Design, in vitro and in vivo Evaluation of Gemifloxacin Mesylate Floating Matrix Tablets

Sushma Appala, Ramesh Bomma and Kishan Veerabrahma*

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal 506 009, Telangana, India

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ABSTRACT

Objective of the investigation was to develop gastro retentive dosage form of gemifloxacin mesylate for local action in the stomach as it has antibacterial activity against Helicobacter pylori. Gemifloxacin mesylate is a synthetic broad-spectrum antibacterial agent for oral administration, having 7 hrs half-life and 71% oral bioavailability. In present study, gemifloxacin mesylate floating matrix tablets were prepared by direct compression method using polymers (HPMC K4M, HPMC K15M and polyox WSR 1105) and evaluated for various parameters like drug content, floating behavior (floating lag time and total floating time), in vitro drug release, swelling index, weight variation, friability, hardness and thickness. Sodium bicarbonate was incorporated as gas generating agent in all formulations. Drug-excipients compatibility was studied by Differential Scanning Calorimetry. Results have shown that the amount of polymer in the formulation affected the drug release. Optimized formulation (F8 containing polyox WSR1105 as release retarding agent) was selected based on in vitro drug release, floating lag time, floating time and other parameters. This formulation followed zero order kinetics and non-Fickian mechanism of drug release. In vivo radiographic study was conducted in healthy human volunteers using tablets containing BaSO4 as radio opaque agent. The average residence time was found to be 4.5±0.86 h (n=3). This design of gastro retentive drug delivery system helps in increasing the local delivery of drug in patients with Helicobacter pylori infection.

KEYWORDS: Gemifloxacin mesylate; floating tablets; in vitro buoyancy; in vitro drug release; in vivo gastric residence time.

Introduction

Oral delivery of drugs is most preferable till today because of its ease of administration and patient compliance. Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended for instant drug release. They are associated with fluctuations in plasma drug levels, which lead to reduction or loss in drug effectiveness or increased incidence of side effects. Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects (Eisen et al., 1990, Getsios et al., 2004, Sansom, 1999). But bioavailability cannot be improved incase of drugs having absorption in upper GIT (Rouge et al., 1996), solubility and stability problems in intestine. So gastroretentive drug delivery systems have been developed to increase gastric residence time (results in higher bioavailability), patient compliance (Fell et al., 1996)and to improve local action of drugs acting mainly in the stomach. Different approaches are used to retain the dosage form in the stomach. They are floating (Deshpande et al., 1996), bioadhesive (Alvisi et al., 1996, Lenaerts and Gurny, 1990), swelling & expanding (Urquhart and Theeuwes, 1984, Mamajek RC and Moyer, 1980), high density systems (Bechgaard H and Ladefoged, 1978; Davis et al., 1986) and modified shape systems (Fix et al., 1993; Kedzierewicz et al., 1993). The floating drug delivery approach is mainly used for drugs which: (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment. The tablets prepared by using floating approach have ability to be buoyant over the gastric contents because of low density thereby exhibited increased gastric retention time.

Gemifloxacin mesylate is a synthetic broad-spectrum antibacterial agent for oral administration, which related to the third generation fluoroquinolone class of antibiotics. It is used in the treatment of chronic bronchitis and community-acquired pneumonia (Reynolds and Prasad, 1996; O’Neil, 2006). It is having more solubility in 0.1 N HCl (pH 1.2), 7 hrs half-life and having antibacterial activity against Helicobacter pylori (Heather et al., 2001). So far, no floating delivery system with gemifloxacin mesylate was reported. Thus, it is a suitable drug candidate for development of gastroretentive drug delivery system.

Objective of the present study was to develop gastroretentive dosage form of gemifloxacin mesylate using floating mechanism. Here, sodium bicarbonate was
used as gas generating agent. In present study, floating tablets were prepared by direct compression method using three different polymers viz., HPMC K4M, HPMCK15M and polyox WSR 1105. The prepared tablets were evaluated for various parameters like weight variation, hardness, thickness, friability, drug content, floating behavior, swelling studies and in vitro release studies. DSC studies were performed to know the compatibility between drug and excipients. In vivo radiographic study was conducted in healthy human volunteers for estimation of gastric retention time of dosage form.

Materials and Methods

Materials

Gemifloxacin mesylate was received as a gift sample from M/s Hetero Labs Limited, Hyderabad, India. Polymers (HPMC K4M, HPMC K15M and polyox WSR 1105) were also generously gifted by M/s Orchid Chemicals and Pharmaceutical Limited, Chennai, India. Sodium bicarbonate, microcrystalline cellulose, magnesium stearate, barium sulphate and concentrated HCl were purchased from S.D fine chemicals, Mumbai, India.

Methods

Drug-excipients compatibility studies

Differential scanning calorimetry

Drug-excipients compatibility study was conducted by Differential Scanning Calorimetry (DSC). It was carried out to know the purity and presence of any interaction among drug and excipients pure drug, drug & excipients mixture (1:1 ratio) were subjected to study. About 5-15 mg of sample to be analyzed was taken in the pierced DSC aluminum pan and scanned in the temperature range of 50–300 °C. The heating rate was 10 °C/min, nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyser (DSC 822 e/200, Mettler Toledo, Switzerland) was used for this purpose.

Preparation of gemifloxacin mesylate floating tablets

Gemifloxacin mesylate (399 mg equivalent to 320 mg of gemifloxacin) was mixed with required quantity of polymer and MCC in a mortar. Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar, powdered with pestle and passed through sieve number 40. This was mixed with previous blend which was also passed through sieve number 40. Finally magnesium stearate and aerosil were added and mixed. The mixture equivalent to 650 mg was compressed into tablets with 13 mm round flat punches on 16 station rotary tablet punching machine (Riddhi, Ahmedabad, India) at a hardness of 6 kg/cm². The compositions of different formulations are shown in Table 1.

Evaluation of gemifloxacin mesylate floating tablets

The prepared tablets were evaluated for uniformity of weight using 20 tablets, hardness (Pfizer tester) using 6 tablets, friability (Vernier caliper) using 6 tablets, in vitro buoyancy using 3 tablets and in vitro dissolution studies using 3 tablets. The results were expressed as mean ± S.D.

In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time, as per the method described (Rosa et al., 1994). The tablets were placed in a 100 mL beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and to float was determined as floating lag time. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the total floating time.

Swelling studies

The swelling behavior of dosage form was measured by studying its weight gain or water uptake ability (Mohammed and Khedr, 2003). This study was performed for all formulations in triplicate. From each formulation, tablet was taken, weighed initially and placed in a beaker containing 200 mL of 0.1 N HCl. At selected intervals, the tablet was withdrawn, blotted to remove excess water and weighed. Percentage swelling of the tablet was expressed as percentage water uptake calculated from following equation (Paula Garcia et al., 2008):

\[
\text{Percentage water uptake} = \frac{(W_t - W_0)}{W_0} \times 100
\]

where ‘W_t’ is the weight of the swollen tablet at time ‘t’ and ‘W_0’ is the initial weight of the tablet.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
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<th>F11</th>
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<td>-</td>
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<td>120</td>
<td>110</td>
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<td>-</td>
<td>-</td>
<td>110</td>
<td>120</td>
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</table>
**In vitro dissolution studies**

*In vitro* drug release study was performed for all formulations using USP type II (Electrolab, TDT-06T, Mumbai, India) apparatus in triplicate. The test was performed by taking 900 mL of 0.1 N HCl, at 37±0.5°C and 50 rpm. A sample (5 mL) was withdrawn from dissolution apparatus at predetermined time intervals such as 1, 2, 3, 4, 6, 8 and 10 h and the samples were replaced with fresh dissolution medium. The collected samples were filtered through 0.45 μm membrane filter and drug content was estimated using UV-Visible spectrophotometer (Elico, SL 159, India) at λ_{max} 271 nm. Cumulative percentage drug release was calculated.

**Drug release kinetics**

The profiles of the *in vitro* release were fitted to different kinetic models to explain the release kinetics of gemifloxacin mesylate from the floating tablets (Dash et al., 2010). The model with the highest correlation coefficient (R²) was considered to be the best fitting one. In the present study, the *in vitro* drug release profiles were fitted to zero-order (Donbrow and Samuelov, 1980), first-order (Merchant et al., 2006), Higuchi (Higuchi, 1965) and Korsmeyer-Peppas kinetic models (Korsmeyer et al., 1983).

**Zero-order:** \[ Q_t = Q_0 + k_0 t \]  
**First-order:** \[ \log C = \log C_0 - k_1 t/2.303 \]  
**Higuchi:** \[ Q_t = k_2 t^{1/2} \]  
**Korsmeyer-Peppas:** \[ Q_t/Q_0 = k t^n \]

Where \( Q_0 \) and \( Q_t \) are the amounts of drug dissolved at zero time and at time \( t \). \( Q_t/Q_0 \) is a fraction of drug released at time \( t \). \( C_0 \) and \( C \) are the concentrations of the drug at zero time and at time \( t \), and \( k_0, k_1, k_2 \) and \( k \) refer to the rate constants obtained from the linear curves of the respective models, and \( n \) refers to the release exponent indicative of the mechanism of drug release. If the value of \( n \) is 0.5 or less, the release mechanism follows Fickian diffusion, while the higher values (0.5 < \( n \) < 1) indicates a non-Fickian model (anomalous transport). The non-Fickian model corresponds to coupled diffusion/polymer relaxation. If the \( n \)-value is 1, the drug release follows zero order and case II transport. The Case II transport generally refers to the dissolution of the polymeric matrix due to the relaxation of the polymer chain. However, the mechanism of drug release is regarded as super case-II transport if \( n \)-values are higher than 1. This mechanism could result from increased plasticization at the relaxing boundary, i.e., gel layer.

**In vivo radiographic studies**

Radiographic study was performed for determination of the anatomical location and behavior of floating tablet in GIT. Barium sulfate was used to make the tablet X-ray opaque. Barium sulfate has a high density (4.48 g/cm³) and poor floating properties. The amount of the X-ray opaque material in these tablets was sufficient to ensure visibility by X-ray, but at the same time this amount of BaSO₄ was low enough to enable the tablets to float.

Formulation F12 was selected for X-ray studies and 13% w/w of drug was replaced with barium sulfate by keeping remaining excipients constant in weight. Three human volunteers, weighing in between 55-75 kg and in the age group of 22-27 yrs, were included in the study. About 30 min before starting the study, the volunteers were fed with low calorie food having 100 g bread and 200 mL water under supervision of a radiologist (Ramesh and Kishan, 2013). First X-ray photograph was taken after 30 minutes of administration of tablet. Further, the next pictures were at different time intervals viz., 1.5, 3.5, 5 h. The volunteers were asked to sit during study and they were not allowed to eat but water was made available during study when required. X-ray photographs were taken at erect position. The study protocol was approved by the human ethical committee (UCPSc, KU, Warangal). The mean gastric residence time was calculated from this study.

**Results and Discussion**

**Drug-excipients compatibility study**

DSC curve of pure drug (Gemifloxacin mesylate) showed a single sharp exothermic peak at 209.25°C. In all other DSC curves, the exothermic peak which corresponded to drug was well preserved with slight changes in broadening or shifting towards higher or lower temperature along with peaks characteristic to individual excipients. Based on results, it was concluded that the Gemifloxacin mesylate is compatible with excipients (HPMC K4M, HPMC K15M, polyox WSR 1105 and NaHCO₃) used in the study and the DSC curves are shown in Figure 1.

**Characterization of tablets**

The floating tablets of gemifloxacin mesylate were prepared by direct compression technique. The results of the physical characteristics of floating tablets are given in Table 2. The weight of all the formulations ranged from 636.2 ± 8.7 to 647.7 ± 2.1 mg. The hardness of the all formulations was found to be in between 5.5 ± 0.5 to 6.0±0.1 kg/cm² and that of thickness from 4.8 ± 0.05 to 4.93±0.1 mm. The friability was below 0.5 %, which was an indication of good mechanical resistance of the tablet. Assay (%) of all formulations varied between 99.47 ± 1.52 to 102.66 ± 1.14%. All physical properties were found to be within permissible limits and complied with the pharmacopoeial specifications for weight variation, drug content and friability (Banker and Anderson, 1987).
In *vitro* buoyancy studies

In this study, sodium bicarbonate was used as a gas generating agent. Upon immersion, sodium bicarbonate starts reaction immediately with the acidic dissolution medium. This reaction generates sufficient amount of CO₂ which get entrapped and protected within the gel layer formed by hydration of polymer. This leads to decreased density of the tablet (reported as 1.004-1.010 g/cm³), as a result of which the tablet becomes buoyant. All the batches showed good *in vitro* buoyancy (with <1 minute floating lag time and >8 hours floating time) properties except F1 formulation. For F1 formulation, the total floating time was less when compared to other formulations. This is because of insufficient amount of gas generating agent (NaHCO₃), so that the F1 formulation was unable to float for a longer period. The floating lag time and duration of floating for the tablets are given in Table 2.

### Swelling studies

Viscosity of the polymer and its content had major influence on swelling process and matrix integrity. The results obtained, it was noted that polyox WSR 1105 demonstrated a faster rate of water uptake and greater swelling than HPMC because of its high viscosity. The tablets showed increase in swelling up to 6 hours. There after it decreased because of rapid erosion. Hence, from the results it was concluded that linear relationship existed between swelling process and viscosity of polymer. The percentage swellings of all formulations ranged in between 147.2 ± 1.5% to 199.4 ± 2.4%. Results of percentages swelling are shown in Figure 2.

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**TABLE 2**

Physical characters of gemifloxacin mesylate floating tablets.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Tablet weight (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>FLT (s)</th>
<th>TFT (h)</th>
<th>Assay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>642.7 ± 7.91</td>
<td>5.8 ± 0.2</td>
<td>4.83 ± 0.05</td>
<td>0.33</td>
<td>4.3 ± 0.2</td>
<td>8</td>
<td>102.6 ± 0.8</td>
</tr>
<tr>
<td>F2</td>
<td>636.2 ± 10.7</td>
<td>5.8 ± 0.2</td>
<td>4.86 ± 0.05</td>
<td>0.17</td>
<td>3.0 ± 0.3</td>
<td>&gt;10</td>
<td>102.66 ± 1.14</td>
</tr>
<tr>
<td>F3</td>
<td>642.3 ± 5.6</td>
<td>5.8 ± 0.2</td>
<td>4.9 ± 0.1</td>
<td>0.23</td>
<td>4.0 ± 0.1</td>
<td>8</td>
<td>101.66 ± 1.03</td>
</tr>
<tr>
<td>F4</td>
<td>647.7 ± 2.1</td>
<td>5.8 ± 0.2</td>
<td>4.9 ± 0.0</td>
<td>0.16</td>
<td>4.0 ± 0.4</td>
<td>&gt;10</td>
<td>101.87 ± 0.75</td>
</tr>
<tr>
<td>F5</td>
<td>642.3 ± 7.3</td>
<td>5.8 ± 0.2</td>
<td>4.86 ± 0.1</td>
<td>0.28</td>
<td>4.4 ± 0.2</td>
<td>&gt;10</td>
<td>100.41 ± 1.02</td>
</tr>
<tr>
<td>F6</td>
<td>642.7 ± 5.8</td>
<td>6.0 ± 0.1</td>
<td>4.8 ± 0.05</td>
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<td>4.4 ± 0.5</td>
<td>&gt;10</td>
<td>99.99 ± 1.56</td>
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<td>F7</td>
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<td>3.7 ± 0.3</td>
<td>&gt;10</td>
<td>100.62 ± 0.6</td>
</tr>
<tr>
<td>F8</td>
<td>645.3 ± 3.7</td>
<td>5.6 ± 0.2</td>
<td>4.88 ± 0.02</td>
<td>0.28</td>
<td>4.7 ± 0.4</td>
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<td>99.99 ± 0.97</td>
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<td>F9</td>
<td>645.7 ± 4.5</td>
<td>5.6 ± 0.2</td>
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<td>22.6 ± 0.5</td>
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<td>100.2 ± 1.34</td>
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<td>F10</td>
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<td>24.6 ± 0.5</td>
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<td>99.47 ± 1.52</td>
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<td>F11</td>
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<td>5.5 ± 0.5</td>
<td>4.93 ± 0.1</td>
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<td>24.3 ± 0.5</td>
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<td>100.41 ± 1.64</td>
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**Fig. 1.** DSC curves of a) pure drug; b) drug and HPMC; c) drug and PolyoxWSR1105; d) optimized formulation (F12).
TABLE 3
Regression coefficient ($R^2$) and release exponent ($n$) values of gemifloxacin mesylate floating tablets for different kinetic models.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
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<tr>
<td></td>
<td>$R^2$</td>
<td>$n$</td>
<td></td>
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<td>0.943</td>
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Fig. 2. Percentage swelling of formulations containing HPMC K15M (F1-F4), HPMC K4M (F5-F8) and Polyox WSR1105 (F9-F13) as release retarding agents.

**In vitro dissolution studies**

Dissolution profiles of formulations F1-F4 prepared with HPMC K15 are shown in Figure 3. Among formulations, F4 was considered as best formulation because of its sustained drug release (97.6 ± 2.5% up to 10 h). The cumulative percentage of drug release from formulations F1 and F2 was 81.87 ± 1.43, 86.45 ± 2.21 in 10 h, respectively. Formulation F3 released about 99.26 ± 2.01% of the drug in 8 h and unable to sustain the drug release for desired period of time. Formulations F1 and F2 did not release the drug within the desired time. Formulation F4 sustained the drug release up to 10 h and was considered as the best formulation in this series.

In vitro drug release profiles of formulations F5-F8 prepared with HPMC K4M are shown in Figure 4. The cumulative percentage of drug release from formulations F5-F7 and F8 was 70.62 ± 3.01, 78.33 ± 2.52, 97.28 ± 0.47 in 10 hours and 95.41 ± 0.47 in 8 h respectively.

Formulations F5 and F6 could not release the total drug within 10 h. Formulation F8 was unable to sustain the drug release for desired period of time. In this series, Formulation F7 was considered as the best formulation because it sustained the drug release for 10 h desired period of time.

Formulations F9-F13 were prepared with Polyox WSR 1105 and their drug release profiles are shown in Figure 5. Cumulative percentage of drug release from formulations F9 to F13 varied between 90.2±0.95 to 97.91 ± 0.47 in 10 h. Total amount of drug was released from formulation F9 at the end of 8 h and it was unable to sustain the drug release up to 10 h. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. In this series, F12 was considered as the best formulation as it released 97.8 ± 0.62% of drug at the end of 10 h.
Fig. 3. Drug release profiles of gemifloxacin mesylate floating tablets prepared with HPMC K15M (mean ± SD, n = 3, SD bars are very small and are not clearly visible).

Fig. 4. Drug release profiles of gemifloxacin mesylate floating tablets prepared with HPMC K4M (mean ± SD, n = 3, SD very are small and bars are not clearly visible).

Fig. 5. Drug release profiles of gemifloxacin mesylate floating tablets prepared with polyox WSR 1105 (mean ± SD, n = 3, SD bars are very small and are not clearly visible).
Drug release kinetics

The $n$ values with corresponding correlation coefficients ($R^2$) for all the formulations are shown in Table 3. Release of the drug from formulations F2, F4-F8 and F12 followed zero order model due to high $R^2$ value (0.980 in F2 to 0.998 in F12) whereas that from F1, F9-F11 and F13 followed Peppas model and the $R^2$ value ranged from 0.955 in F9 to 0.990 in F13 and F1. The value of release exponent $n$ for all the formulations ranged from 0.510 in F10 to 0.670 in F13 and indicated the diffusion and swelling controlled release. Release of the drug from optimized formulations F4, F7 and F12 involved zero-order model.

In vivo radiographic studies

The barium sulphate loaded tablets prepared for radiological studies were evaluated for hardness (5.83 ± 0.28 kg/cm$^2$), thickness (4.9 ± 0.1 mm), friability (0.28%) and floating lag time (62.33 ± 2.51sec). The increased floating lag time of barium sulphate loaded tablets when compared to the original formulation (F12) was expected because of high density of barium sulphate (4.5 g/cm$^3$). The tablets were clearly seen at different positions in GIT during radiographic study (Figure 6). This was evidenced by taking X-rays at different time points (0.5, 1.5, 3.5 and 5 hours). The average gastric residence time was found to be 4.5 ± 0.8 hours (n=3).

Conclusions

The floating tablets of gemifloxacin mesylate were successfully prepared using HPMC K4M, HPMC K15M and polyox WSR 1105 by effervescent floating technique. The drug-excipients compatibility study revealed that the drug was compatible with all the excipients used in the formulations. Formulation F12 was selected for radiographic study because of its sustained drug release, good physical characteristics and buoyancy properties. The non-Fickian diffusion was the release mechanism for all the formulations. The radiographic study was performed on healthy human volunteers and the average gastric residence time was found to be 4.5 ± 0.8 hours (n = 3). From this study, it was concluded that the formulation retained in the stomach for a prolonged period of time and provided controlled release of drug.

Hence, this dosage form was found helpful for improving local action in the stomach of patients suffering from infection caused by Helicobacter pylori.

Conflict of interest: The authors declare that they have no conflict of interest.

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References


Address correspondence to: Prof. V. Kishan, Head, Dept. of Pharmaceutics University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 009 Telangana State, India.
Mob: 9440973245 E-mail: vbkishan@yahoo.com