RESEARCH PAPER

Accepted 23 March 2001
Revised 20 February 2001
Received 9 September 1999
Indian J. Pharm. Sci., 2001, 63(3) 205-210

Development and Evaluation of a Sustained Release Dosage Form: Microencapsulation of Drug-Pectin complex

AJAYKUMAR PATIL*, J. SABOJI[1] AND PURSHOTHAM RAO[2]
K.R.E.S's Karnataka College of Pharmacy, Bidar-585403.
[1]K.L.E.S's College of Pharmacy, Belgaum.
[2]H.K.E.S's College of Pharmacy, Gulbarga.

Diclofenac sodium-pectin complexes were prepared by physical mixture and solvent deposition techniques. Microcapsules of drug and drug-pectin complex were prepared by coacervation phase separation method using ethylcellulose as coating material. The stability of the drug in the formulations were confirmed by TLC and IR studies. Different sizes in a batch of dried microcapsules were separated by sieving. Scanning electron microscopy revealed the morphology of microcapsules. *In vitro* release from complexes and mirocapsules in distilled water and mechanism of drug release are identified. The dissolution rate decreased with an increase in the concentration of pectin and ethylcellulose added in complexes and microcapsules respectively. Dissolution data were fitted into a double log plot equation, a Fickian release (n=0.5) was obtained for all the complexes and microcapsules. The data demonstrates that controlled release formulation of diclofenac sodium can be developed using a combination of two techniques like complexation and microencapsulation. The binding of drug to pectin was investigated using equilibrium dialysis. The binding data were expressed in the form of Scatchard plot, which indicated two classes of binding sites.

Diclofenac sodium is a potent non-steroidal antiinflammatory drug with pronounced analgesic and antipyretic properties. Its half-life in plasma has been reported to be 1-2 h[1]. Commonly it produces bleeding ulceration or perforation of intestinal wall. The short biological half-life and associated adverse effects makes it as an ideal candidate for controlled drug delivery system. Pectin, a conjugated polyuronic acid was reported to complex with cationic and anionic drugs,[2] suggesting its usefulness as a matrix for sustained release preparation. Pectin being a natural product has always constituted a substantial part of man's diet with a long record of safety and also valuable for decreasing plasma cholesterol levels[3] and has antidiarrheal activity.[4] It has gained much attention that favours its use in pharmaceutical applications. It has reported that ethylcellulose can be used as a material for sustained release preparations with an added advantage of enteric coating property.[5] Torres[6] have prepared a complex of diclofenac sodium-ion exchange resins and then microencapsulated with hydroxypropyl-methylcellulose phthalate (HPMCP) to obtain a delayed release of drug and true control over the rate of release with an enteric coating property. Chowdary and Ramesh[7] have formulated microcapsules of nifedipine and its solid dispersions in HPC–MCC with cellulose acetate to obtain sustained release. Sprockel and Price[8] have used a combination of two techniques like complexation and microencapsulation for sustaining the release of chlorpheniramine maleate. Garcia-Encina[9] have also used the same techniques for sustaining the release of diclofenac sodium. The objective of this investigation was to formulate an oral sustained release dosage form of diclofenac sodium using a combination of two techniques like complexation with pectin and then microencapsulating it with ethylcellulose.

*For correspondence

EXPERIMENTAL

Diclofenac sodium was obtained as a gift sample from Tablets India Ltd., Madras. Pectin was purchased from Loba-Chemie, Bangalore. Ethylcellulose was obtained from S.D. Fine Chemicals Ltd., Bangalore. All other chemicals and solvents used were of analytical reagent grade. Inac timed release capsule was purchased from Recon Ltd. Bangalore.

Preparation of Drug-pectin complex[2]:

Diclofenac sodium was dissolved in an adequate amount of ethanol. Pectin was suspended in the drug solution. The solvent was removed under vaccum at 70° and the residue was kept in a dessicator for 24 h. The samples were screened through 125 mm sieve. Different ratios of drug to pectin were used. Alternatively diclofenac sodium was mixed manually with different ratios of pectin and passed through 125 mm sieve to achieve uniformity. The batch size was 3 g.

Preparation of Microcapsules[1]:

The microcapsules of diclofenac sodium-pectin complex and only diclofenac sodium were prepared by coacervation phase separation technique by non-solvent addition using ethylcellulose as a coating material. The complex of diclofenac sodium-pectin prepared by solvent deposition of 1:2 and 1:3 drug to pectin ratios were taken as a core material for microencapsulation. Different ratios of core to coat material were taken for microencapsulation. The batch size was 3 g. Ethylcellulose was dissolved in 30 ml of toluene. The core material was dispersed in the polymer solution using a mechanical stirrer at a speed of 2800 rpm for 10 min. The rpm of mechanical stirrer was previously adjusted with the aid of a Tachometer. Twenty millilitres of petroleum ether was slowly added over a period of 20 min with stirring. The system was then chilled on an ice bath. The resulting microspheres were collected by filtration, washed repeatedly with n-hexane to completely remove even traces of toluene and oven dried at 100° for 4 h to completely remove traces of n-hexane. The product was then washed with water and dried in the oven.

Evaluation:

An assay of diclofenac sodium in the complexes and microcapsules was performed for three randomly collected samples from each formulation. For each, 100 mg of sample was pulverized and dissolved in 50 ml of methanol, the resulting solution was filtered and further dilutions were made with methanol and the absorbance at 282 nm was measured spectrophotometrically. The concentration of the drug was determined from the standard curve. From the results of these studies, weight of samples equivalent to 100 mg of diclofenac sodium were calculated. Different sizes in a batch of dried microcapsules were separated by sieving, using sieve No. 16, 25 and 36. The amount retained on different sieves were weighed. The surface morphology of the microcapsules was observed with scanning electron microscope, JSM Instrument, Model 840 A

Stability Studies:

The stability of the drug in the formulation was confirmed by TLC and IR spectral analysis. The TLC studies were carried out using benzene:methanol:acetone (7:2:3) as the developing solvent and 1% solution of potassium dichromate in 40 % sulphuric acid as the spraying solution on 0.1 mm thick silica gel G plates[1]. The R_f values were compared and it was observed for the presence of any extra spots. IR spectra of the pure and extracted drug by TLC from all types of formulations were determined using Nicolet Impact Model IR Spectrophotometer by KBr Disc method.

In vitro drug release studies:

A quantity of complexes and microcapsules equivalent to 100 mg of diclofenac sodium were tied in a muslin bag. The drug release was studied in distilled water (900 ml, 37°) using USP XXI basket apparatus (100 rpm). Samples (5 ml) were withdrawn at regular intervals and the same volume of fresh medium was replaced. The samples withdrawn were analysed after suitable dilution by Shimadzu 1201 UV-VIS Spectrophotometer at 275 nm. Same process was repeated for marketed timed-release product 100 mg.

Equilibrium Dialysis Studies[2]:

Cellophane membrane bags containing 10 ml of 0.5% pectin in phosphate buffer pH 7.4 (7.69×10^{-5} M) were immersed in 30 ml of drug solutions (3×10^{-4} to 3×10^{-2} M in phosphate buffer pH 7.4) inside the aluminum foil covered 100 ml beakers. The beakers were shaken at 37°. After 24 h, a time sufficient to attain equilibrium, drug concentrations in the beakers were determined at 275 nm spectrophotometrically. And the amount of drug bound to pectin was calculated. Blank experiments were

TABLE 1: DRUG CONTENT AND RELEASE CHARACTERISTIC OF COMPLEXES

Formulations	Drug:pectin	Drug content (mg)	Per cent Drug Released			n
			0.25 h	3rd h	12th h	
P_1	1:1	49.96	22.31	99.84	-	0.6
P_2	1:2	33.28	15.18	83.14	-	0.58
P_3	1:3	24.97	10.14	60.87	96.29	0.51
P_4	1:4	19.97	12.27	50.48	78.32	0.51
S_1	1:1	48.12	52.50	-	-	0.59
S_2	1:2	31.94	30.06	99.81	-	0.59
S_3	1:3	23.37	44.52	99.23	-	0.34
S_4	1:4	17.97	21.31	65.88	-	0.52
DS	-	-	91.25	-	-	0.12

P = Physical mixture. S = Solvent deposition. DS = Diclofenac sodium. n = Diffusion exponent related to mechanism of drug release, according to eqn $M_t/M_\infty=Kt^n$. 100 mg of samples were analysed.

performed in the same manner using only pectin solution. For the preparation of solutions of pectin and drug, a phosphate buffer pH 7.4 was used instead of water to avoid precipitation of the drug at the acidic pH of pectin solution and to reduce the Donnan effect.

RESULTS AND DISCUSSION

The drug content in the various complexes and microcapsules are shown in Table 1 and 2 respectively. TLC studies indicated same or comparable R_f values (0.785 to 0.794). TLC values and IR spectra analytical reports confirmed that there was no interaction between drug and excipients used. The sieve fraction of 25/36 was found to be of major fraction in all the microcapsule formulations having size range of 425–600 mm. This sieve fraction was used in all the further studies. SEM photograph of microcapsules of diclofenac sodium and diclofenac sodium-pectin complex encapsulated with ethylcellulose are shown in figs.1 and 2 respectively with an approximate size of 500 mm and 541 mm respectively, measured on the basis of scale given in the photograph. The microcapsule of fig. 2 is less spherical in shape and having rough surface texture when compared to the microcapsule of fig. 1.

In Vitro release data obtained for the complexes and microcapsules are shown in Tables 1 and 2. From Table 1, it was noted that, pectin caused an appreciable retardation of drug release when compared with pure diclofenac sodium. When the drug–pectin complex is placed in water, a quantity of the liquid is absorbed resulting in the formation of a swollen viscous layer that retains considerable order structure with respect to the polymer, and thus is expected to influence greatly the dissolution of latter. The thickness of this hydrated layer is related to the degree of dissociation of the polymer in the layer. Since pectin is a linear, somewhat fibrous polymer, there will be minimum restrictions on its molecule and swelling will increase progressively in water, controlling the penetration of the latter in the complex and hence opposing the rapid release of the drug. The counterbalancing moiety of the molecule i.e. sodium may have different although small contribution on polymer hydration in the microvicinity of the gel matrix[2]. It was noted that increasing the ratio of pectin in the complexes resulted in increased retardation of drug release in water (Table 1).

The larger concentration of pectin will form a more resistant gelatinous layer to water penetration, drug diffusion and hence release. When the time needed for 50% release was plotted against the quantity of pectin, an almost straight line was obtained with the slope values of 46.5 min and 32.7 min for complexes prepared by physical mixture and solvent deposition respectively. The

TABLE 2: DRUG CONTENT AND RELEASE CHARACTERISTICS OF MICROCAPSULES

Formulations	Core	Core:Coat	Drug content (mg)	Per cent Drug Released			n
				0.25 h	5th h	12th h	
M_1	S_2	1:1	14.37	21.32	78.12	96.91	0.29
M_2	S_2	1:2	9.71	11.02	70.79	91.79	0.36
M_3	S_2	1:3	7.19	9.81	49.35	81.83	0.47
M_4	S_3	1:1	10.53	18.91	76.63	96.85	0.31
M_5	S_3	1:2	7.10	9.91	59.12	89.94	0.52
M_6	S_3	1:3	5.20	8.75	45.21	74.89	0.49
M_7	DS	1:1	43.80	25.14	82.45	99.12	0.21
M_8	DS	1:2	28.93	12.15	60.12	98.82	0.41
M_9	DS	1:3	22.93	10.02	54.53	82.94	0.43
MP	-	-	-	12.11	70.11	94.54	0.33

M= Microencapsulation. S= Solvent deposition. DS= Diclofenac sodium. MP= Marketed product. n=Diffusion exponent related to mechanism of drug release,according to eq^n $M_t/M_\infty=Kt^n$. 100 mg of samples were analysed.

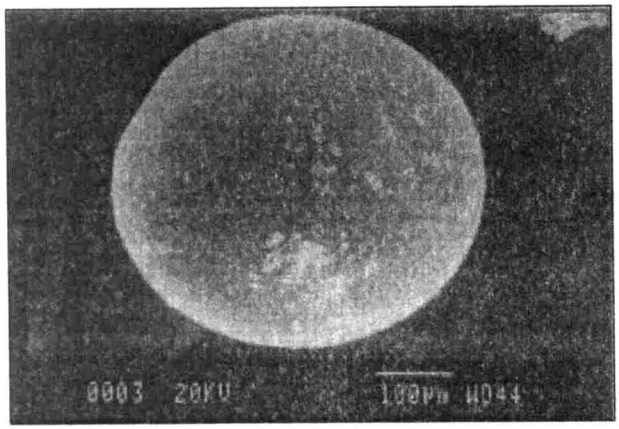

Fig. 1: SEM Photograph of microcapsules of diclofenac sodium encapsulated with ethylcellulose

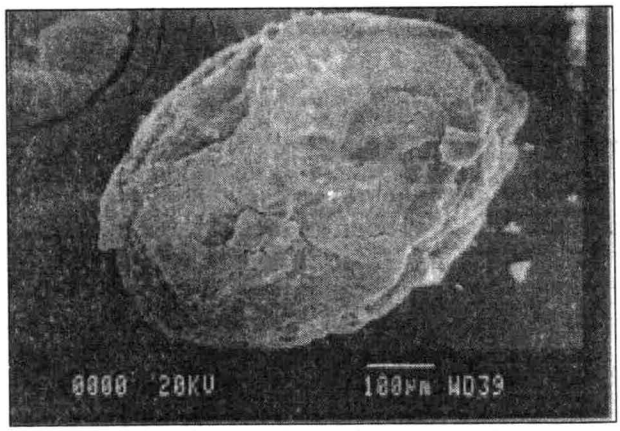

Fig. 2: SEM Photograph of microcapsules of diclofenac sodium–Pectin complex encapsulated with ethylcellulose

magnitude of the slopes were much higher, indicating that, the differences in dissolution rates are consistent with the amounts of pectin added.[2] This slope value also suggests that a major role is played by the pH of the diffusion layer on drug solubility in this layer, with a correspondingly decreased concentration gradient and dissolution.

Concerning the method of preparation of complex, it was noticed that the release of anionic diclofenac sodium from solvent deposition system was much superior than that from the physical mixture. This may result from the fact that the drug, which is deposited on the surface of pectin, will be easily removed in water due to repulsion between the negative charges on both the drug and the polymer. The presence of the drug finely dispersed on the surface of pectin may render its exposure

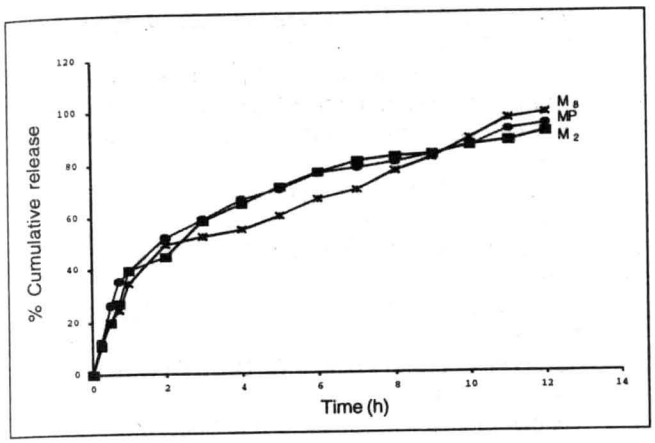

Fig. 3: Release profile of diclofenac sodium in distilled water

M_8=Microcapsules containing pure diclofenac sodium as a core and ethylcellulose as a coating material. MP= Marketed timed release product. M_2= Microcapsules containing diclofenac sodium-pectin solvent deposited complex in the ratio of 1:2 as a core and ethylcellulose as coating material.

to the dissolution medium much easier than in the case of the physical mixture, outweighing the pH effect in the diffusion layer formed of hydrated pectin.[2]

The complexes prepared by physical mixture sustained the drug release sufficiently when compared with that of solvent deposition. If the complexes prepared by physical mixture are given orally as such, may produce gastric irritation, so to prevent this, coating is essential. But it is not possible to coat the physical mixtures because as such it has given sustained release for longer period of time and coating to this may further retard the drug release. Solvent deposited products have sustained the drug release to some extent when compared with physical mixture products. Hence the complex prepared by solvent deposition can be microencapsulated with ethylcellulose to further delay the drug release and to prevent the gastric irritation.[5] The selection of the core material for microencapsulation was made by keeping in view that the quantity of microcapsules equivalent to 100 mg of diclofenac sodium would not be very large which would not be suitable for making formulations such as tablets and capsules.

From Table 2, it is very clear that the sustained action of the drug increases as the polymer (EC) ratio in the microcapsule increases. The high release rate from

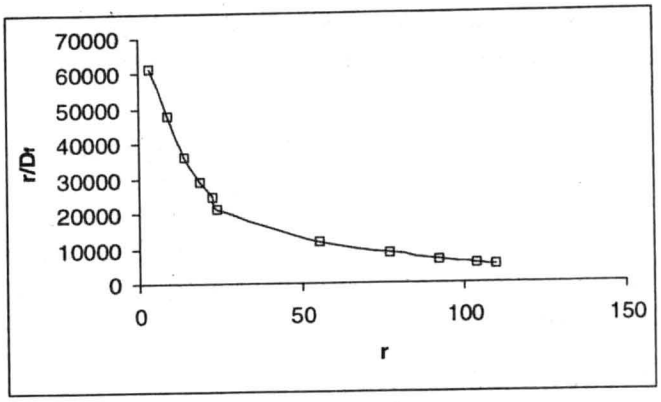

Fig. 4: Scatchard plot

Scatchard plot is r/D_f versus r according to eq^n $r / D_f = kn - kr$ where D_f = Molar concentration of free drug, r= Molar ratio of bound drug to total polymer, n= Number of binding sites and k = Binding constants

the microcapsules of 1:1 of core to coat ratio could be attributed to the presence of uncoated core particles[10], since at this ratio the amount of ethylcellulose might be insufficient to coat all the core particles present as compared to lower ratios.[5]

The data from the release study of complexes and microcapsules were fitted in a Peppas equation[11] in order to understand the mode of drug release. The parameters of the equation are given in Table 1 and 2. All the formulations, including marketed product were best fitted in double log plot (Peppas equation) with the slope value less than 0.5 indicating Fickian release i.e., the mechanism of drug release is by diffusion with obeying the Ficks law of diffusion. Fig. 3 shows the drug release profile of the microcapsules similar to the marketed product. The release profile shown by M_2 was better than M_8, this performance of M_2 might be because of binding of drug with pectin.

To confirm the occurrence of a binding between the drug and pectin, equilibrium dialysis studies were performed. The results of the dialysis study were expressed in the form of Scatchard plot of known advantages.[12] The Scatchard plot as shown in Fig. 4 is not linear but exhibited a curvature indicating the existence of two classes of binding sites. The various parameters calculated by regression analysis are n_1 = 36.18 and n_2 = 151.48 and $K_1 = 18.65 \times 10^2\ M^{-1}$ and $K_2 = 1.22 \times 10^2\ M^{-1}$. Where, n_1 and n_2 are primary and secondary binding sites and K_1 and K_2 are primary and secondary binding constants. It

was observed that, the percentage of drug bound to pectin was decreased with an increase in the concentration of drug.

In conclusion, the solvent deposition technique may be used for complexation of sparingly and slightly water soluble drugs, and then, can be microencapsulated to sustain the action. On the other hand physical mixture can be used for complexation of freely water soluble drugs for sustaining the action.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. F.V. Manvi, Principal, K.L.E.S's College of Pharmacy, Belgaum, for providing the necessary facilities.

REFERENCES

1. Shohba Rani, K.N., Goundalkar, A.R. and Kalyani, P., **Indian J. Pharm. Sci.**, 1994, 56, 45.
2. Naggar, V.F., El-Khawas, M., Ismail, F. A., and Boraie, N.A., **STP. Pharm. Sci.**, 1992, 2, 227.
3. Madan, D. K. and Cadwallader, D.E., **J. Pharm. Sci.** 1970, 59, 1362.
4. Leung, A.Y. and Foster, S., In; Encyclopedia of common natural ingredients used in food, drugs and cosmetics, 2nd Edn., John Wiley and sons, Inc., New York, 1996, 413.
5. Hasan, M., Najib, N. and Suleiman, M., **Drug Dev. Ind. Pharm.**, 1992, 18, 1981.
6. Torres, D., Garcia-Encina, G. and Seijo, B., **Int. J. Pharm.**, 1995, 121, 239.
7. Chowdary, K. P. R. and Ramesh, K.V.R.N.S., **East. Pharm.**, 1994, 443, 127.
8. Sprockel, O. L. and Price, J. C., **Drug Dev. Ind. Pharm.**, 1990, 19, 361.
9. Garcia-Encina, G., Torres, D. and Seijo, B., **J. Control. Release.**, 1993, 23, 201.
10. Chemtob, C., Chaumeil, J. C. and Dongo, M., **Int. J. Pharm.**, 1986, 29, 1.
11. Ritger, P.L. and Peppas, N. A., **J. Control. Release.**, 1987, 5, 37.
12. Martin A., Swarbrick J. and Cammarata A., In; Physical pharmacy, Physical Chemical Principles in the Pharmaceutical Sciences, 3rd Edn., Lea and Febiger, Philadelphia, 1983, 335.