats thus combining both osmotic and erosion characteristics judiciously improved control of release kinetics of poorly soluble drugs. Osmats thus represents a simple, easy to fabricate, versatile, osmotically driven controlled drug delivery system, based on low cost technology.

ACKNOWLEDGEMENTS

Indchemie Health Specialities Pvt.Ltd. for gift sample of drug. BASF & Noveon Inc. for gift samples of polymers.

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SOLUSORB: A NOVEL TECHNOLOGY FOR SOLUBILIZATION OF POORLY SOLUBLE DRUGS

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INTRODUCTION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Celecoxib is diaryl pyrazol class of nonsteroidal anti-inflammatory drug (NSAID). It exhibits anti-inflammatory, analgesic and antipyretic activities by selectively inhibiting cyclooxygenase-2 (COX-2) prostaglandin synthesis. It is indicated to relieve the signs and symptoms of rheumatoid arthritis and osteoarthritis. Since celecoxib is practically water insoluble, its bioavailability is low when administered orally as the crystalline form. Amorphization of poorly water-soluble drugs in solid dispersion increases their dissolution, which can lead to enhance-

ment in their bioavailability. However, reversion from the amorphous to the lower energy crystalline state has been a major limitation in the successful commercialization of solid dispersions. The present paper deals with a novel approach of solubilization using innovative ***Solusorb*** technology, wherein solid dispersions are obtained by sorption of drug-loaded solutions onto carriers.

OBJECTIVE

The aim of the present study included the design of stable solid dispersions using solusorb technology with the following objectives:

a) Evaluation of physical stability of the drug in the solid dispersions

b) Evaluation of in-vitro dissolution rate.

EXPERIMENTAL

The uv spectroscopic method was developed for routine analysis of celecoxib in distilled water, in pH 1.2 buffer and in methanol. The standard curve was found to be linear over the concentration range of 2.5-20 mcg/ml.

A weighed excess of drug was added to 1ml of each of the surfactant/solubilizer. The solution was shaken intermittently for 24hrs and then centrifuged at 3000rpm for 10min. The supernatant was diluted suitably and assayed for drug content. Based on the solubility profile of celecoxib, surfactants/solubilizers showing maximum drug solubility were further studied.

Celecoxib was solubilised in a mixture of surfactants and solubilizers and the resultant solution was adsorbed on solid adsorbent by slowly triturating in mortar. Effect of concentration of surfactants and adsorbents on solubilization of celecoxib was evaluated.

The formulation was evaluated for 1) Drug content- by uv spectroscopy 2) In vitro dissolution- by USP XXIV paddle method 3) Wettability – by contact angle measurement (Kruss contact angle measurement G10) 4) Physical stability- by DSC and XRD. Further the presence of intermolecular bonding was investigated using Fourier transform infrared spectroscopy (FTIR).

RESULTS AND DISCUSSION

The surfactants played an important role in solubilizing celecoxib in the solid dispersions prepared by solusorb technology. As concentration of surfactant increased the solubility of celecoxib increased, inhibiting precipitation of celecoxib on dilution in distilled water. DSC analysis of the solid dispersions prepared using solusorb technology revealed that the celecoxib existed in solubilized form and did not recrystallise even after storing at a stressed condition (40° C/ 75% RH). The contact angle of celecoxib in solid dispersion was found to be lower than pure drug indicating improved wettability.

Thus solusorb technology holds promise for development of physically stable solid dispersions and for bioenhancement of poorly soluble drugs.

ACKNOWLEDGEMENTS

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SPHERULITES: NOVEL VESICULAR DRUG DELIVERY SYSTEM

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INTRODUCTION AND OBJECTIVE

Lyotropic liquid crystalline phases under shear form new kind of multilamellar vesicles with onion like structures called spherulites. These spherulites resemble liposomes, but they are obtained by a simpler process (shearing lamellar phases) and have lamellae up to the very center, like an onion[1]. They can encapsulate hydrosoluble as well as liposoluble molecules and protect them within their multiple layers.

Their size ranges from 1 to 10 microns. Spherulites offer various advantages such as high encapsulation effi-

ciency[2], cost effective method of preparation and stability over other multilamellar drug delivery systems such as liposomes and niosomes, and environment friendly technology.

The limitations of parenteral therapy of gentamicin have prompted the exploration of non-invasive novel drug delivery systems (NDDS) for gentamicin administration. We have already demonstrated the applications of spherulites of insulin nasal delivery system in vivo[2].The objective of the present investigation was formulation and in vitro evaluation of spherulites as a non-invasive NDDS for gentamicin delivery.

EXPERIMENTAL

A fluro-densitometic HPTLC method was developed for the Gentamicin analysis. Method was found to be linear between the concentration range of 40-200 ng.

Sucroester was selected as surfactant for the present investigation. Aqueous solution of gentamicin was mixed with the surfactant. This mixture was then sheared using cup and cone device designed in our research laboratory. The spherulites thus formed were isolated by centrifuging at 5000 rpm for 5 min. The sediment containing spherulites were further freeze-dried using Labconco freeze drier. The effect of following parameters on gentamicin encapsulation and spherulite size were critically studied, A) Ratio of Gentamicin: Sucroester - 1:3 (0.33) to 1:20 (0.05); B) Shear rate - 16.66 to 50.00 sec^{-1}; C) Shearing time - 5 to 30 min. All these parameters were optimized to achieve maximum encapsulation with minimum particle size. The optimized formulation were subjected to stability studies

Gentamicin spherulites were evaluated for drug encapsulation efficiency, drug content, in-vitro drug release, stability as per ICH guidelines, particle size and light scattering (Birefringence).

RESULTS AND DISCUSSION

Spherulite formation was confirmed by light scattering studies, which revealed the birefringent nature of spherulites and a multi-layered structure. As gentamicin/surfactant ratio decreased, drug encapsulation increased. The studies revealed significant increase in drug encapsulation from 61.41 to 80% was observed with an increase in shear rate from 16.66 to 50.00sec^{-1} while the spherulite size decreased from ~30 to ~3 mm. Maximum drug encapsulation efficiency of 80% was found at the ratio of 1:15. In-vitro drug release studies revealed rapid release of gentamicin with no lag time and more than 90% drug release was observed in 90 min. Stability studies confirmed the stability of gentamicin spherulites over a period of 1 year.

CONCLUSION

Spherulites of gentamicin with good stability and high encapsulation efficiency were successfully formulated. Spherulites of gentamicin represent a promising vesicular system for mucosal delivery with significant advantage over other vesicular systems.

ACKNOWLEDGEMENTS

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D-ZOLV PARACETAMOL: A GIFT TO PEDIATRIC PATIENTS

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INTRODUCTION

The demand for solid dosage forms that can be dissolved and suspended in water, chewed or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric market with further application to patients suffering from 'dysphagia'. Mouth dissolve tablets (MDT) are emerging as

patient friendly novel drug delivery system suitable for administration to patients who cannot swallow, who should not swallow and who refuse to swallow. Technologies reported for MDTs like freeze drying, compression moulding, effervescent tablets etc are costly[1]. Hence, there exists a need for a simple method to prepare MDTs. The development of MDT for bitter drugs is a challenging task wherein taste masking is the major hurdle. The challenge becomes even more stringent for high dose bitter drugs[2]. Paracetamol an antipyretic, analgesic is recommended for pediatric administration in a maximum dose of 250 mg. A MDT of paracetamol (250 mg) could provide a patient friendly drug delivery system with high capability.

OBJECTIVE

The study was designed with an objective of development of a MDT of Paracetamol (250 mg) using in-house D-Zolv technology with the features of high palatability and rapid oral dispersion time (DT).

EXPERIMENTAL

Analytical method development:

U V spectroscopy method was developed for the drug content and dissolution studies of MDTs. A stability indicating HPTLC method was developed to assess the stability of the drug in the formulation (mobile phase: Ethylacetate: Ethylmethylketone: Methanol: Ammonia 14:6:1:1).

Formulation development:

The MDTs were prepared by a simple granulation technique. Various GRAS listed excipients were screened and used in formulation development with emphasis on palatability, rapid disintegration, and good mechanical strength. A novel taste-masking agent was screened at various concentrations and was optimized to mask the bitter taste of the drug. Similar studies were carried to compare the effects of superdisintegrants. Various types of sweeteners and flavors were studied and were optimized to enhance the organoleptic properties of MDT. The optimized formulations were subjected to stability studies as per ICH guidelines.

Evaluation:

D-Zolv Tablets were evaluated for a) physical properties: appearance, dimensions, weight variation, hardness and friability; b) organoleptic parameters: taste, mouthfeel, and overall palatability; c) drug content; d) In vitro DT: Measured by dropping the dosage form in the beaker containing 6 ml of water; e) In vivo DT: After administration to human volunteers; f) In vitro dissolution: USP method; g) Stability studies.

RESULTS AND DISCUSSION

The developed formulations of D-Zolv Paracetamol showed good palatability and mouthfeel. Tablets with crosscarmellose calcium as superdisintegrant showed rapid disintegration in comparison with other superdisintegrants. Developed MDT exhibited hardness between 3-4 kg/cm^2 and in vitro and in vivo dispersion time of 45-50 secs. The in vitro dissolution studies revealed more than 80% drug release in 5min. Stability studies confirmed the chemical and physical stability of developed formulation.

CONCLUSION

D-Zolv technology was successfully adopted for the design of mouth dissolve tablets of bitter drugs using a taste-masking agent. This D-Zolv technology is readily amenable to scale up and could be used for a wide range of bitter drugs.

ACKNOWLEDGEMENTS

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IN VIVO EVALUATION OF ORALLY ADMINISTERED INSULIN NANOEMULSION

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OBJECTIVE

To study the efficacy of orally administrated multiple nanoemulsion of insulin in diabetic male albino rats.

INTRODUCTION

Multiple emulsions are complex systems and may be called "emulsions of emulsions" Multiple nanoemulsion are easily absorbed through intestinal lumen via paracellular route as a result of their small size and also move transcellularly through M cells, which line the Peyer's patches region. On the other hand, due to knowledge explosion in biotechnology industry, a wide variety of regulatory and therapeutic proteins including insulin are abundantly and easily produced either by recombinant DNA technology or Merrifield synthesis. Hence the need of the hour is to develop ingenious and efficient methodologies for the safe, selective and effective oral delivery of the available macromolecules.

EXPERIMENTAL

The multiple nanoemulsion was prepared by a double emulsification technique. The formulations were characterized for colour, odour, and visual appearance, pH, short-term stability, stability after centrifugation, and drug content. Selected formulations were analyzed for Globule size distribution by Malvern Mastersizer S ver.2.19.and Transmission electron microscopy.

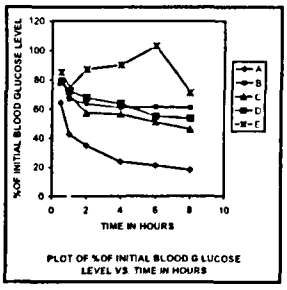
In-vivo evaluation: Male albino rats weighing 180-220 gm (wistar strain) were selected for the study. Rats were made diabetic by giving intraperitonnial injection of streptozotocine. The animals were grouped into six groups as positive control, negative control and to remaining four groups standard formulation A and developed formulation B, C and D were administered. Each group contained 6 animals. The standard formulation was given as intramuscular injection and the three developed formulations were fed orally. Blood samples were collected from the tail vein after ½,1,2,4,6 & 8th hour of drug administration. Blood glucose levels were determined using glucometer.

RESULTS AND DISCUSSION

The results of TEM indicated the preparation of multiple nanoemulsion of insulin. pH of the formulations were in the range of 6.5 – 7.2. The results of Malvern Mastersizer indicated that 10% of particles had particle size less than 150nm, 50% of particles had particle size less than 270nm and 90% of particles had particle size less than 540nm. No creaming, cracking and separation of emulsion was observed on centrifugation at 20,000 rpm for one hour. The stability studies indicated that the developed nanoemulsions were stable when stored at 2-8°C.

Control animals (E) showed hyperglycemia (Fig1). In case of Standard injection (A) the blood glucose levels decreased upto 20 % at 8th hour. The rats were hypoglycemic at this stage. Formulations B, C and D containing Insulin and aprotinin showed decline in blood glucose level but the decrease in blood glucose level was much less as compared to standard formulation.

However the formulation C showed greater decline in blood glucose level and it was much more improved as compared to formulation B.There was 53.71% reduction in blood glucose level at 8th hour. In formulation D containing higher aprotinin concentration did not show any further decrease in blood glucose levels.



PLOT OF %OF INITIAL BLOOD GLUCOSE LEVEL VS TIME IN HOURS

Thus formulation C was found better as compared to other formulations.

CONCLUSION

The present study suggests feasibility of preparation

of multiple nanoemulsion of insulin with mean particle size diameter of 540 nm. *In-vivo* studies in rats revealed that insulin with aprotinin showed 53.71% decrease in blood glucose level at 8th hour and therefore holds promise for oral drug delivery.

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FORMULATION STUDIES OF POORLY SOLUBLE DIURETIC AGENTS

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OBJECTIVES

The purpose of this study was to improve the solubility and dissolution profile of poorly water soluble diuretic agents inorder to optimise their bioavailability. Complexes of these agents were prepared with cyclodextrins and utilized in formulating optimally designed dosage forms to provide desired drug release profiles.

INTRODUCTION

Triamterene is a mild potassium sparing diuretic agent with very poor solubility in water and its bioavailability limited to 30%. The drug is weakly basic and exhibits pH-dependent solubility. It is administered alone as 100 mg dose twice a day and also as an adjunct to the more potent thiazide and loop diuretics, like furosemide, for its potassium sparing effect (1). Furosemide is a frequently used potent loop diuretic with very poor solubility characteristics in water as well as most organic solvents and consequent low bioavailability. It has an absorption window in the upper gastrointestinal tract and has a short duration of action with immediate onset. Cyclodextrins are cyclic oligosaccharides widely used to improve solubility of poorly soluble drugs. Formulation of solid dispersions of these diuretic agents with cyclodextrins has improved their solubility and dissolution rate (2,3). These dispersions can further be formulated into immediate release or modified release systems to optimise dissolution characteristics and bioavailability.

EXPERIMENTAL

Binary systems of triamterene and furosemide with cyclodextrins have been prepared by cogrinding.

Immediate release tablets of triamterene were prepared by direct compression of the drug-cyclodextrin complexes with disintegrants like crosscarmellose and sodium starch glycollate. These were compared for their *invitro* drug release profiles with tablets prepared without cyclodextrin and with marketed formulations. Modified release tablets were prepared by incorporating suitable release retardants like hydroxypropyl methyl cellulose (HPMC). *Invitro* drug release profiles were examined over the entire physiological pH range.

Gastroretentive delivery systems of furosemide were prepared by direct compression of drug-cyclodextin complexes with excipients like HPMC, sodium bicarbonate and microcrystalline cellulose. These systems were evaluated for *invitro* release profiles in the gastric pH.

RESULTS AND DISCUSSIONS

Immediate release tablets of triamterene incorporated as cyclodextrin complexes gave better *invitro* release profiles than tablets prepared without cyclodextrin and marketed formulations; with complete drug release within the first 10 minutes.

Modified release tablets of triamterene gave 16% drug release in the gastric pH in the first 2 hours. Around 25% of the drug was released in the next 2 hours in pH 4.5 acetate buffer. 50% of the drug was released in 6 hours in pH 6.8 phosphate buffer, with complete drug release in 24 hours.

Gastroretentive systems of furosemide started floating *invitro* within 15 – 20 minutes and remained floating for over 24 hours. Around 25% drug was released in the gastric pH in the first 6 hours; with complete drug release in 24 hours.

CONCLUSIONS

Triamterene, a weakly basic, poorly soluble drug, was

formulated as immediate release tablets, with complete drug release within 10 minutes. Modified release tablets gave pH-independent drug release over the entire physiological pH range; with complete drug release in 24 hours, with no dose dumping in any pH condition. Furosemide, a poorly soluble diuretic - with absorption window in the upper gastrointestinal tract – was formulated as a gastroretentive tablet with complete drug release in 24 hours in the gastric pH.

Formulations of both triamterene and furosemide showed improved drug release and are expected to have better bioavailability as compared to conventional preparations.

ACKNOWLEDGEMENTS

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ENTERAL DELIVERY SYSTEM OF INSULIN

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OBJECTIVE

The objective of our study is to investigate the possibility of developing an oral delivery system of insulin, which is designed to release and protect insulin in the small intestine.

EXPERIMENTAL

Insulin (40U) solution, aprotinin and sodium glycocholate were dissolved in ethanolic solution of eudragit L100 and mixed well. The resultant solution was then poured into light liquid paraffin and stirred at 1200 rpm for one hour. The insulin microspheres were formed by addition of gelatin solution (0.5% w/w), the stirring was continued for another one hour. The microspheres were separated, rinsed twice with petroleum ether, vacuum filtered and air dried. Finally, the microspheres were disaggregated by passing them through a sieve of 0.5mm aperture.

A 200 mg sample of insulin microspheres was placed into 70 ml of phosphate buffer solution pH 6.5 at 37°C in constant bath shaker and shaking was maintained at moderate rate for 4 hrs. Samples taken at periodic intervals and assayed by RP- HPLC.

Insulin microspheres (20UI / Kg) were orally administered.

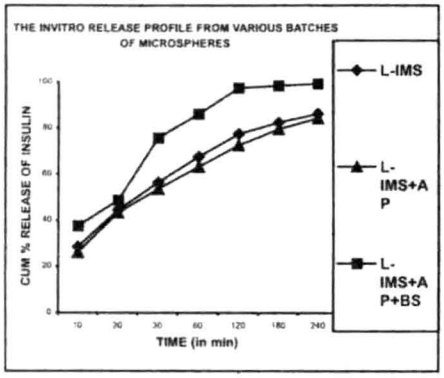
Blood samples were collected, before and at 0.5, 1.0, 3.0, 4.0, 5.0, hour after dosing.

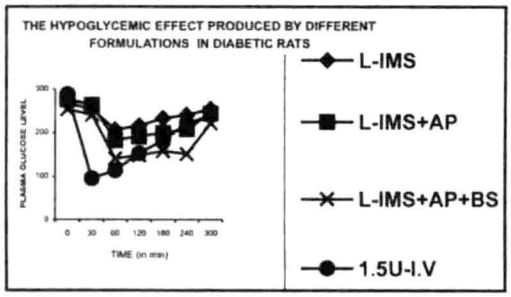
Serum glucose level was determined by using Glucometer. Serum glucose level was determined as a measure of insulin efficacy.

The Biological efficacy of insulin following oral administration of insulin microspheres was evaluated by comparison with the I.V. route.

RESULT AND DISCUSSION

Six batches of insulin -loaded microspheres were prepared using Eudragit L-100. The particle size was determined by optical microscopy. All were free flowing in nature, but showed agglomeration and separated by sieving. In vitro release studies of the insulin microspheres prepared with 1% aprotinin and 1% sodium glycocholate showed a maximum release of 99.3% at end of 4th hr. From the cumulative percentage release vs. time plot, it is apparent that the release of insulin follows first order kinetics. In vivo hypoglycemic effect study, showed that the hypoglycemic effect of





insulin microspheres prepared with Eudragit L-100 was able to reduce blood glucose in controlled manner at least for 3-4 hrs. Our report clearly state that microspheres prepared with aprotinin is able to protect insulin from attack of enzymes and promote absorption rate of insulin by use of sodium glycocholate. The use of Eudragit L-100 as carrier for microspheres gives, a site-specific release of insulin in the upper intestine

CONCULSION

One day in the future our ultimate goal of administering insulin orally may become a reality. This would bring relief to million of diabetics throughout the world.

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NOTE: L-IMS- EUDRAGIT L-100 INSULIN MICROSPHERES, **AP-** APROTININ, **BS-** SOD. GLYCOCHOLATE.

SOLUBILITY ENHANCEMENT OF ANTI-HIV DRUG -NELFINAVIR MESYLATE BY ß-CYCLODEXTRIN COMPLEXATION

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OBJECTIVE

Cyclodextrin shows remarkable ability to form inclusion complexes with various molecules that fit partially or entirely inside the cavity. Aim of our present work was to study ß-cyclodextrin (ß-CD) complexation of Anti-HIV drug – Nelfinavir Mesylate that will maximize its therapeutic effect by improving its solubility and subsequent bioavailability and hence cost reduction of the therapy.

INTRODUCTION

The Anti-HIV drug Nelfinavir Mesylate is selective reversible protease inhibitor which shows good inhibitory activity against HIV-1[1]. It is slightly soluble in water at pH£ 4. Because of less solubility at intestinal pH portions of the drug that are dissolved but not yet absorbed when they pass from stomach into the small intestine may undergo precipitation and loss of their therapeutic benefit. Drug has very low intrinsic dissolution rate which indicates potential for dissolution rate limited absorption problems[2,3]. ß-Cyclodextrin is proven functional excipient, which can be used to improve the solubility of the drug.

EXPERIMENTAL

Preparation and characterization of Inclusion complexes:

Phase solubility studies were performed. The Freeze drying technique was used to prepare inclusion complex of Drug and ß-CD in different molar ratios. Complexes were characterized DSC and XRD Studies.

Dissolution Studies:

The dissolution studies of samples were performed in

distilled water by using USP type II apparatus at 100 RPM. and samples were analyzed at 250 nm.

Intestinal absorption studies:

The rate of intestinal absorption of plain drug and its complex was studied by the *in-vitro* rat everted intestinal sac model. The content of drug in serosal effluent was estimated by developed HPLC method.

Formulation Development of tablet:

The final tablet formulation of complex was developed and optimized on the basis of hardness, disintegration time, friability and dissolution profile

RESULT AND DISCUSSION

Phase solubility studies shows solubility enhancement capabilities of cyclodextrin in higher molar ratios. DSC studies of complex showed changes in the thermogram as compared to plain drug. XRD pattern of complex was found to be diffused and different than that of plain drug confirming formation of new solid phase. These studies further support inclusion of drug in cyclodextrin cavity. These findings were further supported by improved dissolution profile of complex as compared to plain drug.

The rate of drug absorption was found to be 25 % more in case of Complex than plain drug in 1Hr. which further supports scope for enhancement in bioavailability of the drug resulting in reduction in total amount of dose.

Dissolution studies of the tablets (1:1.5 M) showed the order of release rate as complex > physical mixture > milled drug > plain drug. T_{25} value of plain drug, physical mixture and complex was 51.21, 15.91 and < 1min. respectively.

The final tablet formulation of complex was developed and optimized on the basis of hardness (6kg/cm^2), disintegration time (2 min.), friability (0.199) and dissolution profile. The tablet formulations showed the release rate in the order of complex > physical mixture of drug - ß-CD > plain drug. Thus freeze-drying method can be used successfully for complexation. These findings suggest successful attainment of the objective.

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DEVELOPMENT AND PHARMACODYNAMIC EVALUATION OF TABLET CONTAINING INCLUSION COMPLEX OF VALDECOXIB WITH β-CYCLODEXTRIN

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OBJECTIVES

In this study attempts were made to develop valdecoxib (VAL) tablet for better therapeutic efficacy by incorporating inclusion complex of drug with b-cyclodextrin (β-CD).

INTRODUCTION

Valdecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and anti-pyretic activities in animals[1].It inhibits cyclooxygenase-2 mediated prostaglandin synthesis[2]. The present work describes the studies of inclusion complexation of VAL with β-CD, optimization and comparative evaluation of its tablet with marketed formulations.

EXPERIMENTAL

1. Phase Solubility Studies (PSA): Filtrates were analyzed using UV Spectrophotometer (Jasco) at 283 nm for VAL content. 2. Preparation of Inclusion Complexes: The complexes of drug with β-CD in 1:1 M ratio were prepared by solution method, kneading and freeze drying. 3. Characterization of Inclusion Complexes: The complexes were charcterized by using FT-IR Spectrophotometer, NMR Spectrometer XRD and DSC. 4. *In-Vitro* Dissolution Studies of Inclusion Complexes: 5. Development of Formulation: Workable amount of β-CD was found by using Cyclodextrin Utility Number. Pharmacodynamic Studies: Carragenan induced rat paw oedema model for anti-inflammatory activity and acetic acid induced writhing model (mice) for analgesic potential

were adopted. 7.Comparative Evaluation: Devlpoed formulation evaluated against 5 leading marketed brands for dissolution, DSC, anti-inflammatory & analgesic studies.

RESULTS

PSA showed A_L type of curve. Amongst all methods, Freeze-dried complex showed better physical and dissolution profile characteristics. FT-IR, NMR, XRD and DSC analysis showed formation of new physical form. *In vitro* dissolution data showed that complex exhibited faster dissolution rate as compared to the VAL alone or PM. Inclusion complex showed significant enhancement in the % oedema inhibition as compared to the drug alone; in the 1st and 2nd hour. The best analgesic activity was observed at 8 min. for the complex and 29 min. for plain VAL. Comparative dissolution showed that in first 10 min 90.91% drug release occurred from developed formulation while next best and conventional tablet had a release of only 40.91% and 23.51% resp. T_{50}% is less than 1 min for developed tablet whereas for next best and conventional tablets T_{50}% were 46 min and 123 min resp. Complete absence of endothermic peak at 173°C observed only in developed formulation amongst all 5 formulations. Amongst all formulations, developed formulation showed higher % oedema inhibition up to 6 hrs. A significant difference was observed between developed tablet and marketed tablets for % inhibition of writhes.

DISCUSSION

PSA confirmed 1:1 stoichiometry and solubility enhancement capability of β-CD for VAL. It appears that in Freeze-dried complex there is absence of high energy crystalline form of VAL. FT-IR, NMR, XRD and DSC analysis confirmed molecular inclusion phenomenon. Improved dissolution profile of VAL in complex could be attributed to the increased solubility and wettability caused by inclusion. Comparative DSC studies confirmed the presence of true inclusion complex only in tablet formulation developed by our laboratory while in case of 2 marketed formulations there was mere physical presence of β-CD and remaining 3 formulations do not contain cyclodextrin and/or cyclodextrin inclusion complex. Better anti-inflammatory and analgesic activity of developed formulation could be because of true molecular encapsulation of VAL in β-CD.

CONCLUSION

The solubility of VAL was highly improved by complexation with β-CD due to change in crystallinity.Amongst all marketed formulation only tablets of our labortory contains true inclusion complex which subsequenlty resulted in faster onset of action, better bioavialbility and better protection which is evident from pharmacodynamic studies.

ACKNOWLEDGEMENTS

We are thankful to Unichem Pharmaceuticals Ltd. for gift sample of VAL.

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ONCE DAILY SUSTAINED RELEASE FORMULATION OF ANTI-HIV DRUG- STAVUDINE

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OBJECTIVE

Stavudine is one of most important component of HAART regimen used in combating the dreadful disease HIV-AIDS. It has shorter elimination half-life (1.1h) which results in frequent drug administration to achieve the desired therapeutic response[1]. Sustained Drug delivery system was formulated to release 40% of drug in first 4 hrs. and remaining over next 16 hrs.

INTRODUCTION

Stavudine is synthetic thymidine nucleoside analogue active against Human Immunodeficiency Virus. It acts by inhibiting HIV reverse transcriptase by competing with natural substrate deoxythymidine triphosphate and also inhibits viral DNA synthesis by causing DNA chain termination. When adherence of patient towards treatment is less than 80% viral suppression was less than 50%. Even with patients 95-

100% adherence had only 81% suppression, indicating that 100 % adhesion is probably necessary with current medication which can be improved by reducing pill burden [2,3].

Gas generating, floating drug delivery system was designed by using gas generating agent, HPMC and Natural gums.

EXPERIMENTAL

Calibration curve of Stavudine was prepared in 1.2, 4.5, 7.2 buffers and analysis was carried out at 266nm. Different ratios of HPMC, Gas generating agent, swelling agent were tried to achieve desired release profile and floating time.

Tablets were prepared by slugging method and compressed on single punch machine using capsule shaped punches.

Tablets were evaluated for general appearance, thickness, hardness, friability, weight variation, drug content, integrity and in-vitro drug release study.

In vitro drug release profile was studied using USP Type I apparatus by pH change method. Formulations following Higuchi kinetics were selected.

Integrity of tablet was tested in aqueous media agitated with paddle rotating at 75 RPM.

RESULT AND DISCUSSION

Natural gums used in the formulation gels in the aqueous medium. Various gums were tried to get desired release profile. HPMC K100M in the ratio 4.5 with drug was found to sustain the drug over 20 Hrs. Formulation was found to retain the integrity upto period of 24 Hrs. Gas generating agent in the ratio 1.6 is necessary to release carbon dioxide which helps for floating of the tablet in 2 min. Swelling agent in the ratio 1.5 to the drug gives optimum swelling with desired release profile whereas lower amount retards burst release in 4 hrs. and higher amount causes very rapid release of drug. Drug release was found to be Higuchi in all the cases.

Ingredient	Ratio with Drug
HPMC	3, 3.5, 4, 4.5, 5
Gas Generating Agent	0.8, 1.2, 1.6, 2
Swelling Agent	1, 1.5, 2

CONCLUSION

Once daily sustained release formulation of stavudine were successfully developed by using gas generating floating carrier composition. Optimized formulation retains integrity for 24 Hrs. and follows Higuchi kinetics with 90% release in 16 Hrs.

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CLARITHROMYCIN SUSTAINED RELEASE FOR IMPROVED EFFICACY

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INTRODUCTION

Clarithromycin, an advanced generation macrolide antibiotic, is used in treatment of respiratory tract infections like bronchitis and pneumonia[1]. It is currently dosed at 250 mg or 500mg twice daily depending upon severity of infection.

Transitory exposure to sub inhibitory concentrations can lead to re-growth of bacteria[2]. In sustained release formulation, the concentration of antibiotic is far greater than MIC and therefore could reduce drug resistance. Clarithromycin exhibits concentration dependent pharmacodynamics[2] where peak concentration/MIC ratio of approx. 10 has clinical success. Therefore high drug levels should be the goal of the therapy. This is best achieved by high doses taken once daily[3]. Short elimination half-life of clarithromycin (5-7hours)

[4], makes it a useful candidate for sustained release dosage form.

CLT is a poorly soluble basic drug absorbed primarily at small intestine. Due to reduced solubility of drug at intestinal pH; hydrophilic polymers alone result in variant bioavailability. Hence combination of enteric polymer and water-soluble hydrophilic polymers was tried. Channeling agents were also added to enhance drug release.

EXPERIMENTAL

Calibration curves of CLT were prepared in buffers of pH 1.2, 4.5 and 7.2 and analysis done by a colorimetric method developed using para-dimethylaminobenzaldehyde as the reagent. Tablets were prepared by wet granulation method using PVP (5% solution in IPA) as granulating agent and compressed on single punch machine using caplet shaped punches. (17.5'7.5 mm). Different polymers were tried in various grades and concentrations.

In-vitro release was studied using USP type I dissolution apparatus by pH change method and percentage cumulative drug release was calculated using developed colorimetric method.

The developed formulation was compared to marketed extended release formulations with regards to in-vitro release. The optimized formulation was kept for stability studies as per ICH guidelines.

RESULTS AND DISCUSSION

The formulation containing only HPMC as retardant showed slower release at intestinal pH. A combination of Eudragit L 100 and HPMC gave enhanced drug release at alkaline pH. The release of the drug from the matrix was by swelling of the matrix followed by slow erosion. To maintain the integrity of the tablet and slow the rate of erosion, a water soluble polymer added to the formulation showed more consistent results. Addition of B-cyclodextrin as a channeling agent showed further better in-vitro release. In-vitro release profiles of the marketed sustained release formulation of CLT (500 mg) (Klaricid XL, Abbott Laboratories, Indian market and Biaxin XL, Abbott Laboratories, International brand) and the optimized formula showed comparable T90 and k values. Statistical analysis showed that drug release from the tablet matrix followed zero order kinetics. There were no changes in physicochemical parameters tested on tablets during stability studies.

CONCLUSION

CLT sustained release tablets were successfully formulated using combination of Eudragit L 100, HPMC, Polyox and channeling agent. Drug release was found to follow zero order kinetics.

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STUDIES IN DEVELOPMENT OF MICROEMULSION GEL OF HYDROCORTISONE

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OBJECTIVE

The present study aim to develop o/w microemulsion gels of hydrocortisone (HCT) which is widely used as n anti-inflammatory agents in indications like primary irritant dermatitis, contact allergic dermatitis, eczema- atopic, infantile, discoid, seborrhea dermatitis, Lichen Simplex, Pruritus Acne and Flexural Psoriasis.

INTRODUCTION

Controlled release of drug onto the epidermis with assurance that the drug remain primarily localized and does not enter the systems in significant amounts, is a area of research that has only recently been addressed to with success.

Surfactants based formulations which may interact with the lipids in the Stratum corneum and alter their structure, offer a way to modify this protective barrier and specifically to reach and enhance drug penetration over the Stratum corneum and result in improved bioavailability following topical administration.

Microemulsions are thermodynamically stable, transparent,dispersions of oil and water stabilized by an interfacial film of surfactant molecules.They are thermodynamically stable systems and display indefinite stability in absence of chemical degradation of any of its components, spontaneously form, droplets size (typically 10-100 nm), optically isotropic and have ultra low interfacial tension.

EXPERIMENTAL

- O/W microemulsion gels were developed using isopropyl myristate and ethyl oleate as internal phase. Various surfactant and co-surfactants were screened and their concentrations optimized and the microemulsion region was located from the Pseudoternary phas diagrams. HCT (0.5 %w/w) was incorporated in selected formulation

- Selected microemulsions gels were evaluated for various physicochemical parameters like colour, odour, appearance, optical birefringence, pH, globule size determination and *in-vitro* release in pH 7.4 phosphate buffered saline and subjected to stability studies at 4 ± 2°C and 37 ± 2°C. for 2 months.

- Dermal irritation test was carried out for the selected microemulsion gels on Swiss albino rabbits for the period of 72 hrs. Evaluation of the skin reaction was done to the Draize scoring system.

- The *in-vivo* anti-inflammatory study was carried out on Swiss albino mice using Oxazolone induced ear edema and compared with marketed cream.

RESULTS AND DISCUSSION

Selected gels were colourless and transparent with characteristics odour with globule size ranging from 45-270 nm. In *in-vitro* release studies HCT was released over a period of 24 hrs. In stability studies slight liquifaction of gels was evident at 37°C; however samples stored in the refrigerator were stable; also the release profiles of the formulations remained unaffected at both the temperatures. In dermal irritation studies, no signs of erythema and edema were found indicating safety of the formulation. In *in- vivo* efficacy studies the developed HCT gels showed percent inhibition of edema which was comparable to that with marketed cream.

CONCLUSION

Thus within the limits of experimental design it can be concluded that the developed o/w microemulsion gels are suitable carriers for HCT. This systems were stable at refrigerator conditions and safe and efficacious.

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Gift samples: Glaxo India Ltd. (HCT), BASF, Gattefosse (surfactants). M.U.I.C.T (facility for optical birefringence), Bharat Serums and Vaccines Ltd. (facilities for Coulter N4 plus).

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COMPARATIVE PK DATA OF DRF 4367 USING NANOSUSPENSION AND HPßCD FORMULATION

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OBJECTIVE

To improve oral bioavailability of DRF 4367, a novel cox-2 inhibitor

INTRODUCTION

DRF-4367 is 2-Hydroxy methyl -4-[5-(-methoxyphenyl-3-trifluromethyl-1H-1-pyrazolyl] -1-benzenesulfonamide. It has exhibited potent COX-2 selectivity *in vitro* and showed good efficacy in several animal models. Previous oral pharmacokinetics studies in rats with suspension showed bioavailability of 20 and 40% at 100 and 30mg/kg, respectively[1]. This dose dependant decrease in bioavailability could be attributed to poor dissolution as DRF 4367 is a highly permeable drug.

Among various approaches to improve dissolution characteristics, cyclodextrin complexation and disordered drug delivery, an inventive approach, is gaining attention in contemporary research. In this investigation DRF 4367 was prepared as nanosuspension and HPBCD complex, and evaluated for oral PK in rats.

EXPERIMENTAL

pH solubility and phase solubility studies:

Solubility of DRF-4367 across the pH range 1 to 13 and in water was determined by spectrophotometric method. Phase solubility studies were carried out in various concentrations of HPbCD (0-40%) alone and in presence of alcohol and meglumin.

Preparation of amorphous nanosuspension:

DRF-4367 crystalline material was milled using Retsch mixer mill with a 12mm zirconium bead in a 10 ml Zirconium cell for 10 hrs. The amorphous nature was confirmed by XRD, DSC, FTIR and microscopy. The milled material was suspended in 0.5% Tween 80 and homogenized at 300 kPas (5 cycles) using microfluidics high pressure homogenizer. Intrinsic dissolution rate was carried out.

Preparation of Drug-HPßCD Complex:

Stoichiometric proportions of drug, HPBCD and other ingredients were dissolved in alcohol heating at 75°C with constant stirring and heating was continued till complete evaporation of alcohol. Dissolution using USP type 1using water as the medium was carried out.

Preclinical formulation development:

Based on Phase solubility studies the formulation consisting of alcohol, meglumin and HPßCD was developed and evaluated for oral pharmacokinetics in rats.

Single dose pharmacokinetic studies in rats:

PK was carried out using prepared formulation at dose of 100mg/kg for oral and compared with IV data. Samples were withdrawn at regular intervals and analyzed by validated HPLC method using celecoxib as internal standard[1].

RESULTS AND DISCUSSION

DRF-4367 was found to be soluble in the range of 1-5?g/ml in water and pH range of 1 to 8. Phase solubility diagram with HPßCD with meglumine followed the AL-type system. Maximum solubility 1.8mg/ml was achieved.

CONCLUSION

Oral bioavailability of DRF-4367 was enhanced from F~ 0.2 to 1 by HPBCD complexation whereas amorphous nanosuspension showed a marginal enhancement though significant improvement in IDR as compared to the crystalline form.

P-GLYCOPROTEIN MODULATION: PLATFORM FOR IMPROVING *PERORAL* BIOAVAILBILITY OF BCS CLASS IV DRUGS

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OBJECTIVE

To explore the potential of co-administration of P-glycoprotein (P-gp) modulators as a delivery approach to improve *peroral* delivery of Paclitaxel (PCL) and Indinavir (INDI), BCS Class IV drugs.

INTRODUCTION

P-gp mediated efflux mechanism is one of the major hurdles in oral drug absorption for a number of drugs. Co-administration of safe and effective P-gp modulators that inhibits the secretary transport in enterocytes provides a feasible approach for improving oral deliverability of difficult molecules[1]. Therefore present investigation was aimed at evaluating the scope of increasing bioavailability (BA) by modulating P-gp and the potential of grapefruit juice in improving the intestinal permeability of BCS class IV drugs.

EXPERIMENTAL

All animal studies were done according to guidelines of Institutional Animal Ethical Committee (IAEC) of NIPER. Male Sprague Dewley rats (230-250 g) were fasted for 16 h before the experiment with water *ad libitum* and killed by cervical dislocation. Intestinal tissue was removed and the lumen flushed with ice-cold bicarbonate-buffered pH 7.4 Kreb's Ringer solution. Everted sac preparation was made as reported earlier[2]. For apical-to-basal (AàB) transport, drug solution in KRB was placed in the mucosal side and for the investigation of basal-to-apical (BàA) transport; drug was placed in the serosal side. During inhibition studies, the inhibitor was placed in the apical chamber. Integrity of the sac was assessed using propranolol (PPN), a passively transported highly permeable drug. [^{14}C]-PCL in permeability studies was quantified by radio-chemical method, whereas newly developed RP-HPLC method was used for INDI.

RESULTS AND DISCUSSION

PCL exhibited a low absorptive permeability (A→B) along the intestine with relatively small regional variations (Figure 1). Secretory permeability (B→A) across all the segments selected was significantly high with respect to the corresponding absorptive permeability. Efflux ratio was found to be high (15.91±2.17) in the ileum and least in distal colon (2.95±0.95). BàA transport of [^{14}C]-PCL was significantly high ($p<0.01$) in jejunum and ileum segments w.r.t duodenum. Verapamil (VER), a known P-gp inhibitor at 200μM concentration completely inhibited P-gp transport in different segments of the SD rats' gut leading to increase in absorptive transport of PCL and decrease in secretory permeability. Percentage change in the bidirectional transport in the presence and absence of VER was calculated and found that the absorptive transport was approximately 10 fold high in ileum. However the secretory transport was reduced to about 35 to 80% with maximum reduction in ileum. In a similar manner, Cyclosporin (25μM) significantly inhibited INDI BàA transport and improved A→B transport. A change of 29% in the cumulative amount transported in secretary direction and an enhancement of 43.49% in the absorptive direction was observed. PPN showed symmetric bidirectional transport and was not influenced by VER (200μM). Overall the data indicated variability in P-gp expression across various segments of GIT. This, however, should be conformed by western blotting, which is underway in our lab, the observed difference in permeability characteristics of PCL may explain variable bioavailability of various P-gp substrates. Grapefruit juice extract showed the similar trend as that of VER in bi-directional transport studies indicating that grapefruit juice has a profound effect on the intestinal permeability of P-gp substrates.

CONCLUSIONS

In the present investigation, intestinal transport of various classes of drugs was studied to explore the role of P-glycoprotein in impeding the *peroral* drug delivery. Intestinal transport studies with model drugs belonging to BCS class IV, INDI and PCL, indicated that P-gp mediated efflux plays a significant role in limiting their oral bioavailability and thus co-administration with P-gp modulators may improve their deliverability. P-glycoprotein inhibition by grapefruit juice extract may provide a scope for developing differ-

ent components of the same for P-gp modulation activity.

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BIORELEVANT DISSOLUTION TESTING OF RIFAMPICIN CONTAINING FIXED DOSE COMBINATIONS

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OBJECTIVE

To develop the dissolution methodology for evaluation of rifampicin containing FDCs using Biopharmaceutic Classification System (BCS) based approach.

INTRODUCTION

Selection of appropriate dissolution test can be greatly facilitated by considering BCS where drugs are classified based on solubility and permeability[1]. Biorelevant media proposed for evaluation of class II drugs have significant advantage over compendial media for forecasting the *in vivo* behavior of drug product as excellent correlation can be obtained by use of these media. The standard dissolution procedures recommended for evaluation of rifampicin containing FDCs are not able to predict the bioavailability of rifampicin. So it is necessary to develop a dissolution methodology that should be able to predict *in vivo* performance of rifampicin.

EXPERIMENTAL

Dissolution studies were conducted at agitation intensities of 30, 50, 75 and 100 rpm. Dissolutions were performed in various media recommended by USP (0.1 N HCl, 0.01N HCl and pH 6.8 phosphate buffer) as well as media proposed based on BCS for class II drugs {simulated gastric fluid (SGF), fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF)}[2] using passed and failed rifampicin formulations in bioequivalence testing. Equilibrium solubility of rifampicin was determined by adding excess of drug to each medium and equilibrating at 37°C under standard shaking conditions.

RESULTS AND DISCUSSION

Theoretical solubility predictions based on experimental data and literature pKa values indicate rifampicin as a class II drug because of its pH dependent low solubility (permeability is reported to be very high). There is an increase of almost 25- fold between the solubility at pH 3-6 and that at pH 1. Presence of bile salts and solubilizing agents at pH 5 (FeSSIF) and pH 6.5 (FaSSIF) showed no difference in the solubility over the simple buffers of corresponding pH. At lower agitation intensity (30 rpm) high variability in dissolution resulted in nondiscriminatory nature of the test. Higher agitation intensities (75 and 100 rpm) were also not discriminative since the extent of release was almost same in both agitation intensities. BCS based predictions indicated that use of 0.1N HCl as dissolution medium reflects 100% bioavailability, while 0.01N HCl shows 70-90% bioavailability, which is more nearer to the *in vivo* bioavailability of rifampicin of 70 -93% . Hence, 0.01N HCl may be more discriminatory biorelevant medium to distinguish good and poor formulations. These predictions also showed that use of FaSSIF, FeSSIF may underestimate the *in vivo* drug release. Release of rifampicin in pH 6.8 phosphate buffer was higher in case of formulation B (100%) than formulation A (75%). Whereas, more than 75% of rifampicin was released from formulations A and B when dissolution was performed in 0.01N HCl. Thus pH 6.8 phosphate buffer was able to distinguish between two formulations of variable bioavailability in which formulation A had lower bioavailability than formulation B.

CONCLUSION

0.01 N HCl and pH 6.8 phosphate buffer were found to distinguish between formulations differing in bioavailability

as compared to other biorelevant dissolution media. Thus a dissolution methodology with 0.01N HCl and pH 6.8 phosphate buffer using USP apparatus II at 50 rpm is recommended for biorelevant IVIVC for rifampicin from anti TB FDCs.

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STUDIES ON DISSOLUTION ENHANCEMENT OF NIMESULIDE WITH SEMISYNTHETIC CARRIERS

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INTRODUCTION

Nimesulide, a preferential COX-2 inhibitor, is popularly indicated in various pain and inflammatory conditions(1). Being poorly soluble and highly permeable nimesulide can safely be regarded as BCS class II drug. Further, based upon high magnitude Wyatt parameters (like dose volume, dissolution time and absorbable dose), the mechanistics of its oral absorption can unambiguously be regarded as

limited solely to dissolution. Albeit the extent of bioavailability is adequate, yet its rate of absorption is reported is reported to be quite delayed and inconsistent(t_{max}: 1.75-3.25h) [1].

Hence, the current study aims at improving the dissolution of nimesulide through formulation of dispersion with various semisynthetic carriers viz. Polyglycolized glycerites, poloxamers, and cyclodextrins(CDs).

EXPERIMENTAL

Nimesulide was procured *ex-gratis*

from Panacea Biotec Ltd., India. Poloxamers (LutrolsÒ F127, F68), polyglycolized glycerides (GelucireÒ 44/14), b-cyclodextrin (CavitronÒ82900) and hydroxypropyl -b-cyclodextrin (CavitronÒ829006), and sulphobutylether derivative of b-cyclodextrin (CaptisolÒ) were obtained from BASF (Germany), Gattefosse (France), Cerestar (USA) and CyDex Ltd. (USA), respectively. All the other chemicals used were of analytical grade.

Phase solubility studies were carried out with various carriers by shake flask method for 48hrs, as reported by Higuchi and Connors. The dispersions were prepared employing varied ratios of the semisynthetic carriers by hot-melt method, flash cooled, kept under vacuum for 48 hrs and finally sieved. Preparation of inclusion complexes: the inclusion complexes were prepared in various molar ratios by kneading with water:methanol(1:1v/v) for 45 min and subsequently drying under vacuum for 24hr.

Drug release studies were performed in triplicate at 37°C employing USP apparatus II at 100 rpm. Formulations containing 100mg of nimesulide were subjected to dissolution in simulated intestinal without enzymes. Aliqoutes of samples withdrawn periodically wer eanalyzed spectrophotometrically at 393nm and data analyzed using ZOREL software.

The formulations prepared were characterized employing FTIR, XRD and SEM.

RESULTS AND DISCUSSIONS

The phase solubility of nimesulide with different types of carriers were of A_L type revealing linear increase in solubility with the amount of carrier. All the drug formulation, prepared employing varied kind of carriers and the respective physical mixtures, yielded markedly improved dissolution profiles vis-à-vis pure drug. The value of $t_{50\%}$ of pure drug (115min.) decreased appreciably with carriers like CDs and poloxamers (<5min.) indicating manifold improvement

in dissolution rate. Dissolution efficiency of plain drug ($\%DE_{10min}$:2.5) also improved nearly 2-to 26-fold for various formulations (($\%DE_{10min}$:4.8-65.8). this depicts the marked enhancement in both the rate and extent of dissolution, the release increasing from the nigligible (rel_{10min}:7.5% for plain drug) to almost complete (>90% with some of the carriers). The rate and extent of release with GelucireśO, on the other hand, was observed to be relatively less ($\%DE_{10min}$ ranging between 4.8-86.3) than the other carriers but was quite regulated. The XRD and SEM studies revealed that the amorphous nature of drug in the formulations could be responsible for dissolution rate enhancement.

CONCLUSION

the above studies vividly indicate gross improvement in the dissolution rate of nimesulide observed with various types of semisynthetic carriers. Since nimesulide is a BCS classII drug and exhibits dissolution limited absorption, it is highly probable that such improvement in dissolution performance would result in appreciable improvement in drug absorption. In-vivo bioavailability on such formulations are in progress in our laboratory.

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STUDIES ON DESIGN AND EVALUATION OF FLOATING MULTI-UNIT CONTROLLED RELEASE GASTRO RETENTIVE DRUG DELIVERY SYSTEMS OF CELECOXIB

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INTRODUCTION

A controlled release oral drug delivery system with prolonged residence time in stomach is of particular interest for drugs like celecoxib, which show increased bioavailability after oral ingestion when retention time in the stomach is increased. Most gastro retentive system are single unit devices having a common risk of loosing their effect too early and showing varying bioavailability due to their all-or-none emptying phenomenon from the stomach. To over come this problem, multi-unit floating systems have been proposed. They distribute uniformly within the gastric content and gradually empty from the stomach resulting in prolonged effect and reduced inter-product or inter-subject variability.

OBJECTIVE

The objective of the present study was to design and evaluation of floating multi-unit controlled release gastro retentive drug delivery systems of celecoxib. As preformulation work dissolution conditions providing adequate sink condition and simulating gastric fluid was optimized in which the drug is stable. Phase separation coacervation technique was used for encapsulating granules containing drug, gel forming polymer (sodium alginate) and gas generating agents in polymeric membrane. The proportion of the floating agent and the drug to polymer ratio in the granules was optimized. The effect of various polymer proportion in the encapsulation solution was studied on floating and release characteristics of the drug from the formulations.

EXPERIMENTAL

Pure celecoxib was obtained as a gift sample from IPCA Labs, Mumbai. All the polymers, chemicals and reagents used were of pharmaceutical or analytical grade. Dissolution media was optimized based on the criteria of maintenance of sink condition and stability. Rapid, validated UV visible spectrophotometric methods [Jasco, UV-VIS spectrophotometer; model – V570] developed in-house was used for the analysis of the drugs in pure form, in tablets and for application in dissolution studies using 0.1N HCl with 1.0% w/v SLS at 255nm.

Controlled release gastro retentive capsules of celecoxib were prepared, each containing microencapsulated granules of the drug. Varying combination of ethyl cellulose (7 cps) and of PVP (k-30) [1:0 (MG1), 3:1 (MG2), 2:1

(MG3), 1:1 (MG4)] in cyclohexane was used as microencapsulating medium. Micro-encapsulation was ensured by phase separation coacervation technique using temperature change. The granules of celecoxib contained 200 mg of the drug, gel forming swellable polymer (sodium alginate), and also gas generating agents (A:B in 2:1 ratio). This was granulated using 3% w/v solution of PVP (k-30) in isopropyl alcohol. The encapsulated granules were evaluated for physical appearance, micromeritics and drug content uniformity. Three batches of granules were prepared in each case. Encapsulated granules equivalent to 200 mg of the drug was packed in empty gelatin capsules shell and used for release rate studies. Release rate studies were carried out in USP dissolution apparatus (USP XXIII) type 2 (paddle method; 75 rpm) in 0.1N HCl with 1.0% w/v SLS (900 mL) at 37.5 ± 0.5 °C. During dissolution study the formulations were also evaluated for swelling and disintegrating characteristics, buoyancy (lag time to float) and total duration for floating. For all these studies pure drug in gelatin capsules was used as control.

RESULTS AND DISCUSSION

Dissolution media of 0.1N HCl with 1.0% w/v SLS was found to be suitable for providing adequate sink condition and stability for evaluation of controlled release floating multi-unit gastro retentive drug delivery systems of celecoxib. Physical appearance, micromeritics and drug content uniformity for different formulations were found to be satisfactory. The ratio of 2:1 of two gas generating agents was found to provide the granules with good buoyancy and satisfactory controlled release.

Release rate study revealed that all the designed formulations had floating lag time of 10-15 mins corresponding to the time taken for the dissolution of the gelatin shell. The microcapsules of all the formulations floated up to 24 hours. The duration of release of the drug from these formulations was extended beyond 24 hours. Increasing the proportion of EC in coating solution decreased the rate of release of the drug from the microcapsules. Increasing the proportion of hydrophilic polymer in the coat increased the rate and extent of release of the drug from microcapsules and correspondingly maximum release was seen in case of MG4 (EC: PVP, 1:1) with 55% release in 24 hours and minimum in case of MG1 (EC: PVP, 1:0) with 39% drug release in 24 hours.

CONCLUSION

It can be concluded that satisfactory controlled release floating multi-unit gastro retentive drug delivery systems of celecoxib can be prepared by microencapsulation of drug and swellable polymer along with gas generating agent for prolonged residence in the stomach and controlled release of the drug.

COATED PELLETS OF TERBUTALINE: OPTIMIZATION BY RESPONSE SURFACE METHODOLOGY

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OBJECTIVE

The primary objective of the study was to prepare and optimize a sustained release multiparticulate formulation of terbutaline, using RSM.

INTRODUCTION

Sustained release formulation of terbutaline is more beneficial for controlling the nocturnal symptoms of bronchial asthma (1). In the current investigation, we used RSM to design and optimize a sustained release formulation of terbutaline-loaded pellets. MINITAB™ Statistical software (MINITAB Release 13.31, Minitab Inc.) was used for optimization.

EXPERIMENTAL

Surelease® (aqueous polymeric dispersion of ethyl cellulose) coated pellets of terbutaline were prepared by Fluidized bed technique (2). A central composite design was used to evaluate the effect of the critical formulation variables, namely Polymer coating load and HPMC level on the response variables, and to optimize dosage form. Based on the experimental design and factors to be studied, 13 for-

mulations were prepared. The in vitro drug release was studied using the USP XXIII Dissolution apparatus II (paddle).

RESULTS AND DISCUSSION

The percent drug release after certain specific time points such as 1 h, 4 h, and 8 h (Y_1, Y_2 and Y_3) were measured as response variables. A desirability function that combines these three response variables was constructed to simultaneously optimize all the three response variables each having a different target, by the method described by Derringer and Suich (3). The response values (Y_1, Y_2 and Y_3) and overall desirability function (D) were fitted to a second-order polynomial model based on response surface regression. The fitting results were statistically tested for lack of fit. The fitting equations that resulted after model simplification are given below.

% Drug release after 1 h (Y_1) = $36.469 - 3.914X_1 + 1.167X_2 - 0.304X_1^2 - 0.696X_1X_2$

% Drug release after 4 h (Y_2) = $81.507 - 7.506X_1 + 4.392X_2 - 2.762X_1^2 - 1.922X_2^2$

% Drug release after 8 h (Y_3) = $96.429 - 3.853X_1 + 2.402X_2 - 1.94X_1^2 - 1.206X_2^2 + 0.907X_1X_2$

Overall desirability (D) = $0.6613 + 0.1124X_1 - 0.1101X_2 - 0.1213X_1^2 + 0.1278X_1X_2$

Response surface plots (Figures 1-3) showed that the percent of terbutaline release at all three time points was highly dependent on the polymer coating load. When the coating load increased, the percent drug release decreased significantly. On the other hand, the factor X_2 (HPMC level) had a synergistic effect on all the responses.

PREDICTION

A release profile with 35% terbutaline released after 1 h (Y_1), 65% released after 4 h (Y_2) and 90% drug released after 8 h (Y_3) was targeted. Optimum overall desirability was predicted by carefully analyzing the response surface using the computer software MINITAB. The optimum overall desirability (0.8029) can be achieved at intermediate polymer coating load (17.01%) and low HPMC level (1.6%). Thus an optimized formulation was prepared at 17% polymer coating load, and 1.6% HPMC level and evaluated for in vitro release behavior. The response values of the formulation prepared in the predicted optimum condition were satisfactorily close to the predicted values, with a low percentage of bias.

CONCLUSIONS

Terbutaline sustained release pellets with optimal release properties were successfully prepared using RSM. The optimized formulation released 32.8% of drug after the initial 1 h, which is deemed satisfactory to serve as loading dose, 70.91% after 4 h and 90.5% after 8 h, which ensures that most of the drug is released in a period of time comparative to the gastrointestinal residence time. The release profile of optimized formulation appears to be suitable for oral sustained release dosage forms.

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FLOATING BIALYER TABLET CONTAINING CEFUROXIME AXETIL

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INTRODUCTION

Cefuroxime axetil is a broad spectrum antibiotic. The presence of 1-acetoxyethyl group enhances the absorption from the gastrointestinal tract. Cefuroxime axetil is rapidly hydrolysed in intestine producing cefuroxame, which is poorly absorbed. It reduces the bioavailability less than 50%. The amorphous form of cefuroxime axetil is essential for better bioavailability. Processing of this drug by wet granulation affect the amorphous nature of the drug. Therefore, in the present study an attempt is made to formulate bimodal tablet formulation by direct compression. Drug was 300 mg/layer. Type A bilayer tablets containing immediate release layer (IR) and a floating matrix layer (FL) and Type B bilayer tablet containing immediate release layer and a flaoting press-coated layer were prepared.

EXPERMENTAL

Type A tablets: The powder blend of FL (Table 1) was compressed using a manual KBr hydraulic press in a die of 13mm diameter at pressure 50 kg /cm^2 for 1 min. After compression of FL layer, the upper punch was lifted and the powder blend of IR was poured in the same die. This was compressed at pressure 100 kg/cm2 for 1 min.

Using 2.5% w/v PVP solution. IR composition was used to prepare core tablet, which was compressed using 10mm die diameter at 50 kg/cm^2 for 1 min. The press coating was done at 50 kg/cm^2 for 1 min., using 13mm die diameter.

The tablets were evaluated for buoyancy lag time (BLT), floating period, in-vitro drug release and gastro-retentive properties by gamma- scintigraphy.

TABLE 1: COMPOSITION OF FLOATING-BILAYER TABLETS

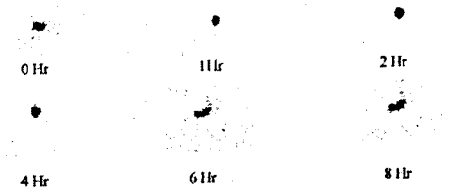
Ingredients	IR (mg)	FL1	FL2	FL3	FL4
HPMC	-	200	100	50	100
Tulsion T-399	15	15	15	15	15
Sodium citrate	15	15	15	15	15
Sodium bicarbonate	-	25	50	50	50
Lactose	25	-	-	-	15

RESULTS AND DISCUSSION

Type A tablets have BLT 7 to 34 min. and remained floated in 0.07 N HCl for more than 18 hrs. The 50% drug released within initial 20-30 min.; thereafter drug release was slower but continuous with 65 to 100 % drug releases at end of 10 hrs. The core tablet showed disintegration time 1.8 min. The press-coated layer of Type B tablets showed BLT 6 to 34 min., floating period 9 hrs and 21 hrs and lag or less than 20% drug release within 4 hrs. In the bilayer tablet press-coated layer retained similar floating and drug release properties. After initial rapid 50% drug release, Type B tablets showed slow release upto 4 hrs followed with rapid release with 70 to 100 % drug release within 8-10 hrs. The tablets were retained in gastric region for more than 8 hrs.

CONCLUSION

Bilayer tablets comprising of immediate layer and HPMC based floating matrix tablet showed floating and controlled drug releases after initial immediate release; whereas bilayer tablets comprising of immediate layer and press coated floating layer have floating and drug release in bimodal fashion after initial immediate drug release.



Gamma Scintigraphs obtained after oral administration.

ACKNOWLDGEMENTS

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STABILITY, BIOPHYSICAL AND *IN VIVO* TOXICITY EVALUATION OF A NOVEL NALOXONE TRANSDERMAL GEL FORMULATION

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OBJECTIVE

The present investigation aims towards the evaluation of a novel Naloxone Transdermal System (NTS) before applying for regulatory approval to commence clinical evaluation.

INTRODUCTION

Transdermal delivery of naloxone (NLX), by maintaining constant blood levels hence avoiding withdrawal symptoms and increased patient acceptance, can be an attractive option in the management of opioid dependence. With the positive feedback of previously performed feasibility and formulation studies, present work aims to complete the evaluation of NTS, developed in our own laboratory [1,2].

METHODS

NTS, containing hydroxypropyl cellulose, ethanol and propylene glycol with 10, 20, and 30 mg NLX/g of gel, was prepared as reported earlier[1]. Gel formulation was subjected to 3 months stability testing at 25°C/60%RH (Stability chamber, WTC Binder, Germany), where refrigeration conditions (4-8°C) served as control. Stability samples were evaluated for drug assay and *ex vivo* permeation through porcine skin after 1, 2, and 3 months. Drug assay was carried out with a newly developed RP-HPLC method. *Ex vivo* permeation studies were performed with porcine and/or Sprague-Dowley rat epidermis using Franz diffusion cells, where ^{3}H-NLX (1μCi/g) served as tracer. NTS was evaluated for in vivo skin irritation potential in female Sprague-Dowley rats (150-160 g) by laser Doppler velocimetry (LDV) and transepithelial water loss (TEWL) measurements. LDV was measured on the NTS application sites (on the dorsal surface of rats) using a Multichannel Laser Doppler System (Perimed, Sweden). TEWL measurement was performed using Tewameter™ (Courage and khazaka, Germany)[3].

RESULTS AND DISCUSSION

Effect of different concentrations of NLX on *ex vivo* permeation is shown in Table 1. It was found that flux of NLX, permeating through porcine and rat skin increased with increase in concentration of NLX in gel. Conversion of porcine and rat epidermis flux values to that across human cadaver skin indicated that NTS is efficient in maintaining the desirable blood-NLX concentrations. Since, only concentration of NLX was increased in all the three cases and composition of rest of the formulation was same, increase in thermodynamic activity of NLX may be a contributing factor in increasing flux across different barriers. Drug assay (75-125%) of stability samples indicated no degradation of NLX at the specified storage conditions. *Ex vivo* permeation studies were performed to assess the stability of penetration enhancer. When flux and lag time values obtained after *ex vivo* permeation studies of stability samples at different concentrations were compared (Figure 1). Samples evaluated at the end of 3 months showed flux values similar/higher to that obtained at previous time point and with control. This indicates the stability of penetration enhancer in the formulation, which retained skin perturbation effect resulting in similar/higher flux values. Assessment of skin irritation potency of the formulations (esp. penetration enhancers) was done by LDV and TEWL measurements. Using LDV technique, no statistical significant difference (P=0.38) was found between 0 and 48 hours of treatment (Figure 2A), while a 10 times increase in the TEWL enhancement ratios after 48 hours of treatment (Figure 2B) was observed. This data indicated that Oleic acid, the penetration enhancer use in NTS, caused the skin barrier perturbation which resulted in increased flux without any significant irritation.

CONCLUSIONS

The newly developed NTS showed to be stable and efficient in maintaining the desirable blood-NLX concentration. *Ex* vivo, biophysical and skin irritation studies showed the influence of NTS on the barrier properties of skin and the permeability of NLX and also indicated insignificant skin irritation nature of the formulation. In a nutshell, NTS is stable and non-toxic and can be carried further for clinical evaluation.

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DEVELOPMENT OF NOVEL VALDECOXIB EMULSION GEL WITH COUNTERIRRITANTS FOR EFFECTIVE PAIN MANAGEMENT

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OBJECTIVE

Development of novel emulsion gel of Valdecoxib and few counterirritants with improved penetration as well as pharmacodynamic activity.

INTRODUCTION

Valdecoxib (VAL) is a highly potent Nonsteroidal Anti Inflammatory Drug (NSAID)[1]. The clinical studies had proved its effectiveness at quite low oral dose as compared to Ibuprofen and Diclofenac[2]. Unfortunately it also have side effect of gastric irritation, which can be bypassed by its topical application. Methyl Salicylate (MS) is well known counterirritant in management of rheumatoid arthritis. Capsaicin (CAP) is natural origin counterirritant widely used in treatment of osteoarthritis, rheumatoid arthritis, neuralgias and diabetic neuropathy[3]. Menthol (MNT) is known for cooling properties.

The VAL emulsion gel as o/w emulsion in Carbapol® base with penetration enhancers as well as counterirritants was prepared. The given formulation of emulsion gel can be used as analgesic for pain management in rheumatoid arthritis, osteoarthritis.

EXPERIMENTAL

Different grades as well as concentration of Carbopol®, Pemulen®were tried to obtain optimum viscosity.

Various surfactants and solubilizers as Twins, Cremophores, Labrafils, Labrasols, Lutrols.

Step I: Preparation of Hydroalcoholic Solution.

Demineralised water (5.0 g), Isopropyl alcohol (3.0 g), Diethylamine(1.0 g) added and mixed uniformly.

Step II: Preparation of Gel phase.

Disodium EDTA(0.1 g) was added in demineralised water(45 g). Carbapol® (1.0 g) was added slowly with continuous stirring until uniform, homogenous slurry of Carbopol® was formed (avoid lump formation).

Step III: Preparation of Oil phase.

Surfactant (3.5g), and Capsaicin (0.025 g) were mixed together in a vessel and warmed.

Butylated hydroxy toluene (0.2 g) and Penetration enhancer-1 (1.0g) were added to the above mixture with continuous stirring. In a separate vessel MNT (5.0 g) was dissolved in MS (10 g) and added to surfactant solution. Step III was added to step II with stirring. The containers was rinsed with hydroalcoholic solution and added to the above mixture. Entire oil phase (step III) was added to the gel base. Globule size was checked (not more than 10 m). The entire mass was passed through colloid mill for two times. Remixed in the main tank (cold water was passed in the jacket).

Step IV: Penetration enhancer-2 (10.0 g) was taken in a vessel and benzyl alcohol (1.0 g), IPA (2.0 g) and water (5.0 g) were added and mixed well. Hydroalcoholic solution (1.0 g) was added to the above solution, mixed well until clear solution was obtained. To this Valdecoxib (1.0 g) was added. Step IV was added to the o/w emulsion slowly with mixing. Remaining hydroalcoholic solution was added and pH was checked (6.5-7.5).

RESULTS

During the various trials of emulsion gel it was observed that with higher concentration of Carbapol® viscosity increased and spreadability decreased. With Pemulene® grade emulsifier emulsion gels can also be obtained without using surfactants. The o/w emulsion breaking was observed with increase in percentage of IPA. .As compared to the conventional formulation VAL emulsion gel showed better physical properties. The appearance of the formulation was white with good spreadability and globule size was below 10m. Stability studies for the said emulsion gel were carried out and emulsion gel was found to be stable as per ICH guidelines.

DISCUSSION

At higher concentration of alcohols in formulation emulsion found to be unstable. Also the addition of oil phase plays important role in reducing globule size. Addition of counter-irritants in gel showed marked improvement in the anti-inflammatory activity as compare to conventional gel formulation.

CONCLUSION

Addition of counterirritants with valdecoxib in stable emulsion gel can give better therapeutic efficacy for better pain management.

ACKNOWLEDGEMENTS

We are thankful to Unichem Labs. Ltd. for gift sample of VAL

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FORMULATION DEVELOPMENT AND EVALUATION OF POLYMER BASED OXYBUTYNIN METERED DOSE TRANSDERMAL SPRAY SYSTEMS

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OBJECTIVE

The objective of the present investigation was (1) To develop metered dose transdermal spray delivery system, in order to provide improvement in bioavailability of oxybutynin by completely avoiding pre-systemic metabolism.

(2) To test the feasibility of novel quick drying and non-occlusive transdermal sprays for enhanced delivery of oxybutynin.

INTRODUCTION

Oxybutynin is a safe and effective drug for the treatment of urinary incontinence due to overactive bladder. Development of metered dose transdermal spray (MDTS) formulations for oxybutynin would offer advantages of lesser anti-cholinergic side effects, increased dosage flexibility and greater ease of use.

The metered dose transdermal spray (MDTS) technology is based around the delivery of a precise dose of the drug to a defined area on the skin in solution form. The MDTS formulations are solutions containing drug, polymeric solvent systems and penetration enhancers.

EXPERIMENTAL

Drug was dissolved in the polymeric solvent system by means of sonication. Ethanol and acetone were used as solvents for transdermal spray systems. Methylal (Dimethoxy methane) was incorporated to increase the rate of drying of the spray film. Solubility of different polymers like Eudragits, Carbopols, Poloxamers and Gantrezes was checked in combinations of solvents (ethanol: acetone: methylal). Glyceryl mono oleate and myristyl lactate were used as permeation enhancers for transdermal spray formulations. The spray pumps of capacity 50 and 100 ml were utilized for delivering MDTS formulations. Spray properties of different actuators (Valois Ltd) were studied. The performance characteristics of formulations were assessed by determining clarity, film forming capacity, pH, drug content, evaporation time, average weight per metered dose and stability.

Draize patch test was performed on rabbits as well as on human volunteers to ensure safety of the spray formulation. In-vitro release studies were carried out using semipermeble parchment paper in Keshary Chein diffusion cells for 24 hours. The in- vivo percutaneous absorption of the developed formulations was confirmed by making use of -1) Animal model-rabbits and 2) Human volunteers.

Predefined metered dose was applied on pre-shaved rabbit skin or on the forearm of volunteers. Blood samples were withdrawn as per the protocol for a period of 24 hours. Concentrations of oxybutynin in blood were analyzed by HPLC-MS/MS method.

RESULTS AND DISCUSSIONS

Good polymeric films were obtained from MDT sprays. Films were non-tacky and quick drying. pH of the developed formulations was between 5-7 and content per spray was about 99- 105 %. Draize patch test did not show any erythema and edema. The in-vitro release was found to be 50-55% over a period of 24 hrs. The extent of absorption of oxybutynin in animal model is shown in Fig.1.

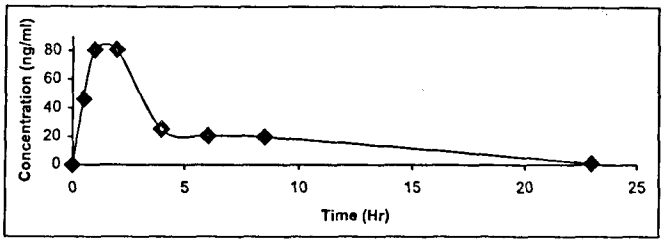

Fig 1: Desired therapeutic levels of oxybutynin were observed in human volunteers.

CONCLUSION

Successful stable oxybutynin metered dose transdermal spray formulations have been developed for percutaneous absorption of the drug. This delivery system will be a preferred mode of administration for patients with urinary incontinence.

ACKNOWLEDGEMENTS

Cipla Ltd. for support.

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CONTROLLED RELEASE GEL FORMUATION OF LIPOSOMAL VITAMIN E ACETATE

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INTRODUCTION

Transdermal liposomal delivery systems have been used to transport the active ingredient directly into the skin through percutaneous absorption. Topical controlled release gels provide uniform concentration and distribution of the drugs within the stratum corneum to provide prolonged action[1]. Vitamin E, as an antioxidant, is therapeutically used to protect the skin from free radical damage.

OBJECTIVES

- To develop liposomal dispersions of Vitamin E acetate
- To prepare controlled release liposomal topical gel formulations
- To characterize liposomes and gel formulations and to study invitro release profile, stability and safety.

EXPERIMENTAL

Phospholipids like, phosphatidyl choline, Centrolex and Percept were used for the formulation development of liposomes of Vitamin E acetate. Liposomes were prepared by thin film lipid hydration method.The process was optimised with respect to proportion of lipids and cholesterol and other process variables. The characterization of optimised formulations was carried out based on following studies: Percent drug entrapment, Differential Scanning Calorimetry, Particle size analysis, Electron microscopy, NMR studies.

Controlled release gels were prepared by using optimized liposomal dispersions. The gelling agent Carbopol 934 P NF in different concentrations was used to prepare the gels. The in-vitro release studies were conducted using animal skin and semipermeable parchment paper attached to Keshary Chein diffusion cell. Safety studies such as Draize test[2] and Microbial limit test[3] were carried out to ensure the safety of the formulation. The stability studies were conducted at refrigeration (4-8°C), room temperature (25±2°C / 60% RH), and accelerated temperature (40°C / 70 % RH). The samples were withdrawn periodically and evaluated for three months.

RESULTS AND DISCUSSIONS

Percept and Vitamin E acetate at 1:3 drug ratios were selected as optimized batch. The size of the vesicles were in the range of 0.5 - 0.8 microns, the vesicles were bilamellar. The drug was entrapped in lipid bilayers and the encapsulation efficiency was 55 ± 3%.The liposomal gel with 2% gelling agent was found to have good consistency and aesthetic feel. The drug release from liposomal dispersion through parchment paper was 80.55 % and from liposomal gel was 66.25 % after 6 hours. The drug release from Plain Vitamin E acetate gel was 46.98 % and from liposomal gel was 27.74% after 24 hours. Liposomal gel was quite stable at all stability storage conditions. Safety and irritancy using Draize patch test showed that the gel was safe for topical applications.As compared to Plain Vitamin E acetate gel, the drug release from liposomal gel was delayed and prolonged the effect for longer duration.

CONCLUSION

Successful controlled release gel formulations containing vitamin E entrapped in liposomal carriers have been prepared and evaluated.

ACKNOWLEDGEMENTS

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VALDECOXIB MICROEMULSION BASED GEL: POTENTIAL FOR PERCUTANEOUS ABSORPTION

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OBJECTIVE

The objective of the study is to formulate a microemulsion based gel system for percutaneous drug delivery of Valdecoxib.

INTRODUCTION

Microemulsion system consists of a mixture of oil, water and amphiphile and is a single, optically isotropic and thermodynamically stable liquid solution. Microemulsions exhibit excellent thermodynamic stability, solubilization potential and clarity unlike the conventional emulsions. Valdecoxib, a diaryl- substituted isoxazole, is a potent and specific inhibitor of Cyclooxygenase-2 (COX-2), which is used for the treatment of rheumatoid arthritis, osteoarthritis & allied inflammatory conditions. Valdecoxib possesses a greater potency and high specificity for COX-2 inhibition like the other drugs of this class. Inspite of its specificity, the poor water solubility of the drug poses a significant problem in formulating the drug in to an efficient topical drug delivery system and hence microemulsion based gel system was investigated as a vehicle in an attempt to overcome this problem.

EXPERIMENTAL

GRAS components were chosen for the study. Oils and surfactants were further screened on the basis of saturation solubility studies of Valdecoxib in the respective components

and those showing maximum solubility of the drug were selected for further studies.

Oil Phase: Medium chain triglycerides,fatty acid esters and propylene glycol, mono and di-glycerides of Caprylic/Capric acid.

Surfactants: Ethoxylated glycerides, Polyoxyl hydrogenated castor oil, Triton-X 100, LAP.

Co-surfactants: Polyols.

Aqueous Phase: Distilled water.

Gelling agents: Carbopols, Xanthan gum, Sodium-CMC, HPMC, HPC, HEC etc.

FORMULATION

Pseudoternary phase diagrams were constructed by titration method and component composition was chosen on the basis of microemulsion region obtained. Microemulsion based gel was then prepared by dispersing the gelling agent in the system.

Characterization of the microemulsion and microemulsion based gel (MBG):

The transparency of the system was characterized by visual inspection and isotropicity by using cross polarizing plates. Samples were evaluated for their thermodynamic stability by subjecting to the freeze thaw cycle and centrifugation at 5000 rpm for 20 minutes. The gel was evaluated for pH, clarity, rheology, drug content. Primary skin irritation testing was carried out using Draize Patch Technique. Evaluation of anti-inflammatory potential was carried out by using carrageenan induced Rat Paw Oedema Model.

RESULTS AND DISCUSSION

Pseudoternary phase diagrams were constructed to screen potential microemulsion based formulations. The microemulsion showed excellent clarity and thermodynamic stability. The microemulsion based gel showed good aesthetic appeal and exhibited pseudoplastic behavior. Drug content as analyzed by UV Spectrophotometric method was 100.03±1.03%. Primary skin irritation test indicated the safety of the formulation and inhibition of inflammation indicated its potential for human use in arthritis and allied conditions.

CONCLUSION

Microemulsion based gel of Valdecoxib at 1%w/w could be formulated successfully and showed promising results in preliminary studies. This novel approach has immense potential for commercialization. However, their efficacy in arthritis model coupled with clinical studies would govern their true business potential.

ACKNOWLEDGEMENT

The authors are thankful to M. The authors are thankful to Macleods Pharmaceuticals Pvt. Ltd for the gift sample of Valdecoxib, Colorcon Asia Pvt. Ltd. for providing Gattefosse excipients, *France*.

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MICROEMULSION BASED GEL OF CELECOXIB: A POTENTIAL TOPICAL DELIVERY SYSTEM

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OBJECTIVE

The main objective of the investigation was to establish and evaluate the anti-inflammatory potential of microemulsion based gel of Celecoxib (CXB) via topical route.

INTRODUCTION

Celecoxib (CXB), a new generation NSAID having COX-2 inhibition potential has been recommended orally for the rheumatoid arthritis therapy[1]. The physicochemical properties of the drug suggest a good potential for topical formula-

tion, especially for rheumatoid arthritis and allied conditions requiring chronic therapy. However, poor water solubility of Celecoxib poses a big challenge in designing an efficient topical delivery system. Hence, solubilisation potential of microemulsions has been exploited for formulating a topical delivery system of Celecoxib.

EXPERIMENTAL

Selection of Components:

Non-irritancy and non-sensitizing properties were the main criteria for the selection of ingredients. Components falling in GRAS (Generally Regarded As Safe) category were selected for study.

Solubility Studies of CXB in Oils:

Saturation solubility of the CXB in various oils was determined by conventional techniques. The oils that solubilized maximum amount of CXB were selected for further studies.

Screening of Potential Micro-Emulsion Components:

OILY PHASE: Fixed Oils, Medium Chain Triglycerides and Modified Oils.

AQUEOUS PHASE: Distilled Water.

SURFACTANT: Polysorbates, Caproyl macroglycerides, Polyethoxylates.

CO-SURFACTANT: Polyols.

Determination of Micro-Emulsion Existence Zone:

To determine existence fields, pseudoternary diagrams were constructed using titration method. Compositions that had minimum surfactant but which could accommodate optimum quantity of oil and water were selected.[2]

Characterization:

Microemulsion prepared was characterized by visual observance for transparency and for isotropicity using crossed polarizing plates. Samples were further subjected to accelerated stability studies that included centrifugation at 5000 rpm for 20 minutes and freeze-thaw cycles to ascertain thermodynamic stability[2].

Formulation of Microemulsion Based Gel (MBG):

The microemulsion based gels were prepared by dispersing various gelling agents (Carbopols, HPMC (K15M, K100M), HPC, Sodium-CMC and Aerosil, Xanthan Gum) and formulated gels were evaluated for Clarity, pH, Viscosity, Drug Content and subjected to stability according to ICH guidelines.

Primary Skin Irritation Testing:

Primary skin irritation study using Draize Patch Technique on rabbits was performed for both microemulsion and MBG.

Evaluation of Anti-inflammatory Potential:

Anti-inflammatory activity of Celecoxib MBG was evaluated carrageenan induced Rat Paw Oedema model.

RESULTS AND DISCUSSION

O/w microemulsion was successfully formulated containing solubilized CXB (2%w/w) with polyethoxylates and modified oils for topical delivery. Microemulsion existence zone was determined by constructing pseudo-ternary phase diagrams using titration method. Isotropicity was confirmed using crossed polarizer. Microemulsion showed no separation when subjected to thermodynamic stability studies. Microemulsion based gels were found to have good clarity, spreadability, aesthetic appeal and exhibited pseudo plastic behavior. Primary skin irritation studies indicated the safety and anti-inflammatory activity indicated the efficacy of the developed formulation.

CONCLUSION

The developed microemulsion and microemulsion based gel of Celecoxib reveal a good potential for commercialization.

ACKNOWLEDGEMENTS

Authors are extremely thankful to Zydus-Cadila for gift sample of Celecoxib and Colorcon Asia Pvt. Ltd. for gift samples of lipophiles.

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FORMULATION AND CLINICAL EFFICACY OF MICROEMULSION BASED ANTIACNE GELS

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OBJECTIVE

To develop non-alcoholic, patient savvy 1% w/w Azithromycin anti-acne gels based on microemulsion approach and to evaluate clinical efficacy, safety & tolerability of the same.

INTRODUCTION

Acne is scientific term for pimples, blackhead, whiteheads, or nodules that form on the face, upper chest, upper back or shoulders. Many causes are associated with acne like infection by *Propionibacterium acne* (being the main), hormonal changes, environmental pollutants, stress etc. Acne is characterized by persistent, recurring reddish blemishes does leading to serious painful inflammatory conditions, if neglected.

The design and development of drug delivery systems with a view to enhance the efficacy of existing formulations is a continuous process in the pharmaceutical industry. In case of topical drug delivery systems, the main barrier to the absorption and penetration of drugs from the formulations is the *stratum corneum* or the upper layer of the epidermis of the skin. Microemulsions offer several potential advantages as drug delivery systems over conventional topical drug delivery systems due to their high penetration ability through the *stratum corneum,* high solubilizing power, transparency, good stability and longer shelf life and ease of manufacturing.[1]

EXPERIMENTAL

All the materials used for preparation of microemulsion based gels were GRAS listed. Oleic acid, rice bran oil, mono/diglycerides of capric/caprylic acid, PEG-40 hydrogenated castor oil, caprylocapryol macrogolglyceride, diethylene glycol monoethyl ether, carbopols. The aqueous phase used was double distilled water.

1) Analytical method Development: The drug content in the developed gels was assessed by UV-spectrophotometrically.[2]

2) Formulation development: The components for the development of were selected depending on AZM solubility in oils, solubilizers, surfactants and cosurfactants. The ratio of selected surfactant and cosurfactant was optimized for greater area of microemulsion existence.

3) Evaluation of microemulsion systems: The developed microemulsions were evaluated by pseudoternary phase diagrams (using cross polarizer), particle size analysis (using Photon Correlation Spectroscopy), accelerated stability studies (freeze thaw cycles, centrifugation) and drug content.

   The developed microemulsion systems containing AZM (1%) were thickened by incorporating carbopols.

4) Clinical evaluation of AZM (1%) gels: After taking written consent & baseline clinical evaluation, adult patients with clinical diagnosis of mild to moderate *Acne vulgaris* were advised to apply Azithromycin gel once a day for 4 weeks. Clinical evaluation was made for non inflammatory & inflammatory lesions (papules, pastules, nodules and cysts). Safety and tolerability evaluation criteria included dryness, erythema, crusting, scaling, burning & pruritis.

RESULTS AND DISCUSSION

Pseudoternary phase diagrams help to choose a small number of formulations from a large pool of formulations. The microemulsion formulation was optimized with respect to low surfactant content, higher area of microemulsion existence and particle size in nanometer range. The optimized microemulsion found to be robust to the accelerated stress conditions. Gelling of ME could be effectively achieved using carbopol as the carrier. The gels were clear, thixotropic having excellent spreadability & emollient properties. Preliminary clinical results indicated potential of developed formulation with respect to safety, efficacy and tolerability.

CONCLUSION

Azithromycin (1%) microemulsion based anti-acne gels could be successfully developed. Clinical data suggests a strong commercial potential of the developed formulation.

ACKNOWLEDGEMENTS

Authors express gratitude to Colorcon-Asia Pvt. Ltd., Noveon, Indoco Ltd, Mumbai.

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FORMULATION AND EVALUATION OF *IN SITU* GEL IMPLANTS OF GLIPIZIDE

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OBJECTIVES

1. To prepare in situ gel implants of glipizide using PLGA.
2. To evaluate implants with respect to various *in vitro* and *in vivo* parameters.

INTRODUCTION

Glipizide is an important drug used in treating non-insulin dependent diabetes mellitus. The oral therapy produces severe hypoglycemia and GI disturbances like nausea, vomiting, heartburn, anorexia and increased appetite. Novel drug delivery systems offer many advantages to overcome these problems. The feasibility of transdermal application of glipizide has already been investigated. Presently, an attempt has been made to formulate and evaluate *in situ* gel implants of glipizide using poly (lactide-co-glycolic) acid (PLGA), a biodegradable polymer.

EXPERIMENTAL

1. **Drug-polymer interaction studies** were carried out by IR spectroscopy, DSC and HPTLC.
2. **Preparation of *in situ* gels:** Initially, a solution of PLGA in triacetin (15% w/v) was prepared. Drug was dispersed in the solution using vortex mixer. Three different ratios (1:5, 1:10 and 1:15) of drug and polymer were attempted.
3. ***In vitro* drug release studies:** The *in vitro* drug release experiments were conducted by vial method upto 30 days using 10 ml phosphate buffer (pH 7.4).
4. **Scanning electron microscopy (SEM):** The morphology of the *in situ* gel implants before and after *in vitro* skin release studies was analyzed by SEM.
5. **Hypoglycemic activity in normal mice:** The over night fasted normal mice were divided into different groups (n=6). Group I received 5 mg/kg of glipizide orally. Group II animals were injected with a solution of PLGA in triacetin (15% w/v) containing glipizide (0.2 ml, drug: polymer 1:15; s.c.). Group III received 0.2 ml sodium CMC. The blood glucose levels were determined at different time intervals at day 1, 3, 5, 10, 15, 20 and 30 day after the implantation.
6. Hypoglycemic, biochemical and histopathological evaluation in diabetic mice

   The hypoglycemic activity was carried out in streptozotocin induced diabetic mice, as explained earlier. After 30 days, lipid profile (high-density lipoprotein (HDL), triglycerides and total cholesterol), alanine transaminase (ALT), aspertate transaminase (AST), urea and creatinine levels were estimated in serum using Auto-analyzer (Hitachi 911, Japan). The glycogen and total protein levels were estimated in liver. Pieces of liver, pancreas and stomach were subjected to histopathological examination.
7. **Skin toxicity study** was conducted by visual observation and histopathological examination.

RESULTS AND DISCUSSION

No changes in the principal peaks (IR spectra), melting point (DSC) and R_f values (HPTLC) of drug in the presence of PLGA, revealed no drug-polymer interactions.

In the *in vitro* release studies, the percentage of drug release was decreased as the proportion of polymer increased. The formulations F1 (Drug-polymer, 1:5), F2 (Drug-polymer, 1:10) and F3 (Drug-polymer, 1:15) released 94, 89 and 82% of drug at the end of 30 days. The drug release from the implants within first day was high, which may be

due to the entrapped drug on the surface and lag period required to form the gel from its sol form. After the burst effect, the release was slow upto 30 days, as the drug after burst release is enclosed in the polymer matrix and hence the diffusion of drug from the matrix would be slow. The drug and polymer ratio, 1:15 was selected for *in vivo* studies based on the *in vitro* release studies.

The results of SEM studies of implants before *in vitro* release studies showed uniform-smooth surface. After the release studies, the surface became rough and pores were formed on the surface, which could be due to the diffusion of drug from the matrix and degradation of polymer.

The hypoglycemic activity of implants was significant compared to control and it was almost comparable to oral glipizide administration. At the end of 30 days oral glipizide and implants produced similar level of hypoglycemic effect in both normal and diabetic mice.

The elevated HDL-C, total cholesterol, triglycerides, urea, creatinine, ALT and AST and decreased levels of protein and glycogen levels in diabetic control mice were significantly reversed by glipizide implants. The inflammation, edema, necrosis, congestion and cellular atypia, which indicate the tissue toxicity, were considerably reduced by implants. These favourable effects were more pronounced with implants in comparison with oral glipizide, which could be due to day-to-day glycemic control. The skin toxicity studies revealed no considerable edema, erythema and inflammation, indicating negligible skin toxicity at the implantation site.

CONCLUSION

The present study showed that glipizide *in situ* gel implants of PLGA exhibited better control of hyperglycemia besides more effectively reversing the complications associated with diabetes mellitus than oral glipizide administration in mice.

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DEVELOPMENT OF DERMAL DELIVERY SYSTEMS FOR A COX-2 SELECTIVE NSAID USING VARIOUS PERMEATION ENHANCERS

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OBJECTIVE

The objective of the present work was to develop an effective dermal delivery system (DDS) for SOC-12N, a cyclooxygenase-2 (cox-2) selective NSAID in order to achieve its therapeutic effect locally at the site of pain, inflammation, or at arthritic joint.

INTRODUCTION

Skin, irrespective of its protective barrier function can serve as a promising portal of entry of drugs for local or systemic action. Targeting topically applied drug to the desired skin layer in therapeutically active concentration and for desired duration of time poses a great challenge in the field of new drug delivery system.

Flux of topically applied drug from a DDS into the skin depends on Physicochemical properties of drug and formulation factors such as vehicle or the base in which the drug is dissolved or suspended and use of penetration enhancers (PEs) which alter the barrier functions of the skin thereby facilitating transport of drug across it.

Present work involved study of effect of various PEs on the flux of SOC-12N when formulated as a topical gel.

EXPERIMENTAL

Preparation of gels: In order to improve aqueous solubility of SOC-12N, its binary

mixes (BM) were prepared with b cyclodextrin (BCD). Gels containing 0.5% w/w SOC-12N or equivalent amount of BM were prepared using carbomer 980 as a gelling agent. Formulations F1, F2 were made without PE; F3, F4 with 8% N,N Dimethyl Formamide (**DMF**), F5 and F6 with

10%Caprylocaproyl Macrogolglycerides (**CM**), F7and F8 with 10% Propylene Glycol (**PG**) and F9, F10 by using a 10% of Diglycol derivative (**DG**). Formulations F1, F3, F5, F7 and F9 contained SOC-12N and F2, F4, F6, F8 and F10 contained BM of drug with BCD.

Assay of formulations: All the prepared formulations were assayed for SOC-12N content by reverse phase HPLC.

***In Vitro* permeation studies:** Flux of SOC-12N from its DDS across full thickness

Abdominal skin of albino Guinea pig was studied using Keshary Chien diffusion cells where in Phosphate buffer saline pH 7.4maitained at 32°Cwas employed as a receptor medium. The receptor medium was withdrawn completely and replaced with the fresh medium at 1,2,4,6,8,12,18 hours and at 24 hours i.e. at the end of study. The aliquots were diluted suitably and absorbances were read spectrophotometrically at 255nm.

RESULTS AND DISCUSSION

SOC-12N is practically insoluble in water. Poor aqueous solubility could limit its permeation through the skin because of its inability to attain saturation solubility when employed in DDS. Cyclodextrins are known to improve aqueous solubility of drugs (1). In order to study the effect of improved solubility of drug on its permeation, BM of SOC-12N and BCD was prepared and formulated in gel as in the case of SOC-12N formulations. Formulations F1 and F2 were made without any PE to investigate the contribution of PE in enhancing the flux of SOC-12N across the skin. Formula F2 containing BCD showed better permeation of drug thus confirming advantage of improved solubility on the drug permeation. In case of formulations F3 and F4, solution of SOC-12N/BM in **DMF** when added to the gel base showed precipitation of drug in the form of long needles which could have resulted in lesser permeation of drug compared to that from F1and F2 thus proving **DMF** ineffective in improving permeation. System F5 containing **CM** as a PE exhibited lesser permeation compared to F1. Although, F6 was remarkably better than F5 in improving the flux of the drug, it was marginally better than F2 indicating limitations of 10% w/w of **CM** in improving permeation of SOC-12N. Formulations F7 and F8 employing **PG** as a PE showed significant improvement in the flux of drug compared to F1 and F2 respectively. Formula F8 exhibited better permeation than F7. Systems F9 and F10 showed the best permeation profiles compared to other formulations. However, no difference in the amounts of the drug permeated was observed from F9 and F10. This could be due to great enhancement in flux caused by **DG** in the concentration used which may have masked the advantage of improved solubility of drug by BCD in F10.

CONCLUSIONS

With the objective of formulating an efficient DDS for SOC-12N, gels incorporating various PEs were prepared and evaluated.

- **DMF** and **CM** in the concentration used were ineffective in improving the flux of the drug, where as **PG** and to a greater extent **DG** helped in improving the permeation of SOC-12N compared to the DDS without PE.
- All the formulations containing drug in the form of BM showed better permeation in comparison with the ones having drug as such except the formulations containing **DG**, which showed comparable permeation results.

EFECT OF NATURAL ABSORPTION PROMOTERS FOR TRANSDERMAL DELIVERY OF CARVEDILOL

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INTRODUCTION

Carvedilol is a beta adreno receptor antagonist which also causes peripheral vasodilatation primarily by alpha adrenergic blockade. The oral absorption is rapid reaching the maximum concentration with 1 to 2 hours. It undergoes excessive hepatic metabolism resulting in low bioavailability of about 23% [1]. The low plasma half life (5-6 hrs) necessitates multiple dosing. So to improve the bioavailability, it was proposed to make transdermal formulation of the drug as it has low melting point and molecular weight. However, to know the dermal absorption of this drug, it was required to carry out preformulation study for the in-vitro skin permeation.

EXPERIMENTAL

A 24 ml modified Franz diffusion cell (diameter 20mm) was used. The receptor compartment was filled with phosphate buffer pH7.4 and thermostatically maintained at 37°C. A piece of hydrated rat abdominal skin was mounted on the diffusion cell facing stratum corneum surface to the donor compartment[2]. The drug solution or suspension (1%) in various solvents was placed in the donor compartment. The amount of carvedilol permeated was quantified by collecting the samples at different time intervals and estimated spectrophotometrically. Different permeation enhancers (eucalyptus oil, cardamom oil and clove oil) were incorporated in the solvent knowing the maximum flux through the skin.

RESULT AND DISCUSSION

The amount of carvedilol permeated through the rat abdominal skin was not sufficient to maintain the therapeutic concentration of the drug for the projected duration of application of the drug (i.e. 48 hrs). therefore, various natural absorption enhancers were evaluated for the improvement in the transdermal flux of the drug. The results (shown in Figure) indicated that the permeation of carvedilol increases with the incorporation of all the three enhancers but the highest flux was obtained with cardamom oil. It is thought that these permeation enhancers interact with some components of the skin causing the stratum corneum to swell and/or leach out some structural components and thus increase the drug penetration through the barrier membrane. Also, according to literature, cardamom oil contains d-alpha-terpineol free and as the acetate, 5-10% cineol and limonene [3]. Although, the part of components such as terpenes or terpenoids have been assessed as skin penetration enhancers, but the combined effect of these terpenes is not fully understood [4]. Thus it is assumed that cardamom oil increases percutaneous penetration of carvedilol by direct effect on the barrier nature of skin

CONCLUSIONS

The preformulation study resulted in the selection of the optimized concentration of cardamom oil (i.e. 5% in ethanol) for the maintenance of carvedilol concentration in the intact system for 48 hrs.

ACKNOWLEDGEMENTS

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DEVELOPMENT OF SALBUTAMOL LIPOSOMAL NEBULIZING DISPERSION FOR IMPROVED STABILITY BY LYOPHILIZATION

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OBJECTIVE

To prepare stable salbutamol liposomal nebulizing solutions and improve their stability by lyophilization.

INTRODUCTION

Liposomes can be used as the particulate carrier systems that are retained in the lungs for a longer time. Nebulization is the most convenient way of administering liposomes via pulmonary route. However, they are susceptible to oxidation and hydrolysis. Lyophilization is the process that gives liposomes in a dry form. These lyophilized liposomes can be administered as Metered Dose Inhalers or Nebulizing Solutions for Reconstitution.

EXPERIMENTAL

Preparation of salbutamol liposomes:

Liposomes of salbutamol sulphate were prepared by thin film hydration method using phospholipids, cholesterol and a-tocoferol. The liposomes were characterized for the morphology, size, bilayer interactions and percent drug entrapment.

Preparation of Nebulizing Dispersion:

The liposomes were dispersed in isotonic phosphate buffer pH 6.4. These dispersions were then subjected to accelerated stability studies at 5oC, 25oC at 60% RH and 40oC at 75% RH.

Lyophilization of liposomal nebulizing dispersions and their characterization:

Lyophilization of the liposomal dispersions of salbutamol was carried out using Edward Moulyo-4k lyophilizer and the lyophilized liposomes were characterized. Development of metered dose inhalers using lyophilized product was attempted. 'Nebulizing Dispersion for Reconstitution' was prepared using the lyophilized liposomes. The product was evaluated for in-vitro deposition pattern by twin Impinger.

RESULTS AND DISCUSSION

The liposomes prepared by Thin Film Hydration method were uniform, bilamellar vesicles of the size 1-3m with almost 50% of salbutamol sulphate entrapped in the aqueous phase.

The results of the stability studies showed that the liposomal nebulizing preparation was stable at 5°C for 12 months The formulation was not stable at 40°C, 75%RH. Lyophilization was carried out to enhance the stability. Lyophilization of the liposomes resulted in the dry substance with moisture content less than 0.1%. Differential

Scanning Calorimetry confirmed the formation of a new entity as a result of lyophilization process. The Scanning Electron Microscopy showed the integrity of vesicular structure even after Fig. 1.

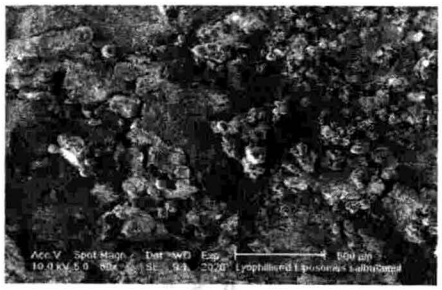

Fig. 1: Scanning Electron Micrograph of Lyophilized Liposomes.

Electron microscopy of the reconstituted solution confirmed bilamellar structure even after lyophilization and its rehydration. In-vitro pulmonary deposition by Twin Impinger method was 20-22% for the reconstituted liposomal dispersions.

CONCLUSION

Stability of liposomal dispersion was found to be improved after lyophilization. The vesicular structure was not changed after the process of lyophilization. Nebulizing dis-

ɔersion for reconstitution is another way of dispensing liposomes in a stable dry.

ACKNOWLEDGEMENT

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INTRA UTERINE DEVICE (IUD) WITH LEVONORGESTREL – A NOVEL WAY TO ACHIEVE CONTRACEPTION

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OBJECTIVE

The primary objective of the present work is to develop a safe, convenient, effective EVA based IUS, which will deliver Levonorgestrel (LNG) at pre-determined rate for a prolonged period of time. Also it should be advantageous over silicone based device.

INTRODUCTION

Convenient long-acting contraceptive methods are becoming more & more appealing. Intra-uterine contraception is entering a new phase with the development of intra uterine systems (IUS's) that will deliver potent progestins directly into the uterus, without affecting the systemic hormonal balance [(1)].

EXPERIMENTAL

The Intra Uterine Device in the shape of cylindrical mould (size 2mm diameter & 20mm length) containing LNG was prepared by hot compression technique [(2)]. Two biocompatible polymers, Ethylene vinyl acetate (EVA) & Poly vinyl acetate (PVA) were mixed at different proportions (1:1, 1:2, 1:3, 1:4 & 1:5). Thus mixed polymers were dissolved in dichloro methane to which calculated quantity of LNG was added & mixed. The LNG containing polymer solution was allowed to evaporate to get LNG containing polymer matrix. The matrix was removed and hot compressed in a stainless steel mould to give desired shape. The device was housed in vacuum for 2-3 weeks for the complete removal of organic solvent.

The device was characterized by X-ray diffraction study & subjected to in-vitro release study as per the USP 24 (2000) [(3)] guidelines and the results were computed for different kinetic models in order to characterize the release pattern. The device was subjected to in-vitro mutation study by Ame's test [(4)] & in-vitro cytotoxicity study by cell culture assay [(5)]. In-vivo anti-fertility study was carried out in cyclic adult female Sparague Dawley rats. The animals in proestrus (PE) stage were anaesthetized under ether and the IUD device was carefully placed within the uterine horn, by laparascopy method [(6)]. Regular vaginal smear was checked to note the estral changes in animals. Animals in proestrus (PE) stage were screened for ovulation rate & for fertilized ova after allowed to mate with males. The uterine histological studies were performed to evaluate the safety and efficacy of the device.

RESULTS AND DISCUSSION

The IUD containing LNG was prepared by hot compression technique using a blend of EVA & PVA. X-ray diffraction study confirms the presence of drug crystals in the polymer matrix. Among the various proportions of polymers used, the ration of 1:4 has showed optimal results, like flexibility, strength and more controlled drug release rate. Linear regression analysis indicated a higher correlation coefficient for Higuchi plot.

The device hasn't showed any positive results for in-vitro mutation study or in-vitro cytotoxicity study. No cyclic changes (or) alteration in ovulation rate were observed in animals receiving 2-4 μg / day of LNG. Where as animals implanted with the device capable of releasing 8 μg/day

showed cyclic changes. Animals allowed for mating with male showed no fertilization. The specially designed IUD for rats is capable of exerting anti fertility effect, by preventing the fertilization rather than preventing the implantation of fertilized ova, as seen in other IUD's!

CONCLUSION

The above results lead us to conclude that EVA & PVA matrix can be used for controlled release contraceptive device. The present study can be extended for further improvement of the device for human application, which will be a real substitute of Cu-T after proper clinical trials.

ACKNOWLEDGEMENTS

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EVALUATION OF SPERMICIDAL ACTIVITY OF INTRAVAGINAL GELS OF *ALBIZZIA LEBBECK* LINN

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OBJECTIVE

To formulate and evaluate the vaginal gels containing the extracts and crude saponins of *Albizzia lebbeck* for spermicidal activity.

INTRODUCTION

Indian folklore and Ayurvedic system of medicine mention the use of some plant products as local vaginal contraceptives. However none of these herbal products have been developed into modern dosage forms. It was, therefore, worthwhile to formulate a drug delivery system for agents from plant origin, which will be safe, convenient to use, and effective.

Albizzia lebbeck (Linn) (Fam: Mimosaceae), is commonly known as Siris. The pods and roots of *Albizzia lebbeck* are known to possess spermicidal activity. This paper reports the evaluation of spermicidal activity of the formulation of alcoholic extract of seeds and crude saponins isolated from them.

EXPERIMENTAL

Seeds of *Albizzia lebbeck* were collected from Maharashtra Nature Park, Mumbai and authenticated from Blatter Herbarium, Mumbai. The seeds were dried, powdered, defatted with petroleum ether and extracted with 90% alcohol. The alcoholic extract was concentrated and successively extracted with hexane, chloroform, carbon tetrachloride and acetone. It was then redissolved in a small volume of boiling alcohol and precipitated by adding dropwise into a large volume of acetone to obtain crude saponin. Vaginal gels were formulated using 1%, 2%, 5% concentrations for each of the alcoholic extract and crude saponin. Normal saline was taken as the control. All the extracts and crude saponin were prepared in the concentration of 1%, 2% and 5% in saline. Both the extracts and the gel formulations were evaluated for the spermicidal activity. 10µl of human semen and 10µl of the extract/gel was taken on the glass slide, mixed with a glass rod and observed under a microscope (10x). The time at which the sperm lost its motility was recorded.

RESULTS AND DISCUSSION

It was observed that as the concentration of the extract/saponin was increased, there was an increase in the spermicidal activity. In the control the sperms maintained its motility for more than 3h, while all the extracts and saponin showed spermicidal activity within 30secs. 1% gel containing extract showed spermicidal effect at 120secs. As the concentration of the extract in the gel was increased (2%, 5%), all the sperms were found to be non-motile within 30secs. Gels containing saponins showed faster spermicidal activity (30secs) as compared to gel containing 1% extract (120secs). With increase in saponin concentration the increase in spermicidal activity was observed.

	Spermatozal motility (%) at various time intervals (secs)							
	0	10	15	20	25	30	60	120
Control Saline	80	80	80	80	80	80	80	80
1% Extract	80					0		
2% Extract	80		0					
5% Extract	80		0					
1% Saponin	80			0				
2% Saponin	80		0					
5% Saponin	80		0					
Control Gel	80	80	80	80	80	80	80	80
1% Extract Gel	80							0
2% Extract Gel	80					0		
5% Extract Gel	80		0					
1% Saponin Gel	80					0		
2% Saponin Gel	80				0			
5% Saponin Gel	80			0				

CONCLUSION

Gels prepared using alcoholic extract of *Albizzia lebbeck* seeds and saponins obtained from them shows promising spermicidal activity and can thus prove useful as vaginal contraceptive.

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EVALUATION OF SPERMICIDAL ACTIVITY OF A NOVEL INTRAVAGINAL CONTRACEPTIVE FORMULATION

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OBJECTIVE

The purpose of the present study was to evaluate the spermicidal activity of some novel intravaginal contraceptive formulations and to study the immobilizing effect of the formulations on sperm cells (spermatozoa).

INTRODUCTION

Vaginal spermicides play an important role in limiting the family size, especially in developing countries. To achieve this, many chemical agents have been tried but these methods are not popular, primarily due to high failure rates and due to side effects such as local reactions and general systemic effects. Up to the present time, hundreds of spermicidal products have been marketed. The synthetic agents available today for fertility control produce severe side effects such as hormonal imbalance, hypertension, increased

TABLE 1: SPERMICIDAL ACTIVITY OF HERBAL OIL AND ITS FORMULATION (DATA ARE MEAN± S.D.)

Spermatozoal motility (%) at various time intervals (seconds)							
	0	10	20	30	40	50	60
A) Herbal oil							
	81.33±1.15	24.33±1.15	Completely immotile (C.IM.)				
B) Formulations % of Oil							
10	81.33±1.15	59.33±1.15	33.66±1.15	14±1.73	C.IM.		
20	81.33±1.15	39.33±1.15	19.33±1.15	C.IM.			
30	81.33±1.15	24.0±1.73	C.IM.				
40	81.33±1.15	24.0±1.73	C.IM.				
50	81.33±1.15	24.0±1.73	C.IM.				

risk of cancer, weight gain etc. Hence there is a need to replace these agents by safe and effective agents such as plant based contraceptive agents. The traditional knowledge of herbal products can be combined with improvised technologies of new drug delivery system to obtain a user-friendly contraceptive system with increased safety and optimized drug delivery.

Oil obtained from plant origin was selected for its spermicidal activity taking into consideration its potential as an intravaginal contraceptive. However, the oil would be messy to use and leak out of vagina during use. To overcome this problem, water-washable formulations of the oil have been prepared for intravaginal administration, which are pharmaceutically elegant and would have a better patient compliance.

EXPERIMENTAL

Spermicidal activity of the formulation as well as the oil was carried out using the *in vitro*, Sander Crammer Immobilization test for determining the spermicidal activity.

Semen samples of healthy male volunteers were used for the study. The samples of motility more than 80% were used for the study. 10ml of sperm suspension and 10ml of the formulations (1:1) were placed on a glass slide. Then it was mixed uniformly and examined under binocular microscope at a magnification of 10X. With the help of stopwatch, the time for the cessation of motility of spermatozoa was studied. The motility of the sperms was observed at different time intervals.

RESULTS AND DISCUSSIONS

Herbal oil showed spermicidal effect within 20 seconds. The formulations showed spermicidal effect, which was found to increase with the increase in the concentration of the oil. The spermicidal effect of the formulations was found to be time and dose dependent. The formulation containing ^{3}30% oil was found to show spermicidal effect within 20 seconds, which was found to be comparable to herbal oil.

CONCLUSION

In conclusion, the developed water-washable, formulations containing the oil showed spermicidal effect *in vitro*. Thus, plant based formulations can be considered promising and can be used as an effective method of contraception in females.

ACKNOWLEDGEMENTS

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COMPARATIVE BIOAVAILABILITY STUDY OF PAEDIATRIC PARACETAMOL RECTAL SUPPOSITORIES IN RABBITS.

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OBJECTIVES

Evaluation of the relative bioavailability of the developed Paracetamol suppository with marketed oral suspension in rabbits using complete cross over design.

INTRODUCTION

Paracetamol is long established non-prescription drug from NSAIDs.It has been clinically proven to be an effective and potent antipyretic agent with analgesic property. It is a drug of choice in fever and is extensively prescribed both in adults and children. Paracetamol is a drug with fewer side effects and with high therapeutic index.

Rectal route has its own certain advantages and is useful route in paediatrics. Rectal dosage of medication can be used effectively to substantially reduce hepatic first pass elimination and to thereby enhance drug bioavailability. Absorption of drug from rectum is affected by physiologic factors, physio-chemical properties of drug and physico-chemical properties of base. Thus it is important to determine whether the desired drug levels have been obtained after rectal administration.

EXPERIMENTAL

Paediatric Paracetamol suppositories were prepared using four types of semisynthetic Suppocire bases:

- Interesterified bases (Std type): e.g. Suppocire D&C
- Esterified bases (N-type): e.g. Suppocire NCX
- Amphiphilic bases (P-type): Suppocire CP

Various adjutants were added and evaluated for their effect on *in -vitro* drug release of paracetamol such as SLS, Span80, DOSS, Miglyol, Labrasol, Lecithin, CPGMC, and Aerosil. Bioavailability studies were carried out in a complete cross over design using New Zealand rabbits weighing 3 to 3.5 kg. Animals were fasted 24h prior to the study but given free access to water. Animals were either administered one paracetamol (250 mg) suppositories rectally or given marketed paracetamol oral suspension. Blood samples were withdrawn at regular intervals from the marginal ear vein of the rabbit and analyzed using a spectrofluorimetric method. Various pharmacokinetic parameters were determined.

RESULT AND DISCUSSION

Suppocire bases gave suppositories with good appearance and with no signs of fissuring, fat blooming or exudation. The type of base and the type of adjuvant had a definite effect on the drug release from suppositories. Suppocire CP and NCX showed much faster drug release as compared to Suppocire D and C. Adjutants such as Labrasol and Capryol PGMC were found to be promising and showed enhanced drug release from Suppocire CP and NCX

Bases. As seen from fig.1 the drug concentration profile obtained after rectal administration of developed paediatric paracetamol suppository is comparable to that of oral marketed suspension. In both the cases peak concentrations were obtained at 1hr post administration with average AUC_0^8 21.43ug.hr/ml and 20.07ug.hr/ml for the test suppository and oral suspension respectively.

CONCLUSION

It can be concluded that paediatric paracetamol suppositories prepared using semisynthetic Suppocire bases have comparable bioavailability to that of marketed oral suspension and can be used as an alternative medication in children.

ACKNOWLEDGEMENTS

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NANOSOLS: BIOADHESIVE DELIVERY SYSTEM WITH ENHANCED MUCORETENTION

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INTRODUCTION

Site-specific oral mucosal delivery aims to the treatment of oral manifestations such as inflammations, physical injuries, pain and mucosal infections. The present work is based on development of bioadhesive polymeric nanoparticles as potential drug carriers for oral mucosal delivery. The DDS could serve as a superior alternative to existing formulations as it would provide enhanced mucoretention thereby improved therapeutic benefit, be easy to administer and patient friendly for the treatment of oral mucosal disorders.

Successful exploitation of such carriers depends on improved formulation technology which requires great deal of optimization based on drug/ polymer properties, particle size, release profile and finally biomedical application. Also, physico-chemical characterization of drug/ polymer carriers is critical in understanding of inner structure and surface properties and, therefore, to a better comprehension of in-vivo behavior.

OBJECTIVE

Process optimization and characterization of bioadhesive polymeric nanoparticles as carriers for Sparfloxacin, for site-specific treatment of mucosal infections.

Providing delivery strategy for nanoparticles in the form of nanosols as a viable alternative to existing approaches for the treatment of most oral disorders.

EXPERIMENTAL

Preparation and Process Optimization of Nanoparticles:

Chitosan, natural and biodegradable polymer with excellent in-situ bioadhesion and Sparfloxacin, wide spectrum fluoroquinolone antibiotic was chosen as polymer and model drug respectively. Chitosan nanoparticles were prepared by controlled precipitation, isolated by ultracentrifugation followed by homogenization and subsequent freeze drying. The process was optimized for various parameters a) polymer: drug ratio b) processing speed c) Volume of solvent d) Amount of precipitating agent e) processing conditions such as speed, stirring time, temperature etc. f) Homogenization period

Process efficiency was determined by study of effect of these parameters on Particle size: using N4 Plus Beckmann coulter counter Percent recovery, loading and encapsulation efficiency using UV spectroscopy.

Nanoparticles were freeze dried with selected cryoprotectants and surfactants and nanosols were prepared by reconstitution of this freeze dried powder mixture in water.

Physico-Chemical Characterization of Nanoparticles:

Various instrumental methods were used for characterization of nanoparticles such as Image analyzer: for size and shape.

Atomic Force Microscopy: for topography and Bioadhesion.

FTIR, XRD and DSC: to study drug to polymer interaction and physical stability of drug in nanoparticles.

Retention time apparatus: to study mucoretention on animal skin.

RESULTS AND DISCUSSION

Chitosan nanoparticles with high encapsulation efficiency of 92-97%, high loading and recovery were optimized. Freeze dried nanoparticles with selected excipients resulted in nanosols without aggregation on reconstitution. Particle size analysis revealed nanoparticles in size range 200-500 nm. DSC, FTIR and XRD spectra confirmed molecular dispersion of drug in nanoparticles, physical stability of drug and drug-polymer interaction. Image analysis and AFM studies revealed spherical shape. Bioadhesive nature was confirmed by AFM using surface roughness estimation. Retention time experiment confirmed enhanced mucoretention of nanoparticles in-vitro..

CONCLUSION

Process optimization and precise characterization significantly enhances product performance as revealed from

high encapsulation efficiency, nanosize and recovery of nanoparticles. Nanosols were formulated as viable delivery strategy for nanoparticulate carriers. The DDS with enhanced mucoretention could serve as a superior alternative to existing formulations for site-specific treatment of most mucosal disorders.

ACKNOWLEDGEMENTS

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ORAL MUCOSAL DELIVERY OF VERAPAMIL: *IN VITRO / IN VIVO* CORRELATION BY FACTORIAL APPROACH

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INTRODUCTION

Oral mucosal drug delivery system (OMDDS) allows drugs to get absorbed through the buccal mucosa, avoiding first pass metabolism and hence rapid onset of action can be achieved. Verapamil, a calcium channel blocker, indicated for the treatment of angina and arrhythmias where rapid onset of action is required, has a low oral bioavailability (20-35%), due to its first pass metabolism. Hence verapamil was selected as the model drug candidate for this study.

OBJECTIVE

The present work has a dual objective:

(1) Development of Oral mucosal delivery system of verapamil designed as buccal tablets.

(2) Optimization of an *in vitro* dissolution procedure by application of factorial analysis to monitor the drug release profile, such that a good *in vitro/ in vivo* correlation can be established.

EXPERIMENTAL

Development of OMDDS: OMDDS of Verapamil was designed as a 100 mg buccal tablet which comprised Verapamil (15 mg), mucoadhesive polymers like sodium alginate and HPC-EXF with standard tablet excipients and compressed into a caplet shape of size 10 X 6 mm. Placebo tablets were also prepared in a similar manner.

Application of factorial design: The *in vitro* dissolution procedure, to obtain a good correlation between the *in vitro* and *in vivo* dissolution was carried out in Modified USP Type I apparatus and was optimized using 2^2 factorial design. The factorial analysis was done on one of the buccal tablet formulations of verapamil with volume of dissolution medium and rpm as two variables shown in Table No.1. Response factor, *invitro* dissolution time was obtained in range 44 - 65 min.

Data obtained was fitted in equation 1: - $Y=b_0+b_1(X_1)+b_2(X_2)+b_{12}(X_1)(X_2)$.

Three new experimental conditions not included in the original set of experimental conditions of factorial design were performed and their results were compared with the predictions determined from the polynomial model.

Evaluation of the OMDDS: Developed OMDDS formulations were evaluated for drug content and other standard tablet properties. *In vitro* drug release (t90%) was determined by *in vitro* dissolution procedure established by factorial analysis. The *in vivo* dissolution time was determined in human volunteers by administration of placebo tablets on to the buccal mucosa.

RESULTS AND DISCUSSION

The predicted values obtained from the factorial design and the experimental values showed good correlation. Table 2

TABLE 1

Level	Volume of Dissolution Medium (X_1)		RPM (X_2)	
Coded	-1	+1	-1	+1
Actual	50	500	50	100

TABLE 2

Formulations	Dissolution Time	
	In vitro t90% (mins)	*In vivo* (mins)
VPM 1	82	86.6
VPM 2	76	71.5
VPM 3	49.5	50
VPM 4	60.65	59.5

CONCLUSION

Mucoadhesive OMDDS of Verapamil was successfully developed which exhibited rapid *in vitro* drug release. A suitable *in vitro* dissolution procedure for oral mucosal delivery system designed as buccal tablets was established by factorial design. The design of an *in vitro* dissolution procedure for buccal tablets, which correlates with *in vivo* dissolution time, represents a novel method for *in vitro* evaluation.

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DEVELOPMENT & *IN VITRO* EVALUATION OF TASTE MASKED BUCCAL DOSAGE FORM OF AN ANTIMIGRAINE AGENT

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INTRODUCTION

Taste masked buccal dosage form of Sumatriptan Succinate (SS) was prepared by wet granulation method. Initially placebo buccal tablets were prepared by using combination of various bioadhesive polymers and normal tablet excipients & optimized on the basis of bioadhesive strength. Various taste masking trials were carried out and finally taste masking was done by complexation with ion – exchange resin. Drug - resin complex was then loaded in the optimized formulations. The final formulation was optimized on the basis of pharmacopoeial tablet tests, bioadhesive strength & *in-vitro* release studies.

INTRODUCTION

SS is a serotonin (5 HT_1) receptor agonist, which is effective in the acute treatment of migraine & cluster headache (1). Following oral administration, SS is rapidly but incompletely absorbed & undergoes extensive hepatic first pass metabolism, resulting in low absolute bioavailability of 14%. Peak plasma concentration occurs within 2 hours. It also has a short elimination half life of about 2 hours (2). The taste of the drug is also very bitter & it is thus needed to mask the taste of the drug. All these parameters clearly warrant the development of a dosage form with improved bioavailability, better patient compliance & hence improved efficacy. Therefore, the aim of the present study was to first mask the taste of the drug and then develop its buccal dosage form.

EXPERIMENTAL

I. Development of Placebo buccal tablets – Placebo buccal tablets were prepared by wet granulation method using PVP K 30 as binder. These tablets were evaluated for bioadhesive strength & work of adhesion using modified physical balance (3) & texture analyzer (4).

II. Taste masking of the drug – It was done by complexation with ion – exchange resin (Tulsion 335). Complex formation was confirmed by FT-IR spectroscopy & DSC studies.

III. Development of drug loaded tablets – Taste masked complex was loaded in the optimized placebo tablets & these tablets evaluated for pharmacopoeial tablet tests, bioadhesive strength & *in-vitro* release studies.

iv. *In – vitro* release studies – These studies were carried out in standard USP II dissolution apparatus (Paddle method) at 50 rpm using IPB pH 6.6 & 0.1N HCl as dissolution mediums.

RESULTS AND DISCUSSION

The present study was an attempt to develop a buccal delivery system for the systemic delivery of SS through the buccal cavity. Since SS is a very bitter drug and has to be absorbed and permeated through the buccal cavity from the delivery system, it was necessary to first mask the taste of the drug & then formulate it as buccoadhesive tablets. The combination of HPMC K4M/Cekol 300/CP 974/Maltodextrin showed good bioadhesive strength in placebo tablets. During complex formation, highest degree of complexation at pH 6.0 (99.25% of the drug was complexed within the resin). Drug loading into the placebo tablets significantly decrease their bioadhesive strength & work of adhesion. Optimized tablets gave maximum in-vitro release of 92.98% in IPB pH 6.6 & 95.70% in 0.1N HCl over a 6h period.

CONCLUSION

The taste masked buccal dosage form of SS was successfully developed. *In-vitro* studies showed that the formulation has good potential in the treatment of migraine & cluster headache. Permeation studies & In-vivo studies are being carried out to prove its clinical usefulness & patient compliance.

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BUCCOADHESIVE DRUG DELIVERY SYSTEM OF ISOSORBIDE DINITRATE – FORMULATION AND EVALUATION

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INTRODUCTION

Unidirectional release, Stability studies.

Buccoadhesive buccal delivery system for Isosorbide dinitrate in the form of unidirectional erodible buccal films were developed and characterized for improving bioavailability. The films were formulated by solvent casting method using different bioadhesive polymers viz. Car-934p, Eu-RL100, PVP by using two different plasticizers Propylene glycol and Diethyl phthalate. The films were characterized on the basis of their physical characteristics, bioadhesive performance. *in-vitro* studies revealed that the release rate of ISDN was higher from Carbopol films containing ratio of Eu-RL100 and PVP in proportion of 1:2, 2:1 respectively by using both plasticizers. Drug diffusion from buccal films exhibited nearly zero order kinetics and release mechanism was diffusion controlled after considerable swelling. All the films exhibited sufficient *in-vitro* adhesion strength. Promising formulations were further studied for temperature dependent stability studies.

OBJECTIVES

The main drawback of conventional ISDN formulation is that it undergoes *hepatic first pass* metabolism by enzymatic denitration. Thus the plasma t ½ is 45-60min., thereby decreasing its bioavailability [1]. The conventional sublingual tablets (5-10 mg) produces maximal concentrations of the drug in plasma by 6 minutes, and fall in concentration is rapid Hence an alternative delivery system for improving the onset of action and $t_{1/2}$ is needed.

EXPERIMENTAL

i) Preformulation studies for Drug Excipient Compatibility[3]:

ii) Standard Curve for ISDN[4] : Beer-Lambert's range ISDN 5-25mg/ml.

iii) Preparation of Drug Loaded Buccoadhesive Film[5]: solvent casting technique.

iv) Evaluation studies on the basis of physical characteristics.

a) Surface pH

b) Folding Endurance

c) Drug content uniformity

d) Percentage swelling

e) Film thickness

f) Bioadhesion strength[6]

g) In-vitro drug release profile of the prepared ISDN buccal films:

H) Temperature dependent stability study [7].

RESULT AND CONCLUSION

The present study was a satisfactory attempt to develop erodible buccoadhesive films, which will overcome the inherent drawbacks associated with conventional drug delivery of ISDN and will have an improved bioavailability, therapeutic efficacy and patient compliance. Buccal formulations of ISDN in the form of films were developed to a satisfactory level in terms of drug release, bioadhesive strength, content uniformity, and all other physical parameters.

Although all buccal films exhibited satisfactory drug release, the best results were obtained with films of Car-934P, and Eu-RL-100 in combination with PVP (1:2 and 1:1) by using diethyl phthalate and propylene glycol as a plasticizer. The various kinetic data plots showed that the drug release is a function of erosion, diffusion and followed nearly zero order kinetic pattern. Results of stability studies indicate that there was not much significant difference in terms of content uniformity, bioadhesive strength, surface pH and in-vitro release profile. Further *In vivo* studies need to be carried out and *in vitro-in vivo* correlation need to be established. Also there is challenge for manufacturer to device suitable manufacturing process to enable large scale production of this buccoadhesive drug delivery system.

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CHARACTERIZATION OF NOVEL BUCCO-ADHESIVE FILMS OF CLINDAMYCIN FOR PYORRHEA TREAMENT

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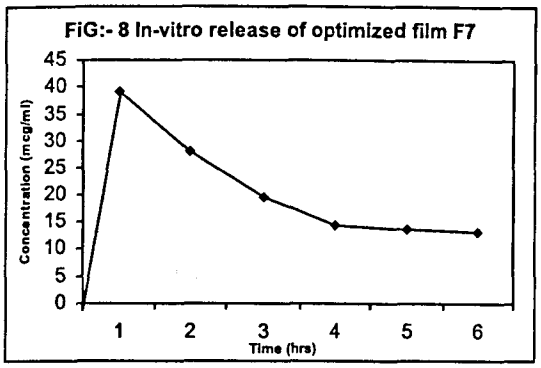
INTRODUCTION

Pyorrhea is a progressive disorder which leads to localized pain, loose teeth, erythrema, swelling and alveolar bone destruction etc. Main causative bacteria involved are anaerobic gram-negative(Bacteroides)and gram positive bacilli(Actinomyces).The potential side effects of systemic antibiotics and inability of conventional formulations to maintain constant drug level enforced interest toward local sustained drug delivery. Thus for local targeting on dental infection bucco-adhesive films of Clindamycin were developed and evaluated.

EXPERIMENTAL

Films of Clindamycin were prepared using polymers like Carbopol-934P(CP-934P),HydroxyPropylCellulose-M(HPC-M) and Eudragit-RS (Eu-RS) by solvent casting method. Seven formulations were prepared. Films were evaluated on the basis of bioadhesive strength, duration of adhesion with mucosa, percentage elongation at break, in-vitro drug re-



lease study etc. In-vitro drug release and duration of adhesion with mucosa was done using flow through cell in simulated saliva of pH 6.6. Bioadhesive strength was measured by modified double beam balance pan using bovine cheek pouch as the model membrane. All seven formulations are listed below.

RESULTS AND DISCUSSION

The optimized formulation was subjected to evaluation parameters like bucco-adhesive strength, adhesion time with mucosa, folding endurance,pH , n-vitro release studies etc. The results obtained were found within satisfactory limit.

CONCLUSION

The present study was an attempt to develop a suitable muco-adhesive drug delivery system of Clindamycin. Bucco – adhesive films were found satisfactory in terms of drug release, bio-adhesive performance, physical & mechanical properties & surface pH. Bucco-adhesive film was found to be satisfactory drug delivery system, which guarantees the release on the target bacteria for extended period of time, without any surgical need.

Codes	CL-HCL	HPC	Eu-RS	PEG-400
	mg	g	g	ml
F1	10	0.3	-	0.3
F2	10	0.3	-	0.2
F3	10	0.3	-	0.1
F4	10	0.4	-	0.1
F5	10	0.3	0.15	0.1
F6	5	0.3	0.05	0.1
F7	5	0.3	0.10	0.1

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FORMULATION AND EVALUATION OF BUCCOADHESIVE COMPACTS OF CARVEDILOL

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OBJECTIVES

The main objective of the study was to formulate and evaluate buccoadhesive compacts (BCs) of Carvedilol and to study the effect of various additives, disintegrants and release enhancers on drug release and bioadhesion of the compacts.

INTRODUCTION

Carvedilol, â blocker with minimal á blocking activity is used in the treatment of hypertension, congestive heart failure and stable angina pectoris. It also possesses some calcium channel blocking effects and anti-oxidant properties. On oral administration Carvedilol undergoes extensive and variable first pass metabolism (with 25% oral bioavailability)

and C_{max} 72 µg/L is reached with in 1-2 hrs causing dose dependent orthostatic hypotension due to its vasodilator property (by á antagonism) (1). Hence Carvedilol can be considered as a suitable candidate for controlled transmucosal buccal delivery, which can bypass hepatic metabolism and provide controlled plasma levels.

EXPERIMENTAL

Compacts containing 10mg of the drug were prepared using polymers namely carbopol 934 and sodium CMC by direct compression on a hydraulic press at a compression pressure of 5 ton for 15 seconds. Polymers were taken in the ratios of 1:1, 1:2, 1:4, 2:1. Acdisol and sodium starch glycollate and PEG 6000 were incorporated at 5 and 10% level whereas diluents were studied at 30% level. All the compacts were evaluated for weight and content uniformity, hardness and bioadhesive strength. Bioadhesive strength was measured by modified balance method described by Gupta et al (2). Compacts were attached to a Teflon block, (fabricated to hold the compact and provide unidirectional drug release and also gives an idea of duration of bioadhesion) by moistening with buffer 6.6 and placed in the dissolution medium (500ml IPB 6.6 buffer containing 0.5% sodium lauryl sulphate). The release study was carried out by USP [22] method at 50 rpm and 37± 0.2°C (3,4).

RESULTS AND DISCUSSION

All the tablets passed the weight variation and content uniformity tests and had acceptable level of hardness. Maximum bioadhesion was observed with compacts containing CP 934 and sod CMC in ratios of 2:1 and 1:4. Drug release increased with increasing CMC ratio upto a certain level (i.e from 1:1 to 1:2), which may be because of faster swelling and erosion of the matrix with increased sod CMC concentration. Beyond that (that i.e from 1:2 to 1:4) the drug release decreased, which might be due to the formation of dense gel structure with reduced erosion and hence drug release. The results obtained can be supported further by the findings of Varshosez and Dehghan (5). Formulation with polymers in the ratio of 2:1 showed optimum release and bioadhesive characteristics (remained adhered after 8hours of the study) and there was minimum inter polymer complexation. The disintegrants showed very little increase in drug release. PEG 6000 increased drug release significantly at 10 % level. Presence of lactose or avicel (30% together with 1% magnesium stearate) improved drug release with minimum effect on bioadhesion and the enhancing effect was more with avicel than with lactose.

CONCLUSIONS

Formulation containing 10 mg drug, 10% PEG 6000, 20% avicel and polymers in the weight ratio of 2:1 provided controlled release (approximately 75% at the end of 8 hrs.) of Carvedilol while maintaining appropriate buccoadhesive characteristics with minimum inter polymer complexation.

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FORMULATION AND EVALUATION OF NOVEL DENTAL IMPLANTS CONTAINING ANTI INFECTIVE AGENTS

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OBJECTIVES

a) To establish the release profiles of the drugs from implants *in-vitro.*

b) To determine pharmacokinetics profiles of these anti-infective drugs in gingival cervicular fluid.

c) To evaluate the clinical efficacy of these drugs as implants in patients with periodontitis.

INTRODUCTION

Periodontal disease is a localized infection with a primary bacterial etiology resulting in tooth loss. Conventional periodontal therapy by root plaguing and scaling along with high doses of orally administered anti bacterial agents results in undesirable systemic side effects, development resistant bacterial strains and superimposed infections.[1,2]

EXPERIMENTAL

The implants containing drugs in biodegradable polymer, poly (e-caprolactone) were prepared by solvent casting technique. The dried film 0.5 *0.5 cm size contains 1 mg of drug complex and 1 mg of tinidazole. *In-vitro* release studies were carried out by the method reported.[3]

Clinical studies were carried out in 10 patients without any systemic disorders and with deep periodontal pockets after informed consent. Implant was placed in the experimental pocket and without any sutures. Gingival cervicular fluid (GCF) and saliva were collected at 0,1,2,3,4,5,6,7,8,24,48 hrs and 10th, 20th, 30th and 40th day. The drugs were estimated spectrophotometrically. Various clinical parameters such as gingival index, gain in attachment, plaque score and pocket depth reduction were measured initially and at 40th day.[4,5]

RESULTS

In-vitro release showed the initial burst effect followed by more sustained release of the drugs for longer periods of time (40 days). Drug complex concentration in GCF reached its maximum of 5.767 ± 2.339 mg/mg at 3rd hour whereas tinidazole reached its maximum of 2.751 ± 1.207 mg/mg at 2nd hour. All clinical parameters evaluated showed a statistically significant changes ($p < 0.001$) after the treatment.

DISCUSSIONS

In-vitro release studies showed that the implants released the anti infective agents in the first order fashion and the release was not dissolution rate controlled.

Evaluation of GCF data showed the immediate release of the drug in higher concentration within few hrs, which is desired for the effective control of inflammation and infection. There after the sustained release of the drug s above the MIC values were obtained for about 40 days. Low salivary concentrations observed which is desirable.

There was a significant improvement in the clinical parameters evaluated at tests sites suggest that some degree of repair of periodontal pocket. Surgical removal of the implant is not required since the polymer is biodegradable.

CONCLUSION

The dental implants developed were able to deliver the anti infective agents in predictable manner for the period of 40 days. Sufficient concentration of antibiotics to inhibit most of the periodontal pathogens was maintained throughout the period of the treatment. Clinically, all patients showed an improvement in diseased condition.

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DESIGN AND EVALUATION OF DRUG DELIVERY SYSTEM FOR RESTORATION OF PERIODONTITIS

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OBJECTIVES

In the present investigation, an attempt was made to design and evaluate controlled drug systems containing anti-inflammatory agents for their direct placement into the periodontal cavity and evaluate its performance in clinics

INTRODUCTION

Systemic administration has been useful in treating periodontitis but repeated and long-term use of systemic drugs is fraught with potential danger including resistant strains and superimposed infections. An important site for drug delivery would seem to be from within the periodontal pocket, where local concentrations at the disease site can be established and maintained at any desired level for any duration required. By means of controlled local delivery from within the periodontal pocket, single administration of a few milligrams of an anti-infective agent can maintain therapeutic concentrations within the crevicular fluid for a longer period of time than, any other mode of delivery.

EXPERIMENTAL

The formulations were devised in the form of *in situ* gels containing ofloxacin using poly (DL-lactide-co-glycolide) (PLGA) as polymer. The formulation was subjected for physicochemical characterization in terms of syringeability and drug content. The *in vitro* drug release studies from the formulation was carried out by vial method. The effect of various precessing parameters such as polymer vehicles, polymer concentration, grades of polymers and effect of excipients on the drug release profile were comprehensively evaluated. The *in situ* gel implants were subjected to stability studies as per the ICH guidelines. The samples were withdrawn at specified time and evaluated for drug content as per given method and observed for any physical changes. *In vivo* evaluation of *in situ* gel implants were carried out in patients with periodontitis visiting to Department of Periodontitis, College of Dental Surgery, Manipal. Ethical Committee of Kasturba Hospital, Manipal, India approved the study protocol.

RESULTS AND DISCUSSION

Poly (lactide-co-glycolide) is soluble in biocompatible solvents such as N, N-dimethyl pyrrolidone (NMP), triacetin, dimethyl sulfoxide etc. When PLGA solution in these solvents come in contact with aqueous fluid in physiological conditions, the solvent being miscible with water diffuses in the aqueous surroundings while the polymer, being insoluble in water is precipitated to form a solid matrix at the site. Thus in the present investigation *in situ* gels are prepared in different solvents, different polymer concentration, PLGA of different grades and also various formulation exicipients were used to study their effect on the formulation characteristics. All the formulations exhibited fairly uniform drug content with good syringeability through 22-gauge needle. The in vitro release studies indicates that the drug release occurred in a biphasic manner characterized with an initial burst effect followed by a slow release for a prolonged period of time. After the preliminary investigation, NMP was chosen as a vehicle for polymer. The drug released from 10%, 15% and 18% PLGA formulations were found to be about 98%, 93% and 85% respectively at the end of 720 hrs. This shows that as the polymer concentration increases, the release rate decreases. The rate of drug release from the formulations prepared with the copolymer ratio of 65:35 was faster than that of other two formulations. As the glycolic acid content decreases, the rate of release decreases. This is probably due to the difference in degradation rate of the polymer, the higher the glycolic acid content, and the faster the degradation rate. The result clearly shows that release of drug enhances after addition of water-soluble additives like sodium chloride and mannitol in this formulations. All the formulations are found to be stable with gel retaining its viscosity and syringeability at the end of the study. Comparison of clinical results reveals that there is a significant reduction in pocket depth, gain in attachment levels and reduction in gingival inflammation. The mean reduction in the pocket depth art treated site was 4.21mm. This was a highly significant reduction on the 60th day as compared to baseline. The plaque index results depict that the study group maintained

a good oral hygiene and there was significant change in the plaque score.

CONCLUSION

The results indicate that these targeted devices for the treatment of periodontal diseases show certain proponent advantages relative to conventional therapy. Effect and prolonged local levels of an antibiotic could be achieved without much systemic load with comparitively less frequency of administration.

DESIGN, DEVELOPMENT AND *IN VITRO* CHARACTERISATION OF CYCLOSPORINE LIPOSOMAL FORMULATIONS FOR PULMONARY ADMINISTRATION

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OBJECTIVES

Cyclosporine a cyclic endecapeptide (mol wt 1202 Da), of fungal origin has been used for clinical transplantation. Cyclosporine is extremely hydrophobic and must be dissolved in lipids or organic solvents before administration. By oral route, variable rate and degree of absorption is observed hence pulmonary delivery of Cyclosporine encapsulated in liposomal carrier systems will provide local cytokine modulating drug for lung transplantation[2].

INTRODUCTION

liposomes offer many attractive features as pulmonary controlled release drug delivery systems. Liposomes are prepared using phospholipids that resemble physiological lipids and hence do not elicit any immunogenic reaction. Liposomal encapsulation of the drug will maintain therapeutic concentration of the drug in the lung for longer period.Peak plasma concentration of cyclosporine, usually occurs within 0.11hr to 1.5 hr of administration[1], liposomal formulation will have longer residence time. It will improve therapeutic action in the pulmonary region and lower drug concentration in blood, thus reduce systemic toxicity, and frequency of dosing.

EXPERIMENTAL

Liposomes were prepared by using, modified Bangham method. A variety of synthetic materials **-á Lecithin** (Phosphatidyl Choline) and **Centrolex -R**, and Cholesterol (high purity) were used.

Preparation of liposomes:

Lipids were dissolved in mixture of solvents and evaporated under vacuum using the rotavapor Model (Super fit R –120) to form a thin film, which was hydrated using PBS buffer (pH =7.4) to get isotonic formulations. Various trials were conducted to optimise the following ratios, Chloroform: methanol, drug: lipid, glass beads: solvent volume, drug: cholesterol, cholestrol: lipid. The formulations were optimised and the process parameters were validated. The liposomal dispersions were further subjected to spray drying and Lyophilization using lactose as cryoprotectant in varying proportions.

RESULTS

Lyophilization of the dispersions for 48 hrs gave dry mass, which redispersed easily to

form the dispersion. The concentration of lactose that gave minimum leakage of the drug from the liposomes was found to be 5%. The dispersions were found to release 80% of the drug in 72 hrs. Spray drying gave a sticky mass with maximum losses.

DISCUSSION

Process of lipid film hydration resulted in formation of spherical liposomes of CsA. Optimisation of the process variables showed that a maximum entrapment efficiency upto 89% was obtained using Egg Phosphatidyl Choline in the ratio of (1:6). Chloroform and methanol in the ratio (9:1) gave thin lipid film. The dispersions can be lyophilized using lactose as the cryoprotectant to give a free flowing powder, with lactose at 5% concentration, which released drug over a period of 72 hrs.

TABLE 1: LIPOSOMAL FORMULATIONS OF CYCLOSPORINE

Sr. No.	Parameter	Method	Results/observations
1	**Morphology and size:**	Malvern Mastersizer	10% below 0.98μ
		Laser diffraction	50% below 4.69μ
		Negative staining	90% below 14.98μ
2	**Entrapment efficiency**	Centrifugation	Max upto 89%
3	***In vitro* release profile**	Diffusion through dialysis membrane	80% drug released within 72 hrs.
4	**Drug lipid interaction**	DSC	Confirms the interaction of lipid with the drug.

CONCLUSIONS

Thus stable, double-layered cyclosporine liposomes in the size range 1-14 microns have been developed and characterised. Pulmonary administration of cyclosporine liposomes is expected to provide controlled and targeted release of the drug.

ACKNOWLEDGEMENT

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PULMONARY DELIVERY OF INSULIN USING NEBULIZING SYSTEMS

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INTRODUCTION

Ever since the discovery of insulin, attempts have been made to alter the route of administration of insulin in the treatment of insulin-dependent diabetes. Pulmonary delivery of insulin has attracted much attention, because it is an efficient route for noninvasive systemic administration. Transpulmonary delivery of peptides and proteins is expected to have higher rates of systemic absorption than other noninvasive routes, since it provides a large surface area, thin alveolar epithelium and low enzymatic activity.

OBJECTIVE

The aim of the current studies was

- To assess the feasibility of delivering a therapeutic dose of insulin as an inhalation aerosol to the lung using ultrasonic / compressed air nebulizer and to evaluate the aerosol performance.
- To prove the efficacy and safety of nebulizing solution of insulin after administration to rats.

EXPERIMENTAL

Formulations: Nebulizing Solutions were prepared containing 100-500 U/ml of human insulin with and without absorption enhancers, proteolytic enzyme inhibitors, preservatives and physico-chemical stabilizers. Solutions were evaluated for appearance, clarity, and pH. Optimized formulations were subjected to stability testing.

Aerosol generation -characterization : Citizen ultrasonic nebulizer and Clenny compressed air nebulizer were used for generating insulin aerosol from nebulizing solution.

Integrity of Insulin molecules was tested using HPLC method. Both the nebulizers were characterized for output efficiency, reproducibility and dead volume. Anderson Cascade Impactor and Liquid Twin Impinger were used to find out Mass Median Aerodynamic Diameter, Geometric Standard Deviation and Respirable fractions.

Efficacy of nebulizing solution: To estimate the dynamics of insulin in the rat lung, nebulizing solution was delivered into the trachea. Blood samples were withdrawn at 15 mins pre-dose, 0, 30, 60, 120, 180, 240 and 300 mins post-dose and glucose level was determined. Placebo group was also kept. Subcutaneous injections were given to control group for determining relative efficacy.

Safety of nebulizing solution: Repeat inhalation dose study was carried out in rats for 28 days. Nebulizing solutions were administered by oral inhalation to rats using nebulizers. On completion of dosing, all animals were euthanized and subjected to a detailed necropsy, organ weight analysis and histopathological evaluation.

RESULTS AND DISCUSSIONS

The optimized formulations were physicochemically stable. The MMAD of insulin aerosol generated using nebulizers was in the range of 1.7-1.9mm and GSD was around 2-2.5. The mass of insulin deposited in lower airways region using Ultrasonic nebulizer was 35% and using Jet nebulizer was 20%. After intratracheal administration of insulin nebulizing solutions to normal rats fasted overnight,

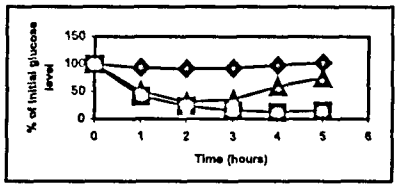

Fig. 1: Hypoglycemic effect of insulin nebulizing solution. ♦-Placebo, ▲-Control-SC, ◘-Nebulizing soln.

significant decrease of glucose level was achieved (Fig.1). No adverse in-life, necropsy or histopathological findings were detected that were related to insulin nebulizing solution.

CONCLUSION

These studies support the argument that pulmonary delivery of insulin for systemic activity is a viable non-invasive alternative to current subcutaneous insulin therapy for treatment of diabetes. The developed nebulizing insulin solutions have proved to be promising pulmonary delivery system.

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DESIGN AND EVALUATION OF NOVEL CARBOPOL BASED OCULAR SOL-GEL PHASE TRANSITION SYSTEMS OF FLUCONAZOLE IN THE MANAGEMENT OF FUNGAL KERATITIS

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OBJECTIVE

Design of carbopol based ocular sol-gel phase transition systems of fluconazole to prolong the residence time of the medicament in the precorneal area, hence potentially increase the bioavailability and therapeutic efficacy of the drug.

INTRODUCTION

Ocular delivery of drugs in an efficient manner has been a major challenge. Fluconazole is a recently developed water soluble bis triazole having novel broad antifungal spectrum In the present study, pH triggered system of gelation was used which involves transformation of carbopol aque-

ous solution into a stiff gel at the physiological pH of the lachrymal fluid.

EXPERIMENTAL

Preparation of Sol to Gel System:

Carbomer stock solutions and viscoliser solutions 1%w/w of HPMC, PVA and MC were prepared in cold saline. They were autoclaved at 121°C, 15p.s.i for 30 minutes. Clarity of the formulations were optically checked. Measurements of pH were carried out. The sols were converted to gels by neutralizing with phosphate buffer pH 7.4 to simulate in-vivo conditions, prior to analysis and then measurement of viscosity was done for all treatment combinations of sols and gels.

The drug content uniformity measurements were done at 261 nm spectrophotometrically.

Compatibility studies were carried out in Solid State by I.R Spectroscopy and in Liquid State by Paper Chromatography using methanol:ammonia in a ratio of 200:3 as the solvent system.

In-vitro studies were carried out in a specially designed apparatus to match in-vivo conditions. The dissolution medium used was phosphate buffer pH 7.4 maintained at a temperature of 37+/-1°C and at 20 rpm. The drug content was determined at 261nm.

Sterility testing was carried out by direct inoculation as per I.P. Before sampling the drug-preservative were inactivated by dilution.

For the in-vitro effectiveness study, Mueller Hinton agar was chosen and conditioned for fungal growth. The scanning electron micrographs were recorded of pure drug and gel formulation at different magnifications using software controlled Digital Scanning Electron Microscope.

In-vivo Effectiveness Study was done by inducing fungal keratitis in rabbit's eyes using candida albicans.

RESULTS AND DISCUSSIONS

Clear sol to gel phase transition was seen on instillation of the devised formulation both in-vitro and in-vivo. Addition of viscolisers to the basic gel former did not interfere with the sol-gel transformation property, on the contrary, improved and strengthened the gel integrity. Individual viscolisers influenced the viscosity of the formulation. For the various formulations, drug content uniformity varied between 99.885% to 103.215%. The I.R study indicates drug's compatibility with the formulation components. The same was also confirmed in the solution state by paper chromatography. In-vitro release studies revealed that a combination of HPMC +PVA and MC+PVA in carbopol formulations are highly effective in sustaining and controlling the drug release.

When all the viscolisers were used in combination F8, the release rate was 93.53% which was considerably reduced, compared to 99.25% for carbopol alone indicating that viscolisers together have a synergistic effect along with carbopol offering a more controlled and reasonably complete release. Data plotted for zero order kinetics were linear while that of first order kinetics did not show linearity. On comparing "r" values for both the plots, all the formulations best fitted in zero order and poorly fitted in first order kinetics. Conclusively, the study reveals that all the formulations follow zero order release kinetics.

Rabbits when subjected to ocular irritancy test did not show any signs of irritation, inflammation, lachrymation and abnormal discharge. The therapeutic effectiveness of devised formulation was found to be excellent as revealed through in-vivo studies. The recovery was seen from the third day onwards of the treatment. Although both formulations produced complete recovery within seven days, the recovery with the devised formulation, was rapid and required less frequency of drug administration. The physical appearance of the sol-gels did not alter or change when the formulation was put to stability studies at room temperature.

CONCLUSION

Aqueous solution of carbopol 934P coupled with added viscolisers are attractive in-situ gel forming systems, promising controlled ocular delivery of fluconazole in effective management of fungal keratitis. All the systems exhibited zero order kinetics and release profile was prominently diffusion associated with initial erosion of the polymer. Devised formulations were found to be effective in management of fungal keratitis. Authors understand that no such systems are commercially available for fluconazole.

ACKNOWLEDGEMENTS

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DEVELOPMENT AND EVALUATION OF NOVEL DICLOFENAC SODIUM-LOADED POLYMERIC COLLOIDAL DISPERSION SYSTEM

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INTRODUCTION

The treatment of ocular inflammations with conventional eye drops is complicated due to limited short duration of effect. Polymeric nanoparticles tend to adhere to the ocular epithelial surface (bioadhesive property). The polymers that seem to have the best potential for this application are poly(lactide-co-glycolide) (PLGA), poly(alkyl cyanoacrylate), (PACA) and poly(ϵ-caprolactone) (PCL). Diepold et al. and Zimmer et al. have reported that the residence time of nanoparticles (NP) was significantly higher in inflammed ocular tissues than in healthy eyes[1]. The increased retention of NP is due to increased cell permeability, a secretion in the precorneal area of substance (eg. albumin, fibrin) that can bind with NP, and a partial blockade of the nasolacrimal duct due to the swollen conjunctive tissue. An effort was therefore, made to develop a bioadhesive-particulate delivery system for diclofenac sodium (DS) applying the concept of bioadhesion on to drug loaded nanospheres with the hypothesis of achieving higher corneal residence with sustained drug release. The optimization of this preparation was carried out by changing the most influencing process parameters during the preparation step. The preparation was then studied *in-vitro* and *in-vivo*.

EXPERIMENTAL

For all NP preparation biodegradable polymer PLGA was used. NP were prepared by using double emulsion (w/o/w) technique using polyvinyl alcohol (PVA) as surfactant, the adjustment was based on the use of sonicator-bath and probe type. The NP suspensions were sterilized by membrane filtration. Freeze-drying was performed using vials covered with 0.22 mm membrane filters in order to preserve the suspensions from bacterial contamination (Fig. 1). Based on the observations an ideal batch was selected and dispersed in aqueous isotonic media. The amount of entrapped drug was measured by a validated HPLC method. In-vitro release was studied in phosphate buffer saline (PBS) pH 7.4 at 37°C (lachrymal pH). In-vivo eye irritation studies was studied by the Draize test, in New Zealand white rabbits.

RESULTS AND DISCUSSION

PLGA (50:50) copolymer because of short half-life seems to be an appropriate choice as matrix material for the production of this nanosphere system. Sterile sub-285nm nanoparticles were produced with good reproducibility and narrow size distributions (0.210-0.566) to avoid discomfort after ocular instillations. The ultrasonication time decreased the NP size and polydispersity at the time interval of 4 min. More polymer load in organic phase increased the size and polydispersity. As PVA concentration was increased, emulsion droplets size decreased. Optimal encapsulation efficiency reached when lowest DS was used. In-vitro release

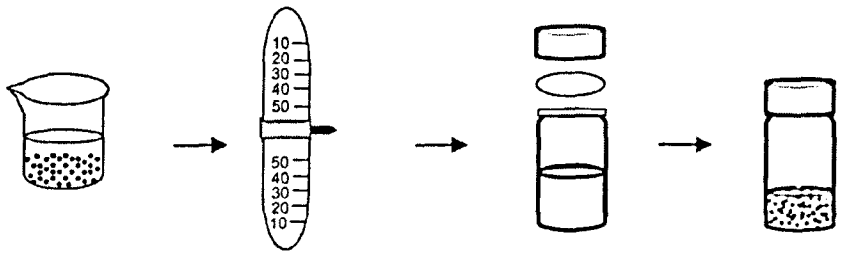

Fig. 1: Schematic procedure for sterilization and package of the sterile nanoparticle suspensions for the freeze-drying in non-aseptic environment.

profiles obtained for each formulation at pH 7.4 showed pH dependent extended release upto 14 h. Sterility testing showed no microbial contamination indicating that sterile nanosphere formulations have been achieved. The mean total scores (MTS) of the Draize test obtained for DS-loaded nanosphere not show irritant effects on the cornea, conjunctiva and iris indicating that the system did not result to be toxic. All final batches formulated were stable at 5°C and room temperature (RT) in terms of mean particle size, drug loading and sterility over a period upto 3 months.

In conclusion, sterile monodispersed submicron-sized formulation of DS is safe for ocular administration and has achieved the objectives of increased contact time, prolonged release, decreased frequency of administration and thus may improve patient compliance. Ocular pharmacokinetic studies are however needed to establish its potential.

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DESIGN & EVALUATION OF SOLUBLE OCULAR DRUG INSERT FOR CONTROLLED RELEASE OF CIPROFLOXACIN HCL

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INTRODUCTION

The ophthalmic drug inserts are defined as sterile preparations, with a solid or semisolid consistency, & whose size & shape are specially designed for ophthalmic application. They are composed of polymeric support containing the drug(s), the latter being incorporated as a dispersion or solution in the polymeric support. Ciprofloxacin HCl is employed in the form of eye drops for the treatment of conjunctivitis. In addition to the inherent drawbacks in conventional eyedrop dosage forms, the frequency of administration for more than six times a day are presumed to cause non compliance to drug therapy. Taking this aspects in consideration, the present study aims at developing the once a day therapy for controlled release of Ciprofloxacin HCl.

INSERT FORMULATION

In the present study Drug reservoir were prepared by film casting method using mercury substrate technique. In the first set, 6 batches (F1 to F6) were prepared using three different concentrations of polymer & two different concentration of the plasticizer. All the 6 formulations were then evaluated for physico chemical properties like uniformity of thickness, uniformity of weight, drug content uniformity, percentage moisture loss & percentage moisture absorption & *in-vitro* drug release characteristics.

In the second set of the experiment, only two different concentrations of the polymer were selected keeping concentration of the plasticizer constant for the casting of the films. The casted films were then crosslinked for four different time intervals. The cross linked formulations (CF1 to CF8) were then evaluated for Physicochemical properties & *in-vitro* drug release profile.

Out of 8 cross linked formulations, the two formulations (CF4 to CF8) were further evaluated for Draize eye irritancy & *in-vivo* drug release profile using rabbits as animal model. Sterilization of these two formulations was carried out using radiation sterilization.

RESULTS AND CONCLUSION

The results of physico chemical tests shown that thickness, weight of individual insert & drug content was found to be uniform throughout the formulations. Moisture loss & moisture absorption study shown that there is considerable effect of moisture on the integrity of the inserts as the polymer used for the preparation of the drug reservoir was hydrophilic.

The *in-vitro* drug release as shown in fig.1 shows that uncrosslinked inserts of Ciprofloxacin HCl extends drug release just up to 2h. which was not satisfactory in achieving

once a day therapy. Since the polymer gelatin & Ciprofloxacin HCl both are hydrophilic in nature, release from the non cross linked gelatin inserts was found to be very rapid. Therefore a suitable cross linking agent (Glutaraldehyde) was identified & utilized in the second set of experiment to control the release from inserts as well as to maintain the mechanical strength of the inserts. The cross linked formulations showed uniform thickness & weight. Drug content was found to be uniform throughout all crosslinked formulation. The *in-vitro* release of drug from cross linked formulations as shown in fig.2 reveals that formulation CF4 & formulation CF8 extends drug release up to 8 & 10 hrs respectively. CF4 & CF8 were also found to be non irritating to the eye & *in-vivo* drug release was also found to be similar as that of *in-vitro* drug release. The release of the drug from the inserts found to follow Higuchi kinetics revealing diffusion of the drug from the inserts. The correlation between *In-vitro* & *in-vivo* release was found to be positive revealing the efficacy of the formulation.

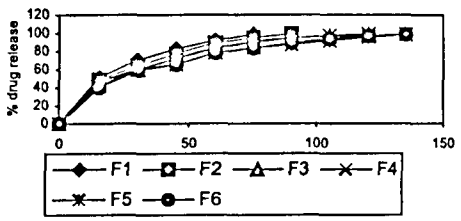

Fig.1. *In-vitro* drug release from uncrosslinked inserts.

In conclusion, results indicates that formulation CF8 has achieved the aim of the present study such as increased contact time, prolong drug release, reduction in frequency & thus may improve the patient compliance.

FORMULATION AND EVALUATION OF BIODEGRADABLE LONG ACTING PARENTERAL DOSAGE FORM OF A BETA LACTAM ANTIBIOTIC

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INTRODUCTION

Lipids have received considerable attention as alternatives to polymeric carriers for controlled release injectable and oral preparations .The major advantages of organogels *versus polymers include their low melt viscosity-thus obviating* the need for organic solvents for solubilization, and the absence of toxic impurities ,such as residual monomers, catalysts and initiators. Also, scale-up and manufacturing of such preparations is relatively uncomplicated compared to microspheres and liposomes. Prolonged therapeutic response from a single dose of an antibiotic intramuscular depot offers many advantages over conventional antibiotic preparations. While water is the preferred suspending liquid, antibiotics are not generally stable in water-based pharmaceutical preparations[1].Moreover, a long acting preparation is desirable to improve the clinical efficacy and patient compliance by reduction of the frequency of injections. Organogels [2], which are increasingly being studied for parenterals have the advantage of being potentially biodegradable and thereby show high tissue compatibility. This paper describes the development of a ready-to use long acting betalactam antibiotic organogel based injectable for prolonged release.

EXPERIMENTAL

In the present investigation intramuscular injectable depot preparations were formulated in several sterilized vegetable oil/derivatized oil bases along with gelling and dispersing agents. The formulations were prepared by dispersing the oleaginous gelling /suspending agent with the natural or derivatized vegetable oil and then sterilized. The Sterile micronized drug was added under Silverson stirring untiluniformly dispersed. The suspension was then passed through a 150 mesh S.S screen and then filled into sterile vials. The entire process was carried out under aseptic conditions.

Physicochemical characterization: The suspensions were evaluated for Particle Size distribution, Sedimentation volume, Redispersibility, Viscosity, Syringeability and Injectability. DSC and FTIR studies were carried out to reveal potential drug-excipient incompatibilities ,if any.

The effects of various combinations of formulation factors such as dispersing agents ,wetting agents and oily vehicles were studied on the in-vitro drug release from both oil suspension and gel systems. The vehicles evaluated were cottonseed oil,peanut oil,Soyabean oil,Ethyl oleate and the medium chain triglycerides. The gelling agents used were aluminium monostearate and glyceryl esters of fatty acids. Effect of wetting agents such as Polysorbate 80 and Lecithin was also evaluated.

The polynomial response equation was established for each of the selected vehicle. With the help of a simple software, 2^3 factorial response surface graphs ,as well as contour plots were constructed with the help of which the optimum formulation was directly identified.

Suitable formulations were further evaluated for further chemical characterization and in-vitro release study. Compatibility with closures was extensively studied and the preparation was put up for stability studies as per ICH guidelines in the proposed pack.

Scale-up studies were carried out to ascertain the reproducibility and ruggedness of the formulation. Scientific approaches based on dimensional analysis were used to determine parameters for large scale technology transfer.

RESULTS AND DISCUSSION

The study demonstrated that a stable formulation could be developed with biodegradable glyceryl esters of fatty acids and derivatized vegetable oil .The product showed prolonged drug release over a period of 48 hours as well as had good syringeability and injectability.

DSC and FTIR studies revealed that there was no potential interaction between the drug and the excipients This was further established by the stability studies on the formulation carried out as per ICH guidelines. Scale-up studies were carried out and rational and scientific approaches [3] for design of manufacturing attributes for technology transfer of the product to large-scale manufacturing were determined.

CONCLUSION

The organogel based formulations showed good prolonged release and have promising potential for Intramuscular depot parenterals.Moreover,the robust nature of the formulation,as well the scientific approach applied for large-scale manufacture would ensure a smooth transition as well as simplify regulatory concerns such as SUPAC related issues for FDA submissions.

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SOLID LIPID NANOPARTICLES: EFFECT OF CRYOPROTECTION

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OBJECTIVES

Preparation and evaluation of solid lipid nanoparticles and investigation of the lyophilization process based on use of different cryoprotectants.

INTRODUCTION

Solid Lipid Nanoparticles (SLNs) are alternative colloidal carrier systems to polymeric nanoparticles, liposomes and emulsions. They are particulate drug carriers of solid lipids with size ranging from 1-900 nm. A prerequisite for particulate drug carriers is maintenance of the particle size even after reconstitution. Therefore, lyophilization of SLNs was investigated and optimized with respect to the cryoprotectants giving good reconstitution performance.

EXPERIMENTAL

SLNs were produced from warm microemulsions, procedure as described by Gasco[1]. The microemulsion consisted of low melting lipids e.g gelucire, a surfactant and a cosurfactant. A novel Cox-2 inhibitor (a class of NSAID) was

chosen as the model drug for incorporation in solid lipid nanoparticles owing to its highly lipophilic nature. The warm microemulsion was diluted in a 10% solution of the following cryoprotectants: sorbitol, lactose, maltose, and mannitol. For the screening of suitable cryoprotectant these dispersions underwent the freeze-thaw test[2]. These dispersions were refrigerated overnight and again thawed to determine the particle size. The performance of these dispersions was checked against a blank containing no cryoprotectant based on the particle size measurement. The average diameter and polydespersity index (P.I) of the lipidic dispersion was determined by photon correlation spectroscopy (PCS) using Beckmann Coulter Counter N4 Plus at a fixed angle of 90° and at room temperature. The dispersion was diluted 1:20 with filtered water before analysis. The dispersion showing lowest particle size in the freeze thaw test was lyophilized using Labconco freeze dryer. The samples were freeze dried for 18 hrs. Drug loading in the lyophilized product containing the cryoprotectant was determined spectrophotometrically using Jasco UV-VIS spectrophotometer.

RESULTS

SLNs of size range below 200nm were produced from warm microemulsion formulations. Of all the cryoprotectants used maltose showed lowest particle size in the freeze-thaw test. So the final lyophilized product was produced using maltose as the cryoprotectant. Drug loading in the freeze dried product was found to be 80%.

DISCUSSION

Freeze-thaw experiments were conducted to select the excipients with the highest potential for cryoprotection. If an excipient can not protect nanoparticles during the first step of lyophilization i.e. freezing, it is not likely to be an effective cryoprotectant. Maltose followed by lactose, both being disaccharide proved an effective cryoprotectant against rest of the monosaccharides.

CONCLUSION

The freeze-thaw studies serve as pre-test to avoid too many time consuming freeze drying processes. Freeze-drying of SLNs with maltose as the cryoprotectant leads to a lyophilizate with good reconstitution performance.

ACKNOWLEDGEMENT

Authors are thankful to Colorcon Asia Ltd for the gift sample of Gattefosse'lipids.

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DEVELOPMENT AND CHARACTERIZATION OF SUBMICRONIC EMULSIONS OF PRIMAQUINE FOR PARENTERAL USE

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OBJECTIVE

The objective of the present study was to formulate and evaluate submicronic emulsions of primaquine suitable for parenteral use.

INTRODUCTION

Primaquine is one of the most widely used drugs in the therapy of malaria especially for the management of relapsing malaria. Primaquine acts specifically on the pre-erythrocytic schizonts (latent form) of malarial parasite, which reside and multiply in liver. However severe tissue toxicity in high doses of Primaquine poses a major challenge limiting its usefulness. Lipid based systems are thought to be readily taken up by the reticulo-endothelial system (RES) present in liver (Kupffer cells) and thus delivered to the site of action thereby, reducing its toxicity to other tissues. The present study reports the feasibility to formulate parenteral emulsions of primaquine for intravenous use.

EXPERIMENTAL

Preparation & characterization of lipid soluble Primaquine base:

Initially, a commercially available moderately water soluble salt, Primaquine phosphate was converted into lipid

soluble Primaquine base by alkalinization followed by extraction with chloroform. The base was characterized by visual appearance, boiling point and infra-red spectra. Absence of phosphate was also confirmed.

Analytical method development:

A colorimetric method for analysis of the drug containing a specific coupling reagent was established over the wavelength of 480 nm.

Formulation development:

Lipid emulsions were prepared by self emulsification technique followed by high pressure homogenization using APV 2000 lab homogenizer. Homogenization pressure and number of cycles were optimized to obtain desired particle size. The particle size was determined by Malvern Mastersizer S ver.2.19

Highly specialized short and medium chain triglycerides (oils) and combinations of various hydrophilic and lipophilic surfactants were used primarily to formulate lipid emulsions. In the selected blank formulations drug was incorporated.

Characterization of lipid emulsions:

The formulations were characterised for pH, creaming, cracking, phase separation, centrifugation, freeze thaw cycling, particle size, drug content. *In vitro* release studies were carried out at 37°C in saline phosphate buffer pH 7.4. Short term stability for three months at ambient and refrigeration temparature were carried out.

RESULTS

1. The Primaquine base obtained was highly viscous yellowish brown liquid having boiling point 176°C (175°C-179°C reported) and was free of phosphate residue.
2. The colorimetric method of analysis was established over 50-300 nm and the value of coefficient of corelation was 0.9964
3. The lipid emulsions had a pH of 7-8 and particle size was in nanometer range. The emulsions were found to be stable with no incidences of creaming, cracking or separation even after centrifugation. The drug loading was found to be about 85%. *In vitro* release profile showed steady and slow release over a prolonged period of time.

DISCUSSION

IR spectra of the primaquine base obtained was super imposable with the IR spectra reported in the monograph. The colorimetric method of analysis followed Lambert-Beer's law. The emulsions so formed are stable and are suitable for parenteral use. The homogenization pressure and number of homogenization cycles had a definite effect on particle size. Increased homogenization pressure and number of homogenization cycles resulted in decreased particle size.

CONCLUSION

The present study suggests the feasibility of preparation of submicronic lipid emulsion of Primaquine suitable for intravenous application. The nature of surfactant, their relative concentrations as well as that of oil were critical factors for stability of emulsion.

ACKNOWLEDGEMENTS

We are thankful to AICTE for sponsoring this project.

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SYNTHESIS OF PEG - CONTAINING ACRYLATE COPOLYMERS WITH IMPROVED MUCOADHESION

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OBJECTIVE

Development of modified copolymers of crosslinked Polyacrylic acid (cr PAA) and Poly ethylene glycol monomethyl ether methacrylate (PEGMM) for improved mucoadhesion.

INTRODUCTION

Adhesion is due to the interaction developed between two condensed phases. In general, an adhesion process is considered to occur in three major stages- wetting, interpenetration or interdiffusion and mechanical interlocking between a substrate and an adhesive, and can be described in terms of both thermodynamic and kinetic aspects. From molecular interaction point of view, the attractive forces between two phases can range from strong bonds (covalent or ionic bonds), to weak secondary molecular interactions (hydrogen bonds and van der Waals interactions). The last stage of adhesion, physical and mechanical bonding, requires the adhesive to form entanglements with the extended mucus chains. For optimal mucoadhesive performance- the polymer should be hydrophilic and contain numerous hydrogen bond forming groups, the surface energies of the polymer should be adequate so that wetting of mucosal surface can be achieved, should have sufficient flexibility to penetrate the mucus network. One of the approaches to enhance hydrogel bioadhesion is by grafting mucophilic polymer chains on to the backbone of the cross-linked polymer. Polyethylene glycol can be used as a typical mucophilic component. Tethered chains have one of their ends attached on the hydrogel surface and leave the other free. These polymer chains penetrate in to the mucous layer and bridge the base hydrogel and the mucous gel, and hence aid in the bioadhesion process.

EXPERIMENTAL

Synthesis of modified polymers:

A mixture containing the polymers cr PAA and PEGMM and the initiator was added with stirring to a solution of magnesium sulfate in distilled water and refluxed at 80°C for 18 hrs. At the end of the reaction, the mixture was diluted with hot distilled water, strained through a 40-mesh screen, and then repeatedly washed with 1L portions of distilled water. The washed polymer was dried in hot air oven at 90°C for 2hrs. The composition of the copolymers were varied by changing the ratios of the cr PAA and PEGMM.

Characterization of the polymers:

The synthesized polymers were characterized by nuclear magnetic resonance (NMR), Infra red (IR) spectroscopy, Differential Scanning Calorimetry (DSC) studies and hydration studies in deionized water. Mucoadhesive performance of the synthesized polymers was measured using a modified pan balance method using 2% NaCMC as the mucoadhesive substrate. Measurement of the adhesive strength was done by using a 5% w/v dispersion of the polymers in double distilled water.

RESULTS AND DISCUSSION

Modified copolymers of cr PAA and PEGMM were obtained as off-white, granular hygroscopic powder. Chemical analysis of the polymer by NMR indicated that PEG side chains were attached to the backbone of the PAA polymer. The IR spectra of the modified polymers showed typical absorption peaks attributed to both crPAA and PEGMM moiety. The modified polymers were found to be more mucoadhesive as compared to both the unmodified polymer, and the mucoadhesiveness of the polymers was increased with increasing content of PEGMM.

CONCLUSION

Polymers containing cr PAA and PEGMM can be synthesized by simple polymerization technique. The addition of PEG moiety into the polymer enhanced the mucoadhesive performance of the polymer. The polymers with higher PEG content were found to be more mucoadhesive as compared to the cr PAA. These polymers can be exploited for development of Mucoadhesive Drug Delivery Systems.

ACKNOWLEDGEMENTS

University Grants Commission for providing financial assistance.

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CHARACTERIZATION and EVALUATION OF NOVEL BIOMATERIAL FOR SUSTAINING DRUG RELEASE BY COATING PROCESS

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INTRODUCTION

The importance and applicability of polymer or Biomaterial films are well established in providing protective coatings and controlling drug release from dosage forms. The main polymers used for film formation have been classified into three categories: Gastrosoluble, enteric or Gastro resistant and insoluble[1]. Cellulosic and acrylic polymers exhibit good film forming properties and hence been extensively studied in pharmaceutical coatings.[2]

However, despite extensive research with such coatings problem may still arise when they are spread on the tablet or pellet surface. Tackiness, unwanted agglomeration and cracking tendency in dry coatings may result with the wrong coating composition or combination. Due to associated limitations with existing film former, there is always a constant quest for novel polymers or bio materials with better film forming characteristics.

In the present study, our aim is to evaluate Damar Batu (DB) as a novel biomaterial for pharmaceutical coatings. DB is yellowish gray transparent semi fossil resin. It is practically insoluble in water and exhibit acid resistant properties. The glass transition temperature (Tg) is 39°C and it softens at 53 – 55°C.

Free film preparation and characterization:

Neat plasticized films of DB were prepared by solvent cast method using 20% w/v solution in Chloroform. Plasticizer (Dibutyl sebacate) was added in concentration of 20 % and 30% w/w and taken as % age of total weight of polymer in solution. The prepared films were investigated for the following characteristics;

- Mechanical properties (Tensile strength and % elongation) by INSTRON instrument.
- Water Vapour Transmission rate (WVTR)
- Moisture absorption properties

Pelletization:

Diclofenac sodium (DS) 10%

Pellets core containing w/w were prepared by extrusion and spheronisation. The DS and Avicel pH 101 were mixed and blended using binder solution to obtain a wet mass which was transferred to a twin screw extruder and screened through a 2mm sieve at an extruder speed of 50 rpm. The extrudes obtained were spheronized at 1000 rpm for 5 minutes. The DS pellets obtained were dried at 40°C for 6h.

Pharmaceutical coating:

The drug containing pellets were coated with various amounts of DB using neat plasticized film coating solutions achieving 2% coat build up without any significant agglomeration or tackiness. *In vitro* drug analysis was performed in 0.1N HCl (pH 1.2, 2h) and phosphate buffer pH 6.8 (up to 10h). coated and cross sectioned pellets were characterized for surface morphology by Scanning Electron Microscopy (SEM).

RESULTS AND CONCLUSION

DB free films were slightly brittle and hence addition of plasticizers was found to be effective in improving the mechanical properties. Plasticized films with mean thickness 0.4 ± 0.02 mm showed moderate tensile strength and high elongation with sufficient flexibility to be bent in dried state.

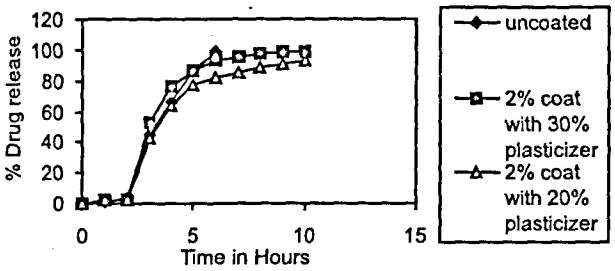

Fig. 1: *In Vitro* Drug Release study.

Very little amount of DS was released (<3%) in first 2h. (pH 1.2) while at pH6.8 the release increased and subsequently sustained up to 10h. this may be possible due to insolubility of DB and DS in acidic milieu. The release from pellets followed first release pattern.

Increase in elongation due to plasticizers addition may contribute in increased adhesion between film and coating surface.[3] The DB films demonstrated low WVTR and poor moisture absorption indicative of hydrophobic features. Sustained drug release up to 10h was achieved with 2%coat build up using 20% and 30% plasticizers concentration.

Due to good mechanical properties low Water Vapour Transmission and sustained release capability, DB seems to be a promising film former for pharmaceutical coatings.

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DETERMINATION OF ETOPOSIDE IN SOLID LIPID NANOSUSPENSIONS BY REVERSE PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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OBJECTIVE

Quantitative estimation of etoposide from solid lipid nanosuspensions.

INTRODUCTION

Etoposide, 4-demethylepipodophyllotoxin-â-D-ethylidene glucoside is a cytotoxic agent, mainly used in combination chemotherapy in small cell lung cancer.[1] Solid lipid nanoparticles represents an alternative way to formulate poorly water-soluble drugs in the form of aqueous dispersions.[2] Entrapment of etoposide inside SLN as carrier improves drug specificity and reduces toxicity to non-diseased cells. A simple, selective, rapid and precise reverse phase HPLC method has been developed for the determination of etoposide in SLN formulations.

EXPERIMENTAL

Chromatographic conditions: A HPLC, TOSOH model comprising of Rheodyne injector (7125) 20îl capacity and UV detector (LC-21) and recorder (SIC12). Analysis was carried out using Shodex C-18 column (5î, 4.6250mm) and UV detection was carried at 240nm.

Reagents Used: Methanol (HPLC grade), glacial acetic acid (AR grade) and doubled distilled water.

Reverse phase HPLC method development for etoposide was carried out in two stages.

1) Calibration curve for etoposide: A mobile phase consisting of Methanol:Water:Acetic acid (65:35:1) having pH of 4.0 at the flow rate of 1ml/min was used.

About 10.0mg of etoposide was accurately weighed and transferred into 10ml volumetric

flask and volume was made up using methanol. Further dilutions were done with the mobile phase to obtain working standard solution of concentrations ranging from

1 µg/ml to 10 µg/ml.

A linear curve was plotted with concentration values on X-axis and area under curve on Y-axis. The method was validated for its linearity, precision and accuracy.

Determination of drug entrapment in SLN dispersions:

Drug entrapment was estimated by injecting a known concentration of blank SLN dispersion and loaded SLN dispersions. A known quantity of SLN dispersions were transferred into a 10ml volumetric flask, dissolved in methanol and volume was made up with mobile phase to obtain sample stock solution. The working sample solution was prepared by diluting 1ml of stock solution to 10ml with mobile phase. The assay data was recorded and concentration of etoposide was calculated by measuring area under curve.

RESULTS AND DISCUSSION

Using the above chromatographic conditions a well-defined and well-separated peak of Etoposide was obtained at retention time of 5.3 min. and the minimum detectable concentration of drug was 10 ηg/ml. The other formulation excipients did not interfere with the elution of Etoposide.The linearity was found to be in the range of 10 ηg/ml to 10 μg/ml with the equation Y= 11626x +817.95 and the coefficient of regression being r =0.9995. RSD was below 2% and recovery was found to be 99.5%. The percent entrapment of etoposide in SLN dispersions was found to be 89.0%.

CONCLUSION

From the results obtained, we can conclude that the above method is simple specific, reproducible, accurate and reliable. This method can be used for determination of etoposide from the SLN formulations.

ACKNOWLEDGEMENT

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EVALUATION OF A NOVEL BIODEGRADABLE POLYMER

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INTRODUCTION

Biodegradable polymers are gaining importance in the pharmaceutical field because of their biodegradability and ease of fabrication into various dosages forms. However limited number of biodegradable polymers are available for pharmaceutical use. One such class of polymers, which is gaining importance, are aliphatic polyester like poly-lactic acid, poly-glycolide, copolymers of lactide-glycolide, because of their biodegradability and ease of synthesis, GRAS status and versatility in pharmaceutical formulations. However this class of polymer has two main disadvantages, high cost and limited hydrolytic stability. Polyesters which are less expensive, hydrolytically stable, with good mechanical properties, easy to synthesize, biodegradable, biocompatible and safe for use in living organisms could therefore provide a major advantage. We have synthesized novel aliphatic polyester by condensation polymerization reaction for application as a biodegradable polymer in pharmaceutical formulation.

OBJECTIVE

The objective of the present study therefore was characterization and evaluation of the novel polymer for

1. Physico-chemical properties.
2. Biodegradation by lipase.
3. Toxicity in animals.

EXPERIMENTAL

Evaluation of the polymer

1) Physico-chemical evaluation

a. Molecular weight by gel permeation chromatography using LYCROGEL PS-400 [250 X 7 mm, 5 microns] as the column and THF as the solvent.

b. Melting point

c. Infra red spectra

2) Biodegradation study: The polymer was assessed for degradation by lipase.[1] The lipase Lipozyme [TL 100 L] was used for the study. Two parameters retained for the evaluation of biodegradation were decrease in molecular weight and increase in acid value. The effect of various concentrations of lipase on polymer degradation was assessed over a period of time The decrease in the molecular weight was evaluated by GPC and increase in acid value was measured by titrimetry.

3) Toxicity studies: Acute and chronic toxicity studies were performed as per OECD guidelines in male albino mice. Chronic toxicity studies were performed for a period of one month. The polymer was administered orally by suspending in PEG 400. Histopathologhical evaluation of the tissues was done to asses tissue damage after acute and chronic toxicity studies. The tissues studied for histophathological changes and tissue accumulation were heart, lungs, liver, stomach, and intestine.

RESULTS AND DISCUSSION

A decrease in the molecular weight and a corresponding increase in acid value was seen which indicated that the polymer degraded in the presence of lipase, indicating its biodegradability. LD_{50} of the polymer was found to be more than 2 g/kg. Histopathological studies revealed no tissue accumulation or tissue damage ascertaining the safety for human use.

CONCLUSION

A novel biodegradable polymer potentially safe for human administration has been successfully synthesized. This polymer could find use in various pharmaceutical applications for oral and parenteral drug delivery as controlled release microparticles for periodontitis, intra-articular drug delivery, molded implants, stents ablated with laser and many more.

ACKNOWLEDGEMENT

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DEVELOPMENT OF NOVEL RADIOSTABLE BIODEGRADABLE POLYMERS FOR DRUG DELIVERY

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INTRODUCTION

The poly (?-hydroxy acids) such as Polyglycolic acids, Polylactic acids and their copolymers are the most popular choice of biocompatible and biodegradable polymers for medical applications. However, they are susceptible to sterilization by ??radiation. They undergo main chain scission and/ or cross-linking as well as structural changes (molecular weight, viscosity and crystallinity), because of generation of free radicals by ionizing radiation. Stabilization of these free radicals by using radiostabilizers might be helpful in improving the polymer property post irradiation.

EXPERIMENTAL

Polylactic acid was synthesized using direct polycondensation of lactic acid at 160°C and 0.5 mm Hg using Sn-octoate as catalyst. The radiostabilizers having a phenylenebisoxyacetate moiety were synthesized and then copolymerized with PLA at similar reaction condition. Polymer characterization was done by HNMR, PXRD, DSC, GPC, FTIR, contact angle, spherulite formation and in-vitro degradation. The effect of gamma radiation (2.5MRad using 60Co as radiation source) on polymer molecular weight was studied and characterized using HNMR, DSC and GPC. Biocompatibility studies were done using cultured cell line.

RESULT AND DISCUSSION

HNMR studies confirmed formation of copolymer of PLA and radiostabilizer. PXRD studies showed all samples were crystalline in nature however annealing studies at 140°C for 24h revealed that incorporation of radiostabilizer affected

the spherulite formation (nature and diameter). The DSC studies pre and post radiation showed changes in melting temperature (Tm). In case of PLA the Tm decreased, which may be attributed to polymer degradation in case of PLA as evident from GPC and DSC. The free radical is generated at the methylene units of PLA and is responsible for chain breaking. In case of copolymers of PLA except in case of sample D, the Tm increased which may be attributed to chain growth as evident from the presence of additional hump in GPC. The present study revealed that stabilization of free radical is possible by copolymerizing the unit with radiostabilizer having aromatic moiety. The distance between the methylene group and aromatic moiety is found to be the key factor for stabilization of free radical. Thus, sample D showed maximum stability against gamma radiation. Incorporation of radiosabilizer affected the hydrophilicity as confirmed by contact angle measurement (L>C>O>H>B>D) as well as in-vitro degradation. Biocompatibility studies carried out using Chinese hampster overies cell lines showed that all the polymer samples were biocompatible, as there was no change in cell morphology or growth.

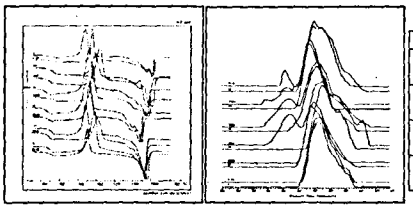

Fig 1. DSC thermogram and GPC of different polymer samples

Batch Coding for polymer samples

L	Poly L lactic acid (PLLA)
D	Copolymer of PLLA and di-methylenephenylenbisoxyacetate
B	Copolymer of PLLA and poly butylene phenylenebisoxyacetate
H	Copolymer of PLLA and poly hexylene phenylenebisoxyacetate
O	Copolymer of PLLA and poly octylene phenylenebisoxyacetate

Table 1: Sample coding for various batches

CONCLUSIONS

Biodegradable aliphatic polyesters resistant to ill effects of gamma radiation sterilization were successfully synthesized. Absence of morphological changes and normal cell proliferation confirmed the biocompatibility. The radiostable polymers can be used in variety of application including implants and microspheres for parenteral drug delivery as well as for sutures, ligatures and prosthetic devices.

ACKNOWLEDGEMENT

Author V.B. Patil is thankful to CSIR, New Delhi for providing senior research fellowship.

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DEVELOPMENT OF CONJUGATES OF CYTOXIC AGENT CISPLATIN WITH SODIUM ALGINATE

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OBJECTIVE

The objective of the present investigation was to conjugate cytotoxic agent, cisplatin (CP) with a biocompatible polymer Sodium alginate, with a view to achieve the controlled release of cisplatin from the conjugate and reduce the toxicity of cisplatin.

INTRODUCTION

Cancer chemotherapy is plagued with a major problem related to drug toxicity, as the effect of cytotoxic drugs is not restricted only to malignant cells, but applies equally to normal proliferating cells as well. Thus, a major direction in research concerning chemotherapy today is the development of means to suppress the toxicity of existing cytotoxic drugs without impairing their therapeutic activity. One possible approach is to use the drug in combination with high molecular weight carriers, either non-specific (polymers) or specific (antitumor antibodies). Polymer-drug conjugates of several anticancer agents like doxorubicin, cisplatin, 5-fluorouracil are reported in literature. Such macromolecularized drug derivatives are expected to increase the efficacy of the drug through more effective distribution, retardation of chemical or metabolic degradation and maintenance of prolonged levels due to slow release of the drug from the complex.

EXPERIMENTAL

The two grades of Sodium alginate were conjugated with CP by direct conjugation method. Conjugates were prepared using different molar ratios of polymer and CP.

Synthesis of Conjugates:

CP dissolved in double distilled water (DDW) was mixed with a solution of sodium alginate, also dissolved in DDW, with stirring. The reaction mixture was continuously stirred for 2 days at R.T. in dark. This was followed by dialysis using DDW for 12 hrs to remove unbound drug. The dialysed solution was concentrated under vacuum and dried at 50 ± 2°C.

Characterization of conjugates:

The conjugates were characterized for colour, odour, visual appearance, TLC studies, infrared (IR) spectroscopy, differential scanning calorimetry (DSC), reversibility of the conjugates, drug content & loading efficiency (UV spectrophotometry). *In-vitro* release profiles of the conjugates were determined by static method, using 50 ml of phosphate buffered saline (PBS) pH 7.4 as dissolution media, maintained at 37° ± 0.5°C.

In vivo bone marrow toxicity study was carried out in Swiss albino mice and percent (%) reduction in total WBC counts and % weight loss on treatment with drug and conjugate were used as the parameters to compare the toxicity of two. In vitro cytotoxic efficacy studies of the conjugates on *Allium cepa* root meristems was carried out and expressed as mitotic index. Mitotic indices of free CP and conjugate were compared.

RESULTS AND DISCUSSIONS

The conjugates were obtained in the form of flakes/films. Formation of the conjugate was confirmed by disappearance of free chloride, which was present in cisplatin IR spectra. DSC study also revealed the formation of the conjugates. The conjugates provided prolonged *in vitro* release upto 48 hrs. A significant reduction in toxicity, to the extent of nearly 80% was observed in case of conjugates. Also *in vitro* cytotoxic activity studies indicated that mitotic index of conjugate to be close to that of the free drug: Free drug (25.2 ± 1.2), Conjugate (37.6 ± 0.9), Control (64 ± 1.0)

CONCLUSION

Conjugates of CP with sodium alginate can be prepared easily by simple process. These conjugates are safe and efficacious and are suitable for development of implantable systems for sustained delivery of CP.

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NOVEL DELIVERY OF ANTIAGING COSMECEUTICALS

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OBJECTIVE

To prepare, characterize and evaluate novel delivery systems for anti aging agents.

INTRODUCTION

Aging of skin is a process, which can not be halted but much less reversed by retinoids, a free radical Scavengers and UV absorbers. There are four major theories on the basic causes of aging. 'The wear and tear', the 'Neuro-Endocrine theory', the 'Genetic Control therory' and the 'Free Radical theory'. Considering any of the above theories the basic visible effects are sagging of skin appearances of wrinkles, fine lines, loss of moisture, etc. these signs though unavoidable can be delayed/ reversed to certain extent by

use of cosmetics with age block actives. The most popular anti aging actives being Vitamins like Vit E and Vit A. the free radical scavengers are known to reduce the appearance of fine lines and wrinkles and nourish the skin. The only problem lies in the stability of these useful vitamins. In the present study, an attempt has been made to increase the stability and prolong the effect of these anti aging vitamins.

EXPERIMENTAL

1. a) preparation of mini globules containing vitamins. The vitamins were encapsulated in water insoluble polymer.

   b) preparation of carbopol gel with and without drug.

2. Characteristics of the anti aging formulations a)blank gel was characterized on the basis of pH, Viscosity, transparency and spreadability.

   b) Gel with miniglobules was characterized on the basis of pH, Viscosity, transparency and spreadability.

3. Evaluation of formulation: efficacy testing of the formulation was done

   a) Sensory testing: it was done by 10 healthy human volunteers.

   b) Histopathological studies: were performed on Guinea pigs.

   c) Measurement of reduction of wrinkles: silicone replicas of wrinkles were taken and reduction in wrinkles were evaluated using SEM.

4. Stability studies as per ICH guidelines.

RESULTS AND DISCUSSIONS

The novel delivery system was prepared and the anti aging actives were incorporated to it. This system showed optimum pH for topical use, showed excellent spreadability and appropriate viscosity. Sensory testing showed that the formulation has a moisturising effect and good aesthetic appeal. Histopathological studies showed an increased elastin and collagen levels, indicating anti aging properties. Also reduction in wrinkles was seen on examination of silicone replicas taken after one month application of the formulation.

CONCLUSION

It was possible to prepare novel delivery system for anti aging agents. From the results it can be concluded that both stability and efficacy of the actives can be increased by incorporation in the novel system.

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MICROEMULSION BASED ANTIFUNGAL NAIL LACQUER FORMULATION: A NOVEL COSMECEUTICAL

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OBJECTIVE

The objective of the study was to develop and evaluate a microemulsion based nail lacquer formulation devoid of harmful organic solvents.

INTRODUCTION

Onychomycosis, a fungal infection of the nails, makes up about 30% of fungus infections of the skin. It involves about 2-5% of general population, increasing to 8-10% in persons over 50 years of age. Although there many potent antifungals drugs currently available, nail infections are very difficult to treat. Because of longer duration of oral treatment (1 week pulse for 2-4 months or continuous therapy for 3-6 months) potential adverse effects such as hepato-

toxicity and drug interactions, are often of concern. To minimize the undesirable side effects associated with systemic treatment, it is highly desirable to have an efficacious topical product to treat onychomycosis. Since the newer antifungal agents have shown a better benefit to risk ratio, topical therapy may help increase overall efficacy, decrease side effects associated with the oral agent. In addition, topical therapy could be used to prevent recurrences. Traditionally, topical treatment alone for onychomycosis are only able to inhibit the growth of fungal nail infections, but not able to cure them. The thick nail plate and its dense keratin nature make it a difficult barrier for a topically applied drug to penetrate. Microemulsions, as a vehicle for topical delivery of actives, offer several advantages like high thermodynamic activity, greater solubilizing potential for hydrophobic moieties, higher permeation through biological barriers and ease of preparation. The present investigation deals with development of microemulsion based nail lacquer preparation for treatment of nail fungal infections like onychomycosis.

EXPERIMENTAL

The components of microemulsion were: a) oil phase: Propylene glycol monolaurate, castor oil. b) Surfactants and cosurfactant: sodium dioctyl sulfosuccinate, Isopropyl alcohol c) Aqueous phase: double distilled water

Drug: fluconazole. Other components used were viscosifying agents opacifiers and secondary resins.

The microemulsion existence region was determined by Pseudoternary phase diagrams using titration method. The formulations were characterized for isotropicity using cross polarizers and globule size was determined using photon correlation spectroscopy. Quantitative analysis of drug in the formulation was carried out by validated HPLC method (r2=0.999, linearity: 500 ng-100 mcg/ml). Viscosity enhancers, opacifiers (optional) and secondary film formers were incorporated into the microemulsion system to yield an elegant nail lacquer. The developed cosmaceutical was evaluated for appearance, uniformity of color, film properties, test of gloss, flexibility, viscosity, water resistance, non-volatile matter, determination of drying time, adhesion test, scratch test, blush test and clarity as per ISI standards.

RESULTS AND DISCUSSION

Pseudoternary phase diagrams helped to screen a small number of formulations from a large pool of formulations. The greater area of microemulsion existence was found at Km ratio 1:3. The globule size ranged between 50-100 nm. The developed fast drying formulation was free from gritty particles uniform in color. Tack free film was flexible enough against sudden pressure. The viscosity was between 300-400 cps. The developed formulation passed the non-volatile matter, adhesion, scratch and blush tests as per ISI standards. The water resistance of the nail lacquer film could be improved by secondary film formers, attempts are going on to impart robustness towards water washability.

CONCLUSION

Feasibility studies undertaken to develop microemulsion based nail lacquer of fluconazole indicate strong potential as a novel cosmaceutical. The results however need to be supplemented by in vitro and clinical testing on onychomycosis patients.

MELT DISPERSION SPHERONIZATION-PROCESS OPTIMIZATION FOR ONCE DAILY NIFEDIPINE FORMULATION.

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OBJECTIVE

Process optimization of melt dispersion spheronization technology for attaining once daily formulation of nifedipine

INTRODUCTION

Nifedipine, a dihydropyridine is a calcium channel blocker used in the treatment of spastic angina and essential hypertension. Its physicochemical and pharmacokinetic parameters suggest a strong rationale for the development of sustained release (SR) dosage forms. Multiparticulate systems are superior over the single unit dosage form and melt dispersion technology is the least used technique for

spheronization process as per literature evidence. Use of surfactant during spheronization process is common in most of the reports and associated with low drug loading. The present investigation aims at modifying melt dispersion technique and to optimize various parameters associated with it.

MATERIAL

Following materials were procured as a gift sample: Nifedipine, Zydus Healthcare. Gelucire & Precirol ATO – Gattefosse France through Colorcon Asia Pvt. Ltd. Hard gelatin capsule shells- Associated Capsules Group Mumbai. Acetone GR commercial sample supplied by Merck India Ltd.

METHOD

Gelucire and Precirol mixture in an optimized ratio was taken and melted in a beaker and the drug dissolved in a suitable solvent was added to this. Solvent was evaporated partially and the resultant molten system was added to preheated water at constant rate of stirring till waxy globules resulted and further solidified to give spherules. Resulting spherules were filtered, dried, sized, evaluated and filled in capsules.

Optimization of Parameters:

Melt temperature: Melt temperature was optimized by determining the critical solution temperature (CST) of Gelucire acetone system.

Solvent content: Solvent content in final ready Gelucire melt which was added to hot water was determined by plotting ternary phase diagram. The solvent corresponding to Gelucire water immiscibility region of ternary phase diagram was chosen as final solvent content.

External phase temperature: Water temperature corresponds to solution temperature of Gelucire-water immiscibility region of ternary phase diagram. Molten Gelucire drug system was added at constant rate of stirring (800 rpm.) to water maintained at different temperatures. The temperature at which maximum sphericity was obtained has been selected.

Stirring speed: Stirring speed was optimized to obtain maximum yield of 20/40 # fraction of spherules. For the purpose different batches were processed at different stirring speeds. The stirring speed which gives maximum yield of particular fraction (20/40 #) has been taken as the optimized stirring speed.

Release parameter: The release parameters were optimized by processing different proportions of Gelucire and Precirol and release profile of each batch was matched with that of marketed formulation by applying F_2 statistical test for two sample variance. The formulation having overlapping release profile to that of marketed product was selected as the final formulation.

Evaluation of Formulation: Spherules were evaluated with respect to:

1. Sphericity by method of Lovgren & Landburg.
2. Porosity, density & flow properties.
3. Moisture pickup studies at 58, 75 & 85% RH.

Selected formulation was filled in size '0' hard gelatin capsules and evaluated for-

1. Content uniformity using UV spectrophotometer at λ_{max} 235 nm.
2. Weight variation.
3. In-vitro release profile using USP XXIII apparatus type I
4. Effect of pH on in-vitro drug release.

RESULTS

Selection of solvent, amount of solvent, Gelucire grade, amount & temperature of external phase and string speed is critical for size and sphericity of granules. .Flow & density of selected batches were adequate for capsule filling. Drug loaded spherules shows no moisture pickup at all the storage conditions listed. Capsule passed for uniformity of weight test as well as content uniformity test (99.5±1.47 %) as per USP. In-vitro release studies indicated first order release profile similar to marketed preparation. Diffusion was the major mechanism of release.

CONCLUSION

Optimized procedure of melt dispersion spheronization technology developed using Gelucire as matrix material was effectively employed for formulation of once daily nifedipine product.

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PARTICLE ENGINEERING USING SPRAY DRYING TECHNIQUE FOR PULMONARY DRUG DELIVERY.

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INTRODUCTION

The Dry Powder Inhalation (DPI) formulations consist of drug particles with aerodynamic diameter of 1-5mm for efficient pulmonary deposition. The conventional particle formation requires milling producing highly cohesive and charged particles. These micronised powders are often blended with 'coarse' inert carriers as loose aggregates to improve deposition in the respiratory tract. Incorporation of drug with suitable excipients and application of alternate particle generation technology such as spray drying and supercritical fluid condensation are used to produce hollow porous 'PulmoSphere' particles with improved drug delivery efficiency and reproducibility.

OBJECTIVE

1) To study particle engineering of the drug by Spray drying technique to produce inhalable particles of favorable size and shape using suitable carriers to improve the delivery to the lower airways.

2) To investigate the in vitro pulmonary drug deposition of Salbutamol Sulphate dry powder aerosol formulations with different proportions and grades of lactose.

EXPERIMENTAL

Particle Engineering by Spray Drying:

An aqueous solution of 2-20% of Salbutamol Sulphate was formulated with various proportions of excipients like a-lactose monhydrate and mannitol. The dispersions were sprayed through a nozzle of 0.7 mm in a Mini Spray Dryer (JISL-LSD-48). The spray drying conditions i.e. pump, aspirator, inlet temperature, airflow were varied according to the feed concentration and composition to get the desired drug entrapment in inhalable particles.

Preparation of Dry Powder formulations:

Six different a lactose monohydrate carriers were used for the study. Three different ratios of coarse is to fine lactose were formulated. The powders were filled into capsules each containing 200mg of the drug.

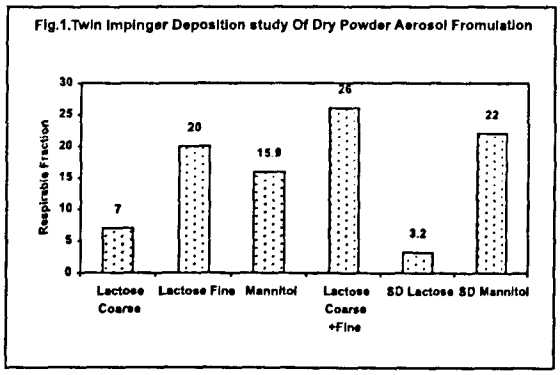
Characterization of inhalable Powder formulations:

The shape and surface morphology of inhalable particles was characterized by Scanning Electron Microcopy. The particle size distribution was determined by laser diffraction using Malvern Mastersizer. Moisture content was analyzed by 737 KF Coulometer, Metrohm, Powder Crystallinity was determined by X-Ray Diffraction. Aerosol characterization

The inhalable powder aerosol formulations were characterized in-vitro by Two Stage Twin Impinger Apparatus. A unit dose dry powder inhaler (Rotahler) was used to determine the emitted dose and Respirable fraction of the powdered formulations.

RESULTS AND DISCUSSIONS

The spray-dried particles were uniform, free flowing and showed no agglomeration. The density of the particles was 1.2-1.7g/cm^3 with a moisture content of 0.4 -0.6%. The Mass Median Diameter of the spray dried mannitol and lactose particles were in the range of 2-10mm & 2-15mm respectively. The X-ray diffractogram for the powder showed no change in the degree of crystallinity. The combination of (Coarse: fine) lactose with the drug was found to give increased deposition in the Stage-II of the Twin Impinger as compared to the other lactose formulations (Fig.1.). The one-step method of preparing the spray dried Salbutamol Sulphate mannitol particles gave increased drug loading with improved pulmonary deposition.



CONCLUSIONS

The spray-dried inhalable particles have similar particle characteristics and in vitro pulmonary deposition to that of the conventional DPI formulations. Thus this technique can be used to formulate hollow porous 'PulmoSphere' particles that are more effectively deposited in the lungs.

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