

Novel Floating Pulsatile Approach for Chronotherapeutic Release of Indomethacin

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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 indomethacin. 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. 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 indomethacin acting as per chronotherapy of rheumatoid arthritis.

Key words: Floating-pulsatile drug delivery, Chronotherapeutic release, Indomethacin, Pellets, 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.¹ 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 but releases drug in early morning would be a promising chronotherapeutic system.

The majority of drugs are preferentially absorbed from the small intestine². Hence, drug release at site of better absorption can improve therapeutic efficacy of drug. This is of more concern for drug delivery that is meant for pulse drug release after a lag period of 6-8 h following oral administration of dosage form. 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 can be released in distal small intestine after a defined time 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,

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maximum drug absorption, reduced inter- and intra-subject variability due to differences in gastric emptying rates, thus greater product safety.

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 distal small intestine to achieve chronotherapeutic release of indomethacin for treatment of rheumatoid arthritis. Indomethacin is a low dose non-steroidal anti-inflammatory drug and is being used successfully for the treatment of rheumatoid arthritis and other joint pains; hence, was used as a model drug.

MATERIALS AND METHODS

Materials. Indomethacin was chosen as a model drug. Microcrystalline cellulose (Alpha chemicals laboratories) was used as a spheronizing agent. Eudragit S100 received as a free gift sample from Degussa Pharma, was used as enteric coating agent. Sodium bicarbonate (Qualigens Fine Chemicals, Mumbai) was used as an effervescent agent with HPMC K100 M (free gift sample from COLORCON Asia Pvt. Limited, India). PVP K-30 (Alpha chemicals laboratories) 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 (Indomethacin; 40% w/w) and the spheronizing agent (Microcrystalline cellulose; 60% w/w) were mixed in tumbling mixer. Sufficient amount of distilled water was slowly added in the powder mixture to achieve a consistency of the 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 in a spheronizer for 15 min at a rotation speed of 1800 rpm. The resultant pellets were dried at 50°C in a fluidized bed apparatus for 45 min.

Coating of the core pellet. 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). The conditions for coating were shown as follows: pellets charged- 200 g, Preheating temperature- 50 °C, Preheating time- 10 min, Inlet temperature- 45 °C, Outlet temperature- 40 °C, Atomizing air pressure- 25 lb/in², 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 effervescent layer of sodium bicarbonate and HPMC K100M using Spheronizer equipment (model S250, Umang Pharmatech). Sodium bicarbonate and HPMC K100M were sieved through 200 µm mesh sieve and then mixed. Afterwards, the obtained mixture was passed again through the 200 µm mesh sieve. The application rate of powder was between 10-15 g/min. An aqueous 7% w/w PVP K-30 solution was used as an adhesive solution. The ratios of sodium bicarbonate to HPMC K100M were 2:8, 5:5 and 8:2 w/w. The pellets were layered with an effervescent agent to achieve a weight gain of 10, 30, 50 and 70% as shown in Table 1.

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

Evaluation of the drug containing core pellets and the complete multiple unit system

Particle size analysis and friability. Particle size distribution of pellets were evaluated by sieve

analysis. Friability was determined as % weight loss after 200 revolutions of 10 g of pellets in a Friabilator.

Scanning electron microscopy. The cross section of dried coated pellets was mounted onto the stages prior to coating with gold to a thickness about 30 nm under vacuum. The morphology of pellets were then observed under SEM.

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 settled pellets was counted visually.

In vitro drug Rrelease studies. The dissolution studies of the pellets 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 was 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, later 2 hrs in phosphate buffer pH 6.4 and finally at phosphate buffer pH 7.4 till complete release of drug. Indomethacin concentrations were determined by UV

spectrophotometry at a wavelength of 320 nm. Percent drug dissolved at different time intervals were then calculated.

RESULTS AND DISCUSSION

Design of complete multiple unit system.

Figure 1 shows the design of 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 gas entrapped in the membrane is sufficient to maintain it. As the HPMC K100M dissolves in medium, the gas entrapped releases and after a particular time the system settles down. Eudragit S100 coating dissolves at $\text{pH} \geq 7$ and complete release of drug occurred. Thus, Outer effervescent layer prolongs the gastric residence time of system and inner layer prevents the drug release in stomach as well as in the proximal part of the small intestine.

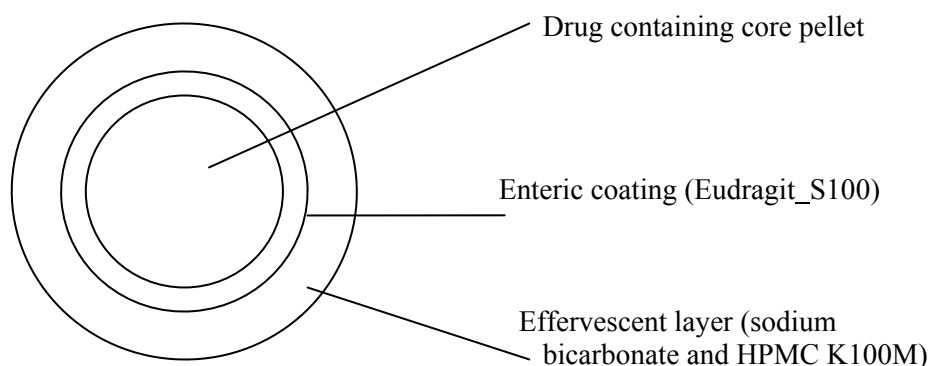


Fig 1. Design of complete multiple unit system (Not to scale)

Pellets characterization. The average size of drug containing core pellets was 1mm. The size of the layered pellets varied from 1.41-1.68 mm for

different batches. SEM pictures of coated pellet showed the uniformity of the coating (Figure 2).

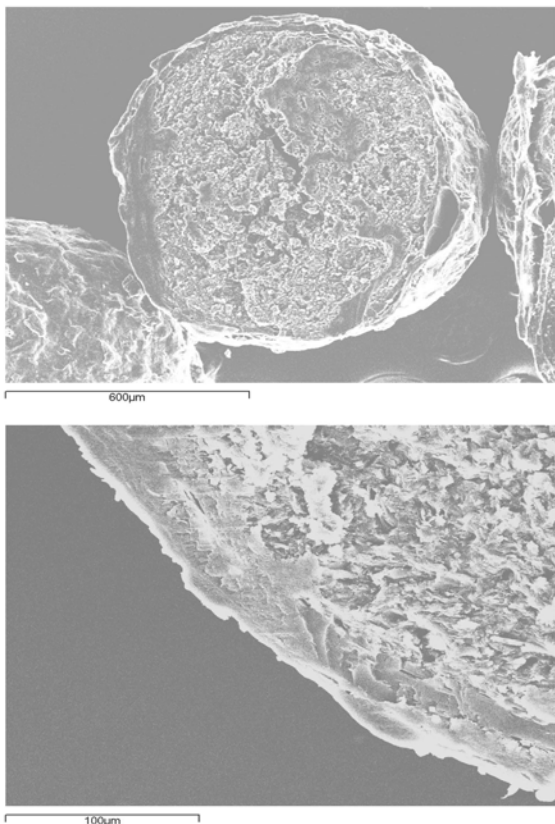


Fig 2. SEM picture of coated pellets (at 85 \times and 400 \times).

delivery system since lag time for pellets is equivalent to their floating time and 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 food³. Floating property of pellets were studied by determining buoyancy and time required for sinking all the pellets under study. The surfactant was used in medium to simulate surface tension of human gastric juice (35-50 mN/m²).⁴ 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 placing in 0.1N HCl. The floating ability of pellets were investigated with respected to amount of effervescent agent (NaHCO₃: HPMC K100M ratio) and the layering level (% weight gain). The prolonged floating time in pellets layered with lower amount of NaHCO₃ was attributed to higher amount of HPMC K100M which possessed higher entrapment capacity of the generated CO₂. As the layering level increases, floating time increases (Figure 3).

Floating ability. Buoyancy of pellets is directly related to performance of floating pulsatile drug

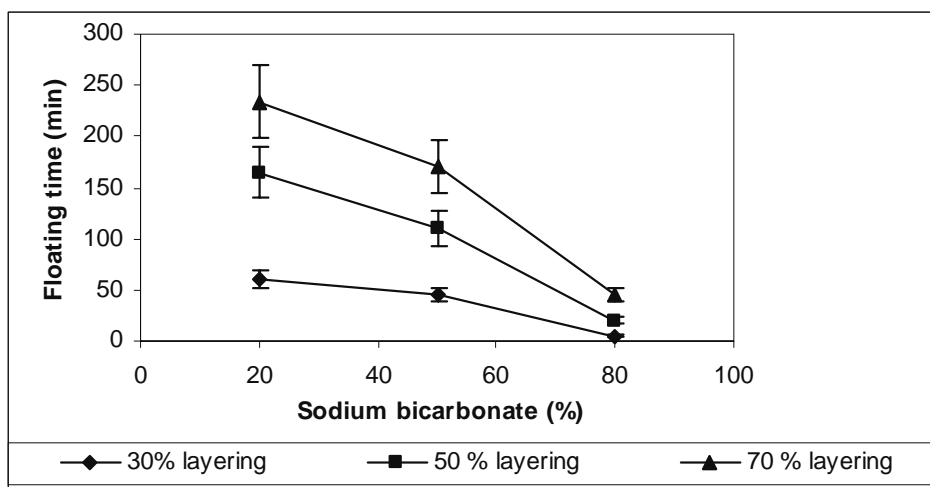


Fig.3. Effect of % NaHCO₃ layered onto the coated pellets and layering level of effervescent agent on floating time of complete multiple unit system

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 pH 6.4 (jejunal transit time is 2 hrs.) and finally at phosphate buffer pH 7.4 till complete release of drug⁵. No release of indomethacin was detected at pH 1.2 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 enteric coating of Eudragit S100 got dissolved (Figure 4).

It is concluded that developed formulations 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 significantly affected performance of pellets. By altering the amount of these two components in formulation floating time of pellets could be controlled ranging from 1-4 h. This approach suggested the use of floating pulsatile pellets as promising drug delivery for site and time specific release of indomethacin acting as per chronotherapy of rheumatoid arthritis.

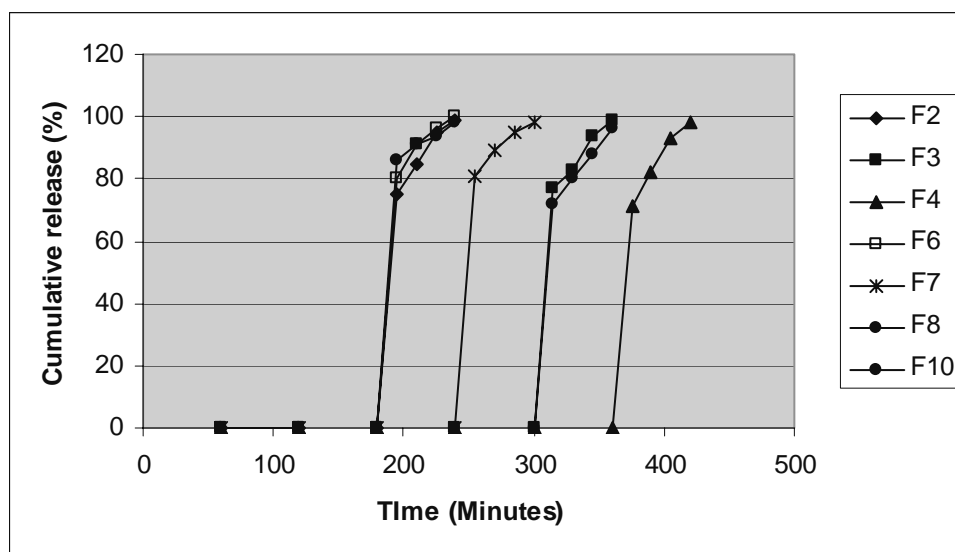


Fig. 4. Cumulative drug release profile.

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