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Floating Drug Delivery Systems: A Review

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ABSTRACT

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Floating drug delivery systems are of particular interest for drugs that are locally active and have a narrow absorption window in the stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This review article summarizes advantages, limitations, polymers used in floating systems, factors affecting floating systems, approaches to design floating systems, evaluation, and applications. These systems are useful to overcome several problems encountered during the development of a pharmaceutical dosage form.

INTRODUCTION

Oral drug delivery is the most preferred route of drug delivery due to ease of administration and patient compliance. The oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. Most of the oral controlled drug delivery systems rely on diffusion, dissolution, or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal tract and the drug profile data, such as dose, absorption properties, and the quantity of drug needed, one can determine the desired release rate of the drug from controlled release dosage form[1, 2].

Floating drug delivery system (FDDS) is a class of gastroretentive drug delivery system. FDDS is a recent advancement in pharmaceutical technology that has also several advantages over conventional drug delivery systems. Those advantages of the floating system can be used in the treatment of the world's most affective diseases like cardiovascular diseases. Floating systems are low density systems that float over the gastric content and tending to keep afloat in the stomach without affecting gastric emptying rate for a prolonged period. While the system is floating on the gastric content drug is released slowly from the system at the desired rate, after the release of the drug; the system is emptied from the stomach[3]. This results in an increase in GRT and better control of fluctuation of plasma drug concentration.

1.1 Advantages:

Floating dosage systems form important technological drug delivery systems with gastric retentive behaviour and offer several advantages in drug delivery. These advantages include:

1. FDDS can remain in the stomach for several hours and therefore prolong the gastric retention time of various drugs[4].

2. FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids.

3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in the floating condition in the stomach to get a relatively better response.

4. FDDS improves patient compliance by decreasing dosing frequency[5].

5. Bioavailability enhances despite the first-pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.

6. Acidic substance like aspirin irritates the stomach wall when coming in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.

7. The FDDS are advantageous for drugs absorbed through the stomach e.g.: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.

8. Site-specific drug delivery.

1.2 Limitations:

1. Drugs which are irritating the gastric mucosa are also not suitable.

2. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated into the systems.

3. Not suitable for drugs that have solubility or stability problems in GIT.

4. The drugs that are significantly absorbed throughout the gastrointestinal tract, which undergo significant first-pass metabolism, are the only desirable candidates.

5. The ability to float relies on the hydration state of the dosage form. To keep these tablets floating, intermittent administration of water is beneficial[6, 7].

1.3 Suitable drug candidates for gastro retention:

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

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa

2. Primarily absorbed from the stomach and upper part of the GI tract, e.g., calcium supplements, chlordiazepoxide and cinnarazine[8]

3. Drugs that act locally in the stomach, e.g., antacids and misoprostol

4. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole[9, 10]

5. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

2. POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM:

Polymers are used in floating systems to target the drug delivery at a specific region in the GI tract i.e. stomach. Polymers are the macromolecule compounds containing many monomer units joined to each other by bonds. Both synthetic and natural polymers are used in the floating drug delivery[11, 12]. Natural polymers used in the floating system are guar gum, chitosan, xanthan gum, gellan gum, sodium alginate, etc. Synthetic polymers used for the floating drug delivery are HPMC, eudragit, ethylcellulose, etc.

A) Natural polymers

Natural gums (obtained from plants) are hydrophilic carbohydrate polymers of high molecular weight. They are generally insoluble in organic solvents like hydrocarbon and ether.

Guar gum

Guar gum is a naturally occurring galactomannan polysaccharide. Guar gum hydrates and swells in cold water forming viscous colloidal dispersions or sols. This gelling property retard the drug release and make it a flexible carrier for extended-release dosage forms[13].

Chitosan

Chitosan is a natural polymer obtained by deacetylation of chitin. It has favorable biological properties such as nontoxic, biodegradable, biocompatible. It is a bioadhesive polymer and has anti-bacterial properties thus making it suitable for site specific delivery. Chitosan is a high molecular weight polycationic weak base with a pKa value of 6.2-7. In addition to acidic pH of 1.2 or neutral media, it becomes buoyant and provides control release.

By increasing the thickness of chitosan film release rate can be decreased[14].

Xanthan gum

Xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture aerobic fermentation of carbohydrates. Xanthan is a long-chained polysaccharide with a large number of trisaccharide side chains. Gum also has excellent solubility and stability

under acidic and alkaline conditions and in the presence of salts and resists common enzymes[15].

Gellan gum

Gellan gum is an anionic, high molecular weight, deacetylated extracellularly, a linear polysaccharide. This gum has an outstanding flavour release, high gel strength, excellent stability, process flexibility, high clarity, good film former, and thermally reversible gel characteristics. Gellan gum is produced as a fermentation product from *Spingomonas elodea.*

Sodium alginate

Sodium alginate chiefly consists of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

B) Synthetic polymers

Synthetic polymers are becoming increasingly important in pharmaceuticals. The use of synthetic polymers ranges from binder, film coating agent, etc. Synthetic polymers are either purely synthetic or they have modified forms of natural polymer known as semi-synthetic.

Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose ethers belong to an extensive family of white to off-white, odorless, water soluble polymers that bind, retain water, thicken, form films, lubricate. It is a semi-synthetic, inert, viscoelastic polymer, used as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

Eudragit

Polymethacrylates (Eudragit) are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. It is soluble in gastric fluid below pH 5. In contrast, Eudragit L, S, and FS types are used as enteric coating agents because they are resistant to gastric fluid. Different types of enteric coatings are soluble at different pH values: e.g. Eudragit L is soluble at pH >6 whereas Eudragit S and FS are soluble at pH >7.

Ethylcellulose

Ethocel has been widely used in the pharmaceutical industry for over 50 years. Ethylcellulose has been used for choice in pharmaceutical formulations for various purposes, such as taste-masking of bitter actives, moisture protection, stabilizer, extended-release multiparticulate coating, micro-encapsulation of actives, extended-release binder in inert matrix systems, solvent and extrusion granulation. The application of Ethylcellulose in wet extrusion processes is limited, since the polymer has considerable elastic properties, but can be successfully used as matrix former in combination with some plasticizing agents.

3. FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM:

a) Density:

The density of the dosage form should be less than the gastric contents (1.004 gm/ml)[16].

b) Size and Shape:

Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT competed to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilo-pond per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes[17, 18].

c) Fed or Unfed State:

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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[19].

d) Nature of the Meal:

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release[20, 21].

e) Caloric Content:

GRT can be increased between 4 to 10 hours with a meal that is high in proteins.

4. APPROACHES OF FLOATING DRUG DELIVERY SYSTEMS:

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation[22].

(A) Non-effervescent systems: This type of system, after swallowing, swells via imbibitions of gastric fluid to an extent that it prevents its exit from the stomach. The formulation methods of such type dosage forms involve the mixing of the drug with a gel, which swells when comes in contact with the gastric fluid and maintains relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer provides buoyancy to these dosage forms. The most commonly used excipients in these systems include hydroxypropyl methylcellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates[23]. This system can be further divided into four sub-types:

(i) Colloidal gel barrier system: These types of systems contain drug with gel-forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its absorption sites in the solution form for ready absorption[24]. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid as hydroxyl propyl cellulose, hydroxyl ethyl cellulose. This hydrocolloid hydrates and forms a colloid gel barrier around its surface after coming in contact with the gastric fluid and also helps in the sustained release of the drug.

(ii) Microporous Compartment system:

In this technology, a drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed. This sealing prevents any direct contact of the gastric surface with the un-dissolved drug. The flotation chamber containing the delivery system to float over the gastric content entrapped air allows, in the stomach. Gastric fluid enters through an aperture,

dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption[25].

(iii) Alginate beads:

To develop Multi-unit floating dosage forms, freeze-dried calcium alginate has been used. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into an aqueous solution of calcium chloride[26]. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, it leads to the formation of a porous system that can maintain a floating force for over 12 hours. These floating beads prolong residence time for more than 5.5 hours.

(iv) Hollow Microspheres/Microballons:

A novel emulsion solvent diffusion method was used to prepare hollow microspheres loaded with a drug in their outer polymer shelf ethanol/ dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of polyvinyl alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of the microsphere of the polymer and drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours[27].

(B) Effervescent Systems:

These buoyant systems utilize matrices prepared with swellable polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid, or tartaric acid) [28]. The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach.

5. EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS:

1. Determination of hardness of tablet:

Randomly sampled twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester[29].

2. Determination of weight variation:

Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated[30].

3. Determination of thickness of the tablet:

The individual crown to crown thickness of ten tablets is determined using slide calipers for each batch.

4. Floating lag time:

It is the time taken by the tablet to emerge onto the surface of the dissolution medium and is expressed in seconds or minutes[31].

5. Measurement of Floating Capacity:

Three individual tablets are put in an individual flask containing 400 ml of 0.1(N) HCL solutions. Then the time in minutes for each tablet to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) are measured. The sample mean and standard deviation are then calculated.

6. Angle of repose:

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at a definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

$\theta = \tan^{-1} (h/r)$

θ = angle of repose

h = height of the heap

r = radius of the heap

7. *In vitro* Dissolution Study:

The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900 ml of 0.1 N HCl as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time.

6. APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS:

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract[32]. It retains the dosage form at the site of absorption and thus enhances bioavailability. These include the following:

a) Site-Specific drug delivery

b) Sustained drug delivery

c) Absorption enhancement

d) Enhanced bioavailability

e) Enhanced first-pass biotransformation

f) Sustained drug delivery reduces the frequency of dosing.

g) Targeted therapy for local ailments in the upper GIT.

h) Reduced fluctuations of drug concentration.

7. CONCLUSION:

Drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Thus gastro retentive dosage forms provide an additional advantage for drugs that are absorbed primarily in the upper segments of the gastrointestinal tract. A floating drug delivery system promises to be a potential approach for gastric retention. Although there are several difficulties to be

worked out to achieve prolonged gastric retention, a large number of companies are focusing on commercializing this technique.

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