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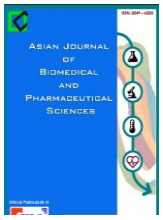

REVIEW ARTICLE

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A Review of Floating Drug Delivery System

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Abstract

Floating drug delivery systems improves the drug bioavailability and patient compliance by increasing the gastric residence time and controlling the drug release. In recent decades, there have been numerous attempts to overcome the barriers like short gastric residence times and unpredictable gastric emptying times. In this review, the technological and research advancements made in floating systems are discussed.

Keywords: Floating drug delivery system, Gastric residence time, bioavailability.

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1. INTRODUCTION

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery patent protected formulation technologies that modify drug release profile, absorption, distribution and elimination of the drug and improving product efficacy, safety, patient convenience and compliance [1].

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation [2]. The primary aim an oral controlled drug delivery system (DDS) should be to achieve more predictable and increased bioavailability of drugs. However, several physiological difficulties preclude the development process. These include inability to restrain and localize the DDS within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. Depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to unpredictable availability and times to achieve peak plasma levels [3]. Furthermore, the relatively short gastric residence time in humans (2–3 h) through the major absorption zone (stomach or upper part of the intestine) can result in incomplete drug release from the DDS and hence diminished efficacy of the administered dose. Thus, control of location of a DDS, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem, in a specific region of the GI tract offers several advantages [4, 5]. These considerations have led to the development of oral controlled-release (CR) dosage forms possessing gastric retention capabilities. In this review the current technological developments in floating drug delivery system and patented or clinically available products are discussed.

BASIC PHYSIOLOGY AND PROBLEMS

The process of gastric emptying occurs both during fasting and fed states; however, the patteren of motility differs markedely in two states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) [6] which is further divided into following 4 phases as shown in figure 1. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. Overall, the relatively brief gastric transit time of most drugs. These problems can be exacerbated by alterations in gastric emptying that occur due to the factors such as age, race, sex and disease states, as they may have seriously affect the release of a drug from the delivery system. So, it is desirable to have a controlled release product that exhibits an extended gastric residence and adrug release profile independent of patient related variables [7].

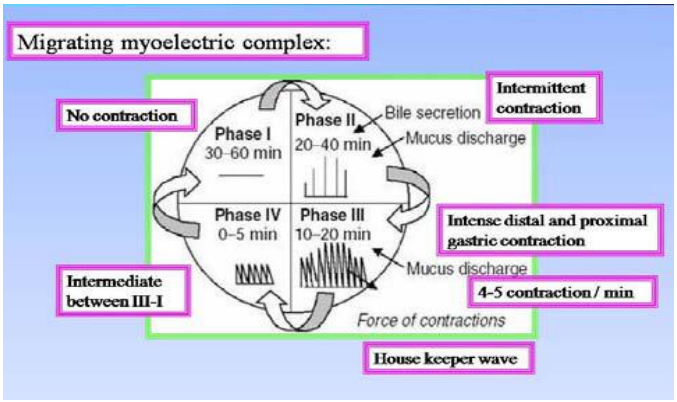

Fig 1: Schematic presentation of MMC

APPROACHES TO GASTRIC RETENTION

Various types of systems have been developed to increase the GRT of dosage forms by employing range of concepts as shown in Fig. 2. These systems have been classified on the basis of principle of gastric retention [6].

- **Floating drug delivery systems (FDDS)**: These systems have low density and so float over the gastric contents.
- **Bioadhesive systems**: They bind with stomach mucosa and hence, enable the localized retention of the system.
- **Swelling and expanding systems**: Such systems absorb water and hence, enlarged size

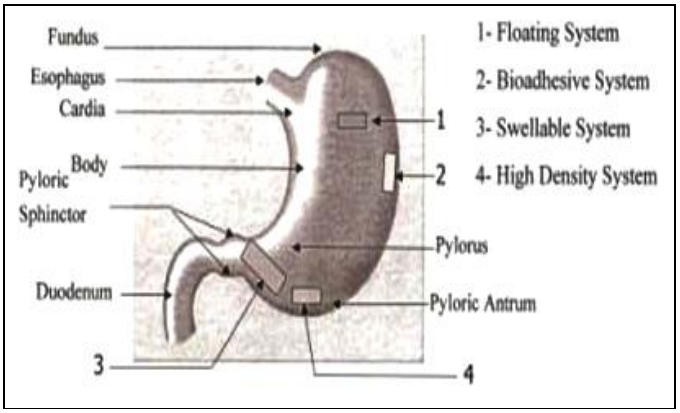

Fig 2: Various Approaches to Gastrortentive systems of system ensures no passage from gastric sphincter.

High density systems: They remain in the stomach for longer period of time, by sedimenting to the folds of stomach.

2. FLOATING DRUG DELIVERY SYSTEMS

These are oral dosage forms (capsule or tablet) that are designed to prolong the residence time of the dosage form within the GI tract [7]. It is formulation of a drug

and gel forming hydrocolloids meant to remain buoyant in stomach. This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence, ready for absorption [8].

The recent scientific and patent literature shows increased interest in academics and industrial research group regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. Table 1 enlists the drugs which have been studied for developing floating systems. The various marketed FDDS are given in table 2.

Merits

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages [9] in drug delivery.

These advantages include:

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach like antacids.

Dosage form	Drug (s)
Microspheres	Aspirin, griseofulvin and p-nitroaniline Ibuprofen, Terfenadine, Tranilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Films	Cinnarizine, Drug delivery device
Powders	Several basic drugs (63)
Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa and benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid
Tablets/Pills	Acetaminophen, acetylsalicylic acid, amoxycilin trihydrate, ampicilin, atenolol, Chlorpheniramine maleate, Cinnarizine, Diltiazem, Fluorouracil, Isosorbide dinitrate, p- Aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5'-phosphate, Sotalol, Theophylline, Verapamil

Table 1: List of drugs explored for developing floating dosage form

3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site [10].
6. Controlled delivery of drugs. It minimizes the mucosal irritation by releasing drug slowly.
7. Treatment of gastrointestinal disorders such as gastro esophageal reflux.
8. Ease of administration and better patient compliance.
9. Site-specific drug delivery system.

Brand name	Delivery system	Drug	Company name
Almagate Flot coat®	Floating dosage form	Al-Mg Antacid	
Cifran OD®	Gas-generating floating form	Ciprofloxacin	Ranbaxy, India
Convoron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol	Pharmacia, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide, Mg carbonate	Glaxosmithkline, India
Madopar ®HBS (Prolopa®HBS)	Floating, CR capsule	Benserazide and L-Dopa	Roche Products, USA
Oflin OD®	Gas generating floating tablet	Ofloxacin	Ranbaxy, India
Topalkan®	Floating liquid alginate preparation	Al-Mg antacid	Pierre FabreDrug, france
Valrelease®	Floating capsule	Diazepam	Hoffmann-LaRoche, USA

Table 2: Marketed FDDS

Types

1. Non effervescent FDDS
2. Effervescent FDDS

Non-Effervescent systems

These are also called as hydrodynamically balanced systems (HBS). They incorporate gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. The buoyancy to these dosage forms is provided by air trapped in the swollen polymer. Sheth and Tossounian [11] postulated that when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. This gel structure then regulates the rate of diffusion of solvent-in and drug-out of the dosage form. As the outer surface goes into solution, the gel barrier is maintained by the hydration of immediate adjacent hydrocolloid layer. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary of the HBS. The whole mechanism of HBS is illustrated in Fig. 3.

- **Colloidal gel barrier systems**

These types of HBS system contains drug with gel forming or swellable polymers like cellulose type hydrocolloids, polysaccharides etc [11]. They contain

high levels (20 to 75 % w/w) of one or more gel forming highly polymers incorporated either in tablets or capsules. After intake of such systems, the hydrocolloid gets hydrated in gastric fluid and forms a colloidal gel barrier around
its surface. The air trapped inside the swollen polymer maintains the density less than unity and confers buoyancy to these dosage forms.

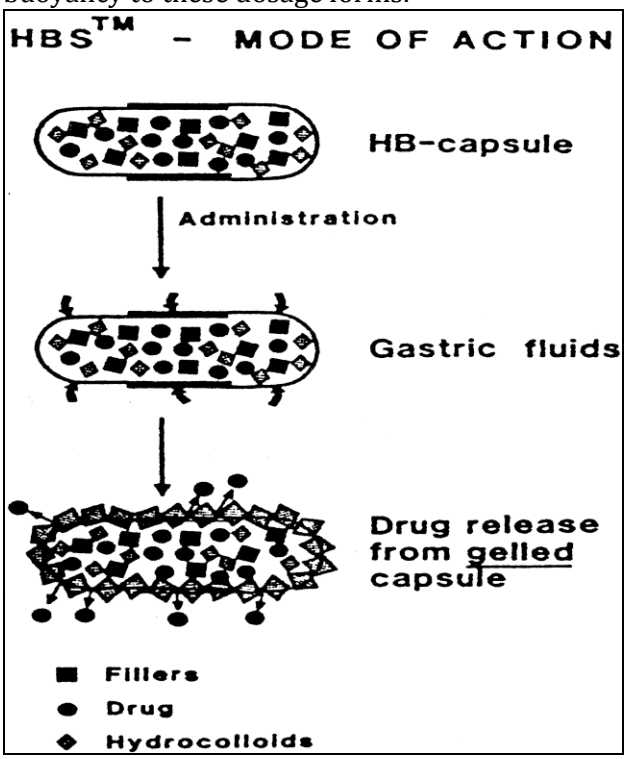

Fig. 3: Principle of HBS

This gel barrier controls the rate of the fluid penetration into the device and hence, release of drug. With time the exterior surface of the dosage form goes in to the solution, the adjacent hydrocolloid layer becomes hydrated and thus maintains the gel layer. The HBS must fulfill the three basic criteria's [12]:

1. It must have sufficient structure to form cohesive gel barrier.
2. It must maintain an overall specific density lower than that of gastric contents.
3. It should dissolve slowly enough to serve as reservoir for the delivery system.

Based upon this principle, a bilayer tablet containing one immediate release and other sustained release layer can be prepared. Immediate release layer delivers the initial dose whereas the other layer absorbs gastric fluid and forms a colloidal gel barrier on its surface [13].

A multi-layer, flexible, sheath-like device buoyant in gastric juice showing sustained release characteristics have also been developed. This device is consisted of at least one dry self-supporting carrier film, made up of water insoluble polymer matrix containing drug in either dispersed or dissolved forms and a barrier film overlaying the carrier film. Both carrier and barrier films are sealed together along their periphery and in such a way as to entrap a plurality of small air pockets, which bring about the buoyancy to the laminated films [14].

- **Micro porous compartment system**

In this type of systems, drug reservoir is encapsulated inside a micro porous compartment with pores along its top and bottom surfaces [11].To prevent any direct contact of gastric mucosal surface, the peripheral walls of the drug reservoir compartment are completely sealed. In stomach, the entrapped air of floatation chamber causes the delivery system to float over the gastric contents. Gastric fluid enters the system only through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

- **Alginate beads**

Multiple unit floating dosage forms [15] have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at – 40ºC for 24 hrs, leading to formation of porous system that maintained structure for over 12 hrs [22]. The floating beads gave a prolonged residence time of more than 5.5-10 hours.

- **Hollow Microspheres**

Hollow microspheres (micro balloons) for ibuprofen were prepared by novel emulsion solvent diffusion method as such type of system is illustrated in Fig. 4. These micro balloons floated continuously for more than 12 hrs over the surface of acidic solution media that contained surfactant.

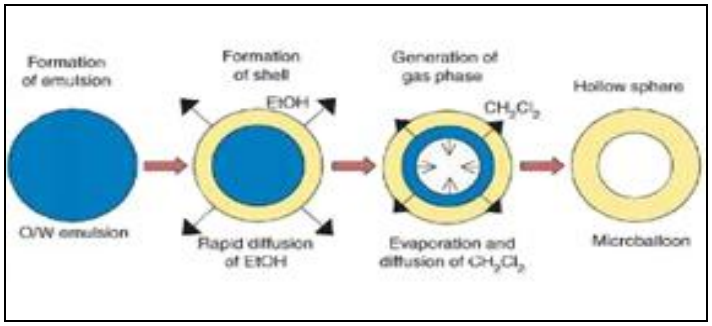

Fig 4: **Formulation of hollow microspheres**

The amount of drug released was more in pH 7.2 than in pH 6.8 [16].

Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air, or inert gas [17]. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.

- **Volatile liquid containing systems**

These devices are osmotically controlled floating systems. These contain a hollow deformable unit that can be transformed from a collapsed to an expanded position and returned to collapse position after an extended period. The deformable unit consists of two chambers which are separated by an impermeable, pressure responsive, movable bladder (Fig. 5) [18]. The drug is

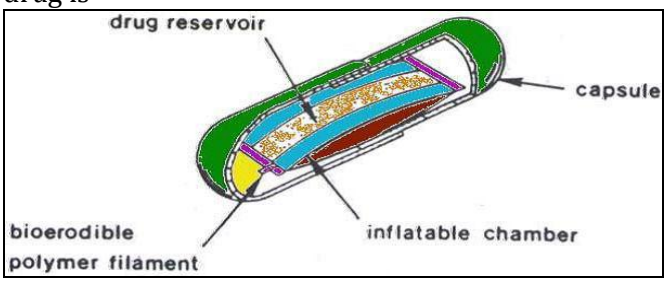

Fig 5: Gastro inflatable drug delivery device (US Patent ≠ 3, 901, 232, August 26, 1975).

loaded in first chamber and the volatile liquid is added into second chamber. Upon administration, the device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made of PVA, polyethylene, etc. 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 [19].

Intra-gastric, osmotically controlled drug delivery system **(Fig. 6)** consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in bioerodible capsule. When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the drug delivery system [20].

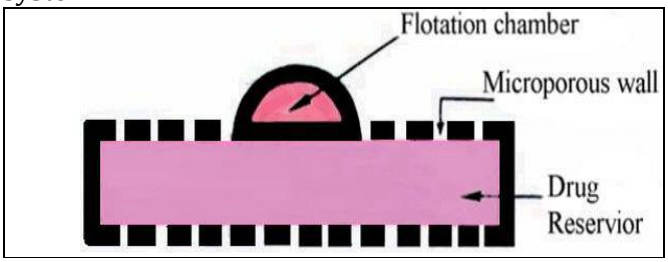

Fig 6: Intra gastric osmotic controlled drug delivery system II (US Patent ≠ 4, 055, 178, October 25, 1977).

The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag.

- **Gas generating systems**

These systems remain buoyant on gastric fluid and contain matrices prepared by using:

1. Swellable polymers such as hydroxyl propyl methylcellulose (HPMC)
2. Polysaccharides such as chitosan.
3. Effervescent components such as sodium bicarbonate, tartaric acid and citric acid or chambers containing a liquid that gasifies at body temperature. The stoichiometric ratio of citric acid and sodium bicarbonate should be optimum for gas generation and is reported to be 0.76:1.

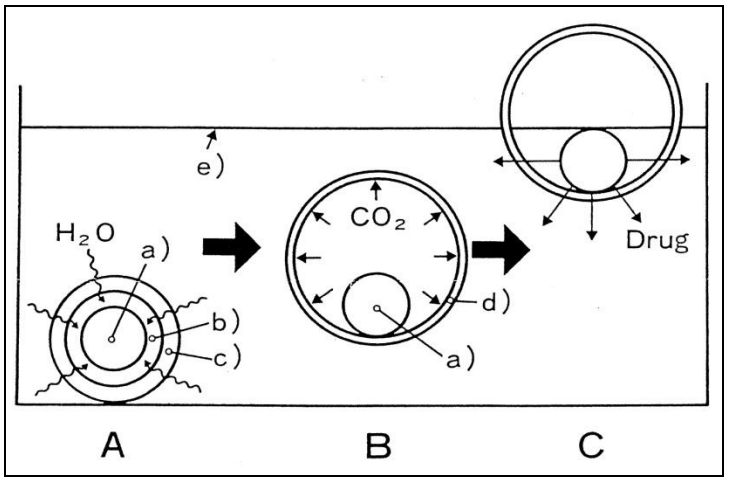

Fig. 7: Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug.

For the preparation of these systems, firstly resin beads are loaded with bicarbonate and then coating with ethyl cellulose is done [21]. This coating is insoluble in water but allows permeation of water through it. This causes liberation of carbon dioxide because of which beads float in the stomach. The mechanism of drug release is illustrated in Fig. 7. The commonly used excipients

are hydoxypropylmethyl cellulose, polyvinyl acetate, polyacrylate polymers, sodium alginate, polyethylene oxide, calcium chloride, Carbopol®, agar, and polycarbonates.

Raft systems

Raft forming systems [22] incorporate alginate gels. These have a carbonate component which upon reaction with gastric acid form bubbles in the gel and hence enables floating. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft (Fig. 8) [23]. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. These systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. A patent assigned to Reckitt and

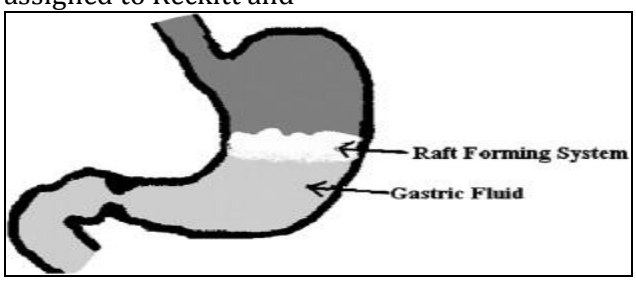

Fig 8: Raft system

Colman Products Ltd., describes a raft forming formulation for the treatment of *Helicobacter pylori (H. Pylori*) infections in the GIT.

3. CONCLUSION

Floating drug delivery system have come forward as an efficient means of enhancing the bioavailability and controlled delivery of drugs. The advancement in delivery technology will lead to the development of large number of floating delivery system to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism.

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