Formulation Development and Evaluation of Gastro Retentive Drug Delivery Systems- A Review

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ABSTRACT

In recent years many advancement has been made in research and development of Oral Drug Delivery System. Concept of Novel Drug Delivery System arose to overcome the certain aspect related to physicochemical properties of drug molecule and the related formulations. Purpose of this review is to compile the recent literature with special focus on Gastro Retentive Drug Delivery Systems to give an update on pharmaceutical approaches used in enhancing the Gastric Residence Time (GRT). Various approaches are currently used including Gastro Retentive Floating Drug Delivery Systems(GRFDDS),swelling and expanding system, polymeric bioadhesive systems, modified-shape systems, high density system and other delayed gastric emptying devices. These systems are very helpful to different problem solve during the formulation of different dosage form. The present work also focuses on the polymers used in floating drug delivery systems mostly from natural origin. Floating drug delivery systems are less dense than gastric fluids; hence remain buoyant in the upper GIT for a prolonged period, releasing the drug at the desired/ predeterminedrate. This review article focuses on the recent technological development in floating drug delivery systems with special emphasis on the principal mechanism of floatation and advantages of achieving gastric retention, brief collection on various polymers employed for floating drug delivery systems etc. In addition this review also summarizes the In–Vitro and In–Vivo studies to evaluate their performance and also their future potential.

KEY WORDS: Controlled release, Floating lag time, Floating duration/ Gastric residence time, Gastro retentive drug delivery systems, Natural gums, Bioadhesive.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. The effective oral drug delivery practice depends on various factors like gastric emptying process, gastrointestinal transit time of dosageform, drug release from dosage form and site of absorption of drug [1-3].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. It has been frequently observed that many drugs which are easily absorbed at upper gastrointestinal tract (GIT), eliminated quickly in the lower GIT because of the peristaltic movement. So it leads to incomplete absorption of drugs from upper part of GIT. To overcome this limitation, the development of oral gastro retentive sustained or controlled release formulations is an attempt to release the drug slowly at upper GIT to maintain effective drug concentration in systemic circulation for a prolonged period [3]. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability [4].

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation,
sedimentation (High density), expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems\(^4\)\(^-\)\(^6\).

Approaches to increase gastric residence time include

- High-density systems
- Bioadhesive or Mucoadhesive systems
- Swelling and Expanding Systems
- Superporous Hydrogels
- Ion Exchange Resins
- Bioadhesive Liposomal Systems
- Raft-forming systems
- Gas-generating systems
- Low-density systems (Floating systems / Hydrodynamically Balanced Systems)

**Floating Drug Delivery Systems (GRFDDS)**
These are the low density systems having their density lesser than the gastric fluid (1.004 gm/cm\(^3\)) and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. GRFDDS are classified into two major categories\(^7\)\(^-\)\(^13\).

**Effervescent systems/ Gas generating systems**
In this system floatability can be achieved by the generation of gas bubbles. They are formulated in such a way that when in contact with the acidic gastric contents, CO\(_2\) is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. In *in vitro*, the lag time before the unit floats is <1 minute and buoyancy is prolonged for 8-10 hours. Bilayer or multilayer systems have also been designed in which drug and excipients can be formulated independently, and the gas generating unit can be incorporated into any of the layers of multiple unit systems, which avoids the ‘all-or-nothing’ emptying process encountered in single unit systems\(^14\)\(^-\)\(^15\). It must form a cohesive gel barrier. It should release contents slowly to serve as a reservoir\(^16\).

**Hydrodynamically balanced systems** are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. HBS are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polyacryl, polyacrylate, polysulphate, agar, carrageenans or alginate acid are commonly used excipients to develop these systems\(^17\)\(^-\)\(^18\).

The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid at body temperature and hydration.

**Table 1: Polymers and other ingredients used for increasing GRT**\(^19\)

<table>
<thead>
<tr>
<th>Polymers and other ingredients</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inert fatty materials (5%-75%)</td>
<td>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, DSGC (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 1000R).</td>
</tr>
</tbody>
</table>
High-density systems
These systems, which have a density of ~3 g/cm³, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm³, such systems can be retained in the lower part of the stomach. Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. A density close to threshold density seems necessary for significant prolongation of gastric residence time. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³.[20–23]

Swelling and Expanding Systems
Swelling and expanding systems are dosage forms that, after swallowing, swell to an extent that prevents their exit from the pylorus[24]. As a result, the dosage form is retained in the stomach for a long period. These systems may be called ‘plug type systems’, since they exhibit a tendency to be logged at the pyloric sphincter. Swelling and controlled release of the drug may be achieved on contact of the drug delivery system with gastric fluid; the polymer imbibes water and swells. Extensive swelling of the polymer is the result of the presence of physical-chemical crosslinks in the hydrophilic polymer network. The bulk enables gastric retention and maintains the stomach in a ‘fed’ state, suppressing housekeeper waves[25,26]. Medicated polymer sheets or swelling balloon hydrogels are examples of such delivery systems. A balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefit and to avoid adverse effects. They are explained as follows (Non-Effervescent systems)[27].

Colloidal gel barrier systems
These systems incorporate a high level (20–75% w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug[27].

Micro porous compartment systems
This technology is based on the encapsulation of a drug reservoir inside a micro-porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.

Multiparticulate system Floating Beads
In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05–2.00 mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet.

Microballons
Various approaches are made in delivering substances to the target site in a controlled release fashion. One of such approach is using polymeric microballoons as carrier for drugs. Hollow microsphere are known as themicroballoons. Microballoons were floatablen in vitro for 12 hrs, when immersed in aqueous media. Radio graphicalstudies proved that microballoons orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movements.

Super porous Hydrogels
In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro meter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is achieved by co-processing with a hydrophilic particulate material, croscarmellose sodium. Which forms a dispersed phase within the continuous polymer matrix during the synthesis (‘superporous hydrogel composites’). The superporous hydrogel composites stay in the upper GIT for >24 hours. Recent advances in the field have led to “superporous hydrogel hybrids”, which are prepared by adding a hydrophilic or water dispersible polymer that can be cross-linked after the superporous hydrogel is formed. Examples of hybrid agents include polysaccharides such as sodium alginate, pectin and chitosan[28–30].

Ion-Exchange Resins
A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin, resultant beads were then
encapsulated in a semipermeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach and exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in a membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly.[31-34].

**Bioadhesive or Mucoadhesive Systems**
The term “mucoadhesion” is commonly used to describe an interaction between the mucin layer that lines the entire GIT and a bioadhesive polymer. Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Thus, they prolong the gastric retention time.[35-36].

Bioadhesion can be explained by[37-38]
- The absorption theory
- The electron theory
- The wetting theory
- The diffusion theory

**Bioadhesive liposomal Systems**
Mucoadhesive liposomal systems are formulated by coating a polymer to facilitate enteral absorption of poorly absorbed drugs. Liposomes are generally coated with mucoadhesive polymers such as chitosan, carboxymethyl chitosan. The mucoadhesion of the resultant liposomes leads to an enhanced GRT of the dosage forms[39-40].

**Raft forming systems**
Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. Floating Rafts have been used in the treatment of Gastric esophageal reflux disease (GERD). The mechanism involved in the raft formation includes the formation of viscos cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO₂. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids . Jorgen et al described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus[41-42].

**FACTORS AFFECTING Gastro Retention Time of Floating Drug Delivery Systems**
The various factors which influence the efficacy of Gastro Retentive Drug Formulation’s as a gastro-retentive systems are:

**Formulation Factors and Idiosyncratic Factors[27,43]**

**Formulation Factors**

**Density**
GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. Drug floatation is a function of time and it could least until hydrodynamic equilibrium is achieved. Dosage forms having larger density then the gastric content sink at the bottom of the atrium where they settle and release the active compound in a controlled manner over a prolonged period of time.

**Size**
Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm. Larger dosage forms tend to have longer gastric retention time than smaller ones because they are emptied in the digestive phase (weaker MMC) and also because their passage through the pyloric sphincter into the small intestine is hindered.

**Shape of dosage form:**
Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have
better GRT = 90% to 100% retention at 24 hours compared with other shapes.

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Viscosity Grade of Polymer:
Drug release and floating properties of GRFDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.

Nature of meal
Feeding of indigestible polymers or fatty acids salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release. Type of meal and its caloric content, volume, viscosity and co-administered drugs affect gastric secretions and gastric emptying time. The rate of emptying primarily depends on caloric contents of the ingested meal. It does not differ for proteins, fats and carbohydrates as long as their caloric contents are the same. Generally, gastric emptying is slowed down because of increased acidity, osmolarity and calorific values. Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 hours has been reported after a meal of fats and proteins.

Frequency of feed
The GRT can be increased by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Idiosyncratic Factors
Idiosyncrasy is genetically determined abnormality to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. The type of reaction is restricted to individuals with a particular genotype. It may also depend on-

Gender
Women have slower gastric emptying time than men. Mean ambulatory GRT in meals (3.4 ± 0.4 hours) is less as compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface. Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counter parts (4.6 ± 1.2 hours) regardless of the weight, height and body surface.

Age
Low gastric emptying time is observed in elderly than do in younger subjects. Intra subject and inter subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have significantly longer GRT. Elderly people, especially those above 70, have a significantly longer GRT.

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

Upright Position:
An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by astral peristaltic movements.

Supine Position:
This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appears to remain buoyant anywhere between the lesser and greater curvature of the stomach.

On moving distally, these units may be swept away by the peristaltic movements that propel the gastric content towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant Intake of Drugs:
Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anticholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of GRFDDS. The co-administration of GI-motility decreasing drugs can increase gastric emptying time.

Biological factors
Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hypothyroidism promote gastric emptying rate.
Advantages of GRFDDS
Increasing the GRT with either of the approaches offers several advantages such as:

- Acidic drug substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- The Floating systems are advantageous for drugs meant for local action in the stomach. e.g., antacids.
- The GRFDDS are advantageous for drugs absorbed through the stomach ex: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site-directed delivery system may also reduce the dosing frequency.
- Administration of prolonged release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- When there is vigorous intestinal movement and a shortened transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages/Limitations of GRFDDS:
- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Drugs showing absorption window at stomach region are only considered to be better candidates.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and also undergo significant first-pass metabolism, may not be suitable candidates for increasing the GRT since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of GRFDDS for drugs that are irritant to gastric mucosa.
- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
- The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm)

Potential Drug Candidate for GRFDDS
- GRFDDS is beneficial for drug candidate which have stability problems at alkaline pH (captopril, ranitidine HCl, metronidazole)
- Drugs having narrow absorption window in stomach, or upper part of small intestine
- (L-DOPA, p-aminobenzoic acid, furosemide, riboflavin)
Drugs that are locally active in the stomach (misoprostol, antacids)

Drugs that exhibit low solubility at high pH values (e.g., diazepam, chlor Diazepoxide, verapamil)

Drugs that disturb normal colonic microbes (e.g., antibiotics)

Miscellaneous

Buoyancy increasing agents

Hydrocolloids

Release rate accelerants

Inert fatty materials

Release rate retardant

Buoyancy increasing agents

Miscellaneous

**Table 2: The Potential Candidates for GRFDDS**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floating microspheres</td>
<td>Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam,</td>
</tr>
<tr>
<td></td>
<td>Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol,</td>
</tr>
<tr>
<td></td>
<td>Tranilast and Terfinedine</td>
</tr>
<tr>
<td>Floating granules</td>
<td>Diclofenac sodium, Indomethacin and Prednisolone</td>
</tr>
<tr>
<td>Films</td>
<td>Cinnarizine, Al bendazole</td>
</tr>
<tr>
<td>Floating tablets and Pills</td>
<td>Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydroxlate,</td>
</tr>
<tr>
<td></td>
<td>Atenolol, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid,</td>
</tr>
<tr>
<td></td>
<td>Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine,</td>
</tr>
<tr>
<td></td>
<td>maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol,</td>
</tr>
<tr>
<td></td>
<td>pentoxyfilline and Diltiazem HCl, Atenolol, ciprofloxacin</td>
</tr>
<tr>
<td>Floating Capsules</td>
<td>Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-</td>
</tr>
<tr>
<td></td>
<td>Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol</td>
</tr>
</tbody>
</table>

**Formulation of Floating Dosage Form**

The following types of the ingredients can be incorporated in to GRFDDS

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous

**Hydrocolloids:**

Suitable hydrocolloids are synthetic, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. e.g., Acacia, pectin, agar, alginites, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and SCMC can be used. The hydrocolloids must hydrate in acidic medium i.e., gastric fluid is having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydro-dynamically balanced to have a bulk density of less than one to assure buoyancy.

**Table 3: Polymers and their Applications in GRFDDS**

<table>
<thead>
<tr>
<th>Name of the polymer</th>
<th>Pharmaceutical applications</th>
<th>Application in GRFDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectin</td>
<td>Adsorbent, emulsifying agent, Gelling agent, thickening agent, stabilizing agent,</td>
<td>Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal (GI) tract. Used in novel tablet formulations and modified release tablets</td>
</tr>
<tr>
<td>Acacia</td>
<td>Emulsifying and suspending agent, binder, viscosity-enhancer</td>
<td>It has been investigated in a number of experimental pharmaceutical applications including as a Sustained release agent in gels, beads, microspheres, and tablets.</td>
</tr>
<tr>
<td>Agar</td>
<td>Emulsifying agent, stabilizing agent, suppository base, suspending agent, tablet binder, thickening agent, viscosity-increasing agent</td>
<td></td>
</tr>
<tr>
<td>Gelatin</td>
<td>Coating agent, film-former, Gelling agent, suspending agent, tablet binder, viscosity-increasing agent</td>
<td>Low-molecular-weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs. Ibuprofen-gelatin micro pellets have been prepared for the controlled release of the drug.</td>
</tr>
<tr>
<td>Alginic Acid</td>
<td>Stabilizing agent, suspending agent, sustained release adjuvant, tablet binder, tablet disintegrant, Viscosity increasing agent</td>
<td>Alginate gel beads capable of floating in the gastric cavity have been prepared, the release properties of which were reported to be applicable for sustained release of drugs, and for targeting the gastric mucosa.</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Coating agent, disintegrant, film former, mucoadhesive, binder, viscosity-increasing agent</td>
<td>Chitosan has been processed into several pharmaceutical forms including gels, films, beads, microspheres, tablets and coatings for liposomes.</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>Coating agent, flavoring fixative, Tablet binder, tablet filler, viscosity-Increasing agent</td>
<td>Studies have also suggested ethylcellulose for use in floating microparticles</td>
</tr>
<tr>
<td>Polycarbophil</td>
<td>Adsorbent, bioadhesive, Controlled release tablet binder, emulsifying agent, thickening agent, suspending agent.</td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Alkalizing agent, therapeutic agent</td>
<td></td>
</tr>
</tbody>
</table>

**Inert fatty materials:**

Edible, pharmaceutical inert fatty material, having a specific gravity
less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy e.g. Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used.

**Release rate accelerant:**
The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60 % by weight. (Super Disintegrant)

**Release rate retardants:**
Insoluble substances such as di-calcium phosphate, talc, magnesium stearate decreases the solubility and hence retard the release of medicaments.

**Buoyancy Increasing agents:**
Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug (dose)</th>
<th>Company, country</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar®</td>
<td>Levodopa(100mg), benserazide(25mg)</td>
<td>Roche Products, US</td>
<td>Floating controlled release capsule</td>
</tr>
<tr>
<td>Valrelease®</td>
<td>Diazepam (15mg)</td>
<td>Hoffmann-La Roche, US</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>Liquid Gaviscon®</td>
<td>Al. hydroxide (95mg), Mg. carbonate (358mg)</td>
<td>GlaxoSmithKline, India</td>
<td>Raft-forming liquid alginate preparation</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Aluminium-magnesium antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Flooding liquid alginate preparation</td>
</tr>
<tr>
<td>Conviron®</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
<td>Gel-forming floating system</td>
</tr>
<tr>
<td>Cifran OD®</td>
<td>Ciprofloxacin (500mg &amp; 1g)</td>
<td>Ranbaxy, India</td>
<td>Gas-generating floating tablet</td>
</tr>
<tr>
<td>Oflin OD®</td>
<td>Ofloxacin (400mg)</td>
<td>Ranbaxy, India</td>
<td>Gas-generating floating tablet</td>
</tr>
<tr>
<td>Cytotec®</td>
<td>Misoprostol (100mg)</td>
<td>Pharmacia, US</td>
<td>Bilayer floating capsule</td>
</tr>
</tbody>
</table>

**Miscellaneous:**
Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporated in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems. A list of Polymers and their Applications in GRFDDS are given in Table 3.

**Evaluation of Floating Drug Delivery System:**
Evaluation of a formulation and parameters to be evaluated is a critical aspect in formulation technology. A schematic on evaluation of GRFDDS is shown as in Schematic Diagram.

**Evaluation of Powder Blend as per general Pharmacopoeial specifications such as Angle of Repose, Bulk Density, Tapped Density, Hausners Ratio, Compressibility Index etc.**

**Evaluation of Floating Tablets**

**Pharmacopoeial Tests**

**Hardness**
The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 Kg/cm² is considered adequate for mechanical stability.

**Friability**
The friability of the tablets was measured in a Roche Friabilator. 20 Tablets were taken, Weighed and Initial weight was noted (W₁) are dedusted in a drum for a fixed time (100 Freefalls, in a Roche Friabilator) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

\[
\text{Friability (\%)} = \left( \frac{(\text{Initial weight} - \text{Final weight})}{\text{(Initial weight)}} \right) \times 100
\]

**Content Uniformity**
In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or not more than 115% (100±15%) of the labeled drug content can be considered as the test was passed.
The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was dissolved in 100ml of 0.1N Hydrochloric acid by sonication for 30 min. The solution was filtered through a 0.45μ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at \( \lambda_{\text{max}} \) of API (nm) using 0.1 N Hydrochloric acid as blank.

Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

In-Vitro Buoyancy Studies

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

\[
\text{Buoyancy (\%)} = \frac{W_f}{W_f + W_s} \times 100
\]

Where, \( W_f \) and \( W_s \) are the weights of floating and settled microspheres respectively.

In-Vitro Dissolution Study

The In-vitro dissolution study for the Floating tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at \( \lambda_{\text{max}} \) of API (nm) using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3)

Kinetic modelling of drug release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modelling of drug release.

In-Vivo Evaluation for Gastro-Retention:

X-ray/ Gamma Scintigraphy:

X-ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of aradio opaque material into a solid dosage form enables it to be visualized by X rays. Similarly, the inclusion of \( \gamma \) emitting radionuclide in a formulation allows indirect external observation using a \( \gamma \) camera or scintiscanner. Incase of \( \gamma \) scintigraphy, the \( \gamma \) rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT.

In-Vivo behavior of coated and uncoated beads, prepared floating beads was monitored using a single channel analyzing study in 12 healthy human volunteers of mean age 34 yrs by Gamma scintigraphy.

Tablet density

Tablet density is an important parameter for floating tablets. The tablet would floats only when its density is less than that of gastric fluid (1.004). The density is determined using following relationship

\[
V = \frac{\pi r^2 h d}{m}
\]

\[
v = \text{volume of tablet (cc)}
\]

\[
r = \text{radius of tablet (cm)}
\]

\[
h = \text{crown thickness of tablet (g/cc)}
\]

\[
m = \text{mass of tablet}
\]

FOR MULTIPLE UNIT DOSAGE FORMS (MICROSPHERES/ MICROBALLONS)

In case of multiparticulate drug delivery systems, differential scanning calorimeter (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and x-ray diffraction studies are performed.

Size and shape evaluation

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation can be determined using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope, Electro scintigraphy.
résistance counting methods, Sedimentation techniques, Laser diffraction methods\[^{31,62}\].

**Morphology and surface topography**
The surface topography and structures were determined using scanning electron microscope (SEM) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profilometer\[^{62}\].

**Percentage drug entrapment**
Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the pre-prepared formulations. The drug is extracted by a suitable method, analyzed and is calculated from:

\[
PDE = \frac{\text{Practical Drug Loading}}{\text{Theoretical Drug Loading}} \times 100
\]

**FUTURE POTENTIAL AND CONCLUSION**
The development of GRFDDS products is currently one of the most important challenges in pharmaceutical research. From the above review we conclude that GRFDDS products by virtue of formulation and product design provide drug release in a modified form distinct from that of the conventional dosage forms mainly at stomach region, aptly applicable to drugs showing absorption at stomach site. The physicochemical properties of the drug, polymer and the drug to polymer ratio govern the release of drug from the formulation. The use of one kind of polymer or another can affect the release kinetics, the presence of burst effect and the mechanisms involved in the release. Natural polymers have been used significantly in designing and synthesis of novel drug delivery systems because of their biodegradable, biocompatible, ecofriendly nature and vast availability. Hence these natural polymers will expand the scope of new drug delivery systems in the future. With proper selection of natural polymers and their blending with other polymers better floating dosage forms with improved floating lag time, floating duration and drug release can be achieved. The use of Natural Polymers can be a good replacement for synthetic polymers in the Formulation development of controlled release floating dosage forms, Formulations prepared by such renewable and eco-friendly plant resources can be considered as promising floating matrix forming agents to bring about sustained release action with site specific delivery for improved bioavailability. FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines).

The kinetic study of drug release helps in obtaining meaningful parameters which are employed for comparative purposes and relating the release parameter with important parameters such as bioavailability which further aids in studying the influence of formulation factors on the drug release for optimization.

**REFERENCES**


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