DEVELOPMENT AND IN VITRO EVALUATION OF AN IN SITU GELLING ORAL LIQUID SUSTAINED RELEASE FORMULATION OF NIZATIDINE

Namrata Hallur¹, Rajashekhar¹, Swamy NGN¹*, Abbas Z²

¹Department of Pharmaceutics, Government College of Pharmacy, Bangalore – 560 027, Karnataka, India.
²Formulation Development Department, Apotex Research Private Limited. Bangalore – 560 099, Karnataka, India.

ABSTRACT

The objective of this study was to develop a novel, floating in situ gelling liquid dosage system for sustained delivery of Nizatidine for the ulcer therapy. The study evaluates gellan gum and sodium alginate as gelling agents, calcium chloride as source of cations and sodium bicarbonate as the gas forming agent. Different Solutions (sols) coded FSA1 to FSA6 were prepared with varying amounts of sodium alginate ranging from 0.5% w/v to 1.75% w/v and formulations FGG1 to FGG6 with 0.25% w/v to 1.25% w/v of gellan gum. The sols were evaluated for pH, surface morphology, rheological properties, in vitro gelation, in vitro floating ability and in vitro drug release. The pH of the prepared in situ gels was found to be in the range of 7.1 to 7.3, suitable for oral delivery. The formulations exhibited thixotropic flow behaviour. With the increase in the polymer concentration, immediate gelation was observed which led to increase in the duration of floating. The in situ gels exhibited drug content uniformity ranging from 97.72 ± 0.6 to 99.25 ± 0.3%. A significant decrease in the rate and extent of drug release was observed with the increase in polymer concentration. Stability studies were carried out on select formulations at 25°C ± 2°C / 60% RH ± 5% RH and 40°C ± 2°C / 75% RH ± 5% RH for 6 months. The drug content was observed to be within permissible limits and there were no significant deviations in the in vitro gelation, floating ability and in vitro drug release characteristics.
Keywords: Nizatidine, Floating in situ gels, Gastroretentive in situ gels, Gellan gum, Sodium Alginate.

INTRODUCTION
The oral route is considered as the most convenient and promising route for drug delivery. The high level of patient compliance in oral drug delivery systems is due to the ease of administration, flexibility in formulation, comparatively low cost of therapy and ease in handling of these systems. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit owing to variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach [1].

For the past few decades, enormous research is being done in the area of oral controlled drug delivery systems. Of special interest are Gastro retentive drug delivery systems (GRDDS) also referred to as Floating drug delivery systems (FDDS) or hydro dynamically balanced systems (HBS). These drug delivery systems are one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract to control the gastric residence time (GRT) [2]. FDDS have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate and release the drug slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations [3].

Gastric retention is advantageous for the delivery of drugs with narrow absorption window in the small intestinal region. Prolonged gastric retention improves bioavailability, reduces drug waste, improves solubility for drugs that are less soluble in a high pH environment and advantageous for drugs that degrade in the colon. It does have applications also for local drug delivery to the stomach and proximal small intestines. Gastro retentive formulations help to provide better availability of new products with new therapeutic possibilities and substantial benefits to the patients [4].

The controlled gastric retention of solid dosage forms may be achieved by different strategies such as FDDS (Ex: non-effervescent and effervescent type tablets, capsules, granules, beads, microspheres, superporous hydrogels [5] and in situ gels), swelling and expanding systems,
low-density systems, raft systems incorporating alginate gels, polymeric bioadhesive or mucoadhesive systems, high-density systems, magnetic systems and other delayed gastric emptying devices \[^6\].

In the past few years, increasing number of *in situ* gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. Smart polymeric systems represent promising means of delivering the drugs; once administered these polymers undergo sol-gel transition \[^7\].

The *in situ* gelling system being one among them is a type of mucoadhesive drug delivery system principally capable of releasing drug molecule in a sustained manner affording relatively consistent plasma profile. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or up on change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. This gelation involves the formation of the double helical junction zones followed by aggregation of the double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages like simple manufacturing processes and ease of administration. Even though the delivery system is widely applicable for ocular therapy \[^8\] and nasal delivery \[^9\], it has several advantages as a dosage form for oral administration like ease of preparation, homogeneous drug distribution, maximum intimate contact of the drug at the absorption site, thus, influencing the rate of absorption compared to other conventional suspensions. By virtue of their mucoadhesive property, the *in situ* gels help in coating of the ulcer lining once the sol comes in contact with the gastric pH \[^10\].

Nizatidine (NIZ), a H\(_2\) receptor antagonist, was used as a model drug. NIZ, is a competitive inhibitor of gastric acid secretion and is used for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer and active duodenal ulcers. It is having an oral bioavailability of 70% with a very short biological half life of 1-2 hours \[^11\]. It mainly acts by inhibiting acid production by reversibly competing with histamine. With the conventional dosage forms of NIZ, the treatment becomes ineffective in some patients with reflux oesophagitis who are being treated with proton pump inhibitors and may continue to produce acid secretion throughout night (nocturnal acid breakthrough). Such patients could be benefited by taking a sustained release formulation of H\(_2\) receptor antagonist. Oral
administration of NIZ in the form of fast dissolving films \cite{12} and immediate release tablets\cite{13} has already been reported.

Thus in the present investigation an attempt has been to prepare a formulation of NIZ as an \textit{in situ} gel forming drug delivery system for oral delivery using gellan gum and sodium alginate as gel forming agents. The Gellan gum commercially available as gelrite is an anionic deacetylated exocellular polysaccharide secreted by \textit{Pseudomonas elodea}, with a tetrasaccharide repeating unit of one alpha-L-rhamnose, one beta-D-glucuronic acid and two beta-D-glucose units. It has a characteristic property of temperature dependent and cation induced gelation \cite{14}, whereas, the sodium alginate undergoes gelation in presence of di- or trivalent metal ions by a co-operative process involving consecutive glucuronic residues in the alpha-L-glucuronic acid blocks of the alginate chain \cite{15}.

\textbf{MATERIALS & METHODS}

NIZ was obtained as a gift sample from Hulcin Research Limited, Chennai. Gellan gum (GG) was generously gifted by Strides Arcolabs Limited, Bangalore. Sodium alginate (SA) and Anhydrous calcium chloride (CaCl$_2$) were purchased from Finar chemicals private limited, Ahmedabad and Sisco Research Labs private Limited, Mumbai respectively. Methyl Paraben and Propyl Paraben were obtained as gift samples from Karnataka Antibiotics and Pharmaceuticals Limited, Bangalore. All other reagents used were of analytical grade.

\textbf{Preparation of \textit{in situ} gelling systems}

The detailed composition of \textit{in situ} gelling liquid formulations is presented in Table 1. Formulations FSA1 to FSA6 containing SA in the concentration range of 0.5 – 1.75\% w/v were prepared by dispersing SA in pH 7.0 citrate buffer. These mixtures were heated to 60°C under continuous stirring. After cooling below 40°C, CaCl$_2$, 0.075\% w/v and NaHCO$_3$, 0.4\% w/v were added under continuous stirring. Later NIZ was added in parts to the resulting alginate solution under continuous stirring to produce homogenous dispersion.

Similarly, formulations FGG1 to FGG6 containing different concentrations of GG in the range of 0.25 – 1.5\% w/v were prepared by dispersing GG in pH 7.0 citrate buffer. These mixtures were heated to 90°C under continuous stirring. After cooling below 40°C, CaCl$_2$, 0.016\% w/v and NaHCO$_3$, 0.4\% w/v were added under continuous stirring. Later NIZ was added in parts to the resulting GG solution under continuous stirring to produce homogenous dispersion\cite{16}. 
For both the formulations, 0.18% w/v of methyl paraben and 0.02% w/v of propyl paraben were used as preservatives. The resulting formulations were finally stored in amber coloured bottles until further use.

**Evaluation of In situ gels**

**Physical appearance, clarity and pH of the Gels**

The developed formulations were inspected visually for clarity in sol and gel form. The pH of the prepared formulation was determined by using calibrated digital pH meter (Model: Systronics micro pH system 362) at 25°C ± 2°C.

**Table 1: Formulation composition of Nizatidine in situ gels**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>NIZ</th>
<th>SA</th>
<th>GG</th>
<th>CaCl₂</th>
<th>NaHCO₃</th>
<th>MP</th>
<th>PP</th>
<th>CB pH 7.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSA1</td>
<td>150</td>
<td>500</td>
<td>-</td>
<td>75</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FSA2</td>
<td>150</td>
<td>750</td>
<td>-</td>
<td>75</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FSA3</td>
<td>150</td>
<td>1000</td>
<td>-</td>
<td>75</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FSA4</td>
<td>150</td>
<td>1500</td>
<td>-</td>
<td>75</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FSA5</td>
<td>150</td>
<td>1750</td>
<td>-</td>
<td>75</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FSA6</td>
<td>150</td>
<td>2025</td>
<td>-</td>
<td>75</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FGG1</td>
<td>150</td>
<td>-</td>
<td>250</td>
<td>16</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FGG2</td>
<td>150</td>
<td>-</td>
<td>500</td>
<td>16</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FGG3</td>
<td>150</td>
<td>-</td>
<td>750</td>
<td>16</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FGG4</td>
<td>150</td>
<td>-</td>
<td>1250</td>
<td>16</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FGG5</td>
<td>150</td>
<td>-</td>
<td>1500</td>
<td>16</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
<tr>
<td>FGG6</td>
<td>150</td>
<td>-</td>
<td>1750</td>
<td>16</td>
<td>400</td>
<td>180</td>
<td>20</td>
<td>Q.S</td>
</tr>
</tbody>
</table>

NIZ: Nizatidine, SA: Sodium Alginate, GG: Gellan Gum, CaCl₂: Calcium chloride, NaHCO₃: Sodium bicarbonate, MP: Methyl Paraben, PP: Propyl Paraben, CB pH 7.0: Citrate buffer pH 7.0, Q.S: Quantity sufficient to make upto 100 mL

**Scanning electron microscopy (SEM)**

The surface morphology of the in situ gels was examined by scanning electron microscopy (SEM JSM 840A JEOL, Tokyo, Japan) to study the structure and arrangement of the formulation. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Gold – palladium alloy of 120 Å was coated on the sample using sputter coating unit (E5, 100 Polaron UK) in Argon at an ambient of 8 -10 pascals with the plasma voltage of about 20 mA to render them electrically conductive. The SEM was operated at low accelerating voltage of about 20 KV with a load current of about 80 mA.
Rheological Studies

NIZ oral suspension (5 mL) and 0.1N HCl (100 mL) were mixed in the ratio of 1:20 v/v and gelation was observed by visual examination. Viscosity of the sols and thereafter in situ gels formed in 0.1N HCl were measured by using Brookfield programmable Rheometer DV III+ model (Brookfield, Engineering Laboratories Inc., Stoughton, MA, USA) with the spindle number 6. For determination of viscosity before gelation, about 20 mL of sample was placed in a beaker and the viscosity values were recorded using a suitable spindle number at different rpm. To measure the viscosity values after gelation in 0.1N HCl, the same procedure as mentioned above was followed. The viscosity measurements before and after gelation was done at rpm of 10, 20, 30, 40, 50 and upto 100 at temperature of 37°C ± 2°C. Rheograms were constructed by plotting the dial readings on the X-axis and RPM values along the Y-axis\(^{[19]}\).

**In Vitro gelation study**

Gelation of in situ gelling solution was carried out by taking 500 mL of 0.1N hydrochloric acid (HCl, pH 1.2) in a beaker\(^{[20]}\). Accurately measured 10 mL of solution was added to HCl with mild agitation that avoids breaking of formed gel. Gelling was observed visually by qualitative measurement and reported in terms of strokes depending on their gelation pattern.  
+ = gels after few minutes, dispersed rapidly  
++ = gelation immediate remains for few hours  
+++ = gelation immediate remains for an extended period.

**In Vitro Floating Study**

The in vitro floating study was carried out using USP dissolution apparatus II having 500 ml of 0.1N HCl (pH 1.2) . The medium temperature was kept at 37°C. Accurately weighed 10 mL of the prepared in situ gel formulations were drawn up using disposable syringe and placed into the petri dish (4.5mm internal diameter) and finally the petri dish containing the formulation was kept in the dissolution vessel containing medium without much disturbance. The time the formulation took to emerge on to the medium surface (floating lag time) and the time over which the formulation constantly floated on the dissolution medium surface (duration of floating) were noted\(^{[21, 22]}\).

**Estimation of Drug Content**

NIZ in 0.1N HCl exhibited absorption maxima at 314 nm. The drug obeyed Beer-lambert’s law in the concentration range of 2.0 – 24.0 µg/ml. A calibration curve was constructed in
0.1N HCl. The linear relationship had a slope value of 0.0368 and an intercept value of 0.0071. The drug concentration in the sample was arrived at by making use of the relationship, \( x = y - 0.0071 / 0.0368 \). A volume of the sample equal to 10 mL was added to 100 mL of 0.1N HCL solution and stirred for 1 h on a magnetic stirrer. The obtained solution was filtered and suitably diluted. Absorbance of this solution was measured at 314 nm in UV-visible spectrophotometer (Elico SL-159) against standard blank. The Drug content was calculated using the formula;

\[
% \text{ Drug content} = \left( \frac{\text{Practical Drug content}}{\text{Label claim of the product}} \right) \times 100
\]

**In vitro drug release studies**

The study of the NIZ release from the in-situ gelling preparation was carried out similar to the method described by Zatz and Woodford with some modification using USP 24 dissolution test apparatus with paddle stirrer at a rate of 50 rpm. The slow speed prevented breaking of the gelled formulation and ensured a low level of agitation. The dissolution medium used was 500 mL of a 0.1 N solution of HCl (pH 1.2), and the temperature was kept at 37\(^\circ\)C ± 2\(^\circ\)C. A 10 mL sample was withdrawn using a disposable syringe; the needle was then wiped clean and the excess sample removed from the needle end. The sample was then gently transferred into a Petri dish which was then immersed into the dissolution medium without much turbulence. At hourly intervals, an accurately measured 10 mL sample of the dissolution medium was removed with the help of a hypodermic syringe, diluted to 50 mL with 0.1N HCl and absorbance of the sample was read at 314 nm using a UV spectrophotometer (Elico SL-159) for analysis of NIZ. Each time, the sample withdrawn was replenished with the same amount of the pre-warmed 0.1N HCl. Each experiment was continued for a period of 8 h in triplicate.

**Stability studies**

Stability studies of the selected formulations were carried out as per ICH guidelines. The selected formulations were stored at accelerated condition of 40\(^\circ\)C ± 2\(^\circ\)C / 75 ± 5% RH and at controlled room temperature of 25\(^\circ\)C ± 2\(^\circ\)C / 60 ± 5% RH for 6 months and were evaluated for their physical appearance, viscosity, pH, *in vitro* gelation, floating lag time, duration of floating, drug content and *in vitro* drug release profile.

**RESULTS & DISCUSSION**

An ideal *in situ* gelling delivery system is required to be a free-flowing liquid with low viscosity under non-physiological conditions to allow reproducible administration into
Stomach condition. It needs to undergo in situ phase transition to form a strong gel capable of withstanding shear forces in gastrointestinal tract and to sustain drug release under gastric environment. The formed in situ gel should preserve its integrity without dissolving or eroding for prolonged period to facilitate sustained release of drugs locally. The developed formulations met all prerequisites to become an in situ gelling floating system, gelled, and floated instantaneously in the pH conditions of the stomach. The relative density of the batches was measured and no significant differences between the batches were found. The relative density values of the batches ranged between 1.012 g/cm³–1.029 g/cm³.

Table 2: Evaluation of Nizatidine in situ gels

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>pH</th>
<th>In vitro gelation</th>
<th>Floating Lag time (sec)</th>
<th>Duration of Floating (h)</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSA1</td>
<td>7.1</td>
<td>++</td>
<td>&lt; 60</td>
<td>20</td>
<td>98.52 ± 0.8</td>
</tr>
<tr>
<td>FSA2</td>
<td>7.0</td>
<td>++</td>
<td>&lt; 60</td>
<td>22</td>
<td>99.10 ± 1.2</td>
</tr>
<tr>
<td>FSA3</td>
<td>7.2</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>99.12 ± 0.6</td>
</tr>
<tr>
<td>FSA4</td>
<td>7.1</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>98.63 ± 0.9</td>
</tr>
<tr>
<td>FSA5</td>
<td>7.3</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>98.52 ± 0.7</td>
</tr>
<tr>
<td>FSA6</td>
<td>7.1</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>98.10 ± 1.3</td>
</tr>
<tr>
<td>FGG1</td>
<td>7.0</td>
<td>++</td>
<td>&lt; 60</td>
<td>22</td>
<td>99.21 ± 0.5</td>
</tr>
<tr>
<td>FGG2</td>
<td>7.1</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>99.25 ± 0.3</td>
</tr>
<tr>
<td>FGG3</td>
<td>7.1</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>98.63 ± 1.2</td>
</tr>
<tr>
<td>FGG4</td>
<td>7.3</td>
<td>+++</td>
<td>&lt; 60</td>
<td>&gt; 24</td>
<td>98.57 ± 0.9</td>
</tr>
<tr>
<td>FGG5</td>
<td>7.2</td>
<td>+++</td>
<td>75</td>
<td>&gt; 24</td>
<td>98.08 ± 0.8</td>
</tr>
<tr>
<td>FGG6</td>
<td>7.1</td>
<td>+++</td>
<td>80</td>
<td>&gt; 24</td>
<td>97.72 ± 0.6</td>
</tr>
</tbody>
</table>

Sol to gel transformation of gellan gum dispersion occurs in the presence of either monovalent or divalent cations upon coming in contact with the gastric fluids. The insoluble CaCl₂ present in the formulation, in presence of gastric acid release calcium ions which interact with the polymer inducing ionic gelation. The carbon dioxide released from the action of gastric acid on sodium bicarbonate results in augmenting the gel with floating characteristics. The carbon dioxide is entrapped in the gel network of the formulation, and the gel rises to the surface of the dissolution medium (in vitro) or the stomach (in vivo). We have observed that in situ gelling formulations of gellan gum, concentration of 0.25% - 1.5% w/v is suitable for sustaining the NIZ in SGF. The gellan gum concentration below 0.25% w/v was not able to sustain the NIZ for long period of time; gellan gum concentration above 1.5% w/v forms gels at room temperature before administration due to high viscosity of solution. All the prepared formulations containing GG and SA were found to be satisfactory in respect to their physical appearance, clarity and pH. The formulations were liquid at room
temperature and revealed pH in the range of 7.0 – 7.3. The pH of the formulations is listed in Table 2.

The SEM photographs of the formulations FSA4 and FGG3 before and after gelation are presented in Figure 1 and 2. The photographs reveal that the formulations have a plate-like arrangement and show greater folding in the polymer structure.

Fig. 1: Scanning electron microphotograph of FSA4 before and after gelation

Fig. 2: Scanning electron microphotograph of FGG3 before and after gelation

The rheological properties of the solutions are of importance in view of their proposed oral administration. In the selection of the concentration of the gelling polymer, a compromise is sought between a sufficiently high concentration for the formation of gels of satisfactory gel strength for use as a delivery vehicle, and a sufficiently low concentration to maintain an acceptable viscosity for ease of swallowing. The rheograms of the in situ gelling formulations
of FSA and FGG series before gelation and after gelation are presented in Figure 3. Before gelation, FSA and FGG series of formulations revealed non-Newtonian pseudoplastic flow behavior in which the bending down curve is superimposed upon the up curve, whereas, after gelation, the down curve is displaced to the left in respect to the up curve indicating the thixotropic nature of the formed gel.

![Rheograms of FSA and FGG in situ gels formulations before and after gelation](image)

Fig. 3: Rheograms of FSA and FGG in situ gels formulations before and after gelation

The *in vitro* gelation study was conducted in 0.1N HCl, pH 1.2. Gelation characteristics of the formulations was assessed on an ordinal scale ranging between + and +++ as shown in Table 2. It can be observed from the results that formulations containing higher concentrations of GG and SA underwent gelation instantly and formed good gels while formulations containing lower concentrations of GG and SA resulted in poor and weak gels that could be attributed to the internal ionotropic gelation effect of calcium ions on GG and SA.
The *in vitro* floating ability of the prepared formulations was investigated using 0.1N HCl, (pH 1.2). The gelation involves formation of double helical junction zone followed by aggregation of the double helical segments to form a three dimensional network by complexation with ca++ ions and hydrogen bonding. Time taken by formulation to emerge on the medium surface (floating lag time) and the duration over which formulation continuously floated (duration of floating) were evaluated and data is recorded in Table 2. In case of formulations containing GG, sodium bicarbonate effervesced upon contact with acidic medium, releasing carbon dioxide. The gelation and cross-linking by ca++ ions result in the formation of a thick gel. The released carbon dioxide was entrapped in the gel matrix producing a buoyant preparation, which resulted in prolonged residence time. In case of formulations containing SA, the calcium ions reacted with sodium alginate to produce a cross-linking 3D gel network and swollen structure that may restrict further liberation of carbon dioxide and drug molecules, leading to an extended period of floating and drug release.

All the batches formulated exhibited drug content uniformity ranging from 97.72 ± 0.6 to 99.25 ± 0.3%, indicating homogenous distribution of drug throughout gel. The % drug content of the prepared batches is shown in Table 2.

**Fig. 4: In vitro drug release from FSA and FGG in situ gels formulations**

The *in vitro* drug release from the *in situ* gelling formulations coded FSA1 to FSA6 and FGG1 to FGG6 is shown in Fig. 4. A significant decrease in the rate and extent of drug release was observed with the increase in polymer concentration and this is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse. Considering the aforementioned results and
in vitro drug release profile, formulations FSA4 & FGG3 were selected for further stability testing.

Stability samples withdrawn at the end of six months of accelerated storage condition and intermediate storage condition showed no change in respect to physical appearance, viscosity, pH, in vitro gelation, floating lag time, duration of floating and drug content. Results of the stability study revealed no remarkable change in the in vitro drug release profile. The results of the stability study at 40\(^\circ\)C ± 2\(^\circ\)C / 75 ± 5% RH and 25\(^\circ\)C ± 2\(^\circ\)C / 60 ± 5% RH at the end of 6 months are compiled in Table 3.

Table 3: Stability data of formulations FSA4 and FGG3 at the end of 6 months

<table>
<thead>
<tr>
<th>Evaluation parameter</th>
<th>40(^\circ)C ± 2(^\circ)C / 75 ± 5% RH</th>
<th>25(^\circ)C ± 2(^\circ)C / 60 ± 5% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FSA4</td>
<td>FGG3</td>
</tr>
<tr>
<td>pH</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td>In vitro gelation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Floating Lag time (sec)</td>
<td>&lt; 60</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Duration of Floating (h)</td>
<td>&gt; 24</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>% Drug content</td>
<td>98.44 ± 1.9</td>
<td>97.87 ± 1.2</td>
</tr>
</tbody>
</table>

CONCLUSION

Floating in situ gelling system is one of the approaches of floating drug delivery system which undergo sol to gel transition in acidic stomach conditions and provide stomach specific release of drug for longer duration while being buoyant on the gastric fluid surface. Such systems provide the advantage of better absorption of drugs which are absorbed from the upper part of the stomach. The present investigation demonstrated the feasibility of developing in situ gelling formulations employing polymers such as gellan gum and sodium alginate along with the source of a calcium ion. The prepared suspensions have the potential to form the gel in situ upon coming in contact with gastric pH and also have the ability of sustain the release of the NIZ beyond 8 h which is desirable for better treatment of gastric and duodenal ulcers in cases of reflux oesophagitis where acid secretion continues. With this we conclude that the administration of Nizatidine as in situ gel formulation using gellan gum or sodium alginate will definitely improve the therapeutic efficacy and patient compliance especially for those suffering with reflux oesophagitis.

ACKNOWLEDGEMENTS

The authors wish to thank Messrs Hulcin Research Limited, Chennai and Strides Arcolabs Limited, Bangalore for sparing gift samples of Nizatidine and Gellan gum respectively. The
authors are thankful to the Principal, Government College of Pharmacy, Bangalore, for
extending the laboratory facilities to carry out the Research work.

REFERENCES
1. Pundlikrao IP, Mohanbhai PK. Design and Development of Floating Gastro Retentive
   Tablets for Mosapride Citrate Dihydrate: In vitro-in vivo Evaluation. Indian Journal of
2. Sharma N, Balekar N, Jain DK. Design and Development of Floating Tablet of Ranitidine
   Hydrochloride and Study the Effect of Formulation Variables. Indian Journal of Novel
5. Shwetha K, Swamy NGN. Development and Evaluation of Superporous Hydrogels for
   Metoprolol Tartrate as a Gastro Retentive System. Indian Journal of Novel Drug
   innovative acceptable approach in gastroretentive drug delivery. Archives of Applied
   Floatable in situ Gel for Stomach-specific Drug Delivery of Ofloxacin. American Journal
8. Eaga CM, Kandukuri JM, Allenki V, Yamsani MR. In situ gels – a novel approach for
9. Swamy NGN, Abbas Z. Mucoadhesive in situ gels as nasal drug delivery systems: an
10. Chandramohan SB, Manjunatha N, Patel K, Samanta MK, Bhaskaran S. Design and
    Development of Oral Sustained In Situ Gelling System of Famotidine. Indian Journal of
11. Sweetman SC. Martindale The complete drug reference. 36th ed., United States of


