RESEARCH PAPER

Accepted 7 December 2001
Revised 21 November 2001
Received 24 May 2001
Indian J. Pharm. Sci., 2002, 64(2): 133-137

Design and Evaluation of a Multiparticulate System for Chronotherapeutic Delivery of Diclofenac Sodium

H. N. SHIVAKUMAR*, SARASIJA SURESH[1] AND S. VENKATARAM[2]
K.L.E.S's College of Pharmacy, Rajajinagar, Bangalore-560 010.
[1]Al-Ameen College of Pharmacy, Hosur Road, Bangalore-560 027.
[2]Recon Ltd., R & D Center, Bannerghatta Road, Bangalore-560 076.

An oral controlled onset dosage form intended to approximate the chronobiology of rheumatoid arthritis is proposed for colonic targeting. The multiparticulate system comprising of nonpareil seeds coated with a mixture of Eudragit S-100 and L100 was designed for chronotherapeutic delivery of diclofenac sodium. The drug was loaded onto non-pareil seeds by powder layering technique using the conventional coating pan. Different coat weights of non-aqueous based Eudragit dispersions were applied onto the drug-loaded pellets using a pilot type spray gun. *In vitro* dissolution tests of the coated pellets were performed in different pH media following pH progression method for a period of 12 h. The *in vitro* dissolution tests showed that the release of diclofenac sodium from the coated pellets depended on the pH of the dissolution fluid and the coat weights applied. All the formulations exhibited an initial lag period characterized by limited dissolution (5.49% to 10.83%) followed by rapid release of the drug. The high ratio of drug solubility relative to the dosing amount promoted rapid release of the drug after the lag period. The release kinetics of diclofenac sodium from the coated pellets in pH 7.4 buffer fitted well into Hixson-Crowell dissolution model.

Chronotherapeutics refers to a treatment method of synchronizing drug administration with biological rhythms to produce maximum health benefits and minimum harm[1]. A colon specific drug delivery system is a controlled onset system used to approximate the chronobiology of certain diseases states. This system could be of a particular value when a delay in systemic absorption is therapeutically desirable. The management of patients with rheumatoid arthritis and inflammation could be improved with such a device[2]. These diseases are affected by circadian rhythms. Symptoms of rheumatoid arthritis were found to be most intense when awaking from a nighttime sleep[3].

Diclofenac sodium, a non-steroidal antiinfammatory drug is frequently prescribed for long-term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis[4]. Gastrointestinal side effects such as bleeding, ulceration and perforation of intestinal wall are commonly seen when the drug is administered orally[4]. In order to eliminate these adverse effects, enteric-coated products[5] and sustained release products[6] are developed and commercialized.

Colon specific delivery can be achieved with a suitable mechanism that triggers off the release of the drug upon reaching the colon. Various approaches have been reported over the last decade to develop new methodologies for site-specific drug release to the colon including pH dependent release[7], time controlled release[8] and microbially controlled release[9]. Methods based on pH sensitive delivery such as enteric-coated dosage forms could be a simple and practical means for colon targeting. These methods are based on the polymers that are insoluble at low pH values but soluble at higher pH values. Several polymers particularly Eudragit

*For correspondence
e-mail: shivakumarhn@yahoo.co.in

S-100 and Eudragit L-100 have been investigated for colonic delivery[10]. A multiparticulate system presents several advantages in comparison to single units forms such as predictable gastric emptying and less local irritation[11]. Multiparticulates also minimize possible intestinal retention of indigestive polymeric material upon chronic administration[12].

With the above considerations in mind, a multiparticulate controlled onset system based on pH-sensitive polymers was designed using the conventional pan-coating technique to deliver a drug to the colon in response to circadian rhythms.

MATERIALS AND METHODS

Diclofenac sodium, Eudragit S-100 and L-100 and nonpareil seeds were generously donated by Recon Ltd., Bangalore. The rest of the chemicals of analytical grade were obtained from S. D. Fine Chemicals, Mumbai and were used as received. These include purified talc, isopropyl alcohol, PVP-K-30, PEG-6000, maize starch, sodium hydroxide, potassium dihydrogen phosphate, disodium hydrogen orthophosphate, hydrochloric acid and glacial acetic acid.

Preparation of drug loaded pellets:

Diclofenac sodium was loaded onto NPS by powder layering technique. A definite quantity of NPS (# 24/30) was charged into a conventional coating pan of 12" diameter. (Sams Machine Tools, India). The mixture of diclofenac sodium, maize starch and purified talc was milled, passed through sieve # 100 and dusted on to NPS using 10% solution of PVPK-30 in isopropyl alcohol (IPA) as binder solution. A pilot type spray gun (Bullows 630) fitted with a 1 mm atomizing nozzle was used to spray the solution. The detailed processing conditions are given in Table 1. The drug-loaded pellets were dried at temperature of 45° for a period of 1 h.

Film coating of the drug-loaded pellets:

As the study aimed at developing a controlled onset system to provide a site specific release to the colon, a preformulation study was undertaken to design a physical mixture of Eudragit L-100 and S-100 having a threshold pH similar to that existing in the proximal colon[13] (pH 6.8). Eudragit L-100 (soluble at pH 6 and above) and S-100 (soluble at pH 7 and above) were physically mixed in different ratios (1:1, 1:2, 1:3 and 1:4) and the resulting mixtures were subjected to solubility studies. The studies revealed that the physical mixture of Eudragit L-100 and S-100 in a ratio of 1:2 had good solubility at pH 6.8 and above. The studies also indicated the mixture bearing the ratio of 1:1 had a threshold pH of 6.5, whereas the other mixtures (1:3 and 1:4) were not soluble at pH 6.8. Hence the physical mixture of the ratio 1:2 of L-100 and S-100 was used for preparing the coating dispersion.

The coating dispersion was prepared by dissolving PEG-6000 in IPA. Purified talc was screened through sieve #100 before addition to the solution. A homogenous suspension was maintained by stirring at a low speed using a variable speed propeller stirrer (Remi Udyog, Mumbai), then the mixture of Eudragit S-100 and L-100 was added. The dispersion was adjusted to have 6.25% w/w of the polymer content by dilution with IPA. The dispersion was stirred for 30 min before coating as well as throughout the coating process.

A # 22/24 fraction of diclofenac-loaded pellets was charged into the same coating pan. The coating dispersion was sprayed on the surface of the drug-loaded pellets under the processing conditions mentioned in Table 2 till 2%, 4%, 6% and 8% of the theoretical weight gain was achieved. The pellets passing through sieve #14 and retained on sieve #18 were used for further studies.

Evaluation of the coated pellets:

Morphology and appearance of the pellets were examined by scanning electron microscopy (SEM-JEOL, JSM-840A, Japan). The cross sections of the pellets were mounted directly onto the SEM sample stab, using double sided sticking tape and coated with gold film (200 nm thick) under reduced pressure (0.00 1 torr) to improve the conductivity. In order to check the integrity of the drug in the formulations[14], IR spectra of the drug and the pellets were obtained and compared using FTIR spectrophotometer (FTIR-8201 PC, Shimadzu corporation, Japan) using potassium bromide pellet method.

Estimation of diclofenac sodium:

Weighed quantity of the pellets were carefully transferred into a volumetric flask and diluted to 100 ml with buffer of pH 7.4 and allowed to equilibrate for a period of 24 h. There after the samples were filtered through a Millipore filter (0.22 µm) and assayed using Jasco V-530 UV/vis spectrophotometer against a reagent blank prepared using control pellets without the drug. Three replicate experiments were performed.

In vitro dissolution studies:

Dissolution tests were performed using USP XXIII Dissolution Test Apparatus-I (ElectrolabTDT-06T) following pH progression method simulating the gastrointestinal tract condition[15]. A definite weighed quantity of the pellets was loaded into the basket of the dissolution apparatus. The pH changes were performed starting with 900 ml of hydrochloric acid buffer of pH 1.2 for 2 h, acetate buffer of pH 4 for 1 h, mixed phosphate buffer of pH 5.5 for 1 h, phosphate buffer of pH 6.8 for 1 h followed by phosphate buffer of pH 7.4 till the end of the test. The temperature through out was maintained at 37±0.5° with stirring speed of 50 rpm. The samples were drawn every h and filtered through a Millipore filter (0.22 µm) and assayed spectrophotometrically at 273 nm for samples with pH 1.2 and at 276 nm for other samples using the same instrument. Dissolution studies were performed in triplicates for each batch of pellets.

RESULTS AND DISCUSSION

SEM photograph of the pellet with 8% weight gain in cross sectional view is shown in Fig. 1. The applied film appears to be continuous and uniform. The IR spectra of diclofenac sodium and its pellets were found to be identical. The principal IR absorption peaks of the drug at 3400 cm^{-1} (N-H stretching of secondary amine), 1560 cm^{-1} (C=0 carboxylate), 1580 cm^{-1} (bending of secondary amine) and 780 cm^{-1} (1,2,3 trisubstituted benzene) 760 cm^{-1} (C-Cl) were all obtained in the spectra of the pure drug as well as the pellets indicating no chemical interaction between the drug and the excipients used.

The theoretical content of diclofenac sodium was found to be 18.24% w/w of the coated pellets. All the investigated

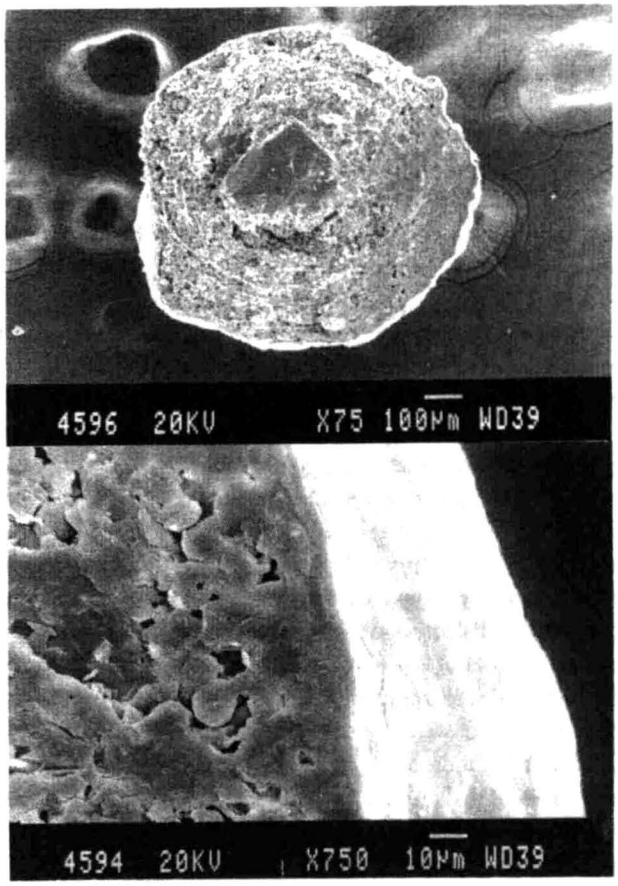

Fig. 1: Cross section of diclofenac sodium pellets coated with Eudragits.

Cross section of pellet of diclofenac sodium coated with Eudragit dispersions (8 % weight gain) as revealed under scanning electron microscope.

TABLE 1: PROCESSING CONDITIONS FOR DRUG LOADING.

Core	Dusting powder composition (g)		Binder solution (10% w/w)	Processing conditions	
Non-pareil Seeds # 24/30 (500 g)	Diclofenac sodium Maize starch Purified talc	300 300 200	PVP-K-30 (100 g) in IPA	Batch size Inlet air temperature Spray rate (ml/min) Dusting rate (g/min) Spray nozzle diameter Spray pressure Pan rotation speed Pan angle	1300g 45-50° 5-10 5-10 1mm 4 kg/cm^2 15 rpm 45°

The composition of the core material along with the processing conditions for loading of diclofenac sodium onto non pareil seeds by powder layering technique.

batches of pellets had acceptable drug content.

The dissolution profiles of pellets with different coat weights are shown in fig. 2. It was seen that the drug release from the coated pellets depended on the pH of the dissolution fluid as well as the coat weights applied. All the curves exhibited an initial lag period charecterised by limited dissolution (5.49% to 10.83%) followed by rapid release of the drug. The *in vitro* lag periods for different formulations were derived by extrapolating the linear portion of the plots to the time axis, (cumulative % release vs time plots) as reported in literature[16]. The *in vitro* lag periods for the formulations were found to range between 3.5 and 4.0 h. The slow release of the drug during the lag period could be attributed to the semi-permeable nature of the pH sensitive polymers used. Both Eudragit L-100 and S-l00 are pH sensitive polymers with a threshold pH of 6.0 and 7.0, respectively. The mixture of the two in a ratio of 1:2 had resulted in a coat having a threshold pH of 6.8 which is evident as a rapid release phase (burst effect) caused by dissolution of the coat and release of the drug when the pellets were exposed to a pH of 6.8. The burst effect could be attributed to certain extent to the pKa (4.0) value of the drug, It has to be noted that the solubiity of diclofenac is pH dependent and the solubility increases rapidly at pH values higher than the pK_a value of the drug. It has been established that the rapid release phase is observed only with drugs possessing a high solubility at the given pH value.[17]

An amount of 50.9, 42.5, 37.3 and 30% of the drug was released from the pellets with 2%, 4%, 6% and 8% weight gain respectively after 5 h. The results proved that there existed a rank order correlation between the amount of drug released at the end of fifth hour and the coat weights. It was observed that in case of pellets with 8% weight gain the burst effect was minimized and the drug was released in a more progressive manner. This may be due to increased coat weight applied when compared to other pellets. The rapid release phase was known to precede the slow release phase.

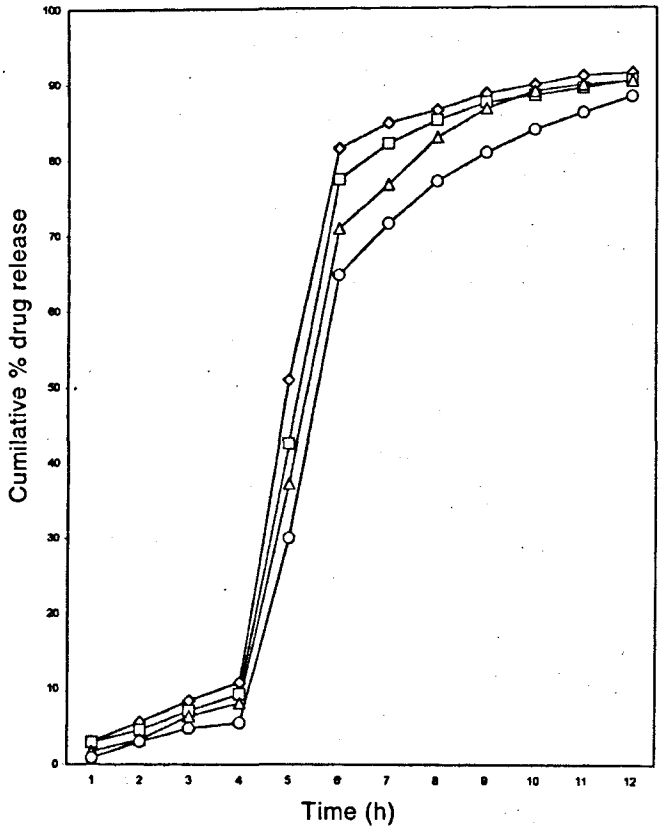

Fig. 2: *In vitro* release of diclofenac sodium from Eudragit coated pellets.

Diclofenac sodium release from coated pellets with 2% weight gain (◇), 4% weight gain (□), 6% weight gain (△) and 8% weight gain (O) respectively.

TABLE 2: PROCESSING CONDITION FOR ACRYLIC COATING.

Composition of polymeric dispersion (% w/w)		Processing conditions	
Eudragit S-100	4.166	Batch size	300 g
Eudragit L-100	2.084	Inlet air temperature	35-45°
PEG-6000	0.5	Exhaust air temperature	25-30°
Purified talc	6.0	Spray rate (ml/mm)	5-10
IPA	Q.S	Spray nozzle diameter	1 mm
		Spray pressure	4 Kg/cm²
		Pan rotation speed	15 rpm
		Pan angle	45°

The composition of the coating material along with the processing conditions for acrylic coating of diclofenac sodium loaded non pareil seeds.

The release kinetics of diclofenac sodium in pH 7.4 buffer was treated according to Hixson-Crowell equation[18]. The rate kinetics was found to be linear with regression coefficient values of 0.982, 0.974, 0.965 and 0.993 for pellets with 2%, 4%, 6% and 8% weight gain respectively. The cube root dissolution rate constants were calculated from the slope of the ($M_0^{1/3}$-$M^{1/3}$) vs time plots and were found to be 0.0056, 0.0063, 0.0091 and 0.0094 $g^{1/3}$/h respectively in increasing order of weight gain.

The results collectively indicate that it is possible to device a multiparticulate controlled onset system comprising of NPS coated with pH dependent polymers using conventional pan-coating technique for site-specific delivery to the terminal ileum and the proximal colon in response to circadian rhythms. Administration of such a dosage form before bedtime may prove to be valuable to patients with rheumatoid arthritis.

ACKNOWLEDGEMENTS

The authors would like to thank Prof. B. G. Shivananda, Principal, Al-Ameen College of Pharmacy for kind support and Prof. B. G. Desai, Principal, K.L.E.S's College of Pharmacy for providing the facilities for carrying out the present research work. The authors would also like to thanks Mr. Mahesh B. K., Srinivas S. and Chandra Shekar A. K. M. from Recon Healthcare. Bangalore for their timely help during the research work.

REFERENCES

1. Traynor, K., Newton, N.W., Hrushesky, W.J. and Reiter, R.J., **Amer. Pharm,** 1992, NS 32, 77.
2. Kinget, R., Willbrord, K., Leisbeth, V. and Guy, M., **J. Drug Targetting,** 1999, 6, 129.
3. Smolensky, M.H. and Gaston, L., **Pharmaceutical News,** 1997, 6, 10.
4. Todd, P.A., and Sorkin, E.M., **Drugs,** 1988, 35, 244.
5. Lin, S. and Kao, Y.H., **Pharm. Res.,** 1991, 8, 919.
6. Lin, L., Lin, S., Ng, S., Froix, M., Ohmo, T. and Heller, J., **J. Control. Release,** 1997, 43, 65.
7. Peeters, R and Kinget, R., **Int. J. Pharm.,** 1993, 94, 125.
8. Ishibashi, T., Pitcairn, G.R., Yoshino, H., Mizobe, M. and Wilding, I.R., **J. Pharm. Sci.,** 1998, 87, 531.
9. Ashford, M., Fell, J.T., Attwood, D., Sharma, H. and Woodhead, P.J., **J. Control Release,** 1994, 30, 225.
10. Dew, M.S., Hugles, P.J., Lee, M.G., Evans, B.K., and Rhodes, J., **J. Clin. Pharm.,** 1985, 14, 405.
11. Kramer, J., Blume, H., In; Ghebre-Sellasie, Y., Eds., Multiparticulate Oral Drug delivery, Marcel Dekker, New York, 1994, 307.
12. Follonier. N., and Doelker. E., **STP. Pharma. Sci.,** 1992, 2, 141.
13. Evans, D.F., Pye, G., Bramley, R., Clark, A.G., and Dyson. T.J., **Gut,** 1988, 29, 1035.
14. Chowdary, K.P.R. and Girija Sankar, G., **Drug Develop. Ind. Pharm.,** 1997, 3, 325.
15. Rodrigiez, M., Jose, L., Vila, J., and Dolores, T., **J. Control Release,** 1998, 55, 67.
16. Ashford, M., Fell, J.T., Attwood, D., and Woodhead, P.J., **Int. J. Pharm.,** 1993, 91, 241.
17. Ching, Cheng. K., Shou Chiung Chen. and Ming Thau, S., **J. Control. Release,** 1997, 44, 263.
18. Martin, A., Bustamante, P. and Chun, A.H.C., In; Physical Pharmacy, 4th Edn., A Waverly Pvt. Ltd., New Delhi, 1994, 333.