International Journal of Drug Delivery 3 (2011) 558-570

http://www.arjournals.org/index.php/ijdd/index

Review Article

ISSN: 0975-0215

Enhancement of Drugs Bioavailability by Floating Drug Delivery System – A Review

Vairappan Kamalakkannan[1, 2], Ayarivan Puratchikody*[2], Viswanadhan Vasantha Prasanth[3], Krishnamoorthi Masilamani [4]

*Corresponding author:

Ayarivan Puratchikody

1. Caplin Point Laboratories Limited, Puducherry, India - 605 502.

2.Department of Pharmaceutical Technology, Anna University of Technology, Tiruchirappalli, Tamil Nadu, India - 620 024.

3.Department of Pharmaceutics, Gautham College of Pharmacy, Bangalore, India – 560 032.

4.Department of Pharmaceutics, School of Pharmaceutical sciences, Vels University, Tamil Nadu, India - 600 117.

Abstract

Gastric emptying is a complex process and one of the most important obstacles in the better absorption and enhances bioavailability of oral drug delivery system. In recent years various scientific and technological advancements have been made in the research and development of oral drug delivery systems to overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying time (GET). In order to avoid such adversities, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hour via floating drug delivery system. Floating delivery systems or hydro dynamically controlled systems are low density systems that have sufficient buoyancy to float over the gastric content and remain buoyant in the stomach. The recent development of these systems includes their physiological and formulation variables affecting the gastric retention and to design the single and multiple-unit floating systems and their formulation, evaluation aspects are covered in detail. This article aims at reviewing the numerous techniques that has been designed till date for optimizing floating drug delivery system (FDDS), and also summarize the evaluation of FDDS of tablet dosage forms.

Keywords: Gastro retentive systems, effervescent systems, non effervescent systems, gastric residence time, floating drug delivery systems, buoyancy.

Introduction

The focus of pharmaceutical research is steadily shifted from the development of new chemical entities to the development of novel drug delivery system of existing drug molecule to maximize their effectiveness in terms of therapeutic action, reducing frequency of dosing and wastage of drugs, patient compliance and reduced adverse effects [1]. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.

Oral drug delivery is the most desirable and preferred method of drug delivery for achieving both systemic and local therapeutic effects. For many drugs, conventional oral formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time [14, 28]

The gastro intestinal tract (GIT) is the major route of drug delivery to the systemic circulation. The normal GE $t_{½}$ is 46.5 ± 5.5 minutes [12, 36, 49, 60]. Oral controlled release dosage forms are not suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT. This is due to the relatively less transit time of the dosage form in these anatomical segments. Thus after only a short period of less than 6 h, the controlled release formulation has already left the upper GIT and the drug is released in short, non absorbing distal segment of the GIT. This results in a short absorption phase, which is then accompanied by lesser bioavailability. These types of problem can be overcome by FDDS.

After oral administration, such a delivery would be retained in the stomach and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption sites. Hence, an advantageous drug delivery system to control and prolong the gastric emptying time and to deliver drugs in higher

concentrations to the absorption site necessitates a specialized delivery system. A significant approach in this regard can be achieved by floating drug delivery systems [29, 63]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion [37, 50], flotation [13], sedimentation [11, 53], expansion [40, 66], modified shape systems [16, 35], or by the simultaneous administration of pharmacological agents [22, 23] that delay gastric emptying.

Definition of floating drug delivery systems

The concept of floating drug delivery system (FDDS), was described in literature as early as 1968 .Floating dosage forms are oral dosage forms of tablets [39], capsules, or micro beads and contain hydrocolloids that allow floating by swelling thereby prolong the residence time of dosage form within gastro intestinal tract (GIT) [55].

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 in plasma drug concentration.

Techniques of gastric retention

Various techniques were used to encourage gastric retention of an oral dosage form. Floating systems have low bulk density [52], so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid in such a situation; there is nothing to float on. Different techniques used for gastric retention [27] are mentioned below,

1.Hydro dynamically balanced system (HBS)
High-density system
Swelling system
2. Expansion or Modified shape system

Bioadhesive or Mucoadhesive system Hydrodynamically balanced systems

While the system is floating on the gastric contents the drug is slowly released from the low density pellets or floating drug delivery systems are also called as hydro dynamically balanced systems (HBS). FDDS or HBS have a bulk density lower than gastric fluid, that is, bulk density of less than one. HBS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach [10]. The incorporated buoyant materials enable the device to float [29, 45]

High-density system

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the 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 fold 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 diameter of the pellets. Commonly used excipients [51] are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5-2.4g/cm3. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part of the antrum [4, 62, 64]. A number of other methods like use of passage-delaying agents [16, 21, 38, 47] and modified shape systems [6, 35] have also been used for gastroretention purpose.

Swelling and expansion systems

These dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach; permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty. It can be referred as Plug-Type systems Polymers in the systems swell at a very faster rate and with higher degree to form a swollen matrix of which size is greater than that of the pylorus [18, 56]. The rate and extent of swelling are important parameters. The rate of swelling and rate of erosion are also important.

Modified shape systems:

Modified shape systems are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extended the GIT depending on the size, shape and flexural modulus of the drug delivery device.

Bioadhesive or Mucoadhesive systems:

Bioadhesive system enabling the localized retention of the system in the stomach. The proposed mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary [45].

Approaches to FDDS

Several techniques are reported in the literature to increase the gastric retention of drugs [7, 44, 57]

Single-unit dosage forms

A. Low density approach of single unit dosage forms

In low density approach [13] the globular shells apparently having low density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn, pop rice and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxypropylcellulose depending upon the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

B. Hydro dynamically balanced systems (HBS) [9]

HBS system containing a homogenous mixture of drug and a hydrocolloid in a capsule which upon contact with gastric fluid acquired and maintained a bulk density less than 1 , thereby being buoyant on the gastric contents of stomach until all the drug was released.

The HBS is a novel dosage form which when in contact with gastric fluid and after dissolution of outer exposed surface of the dosage form, forms a hydrated gel layer and maintained bulk density less than 1g/cm^3. Thus this system remains buoyant in the gastric fluid inside the stomach for 6hrs. The increase in retention time of HBS may also be due to effects the adhesion to the gastric mucosa, rather than the effect of floating.

Conventional dosage form disintegrate within 60minutes and are emptied totally from the stomach shortly afterwards. This dosage form releases the drug through the hydrated layer by diffusion principle. This system is valuable for drugs which are soluble at lower pH and have an absorption window in the upper GIT. By varying the composition of the excipient between 25% to 75%w/w of one or more gel forming hydrocolloids such as hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose and sodium carboxy methylcellulose, the granules are prepared and compressed into tablets or encapsulated into capsules ,which results in the desired release rate of drug. This hydrated gel controls the rate of solvent penetration into the device and the rate of drug release from the device.

Floating drug delivery device with self-activated mechanism for retaining the device in the stomach, which releases the drug under controlled osmotic pressure. The device was found to consist of two chambers, one for the drug reservoir and the other osmogen. In the stomach the gastric fluid dissolves the osmogen, which creates pressure on the drug reservoir compartment; this pressure tends to reduce the total volume of the drug reservoir compartment thereby leading to the continuous release of the drug material from the device.

Next approach is the HBS capsule for the sustained release of the drug in the stomach by incorporation of liquid such as ether in an inflatable chamber. These are designed to prolong the stay of the dosage form in the gastrointestinal tract as an aid in enhancing the absorption. Such systems are best suited for drugs having better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of 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. However, there may be rare exceptions, where the presence or absence of food the stomach has no effect on the absorption of a drug from HBS type dosage forms. The success of HBS capsule as a better system is best exemplified with chlorodiazepoxide hydrochloride comparable blood level time profile as of three 10-mg commercial capsules. The drug is a classical example of a solubility problem where in it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlorodiazepoxide hydrochloride is 150mg/ml and is ~0.1mg/ml at neutral pH)

Multiple-unit dosage form

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lowers [33]. In carbon dioxide-generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature.

Classification of floating drug delivery systems

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

1. **Effervescent system**
   - 1.1 Volatile liquid containing systems
   - 1.2 Gas generating systems
2. **Non-effervescent system**
   - 2.1 Colloidal gel barrier systems
   - 2.2 Microporous compartment system
   - 2.3 Alginate beads
   - 2.4 Hollow microspheres / Microballons

Effervescent system

Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach.

The device may also consist of a bioerodible plug made up of poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release the gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach [31].

Intragastric floating gastrointestinal drug delivery system

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

Inflatable gastrointestinal delivery system

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflatable in the stomach. These systems are fabricated by loading the chamber with the drug reservoir, which can be a drug impregnated polymeric matrix, than encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid [31].

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 [9].

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 vapour liquid and homo drug delivery orifice. The osmotically active compartment contains an osmotically active salt is enclosed within a semi permeable housing. In the stomach, the water in the gastrointestinal fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is then created which acts on the collapsible bag in turn forces the bag reservoir compartment to reduce its volume and activate the drug release through the delivery orifice. Gas generating system

These buoyant delivery systems utilize effervescent reaction between carbonate or bicarbonate salts and citric or tartaric acid to liberate carbon dioxide. The liberated carbon dioxide gets entrapped in the hydrocolloid layer of the system. Thus the specific gravity decreases and the system begins to float [56, 62].

The common approach used for the preparation of these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus carbon dioxide is released, causing the beads to float in the stomach .Other reported approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating

systems based on ion exchange resin technology etc. [17]. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 5-6 hrs [5, 59].

Non-effervescent systems [31, 43, 65, 70]

This type of system after swallowing swells unrestrained via. Imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the "plug type system" since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact after oral administration and maintains a relative integrity of shape and a bulk density of less than 1. This is based on the mechanism of swelling of polymer or bio adhesion to mucosal layer in GIT. The most commonly used excipients are gel forming materials such as polycarbonate, poly acrylate, polystyrene etc. this hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. The various types of this system are as follows:

Single layer floating tablets

This can be formulated by intimate mixing of drug with gel forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than 1. The air entrapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayer floating tablets

A bilayer tablet contains 2 layers, one is immediate release layer which releases the initial dose from system while the other is sustained release layer which absorbs the gastric fluid and maintains a bulk density of less than 1 and thereby it remains buoyant in the stomach (Fassihi and Yang developed a zero-order controlled release) [69]. Multilayer tablet composed of at least 2 barrier layers and one drug layer. All the layers are made of swellable, erodible polymers and the tablet was found to swell on contact with aqueous medium. As the tablet dissolved, the barrier layers eroded away to expose more of the drug. Gas evolving agent is added in either of the barrier layers, this caused the tablet to float and increased the retention of tablet in a patient's stomach.

Colloidal gel barrier systems

This system was first developed by Sheth and Tossounian [58]. It contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporates a high level of one or more gel forming highly swellable cellulose type

hydrocolloids. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

Microporous Compartment System

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall [57]. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un-dissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption.

Alginate beads

To develop Multi-unit floating dosage forms the freeze-dried calcium alginate has been used [67]. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into aqueous solution of calcium chloride. The beads are then separated snap and frozenin liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating force over 12 hours. On the other hand, multiple-unit dosage forms appear to be better suited since they claimed to reduce the inter subject variability in - absorption and lower the probability of dose-dumping

Hollow microspheres

A novel emulsion solvent diffusion method was used to prepare hollow microspheres loaded with drug in their outer polymer shelf [33]. The ethanol: dichloromethane solution of the drug and enteric acrylic polymers is poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours. The drug released was high in pH 7.2 than in pH 6.8 [31]. Hollow microspheres (micro balloons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method [46].

Ideal drug candidates for floating drug delivery

- Drugs those are locally active in the stomach. Eg. Misoprostol, antacids etc.
- Drugs which have narrow absorption window in the GIT. Eg. Furosemide, L-dopa, Para-amino benzoic acid, riboflavin.etc.
- Drugs that exhibit low solubility at high pH values. Eg. Diazepam, Chlordiazepoxide, Verapamil hydrochloride.
- Drugs that are unstable in the intestinal or colonic environment. E.g. captopril, ranitidine HCl, metronidazole.
- Drugs that disturb normal colonic microbes. E.g. antibiotics against Helicobacter pylori.
- Drugs having a specific site of absorption in the upper part of small intestine.
- Drugs having a bulk density of less than 1 to remain in the stomach for a prolonged period of time.

Factors affecting gastric retention

Density

GRT is a function of dosage form buoyancy that is dependent on the density. A buoyant dosage form having a density 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. A density of less than 1.004g/mL i.e. less than that of gastric contents has been reported.

Size

Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.

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 [19].

Single or multiple unit formulation

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state

Under fasting conditions, GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach. However, in the fed state, MMC is delayed and GRT is considerably longer [64].

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 [68].

Caloric content

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

Frequency of feed

The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC [31]

Gender

Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (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. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT [43].

Posture

GRT can vary between supine and upright ambulatory states of the patient. An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size [43].
In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear 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 contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects [7].

Concomitant intake of drugs

Drugs such as Metoclopramide, Cisapride, Codeine, Atropine and Propantheline may affect the performance of FDDS. The co-administration of GI-motility decreasing drugs can increase gastric emptying time [7].

Methodology

Direct compression technique

Involves compressing tablets directly from powdered material without modifying the physical nature of the material itself. Direct compression vehicles or carriers must have good flow and compressible characters these properties are imparted by predisposing these vehicles to slugging, spray drying or crystallization. Most commonly used carriers are di calcium phosphate trihydrate, tri calcium phosphate etc.

Melt granulation technique

It is a process by which the pharmaceutical powders are agglomerated by using a melt able binder and no water or organic solvents are required for granulation. Because there is no drying step, the process is less time consuming and uses less energy. Granules were prepared in a lab scale high shear mixer, using a jacket temperature of 60 °c and an impeller speed of 20000 rpm.

Melt solidification technique

This process involves emulsification of the molten mass in the aqueous phase followed by its solidification by chilling. The carriers used for this technique are lipids, waxes, polyethylene glycols. Drug is incorporated into these carriers to achieve controlled release.

Wet granulation technique

Wet granulation process involves the wet massing of powders, wet sizing or milling and drying. Wet granulation forms the granules by binding the powders together with an adhesive instead of compaction. The wet granulation technique employs a solution suspension or slurry containing a binder which is usually added to the powder mixture however the binder may be incorporated into the dry powder mix and the liquid may be added by itself. The method of introducing the binder depends on its solubility and on the components of the mixture since, in general, the mass should merely be moist rather than wet or pasty, and there is a limit to the amount of solvent that may be employed. Once the granulating liquid has been added mixing continues until a uniform dispersion is attained and all the binder has been activated. Then the wet mass is made to undergo wet screening by passing through a hammer mill or multi mill equipped with screens having large perforations. The milled wet mass is dried by either using tray drier or fluidized bed drier, after complete the drying lubrication materials is blended with dried granules. This lubricated granules is made to undergo compression.

Effervescent technique:

The floating chamber of the drug delivery system can be filled with inert gas [CO_2] by the effervescent reaction between organic acid [citric acid] and bicarbonate salts.

Spray drying techniques:

It involves dispersing the core material in a liquefied coating material and spraying the core-coating mixture in to the environment to effect solidification of coating. Solidification is accomplished by rapid evaporation of the solvent in which coating material is solubilised.

Formulation of FDDS

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

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

Hydrocolloids

Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. E.g. Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, and carboxymethylcellulose sodium can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.

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 accelerants

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.

Release rate retardants

Insoluble substances such as calcium phosphate, talc, magnesium Stearate decreased 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.

Miscellaneous

Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems [48].

Advantages [2, 26]

- The Principle of HBS may not limit to any particular medicament or class of medicament.
- The HBS formulations are not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicament, which absorbed from the intestine.
- Acidic 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 HBS are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
- The efficacy of the medicaments administered utilizing the sustained release principle of HBS formulation has been found to be independent on the site of particular medicaments.
- The HBS are advantageous for drugs meant for local action in the stomach. E.g. Antacids.
- Administration of prolongs release floating dosage forms, tablet or capsules, will results 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 shorted 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 of floating drug delivery system

- Floating system is not feasible for those drugs that have solubility or stability problem in GI tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water [42]
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, may not be desirable candidate. E.g. Nifedipine.
- The ability of drug to remain in the stomach depends upon the subject being positioned upright.
- The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
- Not suitable for drugs that cause gastric lesions e.g. Non steroidalanti inflammatory drugs. Drugs that are

unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastro intestinal tract [41].

- The mucus on the walls of the stomach is in the state of constant renewal, resulting in the unpredictable adherence.
- Faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
- The ability to float relies in the hydration state of dosage form.
- In all the above, the most important and primary requirement for the success is the physical integrity of the system.

Evaluation of FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence *in vitro* floating behavior show prolonged gastric residence *in vivo.* However, it has to be pointed out that good *in vitro* floating behavior alone is not sufficient proof for efficient gastric retention *in vivo*. Various parameters that need to be evaluated in gastroretensive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and X-ray diffraction studies are also performed. Obviously, only *in vivo* studies can provide definite proof that prolonged gastric residence is obtained. Evaluation of FDDS of tablet dosage forms as follows;

Thickness, Uniformity of weight, Content uniformity, Hardness, Friability and Assay

These are the tests can be performed as per the procedures mentioned in the official monographs.

Floating lag time and total floating time determination

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 M hydrochloric acid maintained at 37 °C, by using USP dissolution apparatus containing 900 ml of 0.1 molar hydrochloric acid as the dissolution medium [3].

Weight gain and water uptake

Weight gain or water uptake (WU) can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in simulated gastric fluid at 37 °C and determining the dimensional changes like tablet diameter and or thickness at regular 1 h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation WU = (Wt – Wo) X 100 / Wo in which Wt and Wo are the weights of the dosage form at time t and initially, respectively [20].

In vitro drug release study

Dissolution tests are performed using the USP dissolution apparatus. The test for *in vitro* drug release studies are usually carried out in simulated gastric fluid or 0.1 N hydrochloric acid fluids maintained at 37 °C. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their percentage drug release after an appropriate dilution. Standard methods based on the US Pharmacopoeia or British Pharmacopoeia have been shown to be poor predictors of *in vitro* performance for floating dosage forms.

Conclusion

Gastro retentive floating drug delivery system have emerged as an efficient means of enhancing the bioavailability and controlled drug delivery of many drugs. The currently available polymer-mediated non effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. The research in this area is ongoing on the concept of design of novel polymers according to clinical and pharmaceutical need.

References

[1]. Arora S, Ahuja A. Floating drug delivery system: A Review. J. AAPS Pharm Sci Tech 2005; Vol.6 (03): 372-390.

[2]. Babu VBM, Khar RK. In vitro and In vivo studies of sustained release floating dosage forms containing salbutamol sulphate. Pharmazie 1990; 45: 268-270.

[3]. Baumgartner S, Kristl J, Vrecer F. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195: 125-135.

[4]. Bolton S, Desai S. US Patent, 4 814, 179, March 21, 1989.

[5]. Bolton S, Izevbehai PH, Desai S. Floating sustained release therapeutic compositions, US Patent 4 814, 178. March 21, 1989.

[6]. Cargill R, Cadwell LJ, Engle K, Fix JA, Porter PA, Gardner CR. Controlled gastric

emptying: I. Effects of physical properties on gastric residence times of non disintegrating geometric shapes in beagle dogs. Pharm Res 1988; 5: 533-536.

[7]. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention: A Means to address regional variability in intestinal drug absorption. Pharm Tech 2003; 27: 250-268.

[8]. Cheuh HR, Zia H, Rhodes CT. Optimization of sotalol floating and bioadhesive extended release tablet formulations. Drug Dev and Ind Pharm 1995; 21: 1725-1747.

[9]. Chien YM. Novel drug delivery system, 3rd Ed. Vol. 1. New York: Marcel Dekker 1992; 139-196.

[10]. C.K. Kokate, A.P. Purohit & S.B. Gokhale. Pharmacognosy. Nirali Prakashan, 27th Edition 2004; 190.

[11]. Davis SS, Stockwell AF, Taylor MJ, et al. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm Res 1986; 3:208-213.

[12]. Degen LP, Peng F, Collet A, Rossi L, Ketterer S, Serrano Y, et al. Blockade of GRP receptors inhibits gastric emptying and gallbladder contraction but accelerates small intestinal transit. Gastroenterology 2001; 120:361-8.

[13]. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res 1997; 14:815-819.

[14]. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev and Ind Pharm 1996; 22:631-9.

[15]. El-Kamel AH, Sokar MS, Algamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm 2001; 220: 13-21.

[16]. Fix JA, Cargill R, Engle K. Controlled gastric emptying. III. Gastric residence time of a non-disintegrating geometric shape in human volunteers. Pharm Res 1993; 10:1087-1089.

[17]. Gaba Punam, Gaba Monica, Garg Rajeev, Gupta GD. Available at http://www.pharmainfo.net/reviews/floating-microspheres review, 2008.

[18]. Garg Sanjay, Sharma Shringi. Business Briefing. Pharmtech 2003; 160-166.

[19]. Garima C, Piyush G, Vishal K and Arvind KB. Gastroretention: A Means to Address Regional Variability in intestinal drug Absorption. Pharma Tech 2003; 27: 50-68.

[20]. Gergogiannis YS, Rekkas DM, Dallos PP, Chailis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Dev and Ind Pharm 1993; 19: 1061-1081.

[21]. Greminger JK, Krumer K. Alkyl and Hydroxyalkyl cellulose. In Davidson, RL, editor. Handbook of Water Soluble Gums and Resins, New York: McGraw Hill Book Co 1980; 3-25.

[22]. Groning R, Heun G. Dosage forms with controlled gastrointestinal passage-studies on the absorption of nitrofurantion. Int J Pharm 1989; 56:111-116.

[23]. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev and Ind Pharm 1984; 10:527-539.

[24]. Gu TH, Chen SX, Zhu JB, Song DJ, Guo JZ, Hou JM. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets. Chung Kao Yao Li Hsuesh Pao 1992; 13: 527-531.

[25]. Gustafson JH, Weissman L, Weinfeld RE, Holazo AA, Khoo KC, Kalpan SA. Clinical bioavailability evaluation of a controlled release formulation of diazepam. J Pharmacokinet Biopharm 1981; 9:679–691.

[26]. Hetal N Kikani. A Thesis on Floating Drug Delivery System. The North Gujarat University, Patan 2000-2001; 11-12.

[27]. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol 1985; 19:77S-83S.

[28]. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Crit Rev Ther Drug Carrier Syst 1998;15:243-83.

[29]. Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. Int J Pharm 1998; 174:4754.

[30]. Ichikawa M, Kato T, Kawahara M, Watanabe S, Kayano M. A new multiple-unit oral floating dosage system. II: in vivo evaluation of floating and sustained-release characteristics with p-aminobenzoic acid and isosorbide dinitrate as model drugs. J Pharm Sci 1991; 80:1153-1156.

[31]. Jain NK. Progress in Controlled and Novel Drug Delivery Systems, 1st Ed. CBS Publishers and Distributors, New Delhi 2004; 84-85.

[32]. Jayanthi G, Jayaswal SB, Srivastava AK. Formulation and evaluation of terfenadine micro balloons for oral controlled release Pharmazie 1995; 50: 769-770.

[33]. Kawashima Y, Nima T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci (USA) 1998; 81: 135-140.

[34]. Kawashima Y, Niwa T, Takeuchi H, Hino, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo) . J Cont Rel 1991; 16: 279-290.

[35]. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. J Control Rel 1999; 58: 195-205.

[36]. Kydoneius A. Controlled Release Technologies. 2nd Ed. New York: Marcel Dekker; 1991; 24-109.

[37]. Lenaerts VM, Gurny R. Gastrointestinal Tract- Physiological variables affecting the performance of oral sustained release dosage forms. Bioadhesive Drug Delivery System. Boca Raton, FL: CRC Press; 1990.

[38]. Li VHK, Robinson JR, Lee VHL. Influence of drug properties and routes of administration on the design of sustained and controlled release systems. In Robinson JR, Lee BV, editors Controlled Drug Delivery: Fundamentals and Applications. New York: Marcel Dekker 1987; 3-21.

[39]. Libermann, Lachman, Schwartz. Pharmaceutical dosage forms-Tablets volume1, volume 2, volume 3: 131-158.

[40]. Mamajek RC, Moyer ES, inventors. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.

[41]. Mathur P, Saroha Kamal. Floating drug delivery system: An Innovative acceptable approach in gastroretentive drug delivery. Scholar Research Library 2010; 2: 257-270.

[42]. Mayavanshi AV and Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research Journal of Pharmacy and Technology 2008; 4: 345-348.

[43]. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML. Effects of gender, posture, and age on gastric residence time of indigestible solid: pharmaceutical considerations. Pharm Res 1988; 10: 639-664.

[44]. Muller-Lissner SA, Blum AL. The effect of specific gravity and eating on gastric emptying of slow-release capsules. New Engl J Med 1981; 304: 1365-1366.

[45]. N R Jimenez-Castellanos, H Zia and C T Rhodes. Mucoadhesive Drug Delivery Systems. Drug Dev and Ind Pharmacy 1993; 19: 143.

[46]. Nayak AK, Maji R and Das B. Gastroretentive drug delivery systems: a review. Asian Journal of Pharmaceutical and Clinical Research 2001; 31: 9.

[47]. Palin KJ. Lipids and oral drug delivery. Pharm Int 1985: 11: 272-279.

[48]. Patel GM, Floating drug delivery system: An innovative approach to prolong gastric retention. www.pharmainfo.net, 2007.

[49]. Petrakis IE, Kogerakis N, Vrachassotakis N, Stiakakis I, Zacharioudakis G, Chalkiadakis G. Hyperglycemia attenuate erythromycin-induced acceleration of solid-phase gastric emptying in healthy subjects. Abdom Imaging 2002; 27:309-14.

[50]. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate system for oral delivery to the gastrointestinal tract. Adv Drug Del Rev 1998; 34:191-219.

[51]. Prabahakara Prabhu et.al. Indian journal of pharmaceutical education and research 2008; 193.

[52]. Rajendra Jangde et.al. The Pharmaceutical Magazine. March, 2008: 1-3.

[53]. Rednick AB, Tucker SJ, inventors. Sustain ed release bolus for animal husbandry. US patent 3 507 952. April 22, 1970.

[54]. Rouge N, Cole ET, Doelker E, Buri P. Buo yancy and drug release patterns of floating minutesitablets containing piretanide and atenolol as model drugs. Pharm Dev Technol 1998; 3:73-84.

[55]. Rubinstein A, Friend DR. Specific delivery to the gastrointestinal tract, in: A.J. Domb (Ed.), Polymeric Site-Specific Pharmacotherapy, Wiley, Chichester 1994; 282–283.

[56]. Sangekar S. Evaluation of effect of food and specific gravity of the tablets on gastric retention time. International Journal of Pharmaceutics 1987; 35(3): 34-53.

[57]. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Res 2009; 1(3): 623-633.

[58]. Sheth PR and Tossounian JL. The Hydrodynamically Balanced System: A Novel Drug Delivery System for Oral Use. Drug Dev and Ind Pharm 1984; 10 (2): 313-339.

[59]. Sheth PR, Tossounian JL, Sustained release tablet formulations. US Patent 4 140, 755. February 20, 1979.

[60]. Silang R, Regalado M, Cheng TH, Wesson DE. Prokinetic agents increase plasma albumin in hypoalbuminemic chronic dialysis patients with delayed gastric emptying. Am J Kidney Dis 2001; 37:287-93.

[61]. Simoni P, Cerre C, Cipolla A, et al. Bioavailability study of a new sinking, enteric coated ursodeoxycholic acid formulation. Pharmacol Res 1995; 31:115–119.

[62]. Singh BN and Kim KH. Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery via Gastric Retention. J. Controlled Release 2000; 63 (1-2): 235-259.

[63]. Streubel A, Siepmann J, Bodmeier R. Multiple-unit Gastroretentive drug delivery: a new preparation method for low density microparticles. J Microencapsul 2003; 20: 329 – 47.

[64]. Talukder R and Fissihi R. Gastroretentive Delivery Systems: A Mini review. Drug Dev and Ind Pharm 2004; 30: 1019-1028.

[65]. Timmermans J and Moes A J. Measuring the resulting weight of an immersed tests material II: Examples of kinetic determination applied for monolithic dosage forms Acta Pharma Tech 1990; 36: 176-180.

[66]. Urguhart J, Theeuwes F, inventors. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US patent 4 434 153. February 28, 1994.

[67]. Whitehead L, Fell JT, Collett JH. Development of a gastroretentive dosage form. Eur J Pharm Sci 1996; 4: S182.

[68]. Xu W L, Tu X D and Lu Z D. Development of Gentamycin sulfate sustained-release tablets remaining-floating in stomach. Yao Hsueh Pao 1991; 26: 541-545.

[69]. Yang L, Eshraghi J, Fassihi R. A new intragastric delivery system for the treatment of Helicobacter pyloriassociated gastric ulcer: in vitro evaluation. J. Control. Release 1999; 57: 215–222.

[70]. Yyas SP and Roop KK. Controlled Drug Delivery Concepts and Advances. 1st Ed. New Delhi 2002; 196-217.

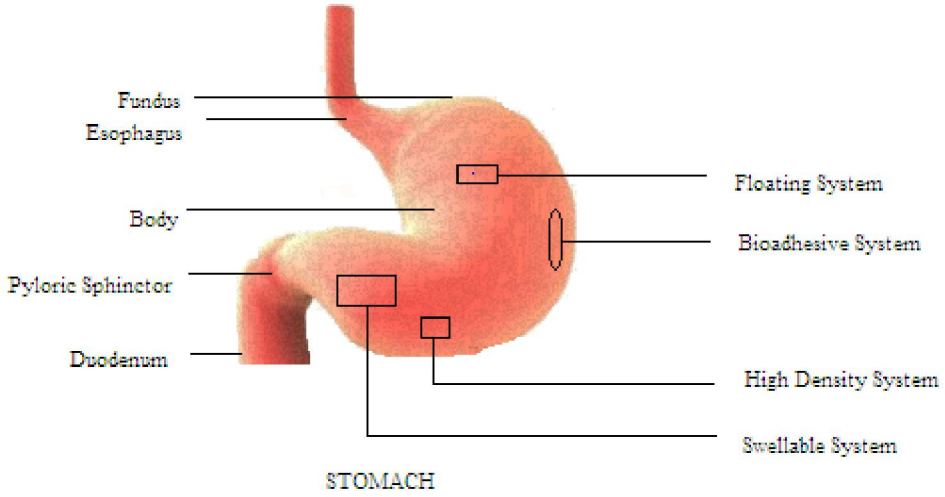

Figure 1:

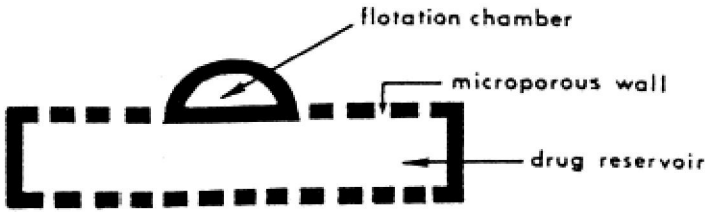

Figure 2: Intragastric floating drug delivery device

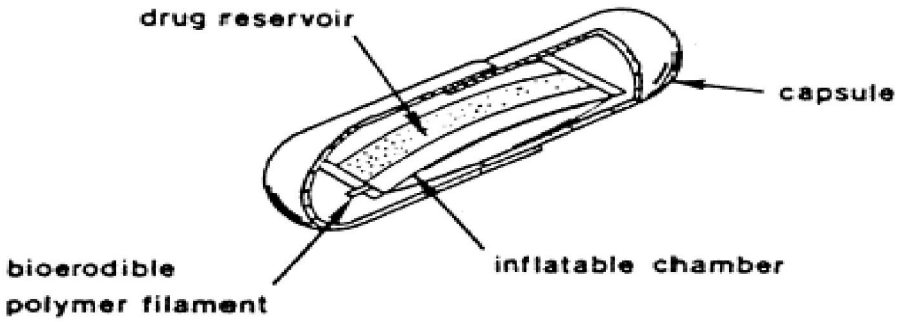

Figure 3: Gastro inflatable drug delivery device

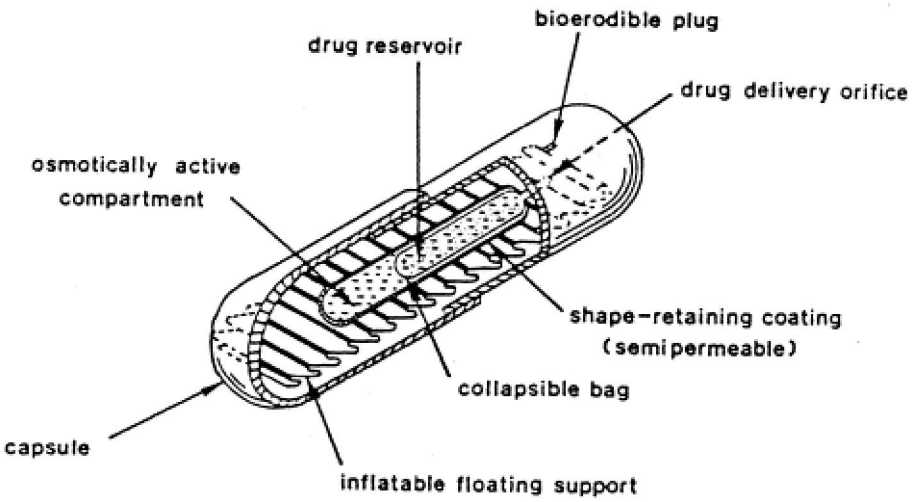

Figure 4: Intra gastric osmotic controlled drug delivery system

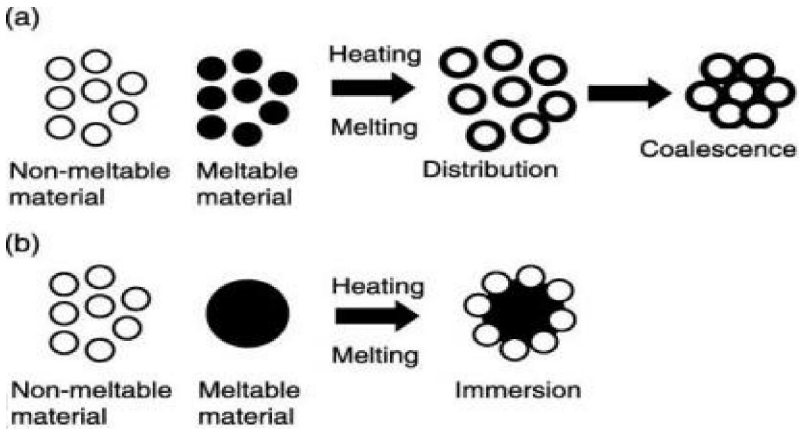

Figure 5:

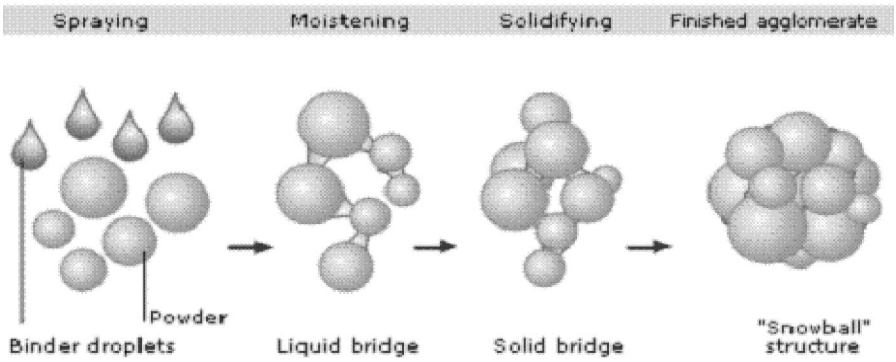

Figure 6:

Ideal candidates for making FDDS with respective dosage forms [8, 15, 24, 25, 30, 32, 34, 54, 61]

S.No	***Dosage Forms***	***Drugs***
1	Floating microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfinadine and Tranilast
2	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
3	Films	Cinnarizine
4	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin
5	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid, Piretamide, Theophylline and Verapamil hydrochloride