

A Review on Techniques and Applications of Gastroretentive Drug Delivery System

Hrishabh Sharma¹, Ashutosh Sharma², Dr. Mayank Bansal³, Dr. Rakesh Kumar Gupta⁴

¹Research Scholar, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

²Associate Professor, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

³Principal & Professor, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

⁴Professor, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

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Corresponding author: Hrishabh Sharma

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Abstract

A Controlled release dose forms have been widely utilized to enhance treatment with a number of significant medications. However, a number of physiological challenges, including the inability to control and localize the system within the target region of the gastrointestinal tract and the extremely changeable nature of the gastric emptying process, pose challenges to the development processes. The bioavailability and periods needed to reach peak plasma levels may be unpredictable as a result of this diversity. The goal of this review on gastro retentive drug delivery systems was to gather the most recent research with a special emphasis on the numerous gastro retentive technologies that have lately emerged as leading approaches in the area of site-specific oral controlled release drug delivery. We have included crucial elements in order to comprehend numerous physiological challenges to achieve stomach retention.

Keywords: Gastroretentive, GRDDS, Oral route, Various Approaches.

Introduction

Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs. The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches:

- (a) Low density form of the DF that causes buoyancy in gastric fluid.
- (b) High density DF that is retained in the bottom of the stomach.

(c) Bioadhesion to stomach mucosa.

(d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or Pharmaceutical excipients.

Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter⁽¹⁻⁶⁾

2. Suitable Drug Candidates for Gastroretention

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper part of the GIT:

Drugs acting locally in the stomach,
E.g., Antacids and drugs for H. Pylori viz.,
Misoprostol

Drugs that are primarily absorbed in the stomach, E.g., Amoxicillin

Drugs that is poorly soluble at alkaline pH, E.g., Furosemide, Diazepam, Verapamil, etc.

Drugs with a narrow window of absorption, E.g., Cyclosporine, Methotrexate, Riboflavin and Levodopa, etc.

Primarily absorbed from stomach and upper part of GI tract, E.g., Calcium supplements,

Chlordiazepoxide and Cinnarazine

Drugs that degrade in the colon, E.g. Ranitidine, Metformin HCl, Metronidazole.⁽⁷⁾

Drugs Those are Unsuitable For Gastroretentive Drug Delivery Systems

- ❖ Drugs that have very limited acid solubility. E.g. Phenytoin etc.
- ❖ Drugs that suffer instability in the gastric environment. E.g. Erythromycin etc.
- ❖ Drugs intended for selective release in the colon. E.g. 5- amino salicylic acid and Corticosteroids etc.⁽⁸⁾

Factors affecting the gastro retentive system

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co- administration of gastric-emptying delaying drugs.⁽⁹⁾ Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system⁽¹⁰⁾.

1. Density: Density of a dosage form plays a vital role in determining its buoyancy and henceforth, its floating efficiency.

2. Shape of dosage form: Compared to other shapes, devices with tetrahedron and ring shape have better floating potential. They have 90-98% better retention for 24 hrs

3. Single or multiple unit formulation: Multiple unit formulations permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

4. Fed or unfed state: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.

5. Nature of meal: Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release⁽¹¹⁾.

6. Caloric content: A meal rich in protein and fat content can increase floating by 4- 10 hrs.

7. Frequency of feed: The floating can increase by over 400 minutes when successive meals are given compared with a single meal

Formulation considerations for GRDDS

It must be effective retention in the stomach to suit for the clinical demand

- 1) It must have sufficient drug loading capacity.
- 2) It must be control the drug release profile.
- 3) It must have full degradation and evacuation of the system once the drug release is over.

Polymers and other ingredients

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

Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC etc.

Inert fatty materials (5%-75%): 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. E.g. Beeswax, Fatty acids, Long chain fatty alcohols, Gelucires.

Effervescent agents: Sodium bicarbonate, Citric acid, Tartaric acid, Di-SGC (Di- Sodium Glycine Carbonate, CG (Citroglycine).

Release rate accelerants (5%-60%): eg. Lactose, Mannitol.

Release rate retardants (5%-60%): eg. Dicalcium phosphate, Talc, Magnesium stearate.

Buoyancy increasing agents (upto 80%): eg. Ethylcellulose.

Low density material: Polypropylene foam powder (Accrued MP 1000[®]).

Advantages of gastroretentive delivery systems

➤ Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.

➤ Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. β -lactam antibiotics (Penicillins and Cephalosporins).

➤ For drugs with relatively short half-life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.

➤ They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).

➤ The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.⁽¹²⁻¹⁷⁾

Disadvantages of floating drug delivery system:

➤ 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-coat, water⁽¹⁷⁾.

➤ The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

➤ Some drugs present in the floating system causes irritation to gastric mucosa.

Limitations^(18, 19):

➤ Require a higher level of fluids in the stomach⁽¹⁸⁾.

➤ Not suitable for Drugs that.

- Have solubility problems in gastric fluid. E.g. Phenytoin,
- Cause G.I irritation. E.g. NSAIDS,
- Are unstable in acidic environment.

➤ Drugs intended for selective release in the colon E.g. 5- aminosalicylic acid and Corticosteroids etc.

Application of gastro retentive drug delivery systems

➤ Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption⁽²⁰⁾.

Eg. A significantly increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

➤ Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased

when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

➤ Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy⁽²⁰⁾.

E.g. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD[®] CO LTD. capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD[®] CO LTD. capsules (8 hours).

➤ Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

➤ Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. E.g. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased.

AUC obtained with the floating tablets was approximately 1.8 times those of conventional Furosemide tablets.

Approaches to gastric retention

Floating DDS (FDDS), with low density providing sufficient buoyancy to float over the gastric contents, Bioadhesive systems, enabling the localized retention of the

system in the stomach, Swelling and expanding systems, preventing transit from the gastric sphincter, High density system, remaining in the stomach for longer period of time by sedimenting to the folds of stomach, Super porous hydrogels, and Modified- shaped system. A number of other methods like use of passage-delaying agents, magnetically controlled systems and combination methods like floating-bioadhesive systems.

Floating drug delivery systems

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir.

Types of floating drug delivery systems

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

- 1) Non- Effervescent FDDS
- 2) Effervescent FDDS

Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most

commonly used excipients in non-effervescent FDDS are gel forming or highly swellable Cellulose type hydrocolloids, Hydrophilic gums, Polysaccharides and Matrix forming materials such as Polycarbonate, Polyacrylate, Polymethacrylate, Polystyrene as well as Bioadhesive polymers such as Chitosan and Carbopol.

A. Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.

A. Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gelbarrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach⁽²¹⁾.

B. Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gelbarrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

C. Alginate Beads

Multi-unit floating dosage forms were developed from freeze-dried Calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping Sodium alginate solution into aqueous solution of Calcium chloride, causing precipitation of Calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The Ethanol: Dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.⁽²²⁾

1) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. Citric acid and Tartaric acid) present in the formulation to produce Carbon dioxide (CO₂) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature. These effervescent systems further classified into two types:

1. Gas generating systems,
2. Volatile Liquid/Vacuum Containing Systems.

1. Gas Generating Systems

A. Tablets

Floating bilayer tablets with controlled release for Furosemide were developed by Ozdemir et al., 2000. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid.

B. Floating capsules

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium

bicarbonate. The systems were shown to float during *in vitro* tests as a result of the generation of CO₂ that was trapped in the hydrating gel network on exposure to an acidic environment.

A. Multiple unit type floating pills

The system consists of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swell able membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO₂ within the system.⁽²³⁾

B. Floating system with Ion-Exchange resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO₂. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO₂ generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads.

1. Volatile Liquid / Vacuum Containing Systems

A. Intra-gastric floating gastrointestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

B. Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated

polymeric matrix, encapsulated in a gelatin capsule.

C. Intra-gastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device.

The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice.⁽²⁴⁾

Bioadhesive drug delivery system

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a thorough understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment. As the mucus layer comes into contact with bioadhesive coated system, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occur between the complimentary structures. However, these interactions last only until the turnover process of mucin and, in order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time.

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles on contact

with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon.

Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter.

Low-density systems ($<1 \text{ g/cm}^3$) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called microballoons⁽²⁵⁾ because of the low-density core.

Formulation Ingredients of Floating Dosage Form

Following types of the ingredients can be incorporated in to floating dosage form,

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Low density material
- Miscellaneous⁽²⁶⁾

Future Potential of Fdds

Floating dosage form offers various future potential as evident from several recent publications. Among the recently used clinical drugs several narrow absorption window drugs may benefit from compounding into a FDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment. It may be believed that it can be possible with FDDS. Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their

absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development of various anti-reflux formulations. Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease, is also an important area of consideration. Combination therapy to treat *H.pylori* infection in a single FDDS needs to be developed. The study of the effect of various geometric shapes in a more excessive manner than previous studies on gastro retentivity needs to be developed. The investigations can be concentrated on the concept of design of novel polymers according to clinical and pharmaceutical need.

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