Design and evaluation of bilayer floating tablets of cefuroxime axetil for bimodal release

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Study aims to design a gastroretentive delivery system for bimodal release of cefuroxime axetil (CA). CA has site-specific absorption from upper gastrointestinal tract and in intestine it undergoes hydrolysis to cefuroxime having poor absorption. Unabsorbed drug causes high concentration of antibiotic entering colon and contributes to the side effects like colitis. Therefore, a gastro-retentive dosage form is required to ensure controlled drug delivery within drug-absorbable regions. Bilayer tablet, each layer containing half the dose of drug was formulated with one immediate release layer (IRL) and another floating matrix layer (FML). The FML showed good floating properties with buoyancy lag time of 12-35 min and floating time of 8-24 h. Thus, bimodal drug release comprising of immediate release for quick onset of action followed by controlled release minimizing the concentration of unabsorbed drug entering colon was achieved. No change in amorphous nature of drug during processing was observed, which was confirmed by differential scanning colorimeter and X-ray diffractometer. The γ-sintigraphy confirmed the gastric residence of tablets in human volunteers.

Keywords: Bimodal drug delivery, Cefuroxime axetil, Floating drug delivery system, Gastroretention

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Introduction

Gastrointestinal (GI) transit time is one of the several physiological limitations that must be controlled in the development of peroral modified release dosage forms¹. Hydrodynamically balanced system based on hydrophilic polymers is one of the floating systems, which on contact with the gastric fluids form a water impermeable colloidal gel barrier and attain bulk density (< 1). These systems not only prolong gastric residence but also do so in an area that could maximize the drug reaching its absorption site². To overcome limitation of controlled drug delivery system, attention have been focused towards developing drug delivery systems that are capable of releasing therapeutic agent at right site and on right time from pulsatile drug delivery systems³.

Multiparticulate floating-pulsatile drug delivery systems were developed in this laboratory using porous calcium silicate (Florite RE®) with sodium alginate⁴ and calcium pectinate⁵, for time and site-specific drug release of meloxicam and diclofenac sodium, respectively. Though the system is useful for drugs following chronopharmacology, its application for multiple pulses in upper GI tract will be very useful where quick onset of action followed by second pulse after a definite time period of no drug release is required.

Cefuroxime axetil (CA), a cephalosporin antibiotic, possesses 1-acetoxy-ethyl group that enhances absorption of cefuroxime from GI tract. But CA is rapidly hydrolyzed in intestine, releasing cefuroxime, which is poorly absorbed, thereby reducing its bioavailability (< 50%)⁶-¹⁰. Apart from other side effects due to high drug plasma levels, CA missing the absorption site in upper GI tract remains unabsorbed causing high concentration of antibiotic entering colon leading to antibiotic associated colitis¹¹,¹². Present research aims to design gastroretentive drug delivery system for CA that could give site specific and bimodal controlled drug release.

Materials and Methods

Materials

CA was gift sample from Lupin Research Park, Pune; hydroxypropyl methylcellulose K4M from
Preparation of Bilayer Tablets with Floating Matrix Layer

Bilayer tablets consist of floating matrix layer (FML) as bottom and immediate release layer (IRL) as top layer. IRL contained: CA (equiv to 250 mg of cefuroxime base), 300; Tulsion T-339, 15; sodium citrate, 15; lactose monohydrate, 27.5; and magnesium stearate, 2.5 mg. Ingredients of FML (Table 1) were weighed, mixed homogeneously and directly compressed in a die (13 mm diam) at 50 kg/cm$^2$ pressure for 1 min using an Infrared-KBr hydraulic press (Spectra Lab, Mumbai). The upper punch was lifted and IRL blend poured as top layer in the die containing initially compressed FML and then compressed at 100 kg/cm$^2$ pressure for 1 min to produce bilayer tablets.

Table 1—Composition of formulations for floating matrix layer

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Ingredients</th>
<th>M1 mg/tab</th>
<th>M2 mg/tab</th>
<th>M3 mg/tab</th>
<th>M4 mg/tab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cefuroxime axetil</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
</tr>
<tr>
<td>2</td>
<td>HPMC K4M</td>
<td>200.00</td>
<td>150.00</td>
<td>100.00</td>
<td>50.00</td>
</tr>
<tr>
<td>3</td>
<td>Sodium bicarbonate</td>
<td>25.00</td>
<td>50.00</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>4</td>
<td>Sodium citrate</td>
<td>15.00</td>
<td>15.00</td>
<td>15.00</td>
<td>15.00</td>
</tr>
<tr>
<td>5</td>
<td>Tulsion T-339</td>
<td>15.00</td>
<td>15.00</td>
<td>15.00</td>
<td>15.00</td>
</tr>
<tr>
<td>6</td>
<td>Lactose</td>
<td>25.00</td>
<td>25.00</td>
<td>25.00</td>
<td>25.00</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>580.00</td>
<td>555.00</td>
<td>505.00</td>
<td>455.00</td>
</tr>
</tbody>
</table>

Physical Evaluation of Tablets

Bilayer tablets were evaluated for mechanical strength using Pharma-Test tablet hardness tester (Incorp Ltd, Hyderabad) and Friabilator (Elactrolab, Mumbai). Buoyancy lag time (BLT) and floating time (FT) of tablets were determined in 900 ml of 0.07 N HCl at 37 ± 0.5°C using USP 24 type II dissolution testing apparatus (Electrolab TDT-06P, Mumbai) with the agitation speed of 55 rpm. Time required for a tablet to float on the surface of dissolution medium was determined and expressed as BLT. The time period for which tablets remained floating was expressed as FT. The time period over which the tablet remains intact was considered as period of Matrix Integrity.

Differential Scanning Calorimetry (DSC)

Thermograms of drug and powdered tablets were obtained using Mettler-Toledo DSC 821e (Mettler Toledo, Switzerland) equipped with an intracooler. Indium/zinc standards were used to calibrate DSC temperature and enthalpy scale. Weighed samples of drug and powdered tablets were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25-180°C. Inert atmosphere was maintained by purging nitrogen gas (flow rate, 50 ml/min).

Powder X-ray Diffraction Studies

The powder X-ray diffractograms of pure drug and powdered tablets were recorded using Phillips PW 1729 X-ray diffractometer (Legroupe Interconnexion, Saint-Julie, Canada). Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2-50° (2θ). Voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were $2 \times 10^3$ cycles sec$^{-1}$ and 10 mm/2θ, respectively.

Dissolution Studies

Drug release from tablets was performed in triplicate using USP 24 type II dissolution testing apparatus (Electrolab TDT-06P, Mumbai) in 900 ml of 0.07 N HCl solution with agitation speed (55 rpm) at 37±0.5°C. Samples were withdrawn at appropriate times and analyzed spectrophotometrically at 278 nm. Analysis of data was done using ‘PCP Disso V 3’ software (PCP, Pune).

In-vivo Gastro Retention Test

In-vivo study protocol was approved by the Institutional Ethical Committee. A written consent was obtained from human volunteers and study was supervised by expert radiologist and physician. In-vivo floating ability was studied in triplicate by $\gamma$-scintigraphy in healthy male human volunteers (25-30 years age and 55-65 kg body wt) who were non-alcoholic, non-smokers and were not taking any other medication. The 0.1 milli curie radiolabeled Tencinium ($^{99m}$Tc) was uniformly mixed with powder components and compressed as described under preparation of tablets. Each volunteer ingested the tablet orally along with water after taking a light breakfast in the morning. The tablets were visualized using a gamma camera (GE Millennium MPR Gamma Camera, Israel). Images were taken with volunteers in supine position immediately after administration of formulation (0 h) and at intervals of 1, 2, 4, 6 and 8 h.
Results and Discussion

CA exhibits broad spectrum of activity against Gram-positive and Gram-negative microorganisms. It is available commercially as film coated tablets containing the equivalent of 125, 250 or 500 mg of CA or as dry suspension, which on reconstitution provides the equivalent of 125, 250 or 500 mg of CA per 5 ml. CA in amorphous form (purity 95 %) has a higher bioavailability than the crystalline form with adequate chemical stability\(^6-10\). To minimize conversion of amorphous drug into crystalline state, tablets were prepared by direct compression technique. DSC thermogram of amorphous CA did not show any endothermic peak. Similarly, DSC thermogram of the amorphous drug after compression was also carried out to check the physical state of the drug. No change in the DSC thermogram was observed which indicates that the amorphous nature of the drug was retained even after compression (Fig. 1). XRD pattern of amorphous CA and tablet powder showed a halo, without any characteristic diffraction peak, which supports the DSC data (Fig. 2).

Drug has absorption window in upper GI tract and drug missing this remains unabsorbed and contributes to the side effects like Pseudomembrane colitis\(^12\). Moreover, on oral administration, CA is rapidly hydrolyzed in intestine, thereby resulting in the formation of cefuroxime, which is poorly absorbed from GI tract. Therefore, it is essential to retain the drug in stomach for better absorption. Modified release formulations suffer from demerits associated with continuous and unnecessary exposure to high plasma levels. Moreover, the controlled release formulations have delayed onset of action. Pulsatile drug delivery systems have been reported to overcome such problems\(^13-18\).

In present work, bilayer tablets consist of IRL (50% dose) for quick onset of action and FML (50%) for gastroretentive controlled drug release in upper GI tract. To arrive at final composition, immediate release (IR) tablets were prepared and evaluated separately. IR tablets were prepared using different levels of excipients with Tulsion T-339 as a disintegrating agent. Amorphous CA forms gel in contact with water, which prolongs the disintegration and retards the dissolution rate of CA from tablet formulation. Addition of sodium salt of citric acid to the formulation containing amorphous CA is reported to prevent its tendency to form a gel\(^6,7\). In present study, monosodium citrate was added in the formulation to prevent gelling. The optimum single layer IR tablet (mean hardness, 4.0 ± 0.5 kg/cm\(^2\), friability, < 1 %) disintegrated within 2 min and showed drug release (> 65%) within 15 min in 0.07 N HCl. This composition of IR tablet was used as top layer in bilayer tablets.

Floating and drug release studies were performed separately for single layer floating matrix tablets (FMT) and bilayer FMT. Single layer FMTs showed BLT of 13-34 min and FT in 8-24 h and the matrix was intact till the end of dissolution study. BLT of tablets was dependent on the amount of swellable polymer. HPMC K4M [average mol wt 10000-1500000, viscosity 4000 mPa (2 % w/v solution)] was the polymer of choice and sodium bicarbonate, a gas-generating agent (Fig. 3). The batch M1 containing highest amount of HPMC K4M and the lowest amount of sodium bicarbonate had BLT of 34 ± 2 min and FT 24 ± 2 h; whereas, it was just 8 ± 2 h for batch M4 with the lowest amount of HPMC K4M and the highest amount of sodium bicarbonate (Table 2). For floating, the ideal matrix should be highly permeable to the media in order to initiate rapid generation of CO\(_2\) and should be impermeable for CO\(_2\) to promote floating. Degree of gelling and strength of HPMC gel govern the floating time. Relaxation, erosion and dissolution of gel lead to sinking of tablets.

The IRL of bilayer tablets also disintegrated within 2 min and the matrix layer was set free for floating.

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Fig. 1—DSC thermograms: a) Pure drug, b) Tablet powder

![Fig. 1—DSC thermograms: a) Pure drug, b) Tablet powder](image1)

Fig. 2—XRD pattern: a) Pure drug, b) Tablet powder

![Fig. 2—XRD pattern: a) Pure drug, b) Tablet powder](image2)
Floating properties of these matrix layers were retained and were similar to those of FMT (Table 2). Batch M1 (Fig. 4) with highest polymer content showed maximum drug release retardation (only 50% after 10 h). Drug release rate was found to be inversely proportional to HPMC content. The batch M4 with lowest polymer content showed maximum drug release (100% after 7 h). Most important factor affecting the rate of release from HPMC K4M matrices is the drug: polymer ratio\(^{19}\). Higher polymer concentration causes increase in the viscosity of the gel as well as the formation of gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release rate.

In case of bilayer tablets with FML, IRL disintegrates within 2 min and the matrix layer, which is in contact with medium starts swelling and builds gel layer around the tablet. Sodium bicarbonate reacts with HCl and generates \(\text{CO}_2\), which is entrapped in the gel reducing the density of matrix. When specific gravity of tablet drops below the specific gravity of medium, the tablets start floating. Tablet surface that was exposed after disintegration of IRL underwent preferential gelling and erosion than the other surface (Fig. 5). This may be due to the comparatively loose compaction and rough surface left after disintegration of IRL. Bilayer tablets show bimodal drug release with initial instant drug release corresponding to IRL within 1 h followed by controlled release from FML (Fig. 6). The drug release from FML was found to be dependent on drug: polymer ratio, which is in

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>BLT (min)</th>
<th>FT (h)</th>
<th>Batch No.</th>
<th>BLT (min)</th>
<th>FT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix tablets</td>
<td></td>
<td></td>
<td>Bilayer matrix tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>34 ± 2</td>
<td>&gt; 24</td>
<td>MI1</td>
<td>35 ± 2</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>M2</td>
<td>20 ± 2</td>
<td>&gt; 24</td>
<td>MI2</td>
<td>21 ± 2</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>M3</td>
<td>15 ± 2</td>
<td>20 ± 2</td>
<td>MI3</td>
<td>15 ± 2</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>M4</td>
<td>13 ± 2</td>
<td>08 ± 2</td>
<td>MI4</td>
<td>12 ± 2</td>
<td>08 ± 2</td>
</tr>
</tbody>
</table>

Fig. 3—Structure of HPMC

Where, \(R = \text{H, CH}_3\) or \([\text{CH}_3\text{CH (OH) CH}_2]\)

Fig. 4—Comparison of cumulative percent release of cefuroxime axetil from floating matrices, M1 (●); M2 (●); M3 (●); M4 (▲)

Fig. 5—Schematic representation of swelling of single layer and bilayer floating matrix tablets with immediate release layer

Fig. 6—Comparison of cumulative percent release of cefuroxime axetil from bilayer floating matrix tablets with immediate release layer from formulations, M1 (●); M2 (●); M3 (●); M4 (▲)
acCORDANCE WITH SINGLE LAYER MATRIX TABLETS. The release profile of batch M3 was suitable for bimodal drug delivery with initial instant drug release corresponding to IRL followed by controlled drug release from FML. Therefore, batch M3 was evaluated for in-vivo gastroretention. Gamma scintigraphy is well known technique to locate dosage form in GI tract on oral administration and has been used for locating matrices, granules, capsules and tablets in GI tract. FML of bilayer tablets after disintegration of IRL was found to retain in the stomach for about 6 h. FML was intact throughout the study period, suggesting the integrity of matrix. Therefore, it can be concluded that the drug release takes place by diffusion through the gel membrane and not by erosion of matrix.

Conclusions
Oral solid dosage form based on bilayer floating drug delivery is promising to achieve bimodal drug release. After an immediate drug release from first layer, controlled release can be achieved from second layer in an area that could maximize drug reaching its absorption site. This system can be useful for pharmaceuticals following chronopharmacology and having limited physiological stability and absorption window in upper part of GI tract. However, further clinical studies are needed to explore potential of system for antibiotics to achieve maximum bioavailability and reduce side effects, and treatment of diseases following circadian rhythm or chronopharmacology.

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References