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Formulation and Evaluation of Sustained Release Tablets Using An Insoluble Rosin Matrix System

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Rosin, a natural resin, was used as an insoluble matrix forming material for studying the release of diltiazem HCl, which was taken as a model drug. The granules prepared were free flowing with good compressibility. The tablets prepared were flat faced, which retained their shape throughout. The method of preparation of matrix system and its concentration were found to have a pronounced effect on the release of diltiazem HCl. Various physical parameters of the granules and the tablets were evaluated. The release mechanisms and the release rate kinetics of the tablets were examined using different release models. The release was found to follow both the first order kinetics and Fickian diffusion. Marked differences in the release rate of the drug from different formulations were observed when % cumulative release was plotted against time. The drug delivery was analyzed using the paddle method according to USP XXIII. All the studies were done in distilled water.

Various natural gums and mucilages have been examined as polymers for sustained drug release, in the last few decades,[1-3] in order to increase the clinical efficacy and patient compliance. The polymers are used in the peroral formulations to deliver the drugs at controlled and predetermined rate, thus maintaining their therapeutically effective concentrations in systemic circulation for prolonged periods of time. The physical and structural properties[4] and the drug release mechanisms and kinetics of these sustained release preparations determine the in vivo performance of these dosage forms[5]. The nature and concentration of the polymer and the method of manufacture have an enormous effect on the kinetics and release mechanism of the formulation.

Diltiazem is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given by mouth in the treatment of angina pectoris and the management of hypertension. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a potential candidate for sustained release preparations.[6-7]

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Rosin, a matrix forming polymer used in the present work, is a solid resin obtained from *Pinus palustris* Miller, and from other species of *Pinus linnae*. The constituents of rosin are 1; sylvic acid, 2; α, β, γ - abietic acids, 3; γ - pinic acids and resin and occasionally 4; pimaric acid. It is contains sharply angular, translucent, amber colored fragments, frequently covered with a yellow dust. Fracture is brittle at ordinary temperatures, shiny and shallow - conchoidal. Odor and taste are slightly terebinthinate, easily fusible and burns with a dense yellowish smoke. Specific gravity is around 1.07-1.09 and residue on ignition is not more than 0.1% and acid value is 150-180. It is insoluble in water, soluble in alcohol, ether, benzene, chloroform, carbon disulfide, dil. NaOH, and KOH or some volatile and fixed oils. Rosin is used as a stiffening agent, has adhesive properties (used in plasters, cerates, ointments and water proofing etc.,) and is stimulant and diuretic.[8] It is also used as a food additive.[9] *In vivo* biocompatibility studies by Dorle *et.al* showed faster degradation in *in vivo* as compared to *in vitro*. It provides

good compatibility compared with poly (DL-lactic-co-glycolic acid).[10]

MATERIALS AND METHODS

Natural rosin (Rosin-N) was locally procured from an ayurvedic supplier. Diltiazem HCl was obtained as a gift sample from Parke-Davis, Hyderabad, Lactose I.P was obtained from Genuine Chemicals, Mumbai. All other chemicals and reagents were of analytical or pharmacopoeial grade.

Diltiazem HCl calibration curves:

Calibration curves of diltiazem HCl were prepared using distilled water in the concentration range of 1-10 µg/ml. The drug was analyzed spectrophotometrically (UV-240 Shimadzu,Japan) at 237 nm (regression coefficient, r^2 = 0.9996 in distilled water).

Preparation of diltiazem HCl tablets:

Both the drug and the polymer material were passed thorough sieve no. 60 and thereafter three different methods were used to prepare the tablets: In the first method (dry mixing), the powders were first mixed in geometric progression in a mortar. Four different formulations with different drug and polymer ratios were prepared i.e., 1:1, 1:2, 1:3, and 1:4. A formulation with lactose as a diluent along with drug and polymer in the ratio 1:0.5 was also studied but did not show any encouraging results. In the second method (wet granulation), the drug and the polymer were mixed as above. Acetone was used as a granulating fluid. It was added drop wise to the mixed powders. After each addition the contents of the mortar were triturated well to ensure uniform mixing. After achieving enough cohesiveness, the obtained dough like mass was passed through sieve no. 22. The granules thus obtained were air dried till acetone evaporated off. After drying, the granules were passed through sieve no. 22/44. The granules retained on sieve no. 44 were mixed with 15% fines (granules which passed through sieve no. 44). Three different formulations of different ratios of drug and the polymer were prepared i.e., 1:1, 1:2, and 1:4.

Preparation of film:

The accurately weighed polymer was dissolved in a known amount of acetone. The drug was added and shaken for some time and poured into a mould. The film was air dried, powdered and passed through sieve no. 60. One formulation in the ratio of drug to polymer 1: 4 was prepared. All the above ratios were obtained by keeping the amount of drug constant at 30 mg and varying the amount of polymer.

Tablet compression:

The tablets of the above formulations were compressed in a single punch tablet compression machine. A weighed amount of the powder or the granules was introduced in the die and the die capacity was adjusted as required. Compression force was adjusted to obtain the required hardness. A batch of 50 tablets was prepared.

Evaluation of Characteristics of Granules and tablets:

The various characteristics of granules like bulk density, total porosity, angle of repose, true density, drug content, particle size etc., were studied.[11,12] .The tablets were evaluated for hardness, friability, uniformity of weight and drug content.

In vitro dissolution studies:[13]

The paddle method was followed for the study (Thermonic, Campbell Elect., Mumbai). The official procedure for dissolution study was adapted for studying the release pattern in order to suit the UV sensitivity of the drug. Dissolution medium (900 ml) was taken in a dissolution flask, which was kept in a thermostatically controlled water bath maintained at 37 ± 0.5°. One preweighed tablet was then introduced into the flask and the paddle was rotated at 100 rpm. At regular intervals over a period of 12 h, the samples of 5 ml were withdrawn and transferred to test tubes and 5 ml of fresh distilled water was replaced into the beaker. The samples were then diluted suitably with fresh distilled water and analyzed spectrophotometrically at 237 nm.

Release models:

The first order and the Higuchi equations were used in order to describe the release from the different formulations prepared by the different methods. The first order equation, Eq. (1) describes the release from systems where release rate is concentration dependent[14-17]. Higuchi[18] (Eqn. 2) described the release of drug from the insoluble matrix as the square root of the time dependent process based on Fickian diffusion[19].$\ln Q_t = \ln Q_o - k.t$. (1) Where, Q_t is the amount of drug released in time t, Q_o is the amount of drug in a tablet; k is the release rate constant for the first order.

$Q = DS (P/\lambda) [A-0.5 SP]1/2 .\sqrt{t}$. (2) Where, Q is the amount of drug released per cm^2 of surface at time t; S is the solubility of the drug in g/cm^3 in dissolution medium, A is the content of drug in insoluble matrix; P is the porosity of matrix; D is the diffusion coefficient of drug; and λ is the tortuosity factor.

RESULTS AND DISCUSSION

In the earlier work matrix tablets of diltiazem hydrochloride were formulated using ethylcellulose and rosin as matrix materials in various quantities (%w/w) to study their ability to retard the release and were evaluated for hardness, friability and drug release .In vitro release from the formulation was studied as per the USPXXIII dissolution procedure. The formulation gave an initial burst effect followed by sustained release for 12 h which indicates bimodal release of diltiazem hydrochloride from the matrix tablets.[20]

An attempt was made to study the efficacy of the insoluble matrix-forming polymer i.e., rosin for the sustained release of diltiazem HCl. Drug-excipients compatibility was studied using TLC and FTIR. It showed no interaction between rosin, drug and various excipients used in the present formulation. In the present study, the various drug to polymer ratios were studied while keeping the drug content constant at 30 mg. Different methods of preparation of the drug and the polymer matrix like, dry mixing, wet granulation, and film forming methods were employed. Granule density, porosity and hardness are often interrelated properties. In addition, granule density may influence compressibility, tablet porosity, dissolution and other properties. Tablets are made from granular particulate solids. Therefore, granulation characteristics are of interest. The quality of tablet depends upon the physico-chemical properties of the granulation. The tablets prepared were flat faced punches with a hardness of 3.5-4.5 kg/cm^2. The release from tablets was studied for about 12 h. All the tablets retained their shape except the 1:0.5 ratio in which the lactose was added as a diluent. Friability remained within 0.75% to 1% showing that the tablets could withstand the mechanical shock during shipment and usage.

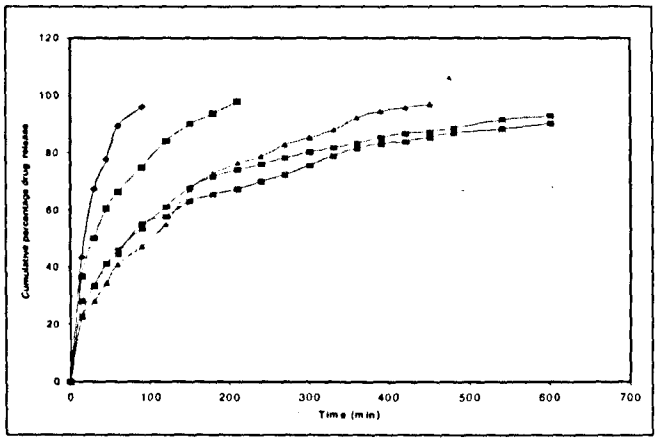

Fig. 1: Drug release from different tablet formulations prepared by dry mixing.

Cumulative percent release of drug from different ratios of drug: polymer tablet formulations, prepared by dry mixing method,in distilled water. Drug:Polymer series1, 1:0.5+Lactose (♦), series2, 1:1(▫), series3, 1:2(▲) , series4, 1:3(X) , series5, 1:4(*).

The method of preparation of granules had a profound effect on the release rate of the drug from the tablets. The formulation prepared by dry mixing method, with 1:0.5 ratio, in which lactose was added as a diluent, gave a fast release of the drug, i.e. 95.94 % (± 0.762) of drug release was observed in 1.5 h (fig. 1). It was observed that, with the formulation in the ratio of 1:1, release of drug was 97.83 % (± 2.031) in 3.5 h (fig.2). Whereas the release was about 95.21% (± 1.392) from the formulation of the same ratio, prepared by wet granulation (fig. 2) in a 12 h study.

It was observed that with the increase of the polymer content the release was retarded, as evident from a 10 h study of formulations in ratio of 1:3 and 1:4. , Fig.1, 90.20 %(± 3.353) release and 92.71%(± 2.455) release, respectively). Nearly 88.63 %(± 1.641) of the drug was released from the formulation of 1:2 ratio, prepared by wet granulation method (fig.2). It was about 65.07% (± 1.486) from the formulation in the ratio of 1:4 (fig. 2), during a study of 12 h The release observed for 1:4, drug: polymer ratio, prepared

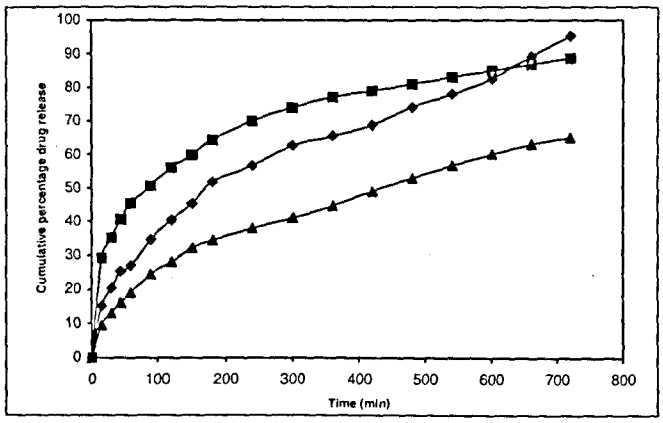

Fig. 2: Drug release from different tablet formulation preared by wet granualtion.

Cumulative percent release of drug from different ratios of drug:polymer formulations, prepared by wet granulation method,in distilled water. Drug:Polymer series1, 1:1(♦), series2, 1:2(▫), series4, 1:4(▲).

by film formation technique was nearly 75.90 % (± 2.722) in 12 h (fig. 2)

All the above studies were done using distilled water as the dissolution medium and the results depicted are an average mean of three trials. The drug release from all the formulations mentioned above followed first order kinetics and the Higuchi model, thus indicating that there was no erosion of the matrix and the tablet maintained its surface area and shape.

REFERENCES

1. Baveja, S.R., Ranga, R.K.V. and Arora, J., **Int. J. Pharm.**, 1989, 51, 115.
2. Bhalla, H.L. and Piyush, C.R., **Indian Drugs**., 1991, 28, 519.
3. Kakkar, A.P., Singh, M. and Medirrata, A., **Drug. Develop. Ind. Pharm**., 1997, 23, 1055.
4. Dabbagh, M.A.., Ford, J.L.,Rubinstein, M.H. and Hogan, J.E., **Int. J. Pharm**., 1996 ,140
5. Gupta, P.K. and Robinson, J.R., Treatise on Controlled Drug Delivery: Fundamentals, Optimization, and Applications. Marcel Dekker, New York, 1992, 255.
6. Chaffman, M. and Brogden, R. N., **Drugs**, 1985, 29, 387.
7. Kim, H. and Fassihi, R., **Pharm. Res**., 1997, 14, 1415.
8. Joseph, R.R., Charles S.L.C Eds., In; Remington: The Science and Practice of Pharmacy, 19th Edn., Vol. II, Mack Publishing Company, Easton, Pennsylvania, 1995, 1665.
9. U.S.Food and Drug Administration, Centre for Food Safety and Applied Nutrition, Agency Response Letter, GRAS Notice No.GRN 000108(21 CFR 172.615,178.38,172.315)
10. Dorle, A.K., Satturwar, P.M.and Fulzule, S.V., **AAPS Pharm Sci.Tech.**, 2003, 4, 55.
11. Ansel, H.C., Popovich, N.G. and Allen, L.V., Eds.,In ; Pharmaceutical Dosage Forms and Drug Delivery Systems,6th Edn., B.I. Waverly Pvt.Ltd, ,New Delhi 1995,213.
12. Lachman, L., Liebermann, A.H. and Kanig, L. J., Eds., In; The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese Publishing Company, Mumbai ,1987, 431.
13. Indian Pharmacoepoeia, Vol II, Controller of Publications, Government of India, New Delhi, 1996,736.
14. Desai, S.J., Singh, P., Simonelli, A.P. and Higuchi, W.I., **J. Pharm. Sci.**, 1996, 55, 1230.
15. Singh, P., Desai, S.J., Simonelli, A.P. and Higuchi, W.I., **J. Pharm. Sci.**, 1967, 56, 1542.
16. Sujja-areevath, J., Munday, D.L., Cox, P.J. and Khan, K.A., **Int. J. Pharm.**, 1996, 139, 53.
17. Panchagnula, R and Sood, A., **Int. J.Pharm.**, 1998, 175, 95.
18. Higuchi, T., **J. Pharm. Sci.**, 1963, 52, 1145.
19. Peppas, N.A., **Pharm. Acta Helv.**, 1985, 60, 110
20. Shirwaikar, A.A. and Srinatha, A., **Indian J. Pharm. Sci.** 2004,66(4): 433-437