Formulation and Evaluation of Itopride Hydrochloride Floating Beads for Gastroretentive Delivery

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ABSTRACT

A gastroretentive sustained release system of itopride hydrochloride was formulated to increase the gastric residence time and modulate its release behavior. Itopride hydrochloride is a prokinetic drug used in the treatment of gastroesophageal reflux disease, Non-ulcer dyspepsia and as an antiemetic. Hence, itopride hydrochloride beads were prepared by emulsion gelation method by employing low methoxy pectin and sodium alginate as sustained release polymers in three different ratios alone and in combination and sunflower oil was used to enable floating property to the beads. The effect of variation in polymer and their concentration was investigated. The beads were evaluated for production yield, particle size, swelling index, density measurement, buoyancy, drug content, drug entrapment efficiency, in vitro release characteristics and release kinetic study. Based on drug entrapment efficiency, buoyancy, swelling and in vitro release, F9 was selected as the optimized formulation. F9 was further subjected to surface morphology by SEM, in vitro release comparison with marketed formulation, in vivo floating study in rabbits and stability study for 90 days. In vitro release follows zero order and fitted in Korsmeyer peppas model (Non-Fickian release). Therefore, the rate of drug release is due to the combined effect of drug diffusion and polymer swelling. The in vivo X-ray studies revealed that the beads were floating in the rabbit stomach up to 10 hours. Thus, it was concluded that the sustained release formulation containing itopride hydrochloride was found to improve patient compliance, minimize the side effects and decrease the frequency of administration.

KEYWORDS: Itopride hydrochloride; floating drug delivery system; low methoxy pectin; sodium alginate; sunflower oil; oil entrapped floating bead.

Introduction

Oral drug delivery is the most widely utilized route of administration for systemic delivery of drugs via pharmaceutical products of different dosage form among all the explored routes. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.

Floating Drug Delivery Systems (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. While the system is floating on the gastric contents, the drug is released 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. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems. It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the gastrointestinal tract is to control the gastric residence time, i.e. gastro retentive dosage form. The continuing effort to improve pharmaceutical formulation in order to optimize therapy and patient compliance, various efforts have been tried to develop a modified release, once a day formulations. As a result of such efforts, many modified formulations are available (Chandira et al., 2010).

Non ulcer dyspepsia (NUD) and gastroesophageal reflux disease (GERD) are commonly encountered disorders of gastric motility in clinical practice. An acetylcholinesterase inhibitor or anticholinesterase agent that inhibits the enzyme acetylcholine esterase (AChE) responsible for degradation of acetylcholine possesses

ABBREVIATIONS: RH—Relative Humidity, GRT—Gastric retention time, GET—Gastric emptying time, SQRT—Square root of time, SEM—Scanning electron microscopy, FLT—Floating Lag Time, IP—Indian Pharmacopoeia, ICH—International Council for Harmonization, SGF—Simulated Gastric Fluid.
gastroprokinetic properties (Badve, 2007; Chandira et al., 2010). Among them itopride hydrochloride is the drug of first choice and is composed of list of approved acetylcholine esterase inhibitor is drug of choice for Gastro esophageal reflux disease and other disorders of gastric motility and help to speed up the passage of food through the stomach and may help with symptoms of bloating and feeling sick. It is a prokinetic drug that activates the gastrointestinal motility through synergism of its dopamine D2-receptor antagonistic action and its acetylcholine esterase inhibitory action. In addition to these actions it has an antiemetic action that is based on its dopamine D2-receptor antagonistic action.

Itopride hydrochloride has its primary site of action in stomach and half life of 5-6 h therefore requires frequent administration of dose. The marketed conventional release products need to be administered 2-3 times daily. Hence it is necessary to develop sustained release formulation which would be once a day formulation to overcome this drawback (Amit et al., 2010; Parmar et al., 2011).

Materials and Methods

Chemicals and Drugs

Itopride hydrochloride was the generous gift from Cipla Goa (India), low methoxy pectin (LMP) was received from Krishna Pectins (India), sodium Alginate (SA) from S.D. Fine Chemicals (India). Other materials used in the study were calcium chloride from Lobachem Pvt. Ltd (India), sunflower oil and Tween 80 from Hi-media laboratories (India). All chemical reagents used were of analytical grade.

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients.

Appearance, solubility and melting point:

The appearance of the drug was compared to the standard description as given in the monograph. The solubility of drug was tested in various solvents such as distilled water, dichloromethane, acetone, ethanol and methanol. Melting point of itopride hydrochloride was determined by capillary method.

Infrared spectroscopy

The FT-IR spectrum of the obtained sample of the drug was compared with the standard FT-IR spectra of the pure drug. FT-IR spectroscopy was carried out to check the compatibility between drug and polymers. The samples were prepared on KBr press.

Formulation of beads

Itopride hydrochloride beads were prepared using emulsion gelation method. Itopride hydrochloride, low methoxy pectin, Sodium alginate was passed through sieve #80 separately. Itopride hydrochloride was dissolved in small amounts of distilled water. Low methoxy pectin and sodium alginate were dissolved in distilled water in three different ratios (1:1, 1:2 and 1:3) as shown in table 1. To the above polymer solution the prepared drug solution was added and stirred and 2 ml of sunflower oil was added. Simultaneously, 2-3 drops of tween 80 was added to form a homogeneous emulsion. The drug loaded emulsion was extruded through a 23 G syringe needle into calcium chloride solution (5% w/v) maintained under gentle agitation. The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. This solution was filtered and the formed beads were allowed to dry overnight at room temperature. Further three more formulations were made using combination of low methoxy pectin and sodium alginate in different ratios (Nimase and Vidyasaga, 2010).

TABLE 1

Composition of itopride hydrochloride bead formulations.

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Drug (mg)</th>
<th>Low methoxy pectin (mg)</th>
<th>Sodium alginate (mg)</th>
<th>Sunflower oil (ml)</th>
<th>Calcium chloride (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1(1:1)</td>
<td>150</td>
<td>150</td>
<td>450</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F2(1:2)</td>
<td>150</td>
<td>300</td>
<td>450</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F3(1:3)</td>
<td>150</td>
<td>450</td>
<td>450</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F4(1:1:1)</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F5(1:2:1)</td>
<td>150</td>
<td>300</td>
<td>150</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F6(1:1.5)</td>
<td>150</td>
<td>450</td>
<td>150</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F7(1:3:1)</td>
<td>150</td>
<td>450</td>
<td>150</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F8(1:1.25:1.25)</td>
<td>150</td>
<td>187.50</td>
<td>187.50</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F9(1:1.5)</td>
<td>225</td>
<td>225</td>
<td>225</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Bead Characterization

Production yield

The obtained itopride hydrochloride beads of each formulation were collected and weighed to determine production yield (PY) using following equation (Kikuchi et al., 1999).

\[
PY (\%) = \frac{\text{Practical Mass (beads)}}{\text{Theoretical Mass (Polymer + Drug)}} \times 100
\]

Determination of particle size

The diameters of dried beads were measured using digital slide callipers (Mitutoyo Corporation, Japan) by inserting the beads in between the space of two metallic plates. The average size was then calculated by measuring the diameter of 3 sets of 100 beads from each batch (Sangeetha et al. 2010).

Determination of swelling index

The swelling behavior of the beads was studied in SGF (pH 1.2). Approximately 100 mg of beads were taken in a dissolution basket and weighed; the basket along with the beads was immersed in SGF. The weight of the basket along with the beads was determined after every hour till almost constant weights are observed. The
swelling index (SI) was calculated using the following equation (Patel et al., 2011):

\[
(\%) \text{SI} = \frac{W_2 - W_1}{W_1} \times 100
\]

Where, \( W_1 \) is weight of the dry beads and basket and \( W_2 \) is weight of the swollen beads and basket.

**Density measurements**

The mean weights and diameters of the beads were measured and used to calculate the densities of these spherical liquid paraffin entrapped calcium alginate beads containing Itopride Hydrochloride using the following equations (Badve et al., 2007):

\[
D = \frac{M}{V} \quad \text{and} \quad V = \frac{4}{3} \pi r^3
\]

Where, \( D \) is the density of the beads; \( M \) is the weight of the beads; \( V \) is the volume of the beads; and \( r \) is the radius of the beads.

**In vitro buoyancy study**

Floating properties of beads were evaluated using USP dissolution XXIII type II apparatus containing 900 ml SGF (pH 1.2). The temperature of medium was maintained at 37 ± 5°C. Fifty beads were placed in the media and the total floating time was measured by visual observation (Badve et al., 2007).

**Drug content and Drug entrapment efficiency**

An accurately weighed sample of beads (100 mg) was crushed in a mortar and added to 500 ml of simulated gastric fluid (pH 1.2). This was sonicated for complete dissolution. From the above solution aliquot of 1 ml was taken and diluted to 10 ml. The mixture was filtered and analyzed spectrophotometrically at a wavelength of 258 nm (UV spectrophotometer, 1601, Shimadzu, Japan). The drug content of each formulation was recorded (Patel et al., 2011).

The percentage drug entrapment efficiency (% DEE) of each bead formulation was calculated using the following equation.

\[
\text{DEE}\% = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100
\]

**Scanning electron microscopy**

Beads were coated with a thin gold palladium layer by sputter coater unit (Diya Labs Mumbai). The surface topography was analyzed with a scanning electron microscope (Nimase and Vidyasagar, 2010).

**In vitro drug release studies**

In vitro release characteristics of itopride hydrochloride floating gel beads were evaluated employing USP XXIII dissolution testing Type I apparatus (UV Shimadzu UV 1700 Pharmaspec). The dissolution test was performed using 900 ml of SGF buffer as dissolution medium maintained at 37±0.5°C. The contents were stirred at 50 rpm. 5 ml aliquot of the solution was withdrawn at predetermined time intervals for 24 hours and fresh 5 ml dissolution media was replaced to maintain sink condition. The above withdrawn 5 ml solution was filtered through whatmann filter paper and from this 1 ml of solution was further diluted and was analyzed spectrophotometrically at a wavelength of 258 nm (Badve et al., 2007).

**Comparison of optimized formulation with Marketed product**

The promising formulation F9 was compared with marketed formulation Ganaton OD Cap 150 mg for *in vitro* drug release.

**Analysis of *in vitro* drug release kinetics and mechanism**

In order to predict and correlate the release behaviour of itopride hydrochloride in simulated gastric fluid (pH 1.2) from these liquid paraffin entrapped calcium alginate beads, it is necessary to fit into a suitable mathematical model. The *in vitro* drug release data of itopride hydrochloride beads were evaluated for kinetics like zero order, first order, Higuchi, and Korsmeyer-Peppas model.

Zero order model: \( F = K_0 t \); where, \( F \) represents the fraction of drug released in time \( t \), and \( K_0 \) is the apparent release rate constant or zero order release constant.

First order model: \( \ln(1 - F) = -K_1 t \); where, \( F \) represents the fraction of drug released in time \( t \), and \( K_1 \) is the first order release constant.

Higuchi Model: \( F = K_H t^{1/2} \); where, \( F \) represents the fraction of drug released in time \( t \), and \( K_H \) is the Higuchi dissolution constant.

Korsmeyer-Peppas Model: \( F = K_p \cdot t^n \); where, \( F \) represents the fraction of drug released in time \( t \), \( K_p \) is the rate constant and \( n \) is the release exponent, indicative of the drug release mechanism.

The Korsmeyer-Peppas model was employed in the *in vitro* drug release behaviour analysis of these formulations to distinguish between competing release mechanisms: Fickian release (diffusion controlled release), Non-Fickian release (anomalous transport), and case II transport (relaxation controlled release). For spheres, a value of \( n \leq 0.43 \) indicates the Fickian release. The \( n \) value between 0.43 and 0.85 is an indication of Non-Fickian release (both diffusion controlled and swelling controlled drug release). When, \( n \geq 0.85 \), it is case II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation (Higuchi, 1963; Korsmeyer et al., 1983; Peppas and Korsmeyer, 1986).

**In vivo floating efficiency (*X-Ray*) study**

Six healthy New Zealand breed Rabbits weighing approximately 2.2-2.5 Kg were used for conducting this study. The rabbits were fasted overnight and allowed free accesses to water only *ad libitum*. To make the beads *X-Ray* opaque the incorporation of barium sulphate (\( \text{BaSO}_4 \)) was necessary. Barium sulphate has a high density (4.7777 g/cm\(^3\)) and poor floating properties. The beads prepared for radiography contained itopride hydrochloride (rabbit dose) where a part of the drug was
replaced with BaSO₄ for in vivo studies and were kept ready.

X-Ray photographs were taken for the rabbits before giving the dosage form to ensure that no material containing Barium sulphate was present in the stomach and these photographs served as control.

Further itopride beads containing barium sulphate that were kept ready were administered to the rabbits using an hollow polyethylene tube with 3-4 ml of water. About 5-10 ml of water was further administered ensuring that the dosage form is present in the stomach. After the ingestion of the beads, the rabbits were exposed to X-Ray photography in the stomach region. At every hour interval, 10 ml of water was administered to animals throughout the study. The X-Ray photographs were taken at different time intervals for 0, 1, 3, 6, 10 hours respectively. The floating efficiency and behaviour was observed (Siddalingam and Mishra, 2007; Kumar et al., 2010; Gangadharappa et al., 2011; Reddy et al., 2011; Kumar et al., 2012). The animal protocol was approved by Animals Ethical Committee within the institution.

Stability studies

As per ICH guidelines, beads were subjected to accelerated stability studies. Weighed quantity of the samples (n=3) were exposed to controlled temperature (40±2°C) and relative humidity (75±5% RH) for a period of 3 months in humidity control oven (Lab Control, Ajinkya IM 3500 Series, India). After 30, 60 and 90 days the samples were taken out and analyzed for buoyancy, entrapment efficiency and in vitro drug release (Kim BH., 2009).

Results and Discussion

Preformulation Studies

Appearance, solubility and melting point

The obtained sample of drug was found to be off white crystalline powder as described in the monograph. The drug was freely soluble in water and soluble in methanol and insoluble in dichloromethane, acetone, and ethanol. Melting point of itopride hydrochloride was found to be 196°C.

Infrared spectroscopy

The characteristic peaks of standard itopride hydrochloride were reported in the IR spectrum which indicated that the obtained sample was of itopride hydrochloride and was pure and when compared indicated there was no interaction between the drug and polymers as all the characteristic peaks of drug were reported in the physical mixture. This confirms the compatibility of the drug with the polymers used for the formulation of oil entrapped gastroretentive beads as depicted in figure 1 and 2.

![Fig. 1. IR spectrum of itopride hydrochloride pure drug.](image-url)
Formulation of beads

Gastroretentive floating beads of itopride hydrochloride (F1-F9) were prepared using low methoxy pectin, sodium alginate each in different ratios alone and in combination, containing 150 mg of itopride hydrochloride using sunflower oil and tween 80. It is well known that the gelation and cross linking of alginate and pectin molecules are due to the stacking of the guluronate blocks in the alginate and pectin chains with the formation of the 'egg-box junction' upon adding chelating divalent cations such as calcium ion (Ca^{2+}).

Bread Characterization

Production yield

The production yield was maximum for formulation F9 containing high drug: polymer ratio (low methoxy pectin + sodium alginate). The practical yield was increased with increasing the concentration of the polymer. The practical yields of different formulations are given in table 2.

Particle size

The prepared beads were almost spherical. The mean surface diameter of all 9 formulations was between 1.248 mm and 1.507 mm tabulated in table 2. The size of the bead was found to be increased as the concentration of polymer was increased.

Swelling index

The results showed that the swelling was related to the polymer concentration with swelling being more significant for beads containing high polymer content. The swelling index was found to be in the range between 0.728% to 1.485% as shown in the table 2.

Density measurements

Density measurement showed that the calculated densities of all the prepared beads were less than the density of SGF (i.e.1.004 g cm^{-3}) imparting floating behaviour to the beads. Their values ranged from 0.754 g cm^{-3} to 0.956 g cm^{-3} as shown in table 2.
TABLE 2
Characterization of floating beads.

<table>
<thead>
<tr>
<th>Formulation Codes</th>
<th>Practical yield (%)</th>
<th>Particle size* (mm) Mean ± SD</th>
<th>Swelling index* (%) Mean ± SD</th>
<th>Density* (gcm⁻³) Mean ± SD</th>
<th>Actual Drug Content* (%) Mean ± SD</th>
<th>Entrapment Efficiency* (%) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 69.666</td>
<td>1.296±0.0024</td>
<td>0.757±0.0579</td>
<td>0.754±0.0054</td>
<td>26.435±0.1953</td>
<td>52.869±0.3906</td>
<td></td>
</tr>
<tr>
<td>F2 74.444</td>
<td>1.378±0.0014</td>
<td>0.932±0.0714</td>
<td>0.883±0.0020</td>
<td>22.268±0.2184</td>
<td>66.311±0.6552</td>
<td></td>
</tr>
<tr>
<td>F3 78.833</td>
<td>1.501±0.0104</td>
<td>1.169±0.0891</td>
<td>0.950±0.0020</td>
<td>21.127±0.0641</td>
<td>72.898±0.3726</td>
<td></td>
</tr>
<tr>
<td>F4 68.666</td>
<td>1.248±0.002</td>
<td>0.728±0.0558</td>
<td>0.775±0.040</td>
<td>24.531±0.6509</td>
<td>49.063±0.3019</td>
<td></td>
</tr>
<tr>
<td>F5 71.111</td>
<td>1.349±0.0028</td>
<td>0.906±0.0693</td>
<td>0.891±0.0003</td>
<td>21.127±0.641</td>
<td>63.387±0.1922</td>
<td></td>
</tr>
<tr>
<td>F6 74.444</td>
<td>1.490±0.0096</td>
<td>1.110±0.0848</td>
<td>0.956±0.0026</td>
<td>17.287±0.0931</td>
<td>69.148±0.3726</td>
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</tr>
<tr>
<td>F7 73.333</td>
<td>1.401±0.0009</td>
<td>1.250±0.0954</td>
<td>0.907±0.0006</td>
<td>22.623±0.0856</td>
<td>76.894±0.1183</td>
<td></td>
</tr>
<tr>
<td>F8 75.238</td>
<td>1.501±0.0058</td>
<td>1.434±0.1096</td>
<td>0.941±0.0061</td>
<td>20.062±0.0499</td>
<td>70.216±0.1746</td>
<td></td>
</tr>
<tr>
<td>F9 79.166</td>
<td>1.506±0.0022</td>
<td>1.485±0.1131</td>
<td>0.955±0.0041</td>
<td>19.223±0.0926</td>
<td>76.949±0.1183</td>
<td></td>
</tr>
</tbody>
</table>

*values expressed as mean of triplicate

In vitro buoyancy studies
All the formulations showed good buoyancy, formulations F1, F2, F4, F5, F7 were floating for more than 12 hour and F3, F6, F8, F9 for 24 hours. F3 and F6 beads showed a longer lag time (10.666 min, 13.333 min) as compared to other formulations F2, F5, F7, F8 and F9 (4.033 min, 5.333 min, 8.333 min and 9.666 min) F1 and F4 (10.33 sec and 13.33 sec.) as shown in table 3.

TABLE 3
In vitro buoyancy studies of beads.

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Amount of oil (ml)</th>
<th>Floating Lag Time* (sec ± SD)</th>
<th>Floating duration (h)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 2</td>
<td>10.333±0.5774</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td>F2 2</td>
<td>4.033±0.5772</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td>F3 2</td>
<td>10.666±0.5774</td>
<td>&gt;24</td>
<td></td>
</tr>
<tr>
<td>F4 2</td>
<td>13.333±0.5774</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td>F5 2</td>
<td>5.333±0.5774</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td>F6 2</td>
<td>13.333±0.5774</td>
<td>&gt;24</td>
<td></td>
</tr>
<tr>
<td>F7 2</td>
<td>7.333±0.5773</td>
<td>&gt;12</td>
<td></td>
</tr>
<tr>
<td>F8 2</td>
<td>8.333±0.5773</td>
<td>&gt;24</td>
<td></td>
</tr>
<tr>
<td>F9 2</td>
<td>9.666±0.5773</td>
<td>&gt;24</td>
<td></td>
</tr>
</tbody>
</table>

*values expressed as mean of triplicate

Scanning electron microscopy
Surface morphology of the prepared floating beads was examined by scanning electron microscopy (SEM). The SEM image was taken for the optimized formulation F9. The beads were spherical and the external surface was slightly rough surface/shrinkage which could be due to drying as shown in figure 3.

In vitro drug release studies
In vitro drug release study of itopride hydrochloride floating beads was carried out. The drug release profiles were presented by plotting the amount of itopride hydrochloride released against time. The cumulative drug release of formulations F1 to F9 was calculated. The beads exhibited a sustained release initially may be by swelling and then diffusion. Formulation F1 and F4 which contained least polymer could sustain the itopride hydrochloride release only up to 12 hour and 10 hour respectively. Whereas formulation F9 containing combination of sodium alginate and low methoxy pectin was found to have maximum release at the end of 24 hour showed a sustained release profile as shown in figure 4,5 and 6.

Comparison of optimized formulation with marketed product
In vitro dissolution profile of marketed product was compared to the optimized formulation F9. Formulation F9 showed release of 96.990 % and the marketed product showed 84.012 % release of itopride hydrochloride at the end 24 hour. Hence, F9 showed better drug release in comparison to marketed product as shown in figure 7.

Analysis of in vitro drug release kinetics and mechanism
The rate constants were also calculated from the slope of the plot of respective models. Higher R² value was obtained in the zero order equation (0.9482 to 0.9939) in comparison to the first order equation (0.7779 to 0.9617). This indicates all the formulations follow zero order kinetics.

Further, dissolution data of all formulations were fitted in Higuchi’s equation and the Hixen crowell equation for all formulations, where R² value was found to be (0.9537 to 0.9885) and (0.9195 to 0.9882)
respectively indicating diffusion to be the predominant mechanism of drug release. To find out exact mechanism, dissolution data of all formulations were fitted in Korsmeyer-Peppas equation. All formulations showed good linearity $R^2$ (0.9906 to 0.9950), with slope (n) values ranging from (0.5512 to 0.7601) and thus follow Non-Fickian or anomalous release as shown in table 3 and depicted in figure 8, 9 and 10. Thus drug release from oil entrapped beads was controlled by swelling as well as diffusion.

**In vivo floating efficiency (X-Ray) study**

The in vivo evaluation of floating beads of Itopride Hydrochloride was conducted. X-Ray photographs were taken for the rabbits before giving the dosage form and they served as control. Than floating Itopride Hydrochloride beads containing barium sulphate were administered and X-rays were taken at 0, 1, 3, 6, 10 h. The X-Ray images showed that the beads were floating in the rabbit stomach. The X-Rays are given in figure 11.

**Stability studies**

In view of potential utility of the formulation, stability studies were carried out on optimized formulation F9 for three months according to ICH guidelines. Formulations were subjected to buoyancy, entrapment efficiency and in vitro release studies after 30, 60 and 90 days. The results showed no much variation indicating that it is stable. As given in table 5.

![Fig. 3. SEM of optimized formulation F9 (a) spherical shape of beads, (b) slightly rough surface.](image)

![Fig. 4. Comparative In vitro release profile of Itopride Hydrochloride floating beads for formulation F1, F2 and F3 in SGF pH 1.2.](image)
Fig. 5. Comparative *In vitro* release profile of Itopride Hydrochloride floating beads for formulation F4, F5 and F6 in SGF pH 1.2.

Fig. 6. Comparative *In vitro* release profile of Itopride Hydrochloride floating beads for formulation F7, F8 and F9 in SGF pH 1.2.
Fig. 7. Comparative *In vitro* release profile of Itopride Hydrochloride floating beads for optimized formulation F9 and marketed formulation in SGF pH 1.2.

Fig. 8. *In vitro* Log % CDR v/s Log time of floating bead according to Koresmeyer Peppas for formulation F1, F2 and F3.
Fig. 9. *In vitro* Log % CDR v/s Log time of floating bead according to Koresmeyer Peppas for formulation F4, F5 and F6.

Fig. 10. *In vitro* Log % CDR v/s Log Time of Floating bead according to Koresmeyer Peppas for formulation F7, F8, and F9.
Fig. 11. X-Ray of floating beads of optimized formulation F9 (a) Control, (b) Test at 0 h, (c) Test at 1 h, (d) Test at 3 h, (e) Test at 6 h, (f) Test at 10 h.

TABLE 4
Model fitting data of release profile for formulations F1-F9.

<table>
<thead>
<tr>
<th>Formulation</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>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order (R²)</td>
<td>0.9871</td>
<td>0.9871</td>
<td>0.9895</td>
<td>0.9939</td>
<td>0.9810</td>
<td>0.9906</td>
<td>0.9838</td>
<td>0.9828</td>
<td>0.9557</td>
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<tr>
<td>First order (R²)</td>
<td>0.8996</td>
<td>0.8326</td>
<td>0.8790</td>
<td>0.7779</td>
<td>0.8229</td>
<td>0.9003</td>
<td>0.8207</td>
<td>0.9027</td>
<td>0.6704</td>
</tr>
<tr>
<td>Higuchi’s (R²)</td>
<td>0.9726</td>
<td>0.9537</td>
<td>0.9656</td>
<td>0.9599</td>
<td>0.9775</td>
<td>0.9386</td>
<td>0.9705</td>
<td>0.9543</td>
<td>0.9833</td>
</tr>
<tr>
<td>Hixen-Crowell (R²)</td>
<td>0.9632</td>
<td>0.9244</td>
<td>0.9496</td>
<td>0.9195</td>
<td>0.9360</td>
<td>0.9577</td>
<td>0.9293</td>
<td>0.9608</td>
<td>0.8819</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td>(R²)</td>
<td>0.9964</td>
<td>0.9909</td>
<td>0.9921</td>
<td>0.9964</td>
<td>0.9906</td>
<td>0.9912</td>
<td>0.9912</td>
<td>0.9936</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>0.6622</td>
<td>0.6650</td>
<td>0.5955</td>
<td>0.7601</td>
<td>0.5844</td>
<td>0.6623</td>
<td>0.6033</td>
<td>0.6258</td>
</tr>
</tbody>
</table>

*R²* - regression coefficient, *n* - slope
TABLE 5
Data obtained for promising formulation F9 after exposing to accelerated stability studies (40±2 °C and 75±5 % RH).

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Buoyancy Mean ± S (n=3)</th>
<th>% Drug entrapment efficiency Mean ± SD (n=3)</th>
<th>In vitro release at end of 24 Hours (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLT (min)</td>
<td>Floating Duration (Hours)</td>
<td></td>
</tr>
<tr>
<td>F9</td>
<td>Initial</td>
<td>9.666±0.5773</td>
<td>&gt; 24</td>
</tr>
<tr>
<td></td>
<td>30 Days</td>
<td>9.989±0.4512</td>
<td>&gt; 24</td>
</tr>
<tr>
<td></td>
<td>60 Days</td>
<td>9.997±0.0317</td>
<td>&gt; 24</td>
</tr>
<tr>
<td></td>
<td>90 Days</td>
<td>10.389±0.9621</td>
<td>&gt; 24</td>
</tr>
</tbody>
</table>

Conclusions
A new sustained release system of oil entrapped beads were designed and prepared and the conclusions were drawn from the study. Preformulation studies were carried out and the results were found to be as given in the literature within the prescribed limits. Nine formulations containing itopride hydrochloride beads were efficiently prepared and characterized by emulsion gelation method using low methoxy pectin and sodium alginate singly and in combination.

The practical yield, particle size and swelling was directly proportional to the increase in the concentration of the polymer. The calculated densities of all the prepared beads were less than i.e.1.004 g cm⁻³ imparting floating behaviour to the beads, some for more than 12 h and others for 24 h. Percentage entrapment efficiency increases as the polymer concentration increases. Formulation F9 was found to have maximum release at the end of 24 hours showed a sustained release profile. Higher R² values were obtained for zero order. Korsmeyer Peppas (Non-Fickian release) was found to be the best fit kinetic model. The beads were spherical and their external surface was slightly rough. Formulation F9 showed better drug release in comparison to marketed product. The in vitro (X-Ray) evaluation of formulation F9 showed that the beads were floating in the rabbit stomach upto 10 hours. Formulation F9 when subjected to stability study concluded that it was stable.

From the studies performed it was concluded that the oil entrapped gastroretentive floating beads of itopride hydrochloride showed excellent buoyancy and sustained drug release upto 24 h and thus enhanced the bioavailability.

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References


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