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Development of a novel floating pulsatile system for chronotherapeutic release of diclofenac sodium

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Abstract

The main objective of the present study was to develop a multiple-unit, floating-pulsatile drug delivery system for obtaining no drug release during floating and in the proximal small intestine followed by pulsed, rapid drug release in distal small intestine to achieve chronotherapeutic release of diclofenac sodium for treatment of rheumatoid arthritis. The system developed consists of drug containing core pellets prepared by extrusion-spheronization process, which were coated with an inner pH-dependent layer of Eudragit S100 and outer effervescent layer of sodium bicarbonate and HPMC K100M (Hydroxypropyl methylcellulose- K100M; HPMC; Methocel K100M premium, Colorcon Asia Pvt. Ltd., India). Developed formulations were evaluated for particle size analysis, friability, scanning electron microscopy, *in vitro* buoyancy studies and *in vitro* drug release studies.

Outer effervescent layer prolongs the gastric residence time and inner layer prevents the drug release in acidic medium. Pellets showed instantaneous floating with no drug release in acidic medium followed by pulsed drug release in basic medium. Concentration of HPMC K100M and layering level of effervescent agent significantly affected performance of pellets. The system showed excellent lag phase followed by burst release in the distal small intestine which gives site and time specific delivery of diclofenac sodium which could serve in the chronotherapy of rheumatoid arthritis.

Keywords: Floating-pulsatile drug delivery; Chronotherapy; Diclofenac sodium; Rheumatoid arthritis

Introduction

Chronopharmaceutics, the drug delivery based on circadian rhythm is recently gaining much attention worldwide. Various diseases like asthma, hypertension, and arthritis show circadian variation, that demands time scheduled drug release for effective drug action (Lemmer, 1991). To follow this principle, one must have to design the dosage form so that it can be given at the convenient time, e.g. bed time for the above mentioned diseases with the drug release in the morning. For this, a pulsatile release profile, where the drug is released completely after a defined lag time, is advantageous. A pulsatile drug delivery that can be administered at bed time, which releases the incorporated active drug early in the morning would be a promising chronotherapeutic system. The majority of drugs are preferentially absorbed from the small intestine (Rouge *et al.*, 1996). It is also known

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that drug release at site of absorption can improve therapeutic efficacy of a given drug. This is particularly of importance for a drug delivery system that is meant for pulse release after a lag period of, say, 6-8 h following oral administration. The floating pulsatile concept was thus applied to increase the gastric residence of the dosage form having lag phase, followed by a burst release in the distal small intestine. A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug could be released in distal small intestine after a defined period of no drug release. Additionally, multiple unit dosage forms provide many relative advantages over single unit dosage forms such as predictable GI transit time, maximum drug absorption, and reduced inter- / intra-subject variability due to differences in gastric emptying rates. These contribute to greater product safety. When orally administering diclofenac sodium conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patients' incompliance of administration in the early morning to coordinate the rhythm of rheumatoid arthritis, due to rapid absorption of the conventional formulation. However, this floating pulsatile drug delivery was not only effective, but also more convenient for administration than the conventional formulation.

The main objective of the present study was to develop a multiple-unit, floating-pulsatile drug delivery system for obtaining no drug release during floating and in the proximal small intestine followed by pulsed drug release in the distal small intestine in order to achieve chronotherapeutic release of diclofenac, a non-steroidal anti-inflammatory drug, used successfully for the treatment of rheumatoid arthritis and other joint pains.

Experimental

Materials. Diclofenac sodium (CIPLA Ltd., Mumbai, India) was chosen as a model drug. Microcrystalline cellulose (Amrut Industrial Products, Thane, India) was used as a spheronizing agent. Eudragit S100 (Degussa India Pvt. Ltd., Mumbai, India) was used as enteric coating agent. Sodium bicarbonate (Qualigens Fine Chemicals, Mumbai, India) was used as an effervescent agent with HPMC K100 M (COLORCON Asia Pvt. Limited, India). PVP K-30 (Alpha chemicals laboratories, Mumbai, India) was used as a binder. All other reagents were of analytical grade.

Preparation of complete multiple unit system

Preparation of core pellets. Drug containing core pellets were prepared by extrusion spheronization process. The drug (Aceclofenac; 40%w/w) and the spheronizing agent (Microcrystalline cellulose; 60%w/w) were mixed in a tumbling mixer. Sufficient amount of distilled water was slowly added to the powder mixture to achieve a damp mass suitable for further extrusion spheronization process. The prepared mass was immediately passed through a radial basket extruder using 1mm diameter screen with the speed set at 15 rpm. The extrudate was then spheronized for 15 min at a rotation of 1800 rpm. The resultant pellets were dried at 50°C in a fluidized bed apparatus for 45 min.

Coating of the core pellets. The core pellets were coated with pH-sensitive layer of Eudragit S100 to achieve a weight gain of 10%. The coating solution was sprayed onto the core pellets in a fluid bed coater (Umang Pharmatech, Thane, India). The conditions for coating consisted of: pellet charge - 200 g, preheating temperature - 50°C, preheating time - 10 min., inlet temperature - 45°C, outlet temperature - 40°C, atomizing air pressure - 25 lb/in^2, spray rate- 3-4 ml/min. Pellets were dried in coating chamber for 30 minutes at 50°C. The coated pellets were subsequently layered with sodium bicarbonate and HPMC K100M using a Spheronizer (Umang Pharmatech, model S250). Sodium bicarbonate and HPMC K100M were sieved

through 200 μm sieve and then mixed. The mixture was again passed through the 200 μm sieve at a rate of 10-15 g/min. A 7% w/w aqueous solution of PVP K-30 was used as an adhesive solution. The ratios of sodium bicarbonate to HPMC K100M employed were 2:8, 5:5 and 8:2 w/w. The pellets were layered such that a weight gain of 10, 30, 50 and 70% was achieved (Table 1).

Evaluation of pellets and complete multiple unit system:

Particle size analysis and friability. Particle size distribution of pellets was evaluated by sieve analysis (Vibratory sieve shaker, Jayant Manufacturing co., Thane, India). Friability was determined as % weight loss after 200 revolutions of 10 g of pellets in a Friabilator (Roche, Campbell electronics, Mumbai, India).

Scanning electron microscopy. The cross section of dried coated pellets was mounted onto the stages prior to coating with gold to a thickness of about 30 nm under vacuum. The morphology of pellets was then observed under a scanning electron microscope – SEM (Model JSM 840, Jeol, Japan).

In vitro buoyancy studies. 25 pellets were placed in 500 ml 0.1 N HCl containing 0.02% w/v tween-80 under stirring rate of 100 rpm. Temperature of medium was maintained at 37.5±0.5°C. At hourly intervals, stirring was stopped for 2 min and the number of pellets that settled was counted manually.

In vitro Drug Release Studies. The dissolution studies of the pellets equivalent to 50mg of diclofenac sodium were performed using USP XXIII Type 1 dissolution test apparatus. Volume of dissolution medium was 900 ml with a stirring speed of 100 rpm and temperature of medium maintained at 37.5±0.5°C. These conditions were kept constant for all dissolution studies. The drug release study was carried out in 0.1 N HCl (pH 1.2) for time period equivalent to floating time which varied for each batch. Phosphate buffer, pH 6.4 and 7.4 was employed until complete release of drug occurred. Diclofenac sodium concentrations were determined by UV spectrophotometry at a wavelength of 273 and 277 nm, respectively, for pH 1.2 and for pH 6.4, pH 7.4. Percent drug dissolved at different time intervals were then calculated.

Results and Discussion

Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and their clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic-pituitary-adrenocortical axis (Crofford *et al.*, 1971; Cutolo *et al.*, 2003). Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with the peak pain and stiffness (Stehlin, 1997).

Formulation development. For the development of Floating-pulsatile systems, swelling properties of HPMC supported the system, reaching a lower density as long as the volume expansion was faster than the weight gain. Different grades of HPMC's were tried to get the maximum entrapment capacity of gas generated i.e. CO_2. It is observed that the high viscosity grade HPMC-K100M shows maximum gas entrapment capacity and hence was used in further studies.

Design of complete multiple unit system. Fig. 1 is a schematic representation of the complete multiple unit system. The system consisted of drug containing core pellets prepared by extrusion-spheronization process, coated with an inner pH-dependent layer of Eudragit S100 and outer effervescent layer of sodium bicarbonate and HPMC K100M. Upon contact with the gastric fluid, carbon dioxide was liberated via neutralization reaction with sodium bicarbonate and was entrapped in the hydrophilic polymeric

membrane of HPMC K100M. The system with a density less than 1.0 g/ml floated and maintained the buoyancy till the gas entrapped in the membrane is sufficient to maintain it. As the HPMC K100M dissolves in medium, the gas entrapped is released and after a particular time, the system settles down. Eudragit S100 coating dissolves at pH≥7 and complete release of drug occurred. Thus, outer effervescent layer prolongs the gastric residence time of the system and the inner layer prevents the drug release in stomach as well as in the proximal part of the small intestine.

Pellet characterization. The average size of drug containing core pellets was 1mm. The size of the layered pellets varied from 1.41-2.00 mm for different batches while SEM pictures of coated pellets showed the uniformity of the coating (Fig. 2).

Floating ability. Buoyancy of pellets is directly related to the performance of floating pulsatile drug delivery system since lag time for pellets is equivalent to their floating time and the proximal small intestinal (jejunal) transit time (i.e.2 hrs.). The system should float in a few minutes after contact with gastric fluid to prevent the dosage form transiting into the small intestine together with food (Sungthongjeen *et al.*, 2006). Floating property of pellets was studied by determining buoyancy and time required for sinking all the pellets under study. The surfactant was used in the medium to simulate surface tension of human gastric juice (35-50 mN/m^2) (Badve *et al.*, 2007). The pellets layered with effervescent agent of 10% weight gain do not float because of insufficient gas entrapment in the gellified hydrocolloid of HPMC K100M. In all the remaining batches, pellets floated within 1 min after exposure to 0.1N HCl. The floating ability of pellets was investigated with respect to amount of effervescent agent ($NaHCO_3$: HPMC K100M ratio) and the layering level (% weight gain). The prolonged floating time in pellets layered with lower amount of $NaHCO_3$ was attributed to higher amount of HPMC K100M which possessed higher entrapment capacity of the generated CO_2. As the layering level increases, floating time increases (Fig.3).

Table 1. Composition of outer effervescent layer of complete multiple unit system.

Formulation code	Sodium bicarbonate: HPMC K100M ratio	% weight gain
F1	2:8	10
F2	2:8	30
F3	2:8	50
F4	2:8	70
F5	5:5	10
F6	5:5	30
F7	5:5	50
F8	5:5	70
F9	8:2	10
F10	8:2	30
F11	8:2	50
F12	8:2	70

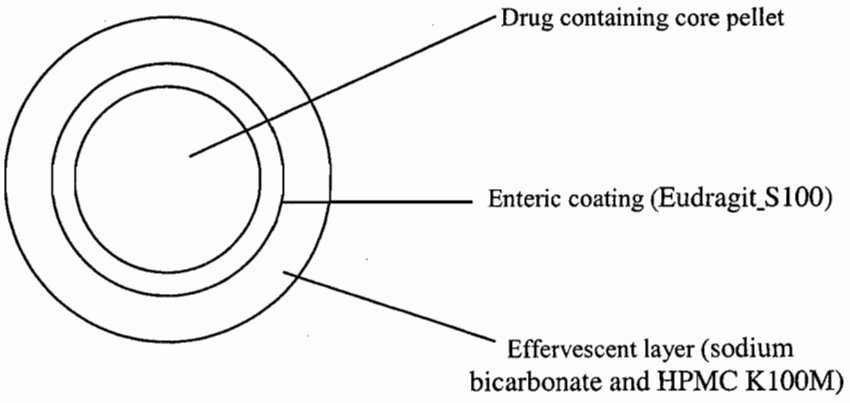

Fig 1. Schematic representation of complete multiple unit system

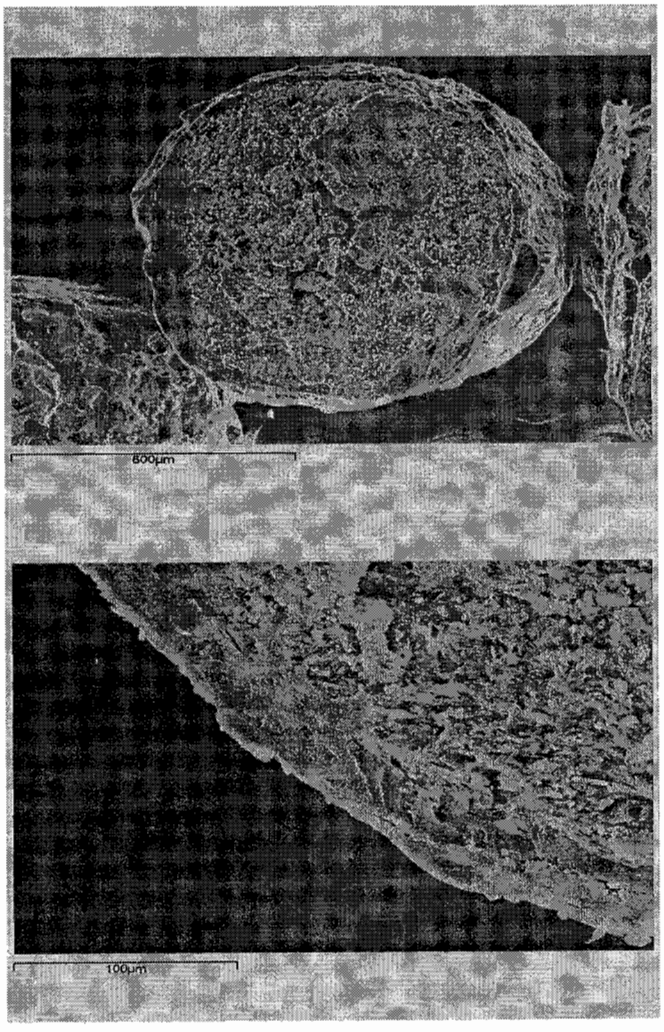

Fig 2. Scanning Electron Microscope picture of coated pellets.

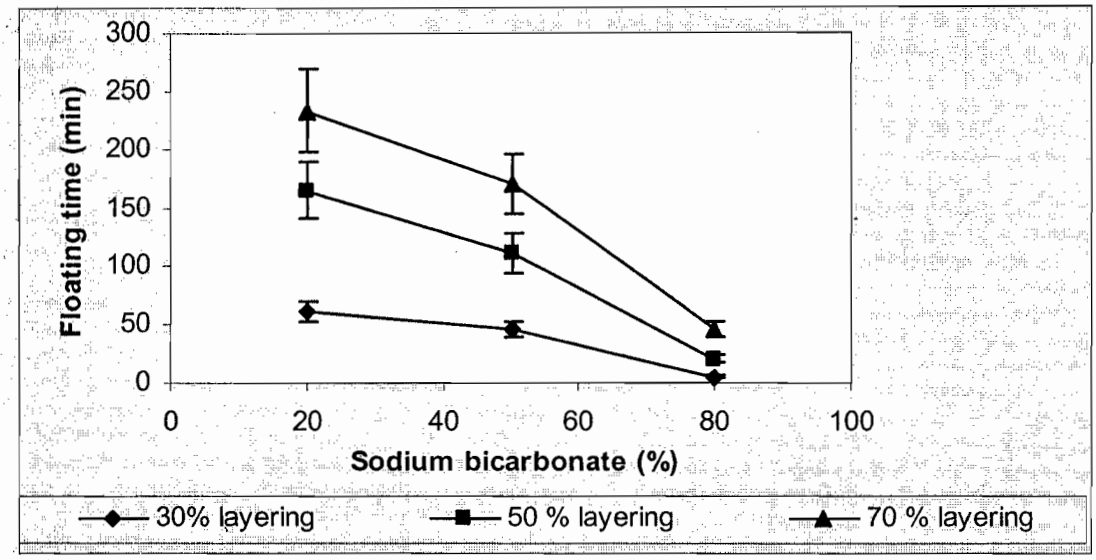

Fig.3. Effect of % $NaHCO_3$ layered onto the coated pellets on floating time of complete multiple unit system

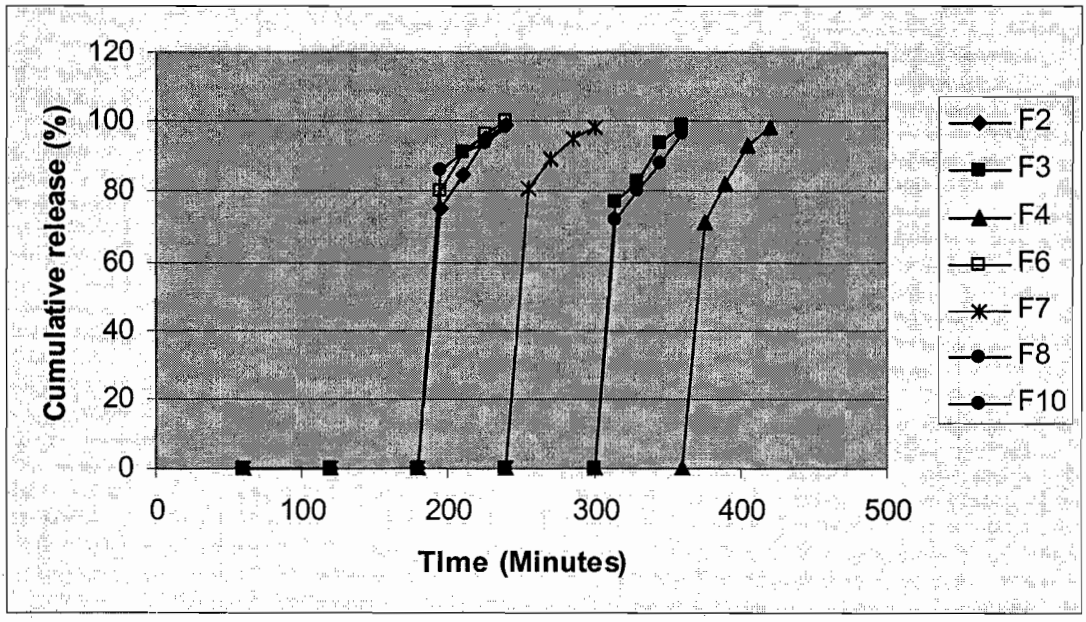

Fig. 4. Cumulative drug release profile.

In vitro drug release studies. To simulate the pH variation of GI tract dissolution studies were performed first in 0.1 N HCl pH 1.2 for time equivalent to floating time(rounded to full hour instead of fraction) and then 2 hours in phosphate buffer pH6.4 (jejunal transit time is 2 hrs.) and finally at phosphate buffer pH 7.4 till complete release of drug (Sharma and Pawar, 2006). Seven batches namely, F2, F3, F4, F6, F7, F8 and F10 were selected for

drug release studies. No release of diclofenac sodium was detected at pH1.2 as well as at pH 6.4. After this lag, complete drug was released within 1 hour in phosphate buffer pH 7.4 in which Eudragit S100 coating got dissolved (Fig. 4).

Conclusion

It is concluded that the formulations studied showed instantaneous floating with no drug release in acidic medium followed by pulsed drug release in alkaline medium. The concentration of HPMC K100M and layering level significantly affected performance of pellets. By altering the amount of these two components in the formulations, floating time of pellets could be controlled that ranged from 1-4 h. This approach is suggestive of the likely use of floating pulsatile pellets as a promising drug delivery system for site and time-dependent release of diclofenac sodium acting in the chronotherapy of rheumatoid arthritis.

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