Review Article

An Update on Floating Drug Delivery System: A Review

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Gastro retentive drug delivery systems.

ABSTRACT

The oral route is the most appropriate and widely used for the delivery of drugs to the systemic circulation. This route has high acceptability for patients, particularly due to the ease of administration. Over the years, oral dosage forms have become increasingly world-wise in the pharmaceutical field, with controlled release drug delivery systems that release the drug at a predetermined rate playing a major role. Various approaches have been designed and utilized to achieve efficient drug delivery for those drugs that have poor bioavailability and shorter gastric residence time. On the other hand, floating drug delivery system, one of the most extensively used approaches of the Gastro retentive drug delivery system has an advantage for the drugs that are absorbed primarily in the upper segments of the Gastrointestinal tract i.e., stomach, duodenum, and jejunum. The main purpose of writing this review article is to emphasize the types of floating drug delivery systems, the principle, and mechanism of floating action to achieve gastric retention. This review also outlines the In-vitro and In-vivo studies used to evaluate the potential, performance, and application of floating systems in to overcome various problems encountered during the development of a dosage form.

1. Introduction

Despite enormous advancements in the drug delivery, the oral route remains the most favorable, desirable route for the therapeutic agent which has high patient acceptability, particularly due to the ease of administration. Over the years, oral dosage forms have become increasingly world-wise in the pharmaceutical field, with controlled release drug delivery (CRDDS) systems that release the drug at a predetermined rate playing a major role. CRDDS provides drug release at a predictable, predetermined, and controlled rate, which is an important pre-requisite for the successful performance of an oral CRDDS. The gastro retentive drug delivery system (GRDDS) is an approach to prolonging the duration of gastrointestinal residence, thereby targeting the site-specific release of drugs in the upper gastrointestinal tract (GIT) to generate local or systemic effects. Gastro retentive systems can remain in the gastric region for several hours which helps in enhancing the bioavailability of the drug, reducing the drug waste, also aids in improving the solubility of poorly soluble drugs in a higher pH environment. Drug absorption in GIT is a highly variable process, which depends on various factors like gastric emptying process, gastro intestinal transit time of dosage forms, drug release from the dosage form, and site of drug absorption[1]. The following two parameters are optimized to develop sustainable orally controlled releasing drug delivery systems that deliver a drug for the required duration for optimal treatment at a therapeutically efficient range to a desirable place.

1) Gastrointestinal transit modulation time: Modulate the transit time for GIT so that dosage form can be taken to or around the target absorption site and thus extend the time limit for maximizing the delivery of drugs.

2) Minimizing the elimination of the first hepatic pass: If the drug to be given undergoes extensive first-pass hepatic removal, preventive measures should be developed to either bypass or minimize the extent of hepatic metabolism.

Gastrointestinal tract Anatomy and Physiology

For successful modulation of GI transit time of a dosage form via GRDDS for drug absorption in GIT and site-specific delivery, a complete understanding of the human GIT is required. Today, the design of the Oral drug delivery system (ODDS) was based on an empirical understanding of GIT anatomy and physiology.
The stomach is used as a depot for the dosage forms of controlled release. It is divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach is composed of the fundus and the body region, which serves as a reservoir for ingested materials, while the distal region (antrum) is the main site for mixing motion, acting as a pump for gastric emptying \cite{2}. Mucus and gastric acid are the two main secretions of the cells lining the stomach. Mucus spreads and covers both the mucosal surface of the wall and the GIT \cite{3}. The main function of the mucus layer is the lubrication and protection of the underlying epithelial cells, the pH of the stomach in the fasted state is approximately 1.5-2.0 and in the fed state is usually 2.0-6.0. The main cause of such variation in the pH of the stomach is that it does not have enough time to produce enough acid before the liquids are emptied. The anatomical structure of the stomach is shown in figure 1.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{stomach_anatomy.png}
\caption{Schematic illustration of the stomach anatomical structure} \label{fig:stomach}
\end{figure}

Gastrointestinal Dynamics (Process of Gastric emptying)
The GIT is always in a state of continuous motility. Gastric emptying is observed in both fasting and fed states. There are two modes of motility pattern; digestive mode and inter-digestive (or fast) mode involved in the digestion of food. An inter-digestive series of electrical events takes place during the fasting state, which cycles through both the stomach and the intestine every 2 to 3 h \cite{2-5}.

**Phase 1 (basal phase):** It lasts from 40 to 60 min with rare contractions.

**Phase 2 (pre-burst phase):** lasts for 40 to 60 min with intermittent action potential and contractions. As the phase progresses the frequency and intensity gradually increases.

**Phases 3 (burst phase):** lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out from the stomach down to the small intestine. This is also known as the housekeeper wave.

**Phase 4:** lasts for 0 to 5 min and occurs between phases 3 and 1 to 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from the fasted to the fed state. This is also known as the digestive motility pattern and comprises continuous contractions in phase 2 of the fasted state. These contractions result in reducing the size of the food particles (to less than 1 mm), which are propelled towards the pylorus in a suspension form. During the fed state onset of MMC, which results in a delay of the gastric emptying rate, scintigraphic studies determining the gastric emptying rate have shown that oral controlled release dosage forms are subjected to 2 complications, including shorter gastric residence time and unpredictable gastric emptying rate \cite{2,3,4}.

**Approaches to GRDDS:** To formulate a successful stomach specific or gastro retentive drug delivery system (GRDDS) several techniques are currently used such as \cite{3,5}.

\begin{itemize}
  \item **Hydrodynamically Balanced Systems (HBS):** In this type of system, the built-in buoyant materials will allow the devices to float.
  \item **Expandable/ Swellable Systems:** In the development of gastro-retentive drug delivery systems, the pyloric sphincter was explored to maintain its size in the stomach by either expanding or swelling. Expansion can be accomplished either by swelling or by unfolding the dosage type.
  \item **Mucoadhesive or Bioadhesive Systems:** These mechanisms typically bind to the epithelial gastric surface and are extended by increasing the intimacy and duration of contact between the dosage form and the biomembrane. The adherence of the delivery systems to the gastric wall increases the time of residence at a given location by improving bioavailability.
  \item **Modified Shape Systems:** These are non-disintegrating geometric forms molded from silastic elastomer or exuded from polyethylene mixtures and prolong the gastric transit time (GIT) depending on the size, shape, and flexural modules of the drug delivery system.
  \item **High-Density Systems:** These contain coated pellets with a density greater than that of the stomach (1.004 g/cm$^3$). This is achieved by coating the drug with thick inert materials like Barium sulfate, Zno, Titanium dioxide. These formulations of high-density pellets are based on the premise that heavy pellets may stay longer in the stomach as they are positioned in the lower part of the antrum.
  \item **Magnetic Systems:** They are a system that includes external stimulation as a magnetic field for the site-specific delivery of drugs. To achieve site-specificity, certain magnetic active compounds are integrated into the dosage type.
  \item **Floating Drug Delivery Systems:** In 1968, Davis first defined floating systems as systems with a bulk density lower than the gastric content. They stay buoyant in the stomach for a long time, with the
potential for constant release of drugs. Swelling delivery systems are capable of swelling up to a size that stops them from flowing through the pylorus. As a consequence, when in contact with gastric fluid, the material retains water and swelling, the dosage form is maintained in the stomach for a prolonged period.

h) Raft-forming systems: In these systems, the gel-forming solvent (e.g. sodium alginate solution containing carbohydrates or bicarbonates) swells and forms a viscous gel containing encapsulated CO2 bubbles in contact with gastric fluid. Formulations often usually include antacids such as aluminum hydroxide or calcium hydroxide to minimize gastric acidity. Since raft-forming devices generate a coating on the surface of gastric fluids, they are also used with gastroesophageal reflux treatment.

Factors controlling gastric retention time in GRDDS [7]

**Density:** GRT depends on the form density of the dose that is less dense than the gastric fluids that have floating behavior, hence gastric retention. GRT is a function of dosage form building up. For the display of floating properties, a density of ≤ 1.0 gm / cm³ is required.

**Size:** The size of the dosage form is another factor that influences gastric retention. The average gastric residences of the fluid-free dosage forms are highly variable and highly influenced by their size (p <0.05). The larger the dose shape, the longer it takes to spawn, because the bigger the form of the dosage would not allow the pyloric antrum to pass into the intestine quickly. Dosage forms are reported to have increased GRT units of a diameter of more than 7.5 mm as against units of a diameter of 9.9 mm.

**The shape of dosage form:** GIT motility is characterized under fasting conditions by periods of strong motor activities or the myoelectric migration complex (MMC) occurring every 1.5 to 2 h. The MMC removes the undigested material from the stomach and, if the timing of the administration of the formulation coincides with that of the MMC, the GRT of the unit may be expected to be very short. In the fed state, however, the MMC is delayed and the GRT is considerably longer.

**Nature of the meal:** Feeding indigestible polymers or salt fatty acids can cause the pattern of stomach motility to change to fed condition and thus lowers the emptying rate of gastric substances and prolonged drug release.

**Caloric Content:** GRT can be increased by 4 to 10 h with a meal that is rich in proteins and fats.

**Frequency of feed:** The GRT can be increased by 40 min when successive meals are given compared with a single meal due to the low frequency of MMC.

**Gender:** Mean ambulatory GRT (3.4± 0.6 h), regardless of weight, height, and body surface.

**Age:** Elderly people, especially those over 70, have a significantly longer GRT.

**Posture:** GRT can vary between supine and upright ambulatory states of the patient.

**Biological factors:** These include Diabetes and Crohn’s disease etc.

2. Floating Drug Delivery System (FDDS)

Floating systems, first described by Davis in 1968, have a lower bulk density than the gastric content. They remain fluid for a long time in the stomach and have the potential to release the drug continuously. In the end, the residual system is vacuumed. Gastric emptying in a fasting state is much faster and floating systems rely heavily on food to delay emptying and provide enough fluid to boost effectively.

![Figure 3: Systematic localization of tablet in the stomach](Image)

FDDS have a bulk density lower than gastric fluids so that they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. Swelling delivery systems are capable of swelling to a size that prevents them from passing through the pylorus. As a result, when in contact with gastric fluid, the polymer imbibes water and swelling, the dosage form is retained in the stomach for a longer

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### Table 1: Technologies adopted for GRDDS [6]

<table>
<thead>
<tr>
<th>S. No</th>
<th>Technology</th>
<th>Company</th>
<th>Product</th>
<th>Active pharmaceutical ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Biodegradable tablets</td>
<td>Lupin, India</td>
<td>Xifaxan</td>
<td>Rifaximin</td>
</tr>
<tr>
<td>2</td>
<td>Effervescent floating system</td>
<td>Ranbaxy, India</td>
<td>Zanocin OD</td>
<td>Olfexacin, Ferrous sulfate</td>
</tr>
<tr>
<td>3</td>
<td>Foam-based floating system</td>
<td>Sato Pharma, Japan</td>
<td>Inon Ace Tablets</td>
<td>Gastrofoam</td>
</tr>
<tr>
<td>4</td>
<td>Coated multi-layer floating and swelling system</td>
<td>Sun Pharma, India</td>
<td>Bactilin GR</td>
<td>Backofoam</td>
</tr>
<tr>
<td>5</td>
<td>Polymer-based swelling technology: AcuForm_</td>
<td>Depomed, Inc. USA</td>
<td>Gabapentin GR</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>6</td>
<td>Floating liquid alginate preparation</td>
<td>Pierre Fabre</td>
<td>Topalkan</td>
<td>Aluminium, magnesium antacid</td>
</tr>
<tr>
<td>7</td>
<td>Erodible matrix-based system</td>
<td>Medicament, France</td>
<td>Cipro XR</td>
<td>Gastrofoam hydrochloride and betaine</td>
</tr>
<tr>
<td>8</td>
<td>Floating capsule Floating, CR capsule</td>
<td>Roche, UK</td>
<td>Vale release Madopa</td>
<td>Diazepam, Levodopa and benserazide</td>
</tr>
<tr>
<td>9</td>
<td>Gastroretention with osmotic system</td>
<td>GlaxoSmithKline</td>
<td>Coreg CR</td>
<td>Carvedilol</td>
</tr>
<tr>
<td>10</td>
<td>Bilayer floating capsule</td>
<td>Pharmacia Ltd, UK</td>
<td>Cytotec</td>
<td>Misoprostol (100/200 μg)</td>
</tr>
</tbody>
</table>
3. Applications of FDDS

FDDS offers several applications for the drug having poor bioavailability because of the narrow absorption window in the upper part of the GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability.\(^{[11,13]}\)

1) Sustained Drug Delivery

HBS may remain in the stomach for longer periods and may therefore release the drug or a prolonged period. A formulation of oral CR overcomes the problem of the shorter gastric residence. The density of these structures is < 1 since they can float on the gastric material. E.g. Nicardipine hydrochloride floating capsules were developed and evaluated in vivo for sustained release. This formulation was compared with commercially available MICARD capsules using rabbits. The plasma concentration-time curve showed a longer residence time (16 h) in the sustained release floating capsules as compared with conventionally MICARD capsules (8 h).

2) Site-Specific Drug Delivery

Targeting the drug to the stomach appears to be useful for all substances intended to produce long-lasting local action in the gastro-duodenal wall. In the intestine, the eradication of H. pylori requires multiple medications to be administered several times a day, resulting in poor patient compliance. These systems are particularly beneficial for drugs that are specifically absorbed from the proximal part of the small intestine. E.g. Riboflavin, Furosemide. Furosemide is predominantly absorbed from the stomach, followed by the duodenum. Monolithic floating dosage form with extended gastric residence time has been reported to have established and improved bioavailability. The AUC obtained with the floating tablets was roughly 1.8 times that of conventional furosemide tablets. Better reliable therapy can be achieved by using FDDS, which allows the reduction of dose and frequency of administration. E.g. the prolonged gastric availability of Misoprostol from such a system may reduce the dosing frequency.

3) Absorption Enhancement

Drugs with poor bioavailability due to site-specific absorption from the upper part of the GIT are potential candidates for use as floating drug delivery systems by maximizing their absorption. E.g. A substantial improvement in the bioavailability of floating dosage forms (42.9 %) could be achieved compared to commercially available LASIX tablets (33.4 %) and enteric-coated LASIX-long product (29.5 %).

4. Approaches to design Floating Dosage Forms\(^{[14,15]}\)

The following are the approaches used for designing floating dosage forms of single and multiple unit systems.

a) Single-Unit Dosage Forms

In low-density approaches, globular shells tend to have a lower density than gastric fluid and can be used as a drug carrier for its controlled release. A buoyant dosage type can also be achieved with the use of a fluid-filled system that floats in the stomach. They are further coated with a drug and polymer mixture. The polymer used can be of choice, i.e. either cellulose ethyl or cellulose hydroxypropyl, depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug over a prolonged period. Fluid-filled floating chamber type of dosage forms includes the incorporation of a gas-filled floating chamber into a microporous component that contains a drug reservoir.\(^{[16]}\) An aperture or opening is present along the upper and lower walls through which the gastrointestinal fluid enters to dissolve the drug. The remaining two walls in contact with the fluid are sealed in such a way that the substance remains undissolved. The fluid that is present can be air, under partial vacuum, or
any other suitable gas, liquid, or solid having a sufficient specific gravity to float in the stomach for an extended time, and after complete release, the shell disintegrates, passes to the intestine, and is expelled.

Hydrodynamically balanced systems (HBS) are designed to prolong the duration of the dosage form in the gastrointestinal tract and ultimately promote absorption. These systems are better suited for drugs with increased solubility in the acidic environment and for drugs with a specific absorption site in the upper section of the small intestine. To remain in the stomach for a prolonged period, the dosage form must have a mass density of less than 1. The dosage form should maintain its structural integrity and permanently release the drug from the dosage form. Single unit formulations are concerned with the problems such as sticking together or being obstructed in the GIT, which have a potential risk of irritating[14].

b) Multiple-Unit Dosage Forms: A stable formulation with all the advantages of a single unit form is designed to create a multi-unit dosage form, without the drawbacks of a single unit formulation. A variety of multi-unit floatable dosage forms have been designed for this purpose. Microspheres have a high load potential and several polymers have been used, such as albumin, gelatin, starch, polymethacrylate, poly acryl amine, and poly alkyl cyanoacrylate. Spherical polymer microsponges, also known as ‘micro balloons.’ The internal hollow structure of the microspheres shows an excellent in vitro floatability. The multi-unit oral formulations generated from CO₂ are the devices with the characteristics which have been described after they have been administered, developed or inflated by carbon dioxide. Such dosage shapes are removed if a 12 to 18 mm diameter in their swollen state is reached from the passage of the pyloric sphincter[16].

Classification of FDDS[17]

- **Floating Drug Delivery System**
  - Effervescent system
  - Volatile liquid/vacuum containing system
  - Single layer floating tablets
  - Alginate beads
  - Hollow/floating microspheres

**Figure 4:** Classification of FDDS

A) Non-effervescent systems

The Non-effervescent FDDS relies on the polymer swell mechanism or bioadhesive mechanism in the GIT mucosal layer. Materials such as polycarbonates, polycrylates, polymethacrylates, polystyrene as well as bioadhesives such as chitosan and carbohydrate are the most widely used excipients of Non-effervescent FDDS gel-formed or highly inflatable cellulose hydrocolloids.

1. Single-layer floating tablets: They are formulated by the intimate blending of the drug with a gel-forming hydrocolloid, which swells in contact with the gastric fluid and maintains a lower bulk density than the unit. These dosage forms are boosted by the air that is captured by the swollen polymer.

2. Bilayer floating tablets: The bilayer tablet contains two layers, one of which is an immediate release layer that releases the initial dose from the system, while the other is a sustained release layer that absorbs the gastric fluid, forms an impermeable colloidal gel barrier on its surface, and maintains a bulk density of less than unit and remains buoyant in the stomach.

3. Alginate Beads: Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of 2.5 mm diameter may be prepared by dropping sodium alginate solution into aqueous calcium chloride solution, resulting in precipitation of calcium alginate resulting in the formation of a porous system capable of maintaining a floating force of more than 12 h. Compared to solid beads, they have a longer period of stay of more than 5.5 h[18].

**Figure 5:** Alginate Beads[18]

4. Floating Microspheres: Better floating properties and better drug release depend mainly on polymers, plasticizers, and solvents. The drug-loaded microspheres have been conventionally developed by emulsification and solvent-evaporation methods. An example was the preparation of hollow micro balloons, loaded with ibuprofen in their outer polymer shell[15]. The ethanol-dichloromethane solution of the drug and the enteric acrylic polymer were poured into an agitated aqueous PVA solution that was dried calcium alginate. Spherical beads of 2.5 mm diameter may be prepared by dropping sodium alginate solution into aqueous calcium chloride solution, resulting in the formation of a porous system capable of maintaining a floating force of more than 12 h. Compared to solid beads, they have a longer period of stay of more than 5.5 h[18].

**Figure 6:** Floating Microspheres[20]

B) Effervescent systems or Gas generating systems

These are matrix types of systems prepared with the help of Swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, citric acid. They are formulated in such a way that when in contact with
gastric contents. CO$_2$ is liberated and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage form. These effervescent systems are further classified into two types:

1. Gas generating systems
   a) Effervescent reaction: It is also possible to achieve floating behavior through the gas bubble generation. CO$_2$ can be generated in-situ by incorporating carbonates or bicarbonates that react with either natural gastric acid or co-formulated as citric acid or tartaric acid. The optimum stoichiometric ratio of citric and sodium bicarbonate for gas generation is reported to be 0.76:1. The CO$_2$ generated which is trapped in the jellified hydrocolloid layer of the system reduces its specific gravity and causes it to float over time\(^9\). These tablets may be either single-layered, wherein the CO$_2$ generating components are intimately mixed within the matrix, or bilayered in which the gas generating components are in hydrocolloid containing layer and drug in other layer formulated for an SR effect\(^{20}\).

   ![Figure 7: Formation of CO$_2$ in the gas generating system\(^{[21]}\)](image)

b) Intra-Gastric Single Layer Floating Tablets or Hydrodynamically Balanced Systems (HBS):
   The most frequently used hydrocolloids, polysaccharides, and matrix-forming polymers, such as polycarbonates, polyacrylates and polystyrene, are gel-forming or highly swelling. This formulation consists of an intimate combination of drug and gel-formation hydrocolloid, which after oral administration swells in contact with the gastric fluid and maintains relative integrity of shape and a volume density below the unity of the outer gelatinous barrier\(^{22}\). The main drawback of this system is the passivity of the operation. It depends on the air sealed in the dry mass centre following hydration of the gelatinous surface layer and hence the characteristics and amount of the polymer.

   ![Figure 8: Hydrodynamically balanced systems\(^{[21]}\)](image)

   Intra-Gastric Bilayer Floating Tablets: These are also compressed tablets as shown in containing two layers: Immediate-release layer and Sustained-release layer.

   ![Figure 9: Intra-Gastric bilayer floating tablet\(^{[21]}\)](image)

   Multiple unit types floating pills: These systems consist of sustain release pills as 'seeds' surrounded by double layers. The inner layer is composed of effervescent agents, and the exterior layer is an expanding membrane. The device sinks quickly and absorbs bloated pills like a balloon as they are dissolved in a dissolution medium at body temperature, which tends to float because they are less concentrated. This lower density is because CO$_2$ is produced and trapped in the system.

   ![Figure 10: Multiple-unit floating oral pill\(^{[21]}\)](image)
2. Volatile Liquid/Vacuum containing systems

a) Intra-gastric floating drug delivery device: These devices are comprised of a drug reservoir encapsulated in a microporous compartment having pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartments were completely sealed to prevent any physical contact of the undissolved drug with the stomach walls. The floating chamber caused the system to float in the gastric fluid, developed Intra-gastric floating SR granules of Diclofenac sodium using polymer solution of hydroxypropyl cellulose L grade (HPC-L) and ethyl cellulose [22]. Calcium silicate as a floating carrier, which has a characterized porous structure with numerous pores and a large individual pore volume. The coated granules acquired floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer.

b) Inflatable Gastrointestinal Delivery systems: These Gastro-inflatable drug delivery devices are osmotic-controlled floating systems that contain a hollow deformable unit, which can convert from a collapsed to an extended position and return to a collapsed position after an extended period. The deformable system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains a drug, while the second chamber contains a volatile liquid. The device may also consist of a bio-erodible plug made of PVA, polypropylene, etc [4,15]. That gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.

c) Intra-gastric osmotically controlled DDS: This system consists of mainly two different parts attached, one is the floating part and the other is the osmotically controlled part. Floating part made up of deformable polymeric bag containing a liquid that gasifies at body temperature. The osmotic pressure controlling part consists of two parts, a drug reservoir, and an osmotically active compartment [4,15]. Inner drug reservoir is an impermeable collapsible bag with a drug delivery orifice and an outer osmotically active compartment consisting of a semi-permeable membrane containing osmotic active salts. When the system comes into contact with gastric fluids, the inflation of the floating part results in buoyancy and osmotic pressure generated in the outer compartment due to fluid intake and the release of drugs via an orifice under osmotic pressure.

### Table 2: Different drugs used in the development of FDDS [25]

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs Formulated in to FDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Antiinfectionics</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Antianginal drugs</td>
<td>Trimethazidine dihydrochloride</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Amoxicillin, Ciprofloxacin, Cefuroxime, Clarithromycin, Cefixime, Cephlexin, Cefpodoxime, Levofloxacin, Ofloxacin, Norfloxacin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Anticancer</td>
<td>5-Flourouracil</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>Metforman, Repaglinide, Glipizide</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Domperidone, Itrapride</td>
</tr>
<tr>
<td>Antiepileptic</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Captopril, Diltaizem, Nitrendipine, Propranolol, Verapamil</td>
</tr>
<tr>
<td>Antilipidemics</td>
<td>Atrovastatin</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>Fenoterol, Tizanidine</td>
</tr>
<tr>
<td>Antidiuretics</td>
<td>Famotidine, Ranitidine, Lansoprazole</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Salbutamol, Theophylline</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Aceclofenac, Ketorolol, Nimesulide, Loraxicam</td>
</tr>
</tbody>
</table>

5. Evaluation of FDDS [27]

1. Pre-compression parameters

a) Angle of Repose: It is a maximum angle between the surface of a pile of powder and its horizontal plane. It is determined by pouring the powder to flow through a funnel and fall freely onto the surface [11,12,13]. Then the height and diameter of the resulting cone are measured by using the following equation.

\[
\tan \theta = \frac{h}{r}
\]

where, \( \theta \) = angle of repose, \( h \) = height of the pile, \( r \) = radius of the pile.
b) Bulk density and Tapped density: It refers to the ratio of the total mass of powder to the bulk volume of the powder, which is determined by pouring a weighed quantity of tablet powder into a graduated cylinder and measuring the height.

Bulk density = (weight of the powder) / (Bulk volume of the powder)

The cylinder containing the sample was tapped using a mechanical tapped density tester (Electrolab) that provides a fixed drop of 14±2 mm at a nominal rate. The cylinder tapping was continued until no further change in the volume was noted. The tapped density was calculated by using the following formula.

Tapped density = (weight of the powder) / (tapped volume)

c) Compressibility Index and Hausner’s ratio: They were measured by using the following formulas.

Carr’s index = Tapped density – Bulk density x 100

Tapped density

Hausner’s ratio = Tapped density / Bulk density

2. Post-compression parameters

a) Weight variation: It is determined by randomly selecting 20 tablets from each formulation and weighing them individually using an electronic balance and the average weight was calculated which was compared with the individual weight of the tablet. In comparison with the percentage given in the pharmacopeia, the deviation for any two tablets should not be more than average weight.

b) Hardness and Thickness: Hardness is the ability of the tablet to withstand mechanical shocks during handling. It is determined by Monsanto hardness tester by randomly selecting three tablets from each formulation, which is measured in terms of kg/cm².

The thickness of the tablet was determined by randomly selecting three tablets from each formulation and measured using Vernier calipers which were expressed in mm. The extent of deviation in the tablet formulation should not exceed the limit of ± 5% of their determined values.

c) Friability: It is used to determine the physical strength of uncoated tablets upon exposure to mechanical shock and attrition with the help of Roche Friabilator, which is expressed in terms of percentage. These ten tablets were weighed and placed in the Friabilator and operated at 25 rpm for about 4min (100 revolutions) [27]. Then the tablets were dedusted and reweighed and friability was calculated using the following equation.

Friability = Initial weight – Final weight x 100

Table 3: Drugs available as Floating dosage forms [26]

<table>
<thead>
<tr>
<th>Floating Dosage Forms</th>
<th>Effervescent systems</th>
<th>Non-effervescent systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floating Microspheres</td>
<td>Iloprost, pilocarpine, and verapamil</td>
<td>Indomethacin, glipizide, Rimipin, rosiglitazone, piroxicam, ranitidine, 5-flurooracil,</td>
</tr>
<tr>
<td>Floating beads</td>
<td>Metronidazole, 5-flurooracil, riboflavin</td>
<td>Famotidine, pantoazole, metronidazole</td>
</tr>
<tr>
<td>Floating tablets</td>
<td>Propranolol, norfloxacin, fenoterol, acetylsalicylic acid, clofibrate, ciprofloxacin, nimodipine, theophylline</td>
<td>Verapamil hydrochloride, captopril, nimodipine, theophylline</td>
</tr>
<tr>
<td>Floating pellets</td>
<td>Ofloxacin, tetracycline, theophylline, riboflavin</td>
<td>Metronidazole, lansoprazole</td>
</tr>
<tr>
<td>Floating capsules</td>
<td>Nicardipine, verapamil</td>
<td>Ofloxacin, propanolol, L-dopa, benserazide</td>
</tr>
</tbody>
</table>

d) Swelling index: This can be measured by examining weight gain or water uptake of the tablet, which includes an increase in tablet diameter and/or thickness over time.

\[ S.I = \frac{W_f - W_o}{W_o} \]
Where, SI = Swelling index; \( W_t \) = Weight of tablet at time \( t \), \( W_0 \) = Initial weight of the tablet

e) Drug content: Ten tablets were taken and placed in a mortar and crushed into a fine powder. An accurately weighed powder equivalent to 100mg of Fenoverine was transferred into a 100 mL volumetric flask containing 100 mL of 0.1N HCl and the absorbance was measured against blank at the respective wavelength.

f) In vitro buoyancy studies: The in vitro buoyancy was determined by finding out the floating lag time and total floating time. This is carried out by placing the tablets in a 100 mL beaker containing 0.1N HCl [20]. The time required for the tablet to rise from the bottom of the beaker to the surface and float was measured as floating lag time (FLT) and the duration of the tablet that constantly floats on the dissolution medium was noted as Total floating time (TFT) [20-22].

g) In vitro dissolution studies: It was performed using USP type I (basket) dissolution apparatus at a rotational speed of 50 rpm. The dissolution medium consists of 900 mL of 0.1 N HCl, maintained at a temperature of 37±0.5°C. At predetermined time intervals, a 5mL sample was withdrawn from the dissolution apparatus and replaced with a fresh dissolution medium. The collected samples were filtered through a 0.45 µm membrane filter and diluted to suitable concentrations with 0.1N HCl [29]. The absorbance of these solutions was measured at the respective wavelength. The cumulative percentage of drug release was calculated using the equation obtained from a calibration curve.

h) Fourier transform infrared analysis (FTIR): Mostly used technique to identify organic, inorganic, and polymeric materials present in the dosage form, analyses pure drug, polymer, and drug-loaded polymer formulations as well as functional group determination [20,21,23]. The spectra were scanned over the wavenumber range of 3600-400 cm⁻¹ at the ambient temperature.

i) Differential Scanning Colorimetry (DSC): Used to characterize water of hydration of pharmaceuticals. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25°C-65°C. The inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 mL/min [26,29].

j) X-Ray method: Frequently used evaluation parameter for floating dosage forms. It helps to locate the dosage form in the GIT so that the gastric emptying time of the dosage form can be expected and correlated. The presence of a radio-opaque substance in a dosage form allows X-rays to be visualized [22].

k) Gamma-Scintigraphy: Gamma-emitting radioisotopes compounded in controlled release dosage forms have become the state-of-the-art estimate of gastro retentive formulation in healthy volunteers. The key disadvantages of this approach are the combination of ionizing radiation for the patient, minimal topographic knowledge, poor technological resolution, and the difficult and costly processing of radiopharmaceuticals [21].

6. Conclusion

The absorption of drugs in the gastrointestinal tract is a highly complex procedure. Prolonged gastric retention of the dosage form increases the time for the absorption of drugs through the floating drug delivery system. Floating controlled drug delivery systems are used to fix this challenge. It often establishes intimate contact between the dosage form and the absorbing tissue, which can result in a high concentration of drugs in the local area and thus a high flow of drugs through the absorbing tissue, producing a long-term pharmacological response of maximum bioavailability and fewer complications for drugs that are absorbed primarily in the upper portion, where FDDS becomes an additional advantage for the drugs that are primarily absorbed in the upper segments of GIT i.e., stomach, duodenum, and jejunum. FDDS is promising to be a future approach to gastric retention. Various types of dosage forms with Sustained GRT would bring new and significant therapeutic opportunities. The one currently available Polymer-mediated Non-effervescent and effervescent FDDS built based on delayed gastric emptying and buoyancy principles, seems to be an effective approach to the modulation of controlled delivery of oral drugs. Several commercial products and patents approved in this area are evidence of it.

References

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