NEW INSIGHTS INTO GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT
In recent year, considerable attention has been focused on the formulation and development of new drug for orally targeted drug delivery systems. The oral route is most popular route of drug administration. Conventional dosage forms are unable to control either the rate or site of action. When a drug is delivered as a conventional dosage form they show very short gastric retention time. As such the drug which act locally in the stomach or get degraded by the colonic bacteria or/and alkaline pH of the small intestine cannot be formulate as conventional dosage form. In conventional dosage forms, fluctuating drug level may lead to some side effect and dosing interval is short, this leads to poor patient compliance. At present a number of approaches are utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding system, mucoadhesive system, high density system, modified system and other delayed gastric emptying systems. Floating drug delivery systems has density lower than gastric fluid, so that it has tendency to float over gastric contents and remain in the stomach for prolonged period of time. The hydrodynamically balanced gastrointestinal drug delivery system is designed to prolong the GI residence in area of the GI tract to maximize the absorption of drug at the desired site in the solution form and hence increase the absorption.

Key words: Gastric retention, FDDS, High density system, Mucoadhesive system

INTRODUCTION
The oral drug delivery systems exhibit variable and short gastric emptying time, which result in incomplete drug release from the delivery system. This leads to diminished efficacy of
administered dose. To overcome these problems gastro retentive drug delivery systems are used. [1, 2]. Gastro retentive drug delivery systems are the systems which are capable to prolong the retention time of the dosage form in the gastric region and improve the bioavailability of drugs that are mainly absorbed from upper GIT (duodenum and stomach).[3] Gastro retentive systems are remain in the gastric region for longer period and therefore significantly extend the gastric residence time of drugs so that increase bioavailability, reduce drug waste, and improve solubility of drugs that are less soluble in alkaline environment.[4] They prolong dosing interval, so that increase patient compliance. For delivery of sparingly soluble and insoluble drugs gastro retentive dosage forms (GRDF) are chiefly effective. [5, 6] Drugs having narrow absorption window in GI tract and give local action in upper part of small intestine are suitable for GRDDS. They are advantageous for the treatment of peptic ulcer disease. One of the most possible approaches for achieving a prolonged drug delivery in the GI tract is to control the gastric residence time by making gastro retentive floating drug delivery system.[5] FDDS applicable for drugs having poor bioavailability because of narrow absorption window in the GIT. FDDS increase the bioavailability of drug by retains the dosage form at the site of absorption. [3]

**BASIC PHYSIOLOGY OF STOMACH**

Stomach is anatomically divided into three portions: Fundus, body and antrum (pylorus). The proximal stomach have fundus and body, serves as a reservoir for material ingested and the distal stomach is site of mixing. Gastric emptying process occurs during fasting and fed state. The pattern of motility is different in this two state. Fasting state is characterised by an interdigestive series of electrical events which cycle through the stomach and small intestine every 2-3 h. [7]. This activity is called the interdigestive myoelectric cycles or migrating myoelectric complex (MMC). MMC have four consecutive phases.[8]

**Phase I** - Quiecent period lasting from 40 to 60 min with rare contraction.

**Phase II** - Period of similar duration consisting of intermittent action potentials and contractions, that gradually increase in intensity and frequency as the phase progress.

**Phase III** - Short period of intense, contraction lasting from 4 to 6 min. The cycle in this phase is called “housekeeper” wave, for the reason that it sweep undigested materials out of the stomach.

**Phase IV** - Brief transitional phase, that occurs between phase III and phase I of two consecutive cycles.[9]
FACTOR AFFECTING GASTRORETENTION- [5, 10, 11]

- **Size** - Dosage form units with a large diameter having large volume. If volume increases density will be decreases, low density help in floating. So that larger size devices are reported to have an increased GRT compared with small diameter.

- **Shape of dosage form** – Tetrahedron and ring shaped devices are reported to have better GRT compared with other shapes.

- **Density** – Low density system tend to float on the gastric fluid surface while high density system sink to bottom of stomach.

- **Single or Multiple unit formulation**- Multiple unit formulations show a more predictable release profile and allow co-administration of units with different release profiles and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or Unfed state**- The migrating myoelectric complex (MMC) occurs every 1.5 to 2 hours under fasting conditions i.e. gastric motility is higher in fasting condition which shows lesser GRT. However, in the fed state, MMC is delayed and GRT is considerably longer;

- **Caloric content** - A meal that is high in proteins and fats, GRT can be increased by 4 to 10 hours.

- **Gender** - GRT in males (3.4±0.6 hours) is less compared with their age and race matched female (4.6±1.2 hours), (regardless of the weight, height and body surface).

- **Age** – Geriatric patient have a significantly longer GRT as compared with children.

- **Posture** – GRT can vary between supine and upright ambulatory position of the patient.

- **Disease state**- GRT is altered during disease state.

- **The time, at which the drug is taken**- When a single unit system is taken during phase III of the MMC, the powerful peristaltic waves increase the chances of expelling the drug into the duodenum.

- **Rate of dissolution of drug**- A drug which dissolving fast will quickly evacuate with water through the pylorus.

- **Nature of drug**- If drug is taken during meal, water soluble drug leave the stomach with water, while lipid soluble drug leave it with lipids and fats are evacuated last.
Table I: Comparison between Conventional and Gastro retentive drug delivery system [12, 13]

<table>
<thead>
<tr>
<th>Conventional drug delivery system</th>
<th>Gastro retentive drug delivery system</th>
</tr>
</thead>
<tbody>
<tr>
<td>- More side effect</td>
<td>- Less side effect</td>
</tr>
<tr>
<td>- Patient compliance is less.</td>
<td>- Improves patient compliance</td>
</tr>
<tr>
<td>- Less gastric retention time</td>
<td>- Improve gastric retention time</td>
</tr>
<tr>
<td>- Not appropriate for delivery of drugs with narrow absorption window in small intestine region.</td>
<td>- Appropriate for delivery of drugs with narrow absorption window in small Intestinal region.</td>
</tr>
<tr>
<td>- Not much beneficial for drugs Exhibit local action in the stomach.</td>
<td>- Beneficial for drugs Exhibit local action in the stomach.</td>
</tr>
<tr>
<td>Degraded in the colon.</td>
<td>Degraded in the colon.</td>
</tr>
<tr>
<td>Having rapid absorption through GIT</td>
<td>Having rapid absorption through GIT</td>
</tr>
<tr>
<td>- No risk of dose dumping.</td>
<td>- High risk of dose dumping.</td>
</tr>
</tbody>
</table>

SUITABLE DRUG CANDIDATE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM- [14, 15]
1. Drugs that have narrow absorption window in GI tract e.g. Riboflavin, Paraamino benzoic acid and levodopa.
2. Primarily absorbed from stomach and upper part of GI tract e.g. Chlordiadepoxide and Cinnarizin.
3. Drugs that locally act in the stomach e.g. antacid and misoprostol.
4. Drugs that degrade in the colonic environment. e.g. Captopril, Ranitidine HCl and metronidazole.
5. Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.
6. Drugs that show low solubility at high pH values e.g. Diazepam, Chlordiazepoxide, verapamil.

APPROACHES TO GASTRORETENTION
1. **High density approach.** These systems have density higher than the stomach fluid (1.004 g/cm³). It would be at least 1.50 g/cm³. [12] These systems are able to withstand peristaltic movement and retained in the stomach for several hours.[16]. These system can be manufacture by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder, etc. [9]
2. **Mucoadhesive Drug Delivery System**- Mucoadhesive drug delivery systems are designed to localize a delivery device within the lumen to increase the absorption and retention time of drugs in a specific site. [16]. Mucoadhesive drug delivery system offer drug release at controlled manner. They bypass the first pass metabolism and avoid degradation of GI enzymes and have good surface area so that they give rapid absorption and good bioavailability. [17] The concept of mucoadhesive polymer to extend the GI transit time is shown in figure 2. [18] Bio adhesive or mucoadhesive polymers are natural or synthetic polymers capable of producing an adhesive interaction with a biological membrane or with the mucus lining on the GI mucus membrane. Some Bioadhesive or mucoadhesive polymers are- Polycarbophil, Carbopol, Pectins, Chitosan, HPMC, CMC and Gliadin, etc. [9]

![Fig. 1- Low density system and High density systems](image)

**Figure 2:** Interaction of a mucoadhesive drug delivery system with the mucus layer on the gastrointestinal surface epithelium.

3. **Swelling and Expandable systems**
If a dosage form is bigger than the pyloric sphincter it will withstand the gastric transit. But the dosage form must be small to be swallowed. There is three configuration are required-A small size for swallowing, An expanded form for gastroretention and finally a small form
for evacuation.[11] After swallowing these systems are swells to an extent that prevent their exit from the stomach through the pylorus. These systems are also called as “Plug type systems”, since they have tendency to remain logged at the pyloric sphincters. [9] Polymers selected with the proper molecular weight and swelling properties then controlled and sustained drug release can be achieved. When polymers come in contact with gastric fluid, the polymer imbibes water and swells. The swelling of these polymers is due to presence of physical-chemical cross links in the hydrophilic polymer network. [16]

Fig.-3: Swellable tablet in stomach

4. Magnetic Systems
In Magnetic systems dosage forms hold a small internal magnet and another magnet positioned on the abdomen externally. The problem in this system is that, the external magnet must be placed at the right position with a degree of precision. [9, 13]

5. Superporous Hydrogel
They are swellable system. They have average pore size >100 micro meter, absorption of water is very fast by capillary wetting, with the help of pores, so that they swell and reach to an equilibrium size within a minute. They have adequate mechanical strength to withstand the pressure by gastric contraction. They are formulated by hydrophilic particulate material Ac-Di-Sol (Crosscarmellose sodium) [11]

FLOATING DRUG DELIVERY SYSTEM
FDDS are significantly used for drugs that are locally act in stomach and small intestine and have narrow absorption window in small intestine region, unstable in the intestinal or colonic environment and shows low solubility at alkaline environment [16]. FDDS have density lower than gastric fluid, due to which they have tendency to float over gastric contents for prolonged period of time without affecting gastric emptying rate. As the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.[19,20]. Conventional controlled release dosage forms go downwards to the bottom of
the stomach once ingested because their density is higher than that of gastric contents. [5] Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs which are less soluble in alkaline pH. [20, 21] Floating drug delivery also used in sustained drug delivery, delivery of drug at specific site and in enhancement of absorption. [22]

APPROACHES TO FLOATING DRUG DELIVERY SYSTEM

Various types of floating system have been developed which may involve generation of effervescent or non effervescent.

1. Hydrodynamically Balanced System

The hydrodynamically balanced system in either capsule or tablet form, is designed to prolong GI residence time. Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Ethyl Cellulose (HEC), Hydroxy Propyl Cellulose (HPC), Sodium Carboxy Methyl Cellulose (NaCMC), Agar, Carrageenans or Alginic acid are the excipients used in the formulation of HBS. The drug and polymer mixed together and administered in gelatin capsule. The capsule is rapidly dissolve when comes in contact with gastric fluid and the hydrocolloids in the floating device start to become hydrate and form a colloidal gel barrier around its surface with thickness growing with time. These gel barrier controls the rate of fluid penetration into the device and consequent drug releases from the barrier. The gel barrier act as a reservoir for sustained release of drug. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density less than 1 and remain buoyant in the stomach for up to six hours. The working principle of HBS is shown in figure 4. [9, 18.]

![Fig. 4-Working Principles of Hydrodynamically Balanced System](image-url)
2. **Gas generating system (Effervescent System)**

These systems are prepared with swellable polymer such as methylcellulose, chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. When they are come in contact with gastric fluid CO$_2$ is liberated and get entrapped in swollen polymer which provide buoyancy to the system.[24] The system consisted of sustained release pills and the pill surrounded by two layers (Fig. 5). The inner layer was an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Furthermore, the effervescent layer was separated into two sub layers to avoid direct contact between tartaric acid and sodium bicarbonate. Tartaric acid was contained in the outer sub layer and sodium bicarbonate was contained in the inner sub layer. When the system was immersed in a buffer solution at 37°C, a swollen pill was formed, having a density less than 1 g/ml. The neutralization reaction occurs between effervescent layers, and CO$_2$ gas evolved. The system was found to float completely within 10 min. [9, 11]

![Diagram of Gas Generating System](image)

**Fig. 5: Gas Generating System.**

(A) A multiple-unit oral floating dosage system,

(B) Stages of floating mechanism

3. **Raft forming system**

In Raft forming system, a gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonate) when comes in contact with gastric fluid, swell and form a viscous cohesive gel and forming a continuous layer called a raft. Because of low bulk density created by the formation of CO$_2$, this raft floats on gastric fluids. Floating raft act as a barrier
to prevent the reflux of gastric contents into oesophagus so that they are used for gastroesophageal reflux treatment e.g. Liquid Gaviscon (GlaxoSmithKline)[11, 16]

4. **Low density system**. The limitation of the gas generating system is that, they have a lag time before floating on the gastric fluid, so that dosage form may undergo premature evacuation from the stomach. Therefore, low density system (<1 g/cm³) have been developed, which exhibit immediate floating. They are composed of low density material entrapping oil or air [11]. In this approach, the density of the device should be less than the density of gastric fluid i.e. 1 g/ml, so as to float in the gastric fluid of stomach for a prolong period of time without affecting the gastric emptying rate. As the system is floating on the gastric contents, the drug is released slowly for longer period of time. After release of drug, the left over system is emptied from the system. [12]

**TYPES OF FLOATING DRUG DELIVERY SYSTEM:**

A. **Single unit system**

Single unit system (e.g. Hydrodynamically balanced system) may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract. These systems are unreliable in prolonging the GRT owing to their ‘all-or-nothing’ emptying process. (23)

B. **Multiple unit system**

Multiple-unit systems (e.g. microspheres) are passing through the GIT uniformly. They avoid the ‘all-or-none’ gastric emptying nature of single unit system. They reduce inter subject variability in absorption and risk of local irritation. (24,25). A variety of multiple-unit floating systems are based on various principles, such as air compartment multiple-unit system (2), micro particles based on porous carriers (26,27,28), hollow microspheres (micro balloons) (29,30), oil-entrapped gel beads prepared by gelation method (31,32)

**Types of FDDS based on buoyancy**

1) **Non-effervescent FDDS**: General approach for preparation of such system involves thoroughly mixing the drug and the gel-forming hydrocolloid. On contact with gastric fluid this dosage form swells and attains a bulk density of less than gastric fluid. The air entrapped within the swollen matrix help in buoyancy to the dosage form [12]. Gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as
polycarbonate, polyacrylate, polymethacrylate and polystyrene are common excipients used in non effervescent FDDS. [33,34]

2) Effervescent System
Effervescent floating drug delivery systems prepared by swellable Polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, and tartaric acid. On contact with gastric fluid they generate gas (CO2), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time. [12]

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM-[13, 35]
- Patient comfort and compliance is improved because of frequency of dosing is reduced.
- The bioavailability of drug is increases due to increased absorption with in stomach.
- Gastric retention time increases due to buoyancy principle.
- Drug releases in a controlled manner for prolonged period of time.
- Drugs are directly target to specific site in the organ.
- There is no risk of dose dumping because drug releases uniformly.
- Gastric irritation can be minimized, due to sustained release effect.
- Inter and intra subject variability is less.
- Minimizes the counter activity of the body leading to higher drug efficiency.
- There is no or minimum fluctuations in drug concentration, therefore, concentration dependent adverse effects can be reduced.
- Prolonged drug release extends the time period of effective concentration over which the drug is released, thus enhances the pharmacological effects and improves the clinical outcomes.
- Gastro retentive systems have flexibility in dosage form design, so that available in various physical designs like tablet, capsule, solution, suspension etc.

LIMITATION OF GASTRORETENTION DRUG DELIVERY SYSTEMS:[13, 15, 16, 36]
1) Solubility: Drugs that have solubility problem in GIT are not feasible for such system.
2) Stability: The drug substances that are degrading in the acidic environment of the stomach are not suitable candidates for gastro retentive systems.
3) First pass metabolism: Drugs which under goes first pass metabolism may not be suitable for gastro retentive systems.
(4) **Gastro irritant drugs**: Drugs which causes irritation to gastric mucosa are also not desirable.

(5) **High level of fluid**:
Floating system require a high level of fluid in the stomach for drug delivery to float and work efficiently. So that Sufficient amount of water (200-250ml) to be taken together with FDDS.

(6) **Absorption throughout the gastrointestinal tract**:
Drugs which undergo equal absorption through all region of the gastrointestinal tract are not desirable candidate. Drug should have narrow absorption window in GIT.

**TABLE-II: POLYMERS AND OTHER INGREDIENTS USED IN FLOATING DRUG DELIVERY SYSTEM- [10]**

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

<table>
<thead>
<tr>
<th>Hydrocolloids (20%-75%)</th>
<th>They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives e.g. Acacia, pectin, Chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inert fatty materials (5%-75%)</td>
<td>Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Examples Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.</td>
</tr>
<tr>
<td>Effervescent agents</td>
<td>Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).</td>
</tr>
<tr>
<td>Release rate accelerants (5%-60%)</td>
<td>Lactose, Mannitol.</td>
</tr>
<tr>
<td>Release rate retardants (5%-60%)</td>
<td>Dicalcium phosphate, talc, magnesium stearate.</td>
</tr>
<tr>
<td>Buoyancy increasing agents (upto80%)</td>
<td>Ethyl cellulose</td>
</tr>
<tr>
<td>Low density material</td>
<td>Polypropylene foam powder (Accurel MP 1000®).</td>
</tr>
</tbody>
</table>
### TABLE III: LIST OF DRUGS USED IN THE FORMULATIONS OF FLOATING DRUG DELIVERY SYSTEM- [4, 10, 13, 21]

<table>
<thead>
<tr>
<th>Floating microspheres</th>
<th>Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen (37), Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast (38) and Terfenadine. (39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floating tablets and Pills</td>
<td>Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Sotalol, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate (40), Para – amino benzoic acid, Piretanide (41), Theophylline, Verapamil HCl, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol (1), Pentoxyfilline and Diltiazem HCl, Furosemide, Ciprofloxacin, Captopril, Nimodipine, Cinnarizine, Riboflavin-5phosphate.</td>
</tr>
<tr>
<td>Floating granules</td>
<td>Diclofenac sodium, Indomethacin and Prednisolone</td>
</tr>
<tr>
<td>Films</td>
<td>Cinnarizine (42), Albendazole.</td>
</tr>
<tr>
<td>Floating Capsules</td>
<td>Nicardipine, Chlordiazepoxide HCl, Diazepam (43), Furosemide, Misoprostol, L-Dopa, Benserazide Ursodeoxycholic acid (44) and Pepstatin, and Propranolol.</td>
</tr>
<tr>
<td>Powders</td>
<td>Several basic drugs.</td>
</tr>
</tbody>
</table>

### TABLE IV: Commericially available Floating Product: [6, 12, 16, 45]

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug</th>
<th>Delivery system</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cifran O.D.</td>
<td>Ciprofloxacin</td>
<td>Gas generating floating tablet</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Oflin O.D.</td>
<td>Ofloxacin</td>
<td>Gas generating floating tablet</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Colloidal gel forming FDDS</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Liquid Gavison</td>
<td>Alginic acid and sodium bicarbonate</td>
<td>Effervescent floating liquid alginate preparation</td>
<td>GlaxoSmithKline, India</td>
</tr>
<tr>
<td>Almagate float</td>
<td>Al-Mg Antacid</td>
<td>Floating liquid form</td>
<td>-</td>
</tr>
<tr>
<td>Coat</td>
<td>Glumetza</td>
<td>Metformin HCl</td>
<td>Tablet</td>
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<tr>
<td>------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Al-Mg</td>
<td>Floating liquid alginate preparation</td>
<td>Pierre Fabre Drug, France</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Diazepam</td>
<td>Floating Capsule</td>
<td>Hoffman-LaRoche, USA</td>
</tr>
<tr>
<td>Madopar HBS</td>
<td>Benserazide and L-dopa</td>
<td>Floating CR Capsule</td>
<td>Roche Product, USA</td>
</tr>
<tr>
<td>Cytotec</td>
<td>Misoprostol</td>
<td>Bi layer floating Capsule</td>
<td>Pharmacia, USA</td>
</tr>
</tbody>
</table>

**EVALUATION OF FLOATING DRUG DELIVERY SYSTEM** [46, 47, 48]

1. **Particle size analysis**

   The size of 300 particles of each batch was measured by using a calibrated micrometer attached with a microscope and the average diameter was calculated.

2. **Test for buoyancy**

   The microspheres (200 mg) were transferred to a series of six 500 ml beakers containing 400 ml of simulated gastric fluid without enzymes maintained at 37 °C. The content of the beakers was stirred at 100rpm by magnetic pellet. At different time intervals (2, 4, 6, 8, 10, 12 h) floating and non-floating microspheres were separated, dried at 45 °C until a constant weight is obtained. Then the microspheres were weighed and percentage of buoyancy is calculated by using following equation

   \[
   \text{Buoyancy (\%) = } \frac{Q_f}{Q_f + Q_s}
   \]

   Where \(Q_f\) = weight of floating microspheres, \(Q_s\) = weight of settled microspheres collected at different time intervals.

3. **Scanning electron microscopy** [46]

   The sample for the scanning electron microscopy (SEM) analysis was prepared by sprinkling the microspheres one side of double adhesive stub. The stub was then coated with gold using Jeol JFC 1100 sputter coater. The SEM analysis of the microspheres was carried out by using Jeol JSM 5300, Japan. The microspheres were viewed at an accelerating voltage of 15 kV.

4. **Determination of drug loading and encapsulation efficiency** [49]

   The drug content in the microsphere can be determined by pulverising the drug loaded microspheres (10 mg) and then immersing into 100ml simulated gastric fluid (pH 1.2) with
agitation at room temperature for 12 h. After filtration through membrane filter drug concentration can be determined by spectrophotometer at appropriate wavelength. The filtered solution from empty microsphere (without drug) taken as blank. Then drug loading and encapsulation efficiency can be calculated by the following equation.

\[
DL (\%) = \frac{W_D \times 100}{W_T}
\]

DL = drug loading, \(W_D\) = the weight of the drug loaded in the microsphere, \(W_T\) = the total weight of the microspheres.

\[
EE (\%) = \frac{W_A \times 100}{W_T}
\]

EE = encapsulation efficiency, \(W_A\) = Actual drug content, \(W_T\) = theoretical drug content.

5. **In vitro drug release studies** [50]

In vitro drug release studies performed in USP type II apparatus at 50 rpm maintained at 37 ± 5°C. A capsule is placed into 900 ml of 0.1 N HCl (pH 1.2). Then 5 ml sample withdrawn from the dissolution vessel at specific time intervals and replaced with equivalent volume of fresh medium. Then samples were filtered by using Whatmann filter (Grade I) paper and then, determine drug concentrations by using spectrophotometer, against a blank.

6. **Floating lag time and total floating time determination** [16].

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 M HCl maintained at 37°C, by using USP dissolution apparatus containing 900 ml of 0.1 M HCl as the dissolution medium.

7. **Swelling studies**[51]

A known weight of microsphere without drug was placed in 500 ml of different solutions: distilled water and enzyme free simulated gastric fluid (pH 1.2) and allowed to swell for sufficient time at 37 ± 0.5°C using the USP type 1 dissolution apparatus at 50 rpm. The microspheres are removed, blotted with filter paper and their change in weight were measured during swelling until equilibrium was attained. Finally the weight of swollen microsphere was recorded after 4 h and swelling ratio (SR) was calculated by the following formula

\[
SR = \frac{W_E - W_o}{W_o}
\]

Where, \(W_E\) = weight of the swollen microsphere at equilibrium state, \(W_o\) = initial weight of dry microsphere.
8. Stability studies [52]

Stability studies were performed to check the effect of environmental or storage conditions on formulation. Sample was kept in accelerated stability condition at 40°C temperature 75 ± 5% relative humidity for 3 months as per International Conference on Harmonization (ICH) guidelines [53] The samples were withdrawn at 1, 2, and 3 months intervals evaluation was carried out for appearance, thickness, hardness, friability, buoyancy lag time, drug content, floating behaviour, and cumulative% drug released.

CONCLUSION

Among various types of gastro retentive system floating drug delivery system (FDDS) is most promising. Floating drug delivery system can be prepared by two different approaches effervescent and non effervescent system. The drug which act locally in the stomach or get degraded by the colonic bacteria or alkaline pH of the small intestine can be delivered by formulating floating dosage form. The dosage form retains at the site of absorption for prolong period of time and there by increase the bioavailability of drug. It exhibit good stability and better drug release than other conventional dosage forms.

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