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DEVELOPMENT OF MULTIPLE UNIT FLOATING-PULSATILE SITE SPECIFIC DRUG DELIVERY SYSTEM FOR CHRONOTHERAPEUTIC RELEASE OF ACECLOFENAC

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ABSTRACT

Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of diseases or symptoms.

We were prepared core pellets of Aceclofenac (40% w/w) by Extrusion spheronization process. These core pellets were coated with Eudragit S100 and analyzed for their floating ability and in vitro drug release. Developed formulations showed instantaneous floating ability with no drug release in acidic medium.

Introduction

Recent studies in the area of oral controlled drug delivery include novel approaches, which prolong the GRT and Chronotherapeutic delivery system which release the drug in a pulsatile fashion, is recently gaining much attention worldwide. Pulsatile drug delivery system are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time[1].

Various diseases like asthma, hypertension, and arthritis show circadian variation, that demand time scheduled drug release for effective drug action for example inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day. Result of several epidemiological studies demonstrates the elevated risk of several pathologies during a 24 h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Ischemic disease such as angina pectoris and myocardial infarction, and manifested more frequently during these times. Blood pressure which arises notably just before waking up is usually responsible for these attacks. Aceclofenac was chosen as a model drug, which is effective for preventing the time related occurrence of rheumatoid arthritis and osteoarthritis.[2] Aceclofenac was widely accepted as a NSAID agent.[3] So Aceclofenac is a typical example of drug, which is used in the therapy of symptoms or disease as described. However for such cases, conventional drug delivery system are inappropriate for the delivery of Aceclofenac, as they cannot be administered just before the symptoms are worsened, because during this time patient are asleep.[4,5]

To follow this principle one must have to design the dosage forms so that it can be given at the convenient time for example bed time for the above mentioned diseases with the drug release in the morning. Using current release technology, it is possible for many drugs oral delivery for a pulsed or pulsatile release, which is defined as the rapid and transient release of a certain amount of drug within a short time-period immediately after a predetermined off-release period. Chronotherapeutical devices based on multiphase drug release were achieved by using a three layer tablet while similar devices were also developed. Time controlled coating system was also developed including single and multiple unit dosage forms [6]. The concept of the multiple unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates, which include mini tablets, pellets and granules[7]. These systems provide flexibility during formulation development and gives therapeutic benefits to patients. A significant advantage of multiparticulates is that they can be divided into desired doses without making formulation or process changes. They can also be blended to deliver simultaneously incompatible bioactive agents or particles with different drug release properties. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release

profile does not depend on the drug release properties of a single unit[8].

Pellets offer advantages as they constitute multiple unit dosage forms, studies have indicated that they are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter- and intra-subject variability due to differences in gastric emptying rates[9-12]. Pellets can be filled into hard gelatin capsules or compressed into tablets, which rapidly disintegrate into multiple units. Multiple units include Pellets, Granules, Microcapsules, and Beads etc.

Materials:

Aceclofenac was chosen as a model drug (Gift sample from Unique Chemicals Division of J.B.Chemicals & Pharmaceuticals Ltd, Mumbai). 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, HPMC K4M, HPMC K15M (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.

Experimental methods:

a) Preparation of core pellets:

Drug containing core pellets were prepared by extrusion spheronization process. The drug (Aceclofenac; 40%w/w) and the spheronizing agent (Avicel® PH 101; 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 1-mm diameter screen with the speed 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 $\pm$ 1°C in a fluidized bed apparatus for 45 min.

b) 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 coated pellets were subsequently layered with effervescent layer of sodium bicarbonate and HPMC K100M by using PVP K30 as a binder. The ratios of sodium bicarbonate to HPMC K100M were 2:8, 5:5 and 8:2 w/w. The pellets are layered with an effervescent agent to achieve a weight gain of 10, 30, 50 and 70%.

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

The pellets were evaluated for particle size analysis, friability, surface morphology, floating ability and in-vitro drug release study. For floating study, 25 pellets were placed in 500 ml beaker containing 0.1 N HCl under stirring rate of 100 rpm. In-vitro studies were carried out in 0.1 N HCl (pH 1.2) till the pellets was in floating condition. After pellets are settled down, they are studied for further 1 hr. in 0.1 N HCl, subsequently 3 hours in pH 6.5 and finally at pH 7.4 till complete release occur. Aceclofenac concentrations were determined by UV spectrophotometry (V-550 Jasco) at a wavelength of 275 nm.

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

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

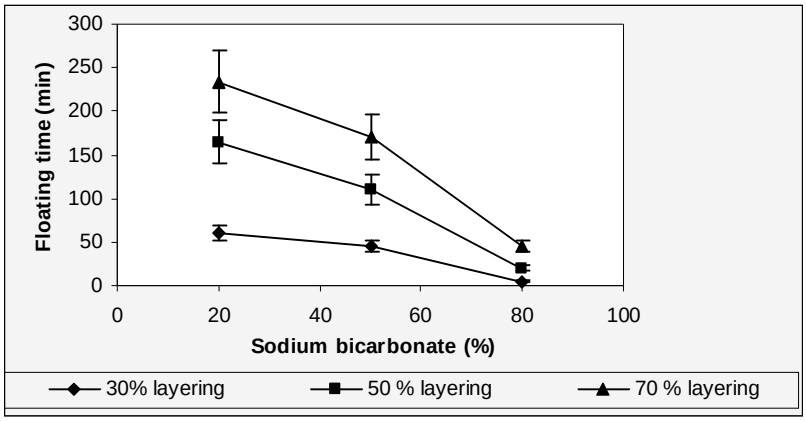

Figure 1. Effect of % $NaHCO_3$ layered onto the coated pellets and effect of % layering of effervescent agent on floating time of the complete multiple unit system.

Results and discussion:

The average size of drug containing core pellets was 1mm. Coated pellets showed narrow size distribution and the dominant size fraction of 1.68-2.00 mm. The surface of drug containing core pellets, coated pellets as well as complete multiple unit system were examined by SEM. Core pellets and effervescent layered pellets were spherical agglomerates with a slightly rough surface. The surface of coated pellet was slightly smoother.

Floating ability:

The pellets layered with effervescent agent of 10% weight gain do not floated because of insufficient gas entrapment in the gellified hydrocolloid of HPMC K100M. In all the remaining Batches (F1 to F9), pellets floated within 1 min after placed in 0.1N HCl. The floating ability of pellets were investigated with respected 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.

In-vitro drug release studies:

Of the Nine batches, seven batches namely, F1, F2, F3, F5, F6, F7 and F9 were selected for drug release studies. Less than 10 % release of aceclofenac 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 enteric coating of Eudragit S100 got dissolved

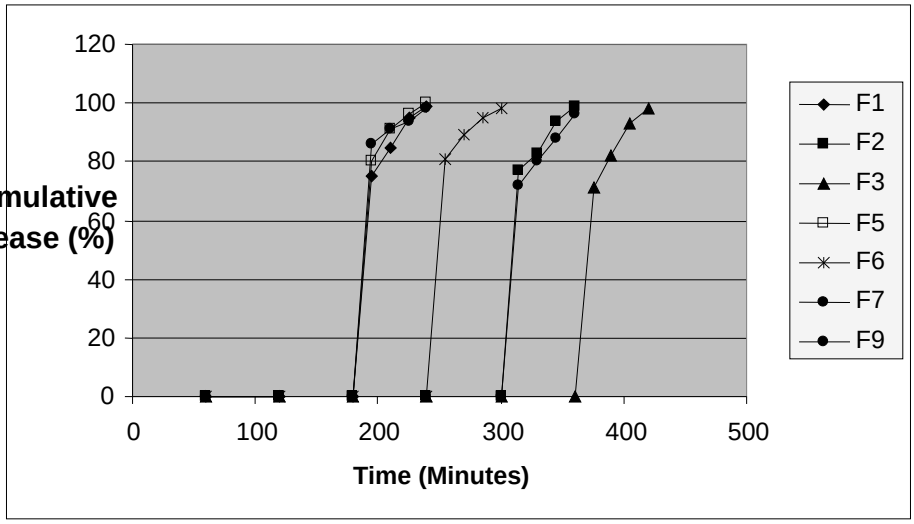

Figure 2. Cumulative % Drug Release Profile.

Aceclofenac was analyzed as per certificate of analysis and were found within the range of the given specification. Aceclofenac was characterized with the help of UV spectrophotometer, DSC and Infrared spectrophotometry. The ultraviolet spectrum of methanolic solution of aceclofenac was found to have λ_{max} of 275 nm which matches with given literature value.The thermogram of drug was characterized by single melting endotherm at 153.06 ^{0}C. Thus the DSC thermogram of the drug was found to be in agreement with the specification. The FTIR spectra of aceclofenac showed a characteristic –N-H Stretching at 3319.3 $cm^{-1,}$ Aromatic -C-H Stretching at 2937.4 $cm^{-1,}$ and $-COO^{-}$ Stretching at 1770.5 cm^{-1} Analysis of aceclofenac was carried out by UV spectrophotometric method. Standard plot of aceclofenac was prepared in methanol, pH 1.2 Buffer, pH 6.4 phosphate buffer and pH 7.4 phosphate buffer.

Standard curve of aceclofenac in methanol was used to determined drug content from the formulation, whereas standard plot of aceclofenac in pH 1.2 buffer, Buffer pH 6.4 phosphate buffer and pH 7.4 phosphate buffer were used to characterize in-vitro release of aceclofenac from the formulation in different medium.

Drug-Excipients compatibility studies were carried out. The possible interaction between the drug and the excipients was studied by DSC and IR spectroscopy. There was no considerable change in the DSC endotherm values when aceclofenac was mixed with excipients compared to that of pure aceclofenac. The results

revealed no considerable changes in the IR peaks of aceclofenac when mixed with excipients compared to pure aceclofenac.

The core pellets of aceclofenac were prepared using microcrystalline cellulose as diluent by extrusion spheronization method. Different ratios of drug: microcrystalline cellulose was taken for preparation of core pellets. Effect of moisture level, spheronization speed and time on physical properties of pellets were studied

The aceclofenac pellets was coated upto 5, 10, 15 and 20% weight gain. The coated pellets were then subjected to dissolution studies in pH 1.2 and 6.4 buffer. Data revealed that 10, 15 and 20 % coating levels had released < 10 % of aceclofenac in acidic buffer, complying with the official requirement for enteric coated dosage formulations. But, 15 % and 20 % coating fails to give immediate release in pH 7.4 buffer. Hence 10 % weight gain was selected as optimum coating level which not only give the enteric effect but also give immediate release in pH 7.4 buffer.

The coated pellets were subsequently layered with effervescent layer of sodium bicarbonate and HPMC K100M using Spheronizer equipment. 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%. The floating ability of pellets were 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.

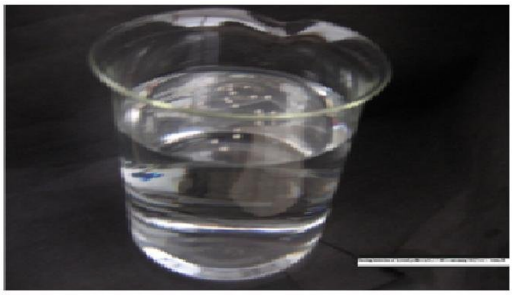

Figure 3. Floating behavior of layered pellets in 0.1 N HCl containing 0.02% w/v tween-80.

Developed Formulations were characterized for Drug content, Particle size analysis, friability, Shape analysis, Surface morphology, in- vitro buoyancy studies and In-vitro Drug Release Studies. Pellets have shown circularity factor of 0.912±0.032 and the aspect ratio of 1.121±0.092. This shows that pellets were of ideal shape for further processing. The dominant size fraction of drug containing core pellets was 0.84-1mm and that of the layered pellets was 1.41-2.00 mm for batch F13. The friability of the formulation was 0.08±0.02%. This indicated that the core pellets were quite hard and able to withstand the mechanical stresses of the subsequent process.

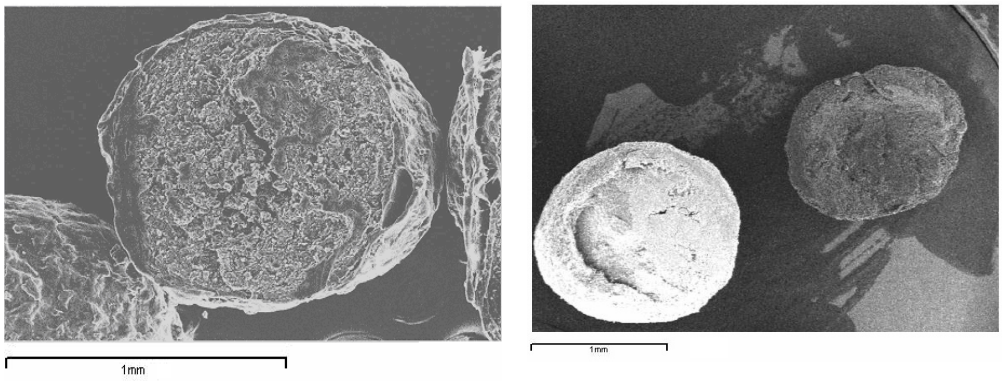

Figure 4. SEM pictures of pellets.

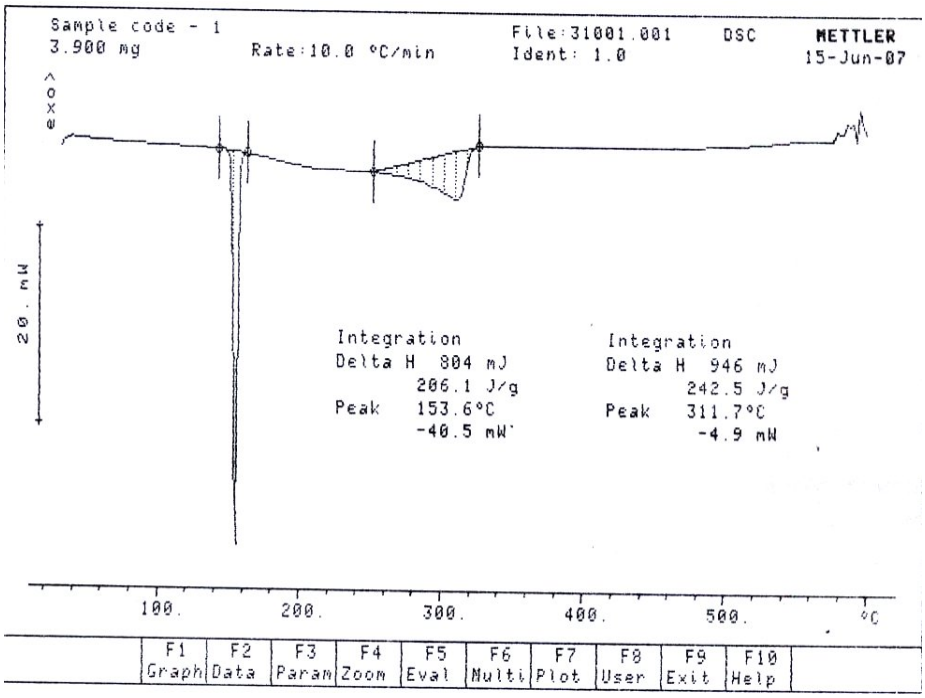

Figure 5. DSC scan of Aceclofenac

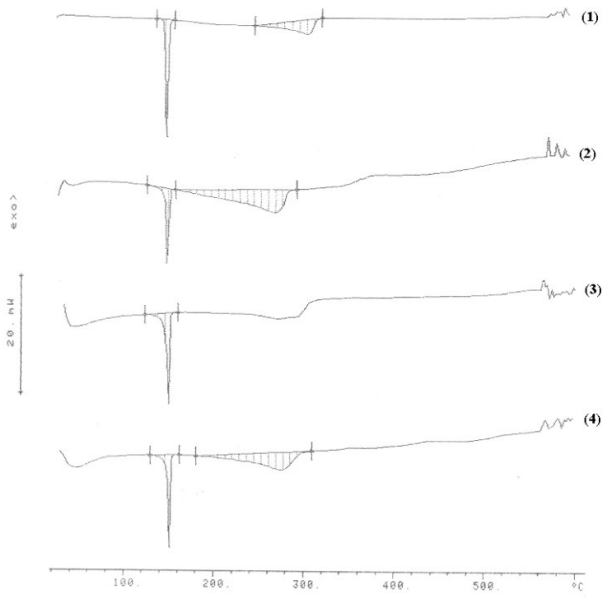

Figure 6. DSC Thermograms. (1) 153.6=A. (2) 152.0=A+MCC. (3) 153.5= A+ MCC+ PVP K30. (4) 152.8= A+ MCC+PVP K30+ Eudragit S100. A= Aceclofenac; MCC= Microcrystalline Cellulose.

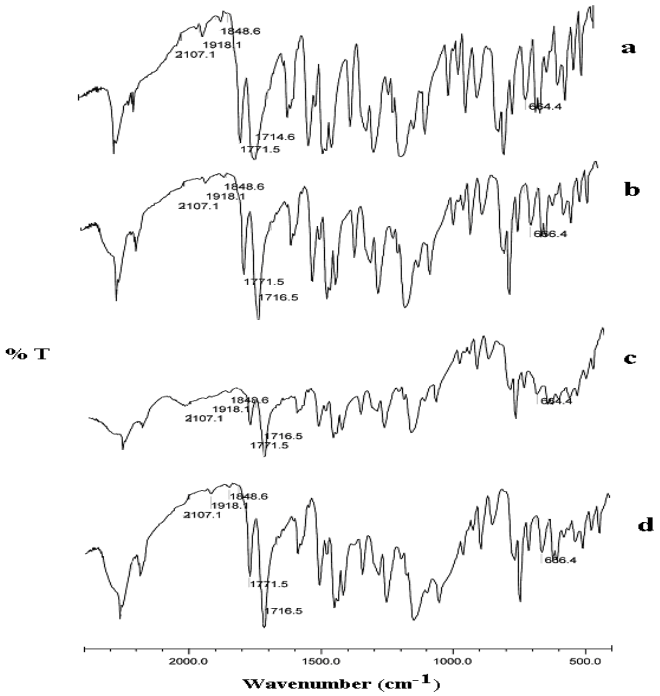

Figure 7. IR Spectra of aceclofenac and its physical mixtures with different excipients. a= A, b==A+MCC, c= A+ MCC+ PVP K30, d= A+ MCC+PVP K30+ Eudragit S100. A= Aceclofenac; MCC= Microcrystalline Cellulose.

Stability study for the optimized formulation batch was performed for a period of three months at room temperature and at accelerated conditions. The drug content and drug release was determined. From the above stability study it was observed that all three formulations were stable at 40^{o}C ± 2^{o}C / 75% RH ± 5% and 25^{o}C ± 2^{o}C /60% RH ± 5% for three months. Assay of the formulation was found to be within specified range. There was no degradation of Aceclofenac in all three formulations. All three formulations were found satisfactory with respect to physical appearance and drug release. All the three developed pellets showed no drug precipitation till 24 hr at room temperature and at 40^{o}C ± 2^{o}C / 75% RH ± 5%. Optimized pellets remain spherical and stable for 3 months at ambient temperature and at 40^{o}C ± 2^{o}C / 75% RH ± 5 %.

Conclusion:

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 aceclofenac acting as per chronotherapy of rheumatoid arthritis.

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