
Ramireddy Amarnath Reddy, Bomma Ramesh and Veerabrahma Kishan*

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 009, Andhra Pradesh, India.

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ABSTRACT

The present investigation deals with the development and evaluation of floating tablets of nizatidine to prolong the gastric residence time, increase local delivery of drug to the \(H_2\)-receptor of the parietal cell wall to reduce stomach acid secretion. The drug-excipient compatibility studies were conducted by using FTIR, DSC and visual observations. Citric acid inclusion in formulations resulted in incompatibility and the composition was modified to eliminate the problem of incompatibility. Floating matrix tablets of nizatidine were developed by direct compression method using hydroxypropyl methylcellulose (HPMC K4M) and polyox WSR 1105 alone as release retardants and sodium bicarbonate as a gas-generating agent. Alleleven formulations exhibited satisfactory physicochemical characteristics and \textit{in vitro} buoyancy. Formulations F6 and F10 exhibited controlled and prolonged drug release for 10 h with zero order release. Formulation (F10) was selected as optimized formulation based on physicochemical properties and \textit{in vitro} drug release and was used in radiographic studies by incorporating BaSO\(_4\). The radiographic studies were conducted in comparison with plain controlled release tablets. These studies revealed that gastric retention time of floating and plain controlled release tablets in fasting state were 2 ± 0.86 h and ≤ 0.5 h respectively in human volunteers. Gastric retention time of floating and plain controlled release tablets in fed state were 5.33 ± 0.57 h and 1.66 ± 0.28 h respectively in human volunteers. In conclusion, optimal floating matrix tablet for nizatidine with desired \textit{in vitro} buoyancy, \textit{in vivo} gastric retention time and prolonged release could be prepared.

KEYWORDS: Floating tablets; drug-excipients compatibility; gastric residence time; nizatidine.

Introduction

Oral drug delivery is the preferred route for drug administration because of its convenience, low cost, and high patient compliance when compared with several other routes. About 90 percent of drug products are administered via the oral route (Kokate et al., 2006). Controlled-release (CR) pharmaceutical dosage forms may offer one or more advantages over immediate release dosage forms of the same drug, including a reduced dosing frequency, a decreased incidence and/or intensity of adverse effects, a greater selectivity of pharmacologic activity, and a reduction in drug plasma fluctuation resulting in a more constant or prolonged therapeutic effect (Malinowski and Marroum, 1999). However, this CR approach is facing problems with several physiological difficulties such as inability to restrain and locate controlled drug delivery system within the desired region of gastrointestinal tract (GIT), due to variable gastric emptying and motility. Control of placement of drug delivery system in specific region of GIT offers advantage for variety of important drugs characterized by narrow absorption window in GIT or drugs with stability problem (Garg and Gupta, 2008).

Various approaches that have been proposed to control the gastric residence time of drug delivery systems in the upper part of the GIT include floating drug delivery systems (FDDS) (Brahma and Kim, 2000), high-density DDS (Caldwell et al., 1998), mucoadhesive systems (Lehr, 1994), swelling and expanding DDS (Urquhart and Theeuwes, 1984; Mamajek and Moyer, 1980), modified shape systems (Fix et al., 1993), and other delayed gastric devices (Gröning and Heun, 1989).

FDDS have a bulk density lower than the gastric fluid and thus remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the druggets released slowly (Arora et al., 2005). Based on the mechanism of buoyancy, two distinctly different technologies, i.e., non-effervescent and effervescent system, have been utilized in the development of FDDS. The effervescent system utilizes matrices prepared with swellable polymers and effervescent components, e.g., sodium bicarbonate and...
citric acid or adipic acid. The matrices are fabricated such that in the stomach carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the swollen gel of hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy (Rubinstein and Friend, 1994). In non-effervescent FDDS, the drug is mixed with a gel-forming hydrocolloid, which swells on contact with the gastric fluid after oral administration and maintains relative integrity of shape and a bulk density of less than unity within an outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms (Sheth and Tossounian, 1979).

Ranitidine HCl was formulated as FDDS by lowering the density. The local delivery of Ranitidine HCl increased the stomach wall receptor site bioavailability to reduce stomach acid secretion (Raval et al., 2007). Similarly, nizatidine is also an histamine H2-receptor antagonist that inhibits stomach acid production and commonly used in the treatment of peptic ulcer and Gastro Esophageal Reflux disease. It reduces the acid secretion by directly acting on parietal cell wall (Davis, 1997). It is having an oral bioavailability of 70% with a biological half-life of 1-2 h. Due to the above mentioned characteristics it becomes a suitable candidate for the development of gastroretentive delivery system.

The present investigation was concerned with the development and evaluation of floating tablets of nizatidine by using hydroxyl-propyl-methyl cellulose (HPMC K4M) or polyethylene oxide (Polyox WSR 1105) as sole release retardant, and sodium bicarbonate and citric acid were incorporated as gas-generating agents in the formulations to prolong the gastric residence time, increase local delivery of drug to the H2-receptor of the parietal cell wall. Initially, drug-excipients compatibility problems were studied by using Fourier transform infrared (FTIR), differential scanning calorimetry (DSC) and visual observation of the prepared tablets for one month. The optimized formulation possessed good floating, extended and controlled drug release properties and was chosen for further in vivo radiological investigation to determine the mean gastric retention time.

Materials and Methods

Materials

Nizatidine was obtained as a generous gift sample from Dr. Reddy's laboratories, Pydibheemavaram, India. Hydroxypropyl methyl cellulose (HPMC) K4M and polyethylene oxide (PEO) WSR 1105 were obtained as gift samples from M/s Orchid Chemicals and Pharmaceuticals Ltd., Chennai, India. Microcrystalline cellulose (Avicel pH102), Sodium bicarbonate were purchased from M/s S.D Fine chemicals Ltd., Mumbai, India. All other ingredients used were of laboratory grade.

Methods

Drug-excipient compatibility studies

(i) Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of samples were obtained using FTIR spectrophotometer (BX I, Perkin Elmer, USA). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide (KBr) of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm⁻¹.

(ii) Differential scanning calorimetry (DSC)

The DSC experiments were carried out to find out the presence of any interaction among drug and the excipients. Pure drug, individual polymers and optimised formulation were subjected to the study. About 5–15 mg of sample to be analysed was taken in the pierced DSC aluminium pan and scanned in the temperature range of 50–250 °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.

(iii) Visual observation

Initially, the tablets of nizatidine were prepared by using either HPMC K4M or Polyox WSR 1105 as release retardant, sodium bicarbonate and citric acid as gas generating agents, Avicel pH102 as bulking agent, magnesium stearate as lubricant and talc as glidant in the formulations. After compression of the mixture into tablets, the change in physical appearance was observed during storage at room temperature. The visual observation was carried out for one month by excluding one of the ingredients from the composition. Finally, the composition was modified to eliminate the problem of incompatibility due to citric acid.

Development of tablets

Accurately weighed quantities (Table 1) of polymer and Avicel pH102 were taken in a mortar and mixed geometrically. To this required quantity of nizatidine was added and mixed slightly with pestle. Weighed quantity of sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder was passed through sieve no. 40 and mixed with the drug blend which was also passed through sieve no. 40. The whole mixture was collected in a plastic bag and mixed for 3 min. To this talc was added and mixed for 2 minutes, later magnesium stearate was added and mixed for 3 min. The mixture equivalent to 500 mg was compressed into tablets using rotary tablet machine (Riddhi, Model-RDD3, Ahmedabad) with 10 mm round concave punches at a hardness of 6 kg/cm².
TABLE 1
Composition of various formulations of nizatidine floating tablets.

<table>
<thead>
<tr>
<th>Name of ingredients</th>
<th>Formulation codes and ingredients (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>270</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>100</td>
</tr>
<tr>
<td>Polyox WSR 1105</td>
<td>-</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>50</td>
</tr>
<tr>
<td>Citric acid anhydrous</td>
<td>10</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>7</td>
</tr>
<tr>
<td>Talc</td>
<td>7</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>7</td>
</tr>
<tr>
<td>Total tablet weight</td>
<td>500</td>
</tr>
</tbody>
</table>

TABLE 2
Physical parameters of nizatidine floating tablets.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Floating lag time (s)</th>
<th>Assay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>506 ± 9.06</td>
<td>5.1 ± 0.2</td>
<td>6.13 ± 0.05</td>
<td>0.27</td>
<td>50 ± 3</td>
<td>100.85</td>
</tr>
<tr>
<td>F2</td>
<td>506 ± 8.43</td>
<td>5 ± 0.3</td>
<td>6.19 ± 0.03</td>
<td>0.35</td>
<td>5 ± 0.3</td>
<td>99.03</td>
</tr>
<tr>
<td>F3</td>
<td>502.5 ± 9.78</td>
<td>6.1 ± 0.3</td>
<td>6.16 ± 0.04</td>
<td>0.24</td>
<td>46 ± 3</td>
<td>99.21</td>
</tr>
<tr>
<td>F4</td>
<td>501 ± 11</td>
<td>6.1 ± 0.5</td>
<td>6.11 ± 0.08</td>
<td>0.30</td>
<td>44 ± 5</td>
<td>99.91</td>
</tr>
<tr>
<td>F5</td>
<td>501.5 ± 6.25</td>
<td>6 ± 0.3</td>
<td>6.13 ± 0.05</td>
<td>0.32</td>
<td>38 ± 3</td>
<td>100.7</td>
</tr>
<tr>
<td>F6</td>
<td>501.5 ± 7.83</td>
<td>6.1 ± 0.2</td>
<td>6.13 ± 0.04</td>
<td>0.18</td>
<td>85 ± 5</td>
<td>98.3</td>
</tr>
<tr>
<td>F7</td>
<td>500.5 ± 7.24</td>
<td>5.9 ± 0.4</td>
<td>6.16 ± 0.04</td>
<td>0.19</td>
<td>92 ± 4</td>
<td>98.9</td>
</tr>
<tr>
<td>*F8</td>
<td>507 ± 8.56</td>
<td>5.1 ± 0.3</td>
<td>6.30 ± 0.03</td>
<td>0.18</td>
<td>65 ± 3</td>
<td>99.28</td>
</tr>
<tr>
<td>*F9</td>
<td>506.5 ± 10.28</td>
<td>6.2 ± 0.2</td>
<td>6.34 ± 0.04</td>
<td>0.20</td>
<td>83 ± 4</td>
<td>97.48</td>
</tr>
<tr>
<td>F10</td>
<td>504.5 ± 10.91</td>
<td>5.9 ± 0.3</td>
<td>6.32 ± 0.04</td>
<td>0.17</td>
<td>114 ± 5</td>
<td>98.96</td>
</tr>
<tr>
<td>F11</td>
<td>504.5 ± 8.64</td>
<td>6.1 ± 0.2</td>
<td>6.33 ± 0.04</td>
<td>0.18</td>
<td>171 ± 6</td>
<td>98.29</td>
</tr>
</tbody>
</table>

Note: All the formulations floated for more than 10 h. Formulations *F8 and *F9 floated for 6 h and 8 h respectively.

Physical evaluation of floating tablets of nizatidine

The prepared tablets were evaluated in terms of their weight variation, hardness, thickness, friability and drug content (Table 2).

In vitro buoyancy studies

The in vitro buoyancy studies were carried out for the prepared floating tablets as per published method (Rosa et al., 1994). The tablets were placed in a 100 mL beaker containing 0.1 N HCl. The time required for a tablet to rise to the surface for floating 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.

In vitro drug release studies

In vitro dissolution studies were carried out using a USP 29 type II (paddle type) dissolution apparatus (Electro Lab, TDT 06P). A floating tablet of nizatidine was dropped into 900 mL of 0.1 N HCl (pH 1.2), maintained at 37 ± 0.5°C and stirred at a speed of 50 rpm. At different times, 5 ml aliquots were withdrawn and replaced with an equivalent amount of plain dissolution medium kept at 37°C. The collected samples were filtered and analysed at λmax 314 nm using a UV-Visible spectrophotometer (Elico Pvt. Ltd., SL 159). The cumulative percentage of drug released was calculated using standard calibration curve of nizatidine.

Analysis of in vitro drug release data

Model dependent methods

To analyze the mechanism of drug release from the tablets, the in vitro dissolution data was subjected to the zero-order (Chen and Hao, 1998), first-order (Shah et al., 1987), Higuchi (Higuchi, 1961), and Korsmeyer-Peppas kinetic models (Ritger and Peppas, 1987; Korsmeyer et al., 1983). The equations for the kinetic models are given below.

Zero-order: \( Q_t = Q_0 + k_0 t \)    \( (1) \)

First order: \( \log C = \log C_0 - k_1 t / 2.303 \) \( (2) \)

Higuchi: \( Q_t = k_2 t^{1/2} \) \( (3) \)

\( Q_t / Q_\infty = k_p t^n \) \( (4) \)

Where \( Q_0, Q_t, Q_\infty \) are the amounts of drug dissolved initially, at any time \( t \) and at \( \infty \) time. \( C_0 \) and \( C_t \) are the concentration of the drug initially and at any time \( t \), and \( k_0, k_1, k_2 \) and \( k_p \) are the rate constants obtained from the linear curves of the respective models.

Model independent methods

For the comparison of release profiles of reference and test products, “difference factor” \( f_1 \) and “similarity factor” \( f_2 \) were calculated (Moore and Flanner, 1996). The difference factor (\( f_1 \)) measures the percent error between the two curves over all time points and is calculated by the following equation:

\[ f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \]
where \( n \) is the number of sampling points, and \( R_i \) and \( T_j \) are the percent dissolved of the reference and test products at each time point \( j \). The two release profiles are considered to be similar if \( f_1 \) value is lower than 15 (between 0 and 15). The similarity factor \( (f_2) \) is a logarithmic transformation of the sum of squared error of differences between the test \( T_j \) and the reference products \( R_j \) over all time points. It is calculated by using the following equation:

\[
f_2 = 50 \log \left( \left[ 1 + \frac{1}{n} \right] \sum_{i=1}^{n} W_i \left| R_i - T_i \right|^2 \right)^{0.5} \times 100
\]

Where \( W_i \) is an optional weight factor and other terms are as defined earlier. The two dissolution profiles are considered to be similar if \( f_2 \) value is more than 50 (between 50 and 100).

**Tablet preparation for *in vivo* radiographic studies**

Radiological (X-Ray) study was used for determination of the anatomical location of nizatidine floating tablets in the GI tract. To make the tablets X-ray opaque, the incorporation of \( \text{BaSO}_4 \) was necessary. For this purpose, the GI tract. To make the tablets X-ray opaque, the composition, in which gas generating agent \( \text{NaHCO}_3 \) was controlled release tablets were prepared with same formulation \( F10 \) was selected for the radiological study, which contained 41% drug, 13% \( \text{BaSO}_4 \) as radio opaque agent, 22% polyox WSR 1105 as polymer and 12% \( \text{NaHCO}_3 \) as gas generating agent, 9.2% Avicel pH 102, 1.4% magnesium stearate and 1.4% talc. The plain controlled release tablets of nizatidine were used as a control. The optimized formulation \( F10 \) was selected for the radiological study, which contained 41% drug, 13% \( \text{BaSO}_4 \) as radio opaque agent, 22% polyox WSR 1105 as polymer and 12% \( \text{NaHCO}_3 \) as gas generating agent, 9.2% Avicel pH 102, 1.4% magnesium stearate and 1.4% talc. The plain controlled release tablets were prepared with same composition, in which gas generating agent \( \text{NaHCO}_3 \) was replaced with Avicel pH 102.

**In vivo radiographic studies**

Six healthy male volunteers participated in the studies after giving informed written consent. The studies were approved by the Ethical Committee of University College of Pharmaceutical Sciences (UCPSc), Kakatiya University, Warangal, India. The study was conducted by administering to each subject one floating/plain controlled release tablet in one session. The healthy male volunteers, weighing between 65±10 kg and in the age group of 25±2 years were included in the study. Study was conducted in fasted and fed state, 3 volunteers each.

**Fasting state:** The \( \text{BaSO}_4 \)-loaded floating/plain controlled release tablet was administered orally to each volunteer with 200 mL of water. During the study they were not allowed to eat but the water was made available *ad libitum*. The first X-ray photograph was taken 30 min after administration of tablet. Further, the next pictures were taken at different time intervals viz., 1.5, 3, and 5 h in a standing position under the supervision of an expert radiologist. The source of X-rays and the subject was kept constant for all images. Thus, the observation of the tablet movements could be easily noticed. The mean gastric residence time was calculated.

**Fed state:** After overnight fasting, the volunteers were fed with a low calorie food. Half an hour later, a \( \text{BaSO}_4 \)-loaded floating/plain controlled release tablet was administered orally to each volunteer with 200 mL of water. At different time intervals (0.5, 1.5, 3, 5 and 7 h post administration of tablet), the volunteers were exposed to abdominal X-ray imaging and the mean gastric residence time was calculated.

**Results and Discussion**

**Drug-excipient compatibility studies**

(i) **Fourier Transform Infrared (FTIR) Spectroscopy**

Chemical interaction between drug and polymer could change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and excipients, samples were analyzed over the range 400 – 4000 cm\(^{-1}\).

The FTIR spectra of pure drug, drug-HPMC K4M and drug-Polyox WSR 1105 were obtained and shown in Figure 1. The major peaks were observed at 754.5, 1017.8 and 1229.8 cm\(^{-1}\) for pure drug. These results suggested the compatibility between nizatidine, HPMC K4M and polyox WSR1105, because FTIR spectra of nizatidine-HPMC K4M and nizatidine-Polyox WSR 1105 mixture displayed all the characteristic bands of drug, without any significant spectral shift.

Figure 1d suggested that there was incompatibility between nizatidine and citric acid because FTIR spectrum of nizatidine and citric acid mixture (1:1), which was immediately analyzed after preparation, showed an extra peak at 1700 - 1800 cm\(^{-1}\) indicated by an arrow other than characteristic bands of drug. This was confirmed further byFT-IR spectrum of nizatidine and citric acid mixture (Figure 1e), which was preserved for one month and analyzed, showed entirely different peaks and lacking characteristic bands of drug. But, in contrast the Figure 1f and 1g showing FTIR spectra of the formulation F5 containing citric acid displayed all the characteristic bands of drug, without any significant spectral shift. This suggested absence of chemical interaction between the components of the formulation and probably, due to very low concentration of citric acid in formulation (0.02 % w/w).
(ii) **Differential Scanning Calorimetry (DSC)**

The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC curve of pure nizatidine (NIZ-1) showed in Figure 2, a single sharp endothermic peak at 136.32°C (−130.50 J/g) corresponding to its melting point (130–134°C) being started at 132°C and ended at 138°C. The 1:1 mixture of nizatidine and HPMC K4M (NIZ-7) was showing an endothermic peak of drug at 139.79°C which was well preserved with slight change in terms of broadening or shifting towards the higher temperature. Similarly, Figure 3 (obtained from 1:1 mixture of nizatidine and polyox WSR 1105, NIZ 8) showed an endothermic peak of drug at 141.60°C, which was well preserved with slight changes in terms of broadening or shifting towards the higher temperature. The minor change in the melting endotherm of drug could be due to the mixing of the drug and polymer, which lowered the purity of each component in the mixture and indicated no potential incompatibility. Thus, it was concluded that the drug had compatibility with HPMC K4M and polyox WSR 1105 when used in the formulation.

The DSC thermogram (Figure 4) of citric acid anhydrous (NIZ-2) showed a single sharp endothermic peak at 162.76°C corresponding to its melting point (155°C). Decomposition of the organic acid started immediately after the melting event since the signal did not return to the baseline level, but continued its downward shift. This thermal instability of citric acid anhydrous at temperatures above its melting point was consistent with the thermo gravimetric analysis (TGA) findings and was detectable in all the physical blends as a broad peak around 190°C exhibiting concentration-dependent intensity (Schilling et al., 2008). In NIZ-3 and NIZ-4 endothermic peak of drug disappeared, indicating the potential interaction between nizatidine and citric acid consequently, nizatidine was incompatible with citric acid.

Further in Figure 5, the DSC curves suggested that NIZ-9 (Formulation, F5 containing citric
acidity showed an endothermic peak of drug at 140.01°C and was well preserved with slight changes in terms of broadening or shifting towards the higher temperature. NIZ-10 showed endothermic peak of drug at 134.58°C and was well preserved with slight changes in terms of shifting towards the lower temperature. But in both NIZ-9 and NIZ-10 citric acid endothermic peak (NIZ-2, 162°C) disappeared, which indicated that there might be potential interaction between nizatidine and citric acid.

Fig. 2. DSC curves of pure drug nizatidine (NIZ-1), pure polymer HPMC K4M (NIZ-5), and 1:1 mixture of nizatidine & HPMC K4M (NIZ-7).

Fig. 3. DSC curves of nizatidine pure drug (NIZ-1), pure polymer polyox WSR 1105 (NIZ-6), and 1:1 mixture of nizatidine & polyox WSR 1105 (NIZ-8).
(iii) **Visual observation**

From both FTIR and DSC studies it was concluded that nizatidine was incompatible with citric acid. It was also visually observed in punched tablets with citric acid and showed in Figure 6. Whenever both nizatidine and citric acid were present the scope of brown coloration started. Brown color was not clearly visible immediately after preparation and after one day, but gradually developed. When either of the ingredients, citric acid or drug was excluded no coloration was noticed (Figure 6 m and n). This clearly proved the existence of interaction between nizatidine and citric acid.

**Physical evaluation of floating tablets of nizatidine**

The physico-chemical characters of tablets are shown in Table 2. The average weight of all the tablets for different formulations (F1 – F11) was found to range from 500.5 ± 7.24 to 507 ± 8.56 mg. The hardness of formulations F3 - F11 was found to be in between 5.8 ± 0.5 to 6.2 ± 0.2 kg/cm², except for F1 and F2 with hardness of 5 ± 0.3 to 5.1 ± 0.2 kg/cm². The thickness varied from 6.11 ± 0.06 to 6.34 ± 0.04 mm and friability was in the range of 0.17 to 0.35% for all the formulations indicating good mechanical resistance. The assay of the tablets of all the formulations gave a value of 97.45% to 100.85%. Tablets of all the formulations showed acceptable physicochemical properties and complied with pharmacopeial standards.
specifications for weight variation, drug content and friability.

**In vitro buoyancy studies**

The investigated floating systems employed NaHCO₃ as gas-forming agent dispersed in a hydrogel matrix. The in vitro buoyancy experiments revealed the ability of most of the formulations to remain buoyant for more than 10 h except F8 and F9. It was suggested that the gel layers formed by the polymers, enabled efficient entrapment of generated gas bubbles. The possible increase in the tablet porosity made it to float on dissolution medium (0.1 N HCl) for longer period of time. The formulations were developed so that upon arrival in the stomach, the carbon dioxide gas could be liberated by the acidity of gastric contents and got entrapped in the gel of hydrocolloid. A decrease in the density would cause the dosage form to float on the chyme (Brahma and Kim, 2000). The extended residence time of this drug in the stomach could increase local delivery of the drug to H₂-receptor of the parietal cell just like Ranitidine HCl DDS and result in the improvement of receptor site bioavailability of nizatidine to reduce acid secretion (Raval et al., 2007).

One of the parameters influencing the behaviour of the effervescent systems is their floating lag time. As shown in Table 2, the tablets prepared with HPMC K4M (F1-F5), constant NaHCO₃ ratio, 10% w/w and 2 % w/w of citric acid exhibited short floating lag time. The lag time of formulations F6 and F7 containing NaHCO₃ without citric acid were 85 and 92 s respectively. This time was slightly longer than that obtained with other formulations (F1-F5). The formulations (F8-F11) prepared with Polyox WSR 1105 containing 12% w/w of NaHCO₃ exhibited floating lag time in the range of 65 to 171 s and in these formulations the floating lag time increased with increasing concentration of Polyox WSR 1105.

Fig. 6. Tablets showing the interaction (brown colored spots) due to the presence of citric acid and nizatidine (a-l), when either of these is absent no interaction is seen (m & n).
**In vitro drug release studies**

Initially, we calculated the theoretical drug release profile of nizatidine for 10 h. The calculation was based on the reported pharmacokinetic parameters of the drug (PDR, 2011). It was expected that the developed formulation should have the theoretical drug release profile as 20±3% in 1 h, 28±3% in 2 h, 37±3% in 3 h, 46±3% in 4 h, 64±3% in 6 h, 82±3% in 8 h and 100±3% in 10 h.

From the Figure 7, it could be observed that the polymer HPMC K4M had sustaining effect on the release of drug from the floating matrix tablet. The cumulative percentage of drug release from formulations F1, F2, F3, F4 and F5 was 81.18 ± 0.4, 87.56 ± 2.7, 94.08 ± 1.4, 100.61 ± 4.0 and 99.12 ± 2.3 in 10 h respectively. All these five formulations (F1-F5) floated for 10 hours. Formulations F1 and F2 were unable to sustain the drug release as theoretical profile and also didn’t release the drug within the desired time. Formulations F3 and F4 were unable to sustain the drug release as theoretical profile but released the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. Formulation F5 sustained the drug release as theoretical profile and also released the drug within the desired time. But these formulations were containing citric acid, which was incompatible with nizatidine. So the formulations were further developed by excluding citric acid.

The cumulative percentage of drug release from formulations F6 and F7 was 97.82 ± 1.4 and 92.72 ± 1.4 in 10 hours respectively. These two formulations also floated for 10 h. Formulation F7 was unable to sustain the drug release as theoretical profile but released the drug within the desired time. Formulation F6 sustained the drug release as theoretical profile and also released the drug within the desired time. So formulation F6 was considered as best formulation among all these prepared with HPMC K4M. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer.

The formulations F8-F11 were prepared with Polyox WSR 1105. From Figure 8 it could be observed that the polymer polyox WSR 1105 had sustaining effect on the release of drug from the floating matrix tablet. Cumulative percentage of drug release from formulations F8, F9, F10 and F11 were 99.14 ± 1.7, 100.39 ± 1.0, 98.01 ± 1.4 and 97.19 ± 0.4 in 6, 8, 10 and 10 hours respectively. Formulations F8 and F9 were unable to sustain the drug release for the desired time. Formulations F10 and F11 were able to sustain the drug release as theoretical profile and also released the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. Formulation F10 was considered as best optimized formulation among all the four formulations as it showed good sustained release very near to theoretical release profile.

![Fig. 7. In vitro dissolution profiles of nizatidine floating tablets prepared with HPMC K4M (n = 3).](image-url)
**Analysis of *in vitro* drug release data**

The data obtained from *in vitro* dissolution studies was analysed by using different models viz., zero order, first order, Higuchi and Peppas equation. Different n values of Korsmeyer-Peppas equation indicate different mechanisms of drug release. If the n value is 0.45 then Fickian diffusion is apparent, if the n value ranges from 0.45 to 0.89 it represents anomalous diffusion transport. If the n value reaches 0.89 and above then case II and Super case II transport are indicated, which show that the release would follow zero order. From table 3 it is clear that F6, F7, F10 and F11 followed the zero-order because they showed high regression coefficient (R²) for zero-order when compared to others. The formulations F1-F5 and F8 followed the Peppas model. Whereas F9 followed the Higuchi model. The optimized formulations F6 and F10 followed zero-order release. All the formulations (except F3, F4, F8 and F9) have n value between 0.45 and 0.89 indicating anomalous transport.

For the comparison of release profiles of reference and test products, “difference factor” f₁ and “similarity factor” f₂, were calculated. The similarity factor for the optimized formulations (F6 and F10) were 78 and 86 respectively. Similarly, the difference factor was 4 and 3 respectively.

**In vivo radiographic studies**

The *in vitro* buoyancy lag time of BaSO₄-loaded floating tablets were 240 ±35 s. The increase in lag time, compared to the original formula of F10 (105 ±15 s), was expected because BaSO₄, as reported by its manufacturer, has a higher relative density (4.5 g/cm³). Figure 9 shows the radiographic images taken at different time periods of BaSO₄-loaded floating tablet in one volunteer under fasting state. Here, the tablet appeared at the same position in the stomach for about 1.5 h. Later, the tablet moved down from stomach into the intestine. The mean gastric retention time of the floating tablet in fasting state was 2.0 ±0.86 h (n=3). Similarly, mean gastric retention time of the plain controlled release tablet (CRDDS) in fasting state was only ≤ 0.5 h, shown in Figure 10.

Figure 11 shows the radiographic images taken at different time periods of BaSO₄-loaded floating tablet in one volunteer under fed state. The tablet remained in the stomach for the first 3 h at different positions. Later on, the tablet slightly moved downwards, yet remained within the stomach till 5 h. In the next picture, the tablet moved from stomach into the intestine. The mean gastric retention time of the floating tablet in fed state (Figure 12) was 5.33 ± 0.57 h (n=3). Whereas, mean gastric retention time of the plain controlled release tablet in fed state was 1.66±0.28 h (n=3).
TABLE 3

Regression coefficient ($R^2$) values of nizatidine floating tablets for different kinetic models.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero-order $R^2$</th>
<th>First-order $R^2$</th>
<th>Higuchi $R^2$</th>
<th>Korsmeyer – Peppas $R^2$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.936</td>
<td>0.996</td>
<td>0.995</td>
<td>0.997</td>
<td>0.609</td>
</tr>
<tr>
<td>F2</td>
<td>0.896</td>
<td>0.987</td>
<td>0.999</td>
<td>0.999</td>
<td>0.461</td>
</tr>
<tr>
<td>F3</td>
<td>0.904</td>
<td>0.924</td>
<td>0.992</td>
<td>0.994</td>
<td>0.377</td>
</tr>
<tr>
<td>F4</td>
<td>0.818</td>
<td>0.921</td>
<td>0.976</td>
<td>0.984</td>
<td>0.252</td>
</tr>
<tr>
<td>F5</td>
<td>0.980</td>
<td>0.789</td>
<td>0.974</td>
<td>0.988</td>
<td>0.501</td>
</tr>
<tr>
<td>F6</td>
<td>0.979</td>
<td>0.804</td>
<td>0.958</td>
<td>0.971</td>
<td>0.472</td>
</tr>
<tr>
<td>F7</td>
<td>0.980</td>
<td>0.789</td>
<td>0.955</td>
<td>0.968</td>
<td>0.473</td>
</tr>
<tr>
<td>F8</td>
<td>0.820</td>
<td>0.893</td>
<td>0.974</td>
<td>0.992</td>
<td>0.255</td>
</tr>
<tr>
<td>F9</td>
<td>0.944</td>
<td>0.831</td>
<td>0.985</td>
<td>0.965</td>
<td>0.393</td>
</tr>
<tr>
<td>F10</td>
<td>0.987</td>
<td>0.834</td>
<td>0.954</td>
<td>0.941</td>
<td>0.470</td>
</tr>
<tr>
<td>F11</td>
<td>0.995</td>
<td>0.830</td>
<td>0.928</td>
<td>0.962</td>
<td>0.655</td>
</tr>
</tbody>
</table>

Fig. 9. X-ray photographs of GRDDS tablet containing BaSO$_4$ (shown by an arrow) in fasting state at different time points.

Fig. 10. X-ray photographs of CRDDS tablet (shown by an arrow) in fasting state at different time points.
Conclusions

The controlled release floating tablets of nizatidine were successfully developed by effervescent technique using HPMC K4M and Polyox WSR 1105 as polymers and NaHCO₃ as effervescent agent. From the drug-excipients compatibility study, it was observed that nizatidine had an interaction with citric acid and no incompatibility existed between the drug and other excipients. Drug release data of formulations was subjected to curve fitting analysis. Formulations, F6 and F10 were best fits for zero-order release and considered as optimized. One of the optimized formulations, F10 was selected for the radiological study by including BaSO₄. These studies were conducted in comparison with plain controlled release tablets. This revealed that gastric retention time of floating tablets and plain controlled release tablets in fasting state were 2 ± 0.86 hours (n=3) and ≤ 0.5 hours respectively. Gastric retention time of floating tablets and plain controlled release tablets in fed state were 5.33 ±0.57 h and 1.66±0.28 h (n=3) respectively in healthy human volunteers. These studies confirmed the superiority of GRDDS design in gastric retention over plain or controlled release tablets.

Conflict of interest

The authors declare that they have no conflict of interest.

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References


Address correspondence to: Prof. V. Kishan, Department of Pharmacaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506009, AP, India. Tel: +91 870 2438844; E-mail: vbkishan@yahoo.com