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FLOATING DRUG DELIVERY SYSTEM: A NEW DOSAGE FORM

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Abstract

Floating drug delivery system is a recent advancement in pharmaceutical technology which has also several advantages over the conventional drug delivery systems. With an increasing understanding of polymer behavior and the role of the biological factors, it is suggested that future research work on the way of floating drug delivery system should be aimed to control accurately the drug input rate into the gastrointestinal tract. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

INTRODUCTION

In recent year scientific and technological advancement have been made in the research and development of rate-controlled oral drug delivery systems. However, to achieve more predictable and increased bioavailability of drugs, short gastric residence times, unpredictable gastric emptying times, and other physiological adverse conditions must be overcome (Zhenqiu et al., 2004).

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance to other modes of drug intake. However oral administration has only limited use for important drugs, from various categories, that have poor oral bioavailability due to incomplete absorption and/or degradation In the GI track (Hoffmann et al., 2004).

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing

controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

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

The concept of floating drug delivery system was described in the literature as early as 1968 (Davis; 1968). Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicine pills. It was suggested that this difficulty would be overcome by providing pills having density less than 1.0 g/ml so that pills will float on water surface.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems

(Arora et al., 2005).

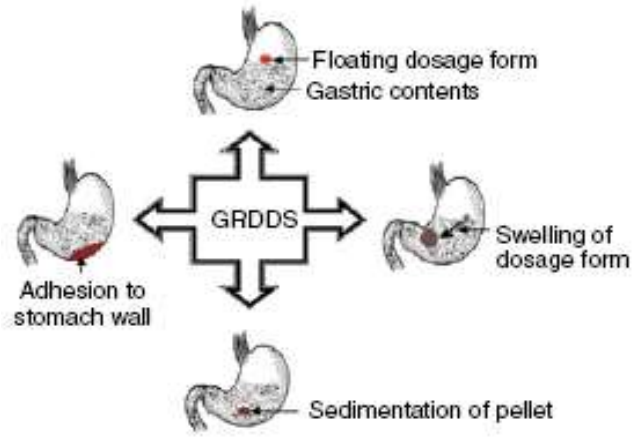


Figure 1: Classification of gastroretentive drug delivery system (Chawla *et al.*, 2003)

BASIC PHYSIOLOGY OF THE GASTROINTESTINAL TRACT

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made up of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (Desai S.A et al., 1984)

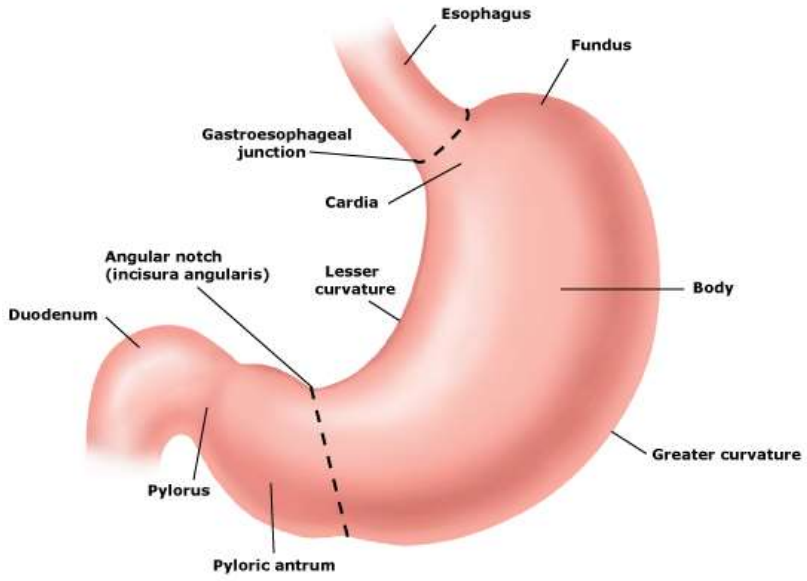


Figure 2: Pictorial representation of anatomy of stomach

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take

place, which cycle both through stomach and intestine every 2 to 3 hours (Vantrappen GR., et al). This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Wilson CG et al) (Figure 3)

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slow down of gastric emptying rate .(Bolton S et al)

Scintinographic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate.

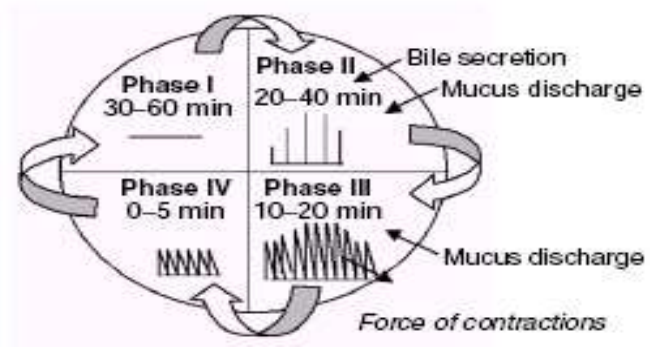


Figure 3: Motility patterns of the GIT in fasted state

GASTRIC EMPTYING AND PROBLEMS

It is well recognized that the stomach may be used as a depot for sustained release dosage forms, both in human and veterinary applications, stomach is anatomically divided in to three parts: Fundus, body and pylorus (Mamajek RC et al).

The proximal stomach made up of the fundus and body region serves as a reservoir for ingested materials, while the distal region (antrum) is the major site for the mixing motion, acting as a pump to accomplish gastric emptying. The process of the gastric emptying occurs both during fasting and fed stages.

Scintinography study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered Controlled release dosage form is mainly subjected to two physiological adversities (Mamajek RC et al).

Yet another major adversity encountered through the oral route is the first pass effect, which leads to reduce systematic availability of a large number of a drug. These problems can be exacerbated by alteration in the gastric emptying that occur due to factors such as age, race, sex and disease states, as they may seriously affect the release of a drug from DDS. It is therefore desirable to have a Controlled release product that exhibits an extended GI residence and a drug release profile independent of patient related variables.

SUITABLE DRUG CANIDATE 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 parts of the GIT .Garg et al., (2008).

Table 1. Drug properties for formulating as a CRGRDF

S. No.	Properties	Drugs formulated as CRGRDF
1.	Act locally in the stomach	Tetracycline and Antacids

2.	Low solubility at high pH	Diazepam and Propranolol
3.	Primarily absorbed in stomach	Albuterol and Levodopa
4.	Narrow absorption window	Riboflavin and Allopurinol
5.	Absorb rapidly from GIT	Amoxycillin
6.	Degrade in colon	Ranitidine and Metoprolol
7.	Unstable in intestinal fluids	Captopril and Famotidine

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The gastric retention time (GRT) of dosage forms is controlled by several factors such as:

Table 2: Factors controlling gastric retention of dosage forms

S.No	Factor	Characteristic	Effect
1.	Density of dosage form	Less than the gastric fluid density (<1.0gm/cm^3)	Buoyancy of the dosage form is retained in stomach-prolong release
2.	Type of meal	Indigestible polymers or fatty acid salts	This changes the motility pattern of stomach-prolong release
3.	Frequency of food	Successive meal over 6 hours	GRT increases-prolong release
4.	Size of the dosage form	Increases around to 13 mm for tablets	Retained for the longer period in stomach-prolong release
5.	Gender	Male have higher GRT than females	Male=3.4±0.6 hours Females=4.6±1.2 hours

6.	Age	Elderly people (>70 years)	Shorter GRT-rapid release
7.	Posture	Upright position	Increase in GRT-prolong release
8.	Shape of the dosage form	Tetrahedrons and rings	Nearly 100% retention at 24 hours

APPROACHES FOR GASTRIC RETENTION

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include

a) Floating Systems

b) Bio/Muco-adhesive Systems

c) Swelling and Expanding Systems

d) High Density Systems

e) Incorporation of Passage Delaying Food Agents

f) Ion Exchange Resins

g) Osmotic Regulated Systems

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- Enhanced bioavailability e.g. furosemide and riboflavin.
- Enhanced first-pass biotransformation.
- Sustained drug delivery/reduced frequency of dosing e.g. Diazepam.
- Targeted therapy for local ailments in the upper GIT.
- Reduced fluctuations of drug concentration.
- Maximum utilization of drug and decrease in the total side effects.
- Improved patient compliance due to less frequent dosing.
- FDDS is utilized in treatment of gastric duodenal cancers and ulcers and in development of various anti reflux formulations

APPROACHES TO DESIGN FDDS

The following approaches have been used for the design of floating dosage forms of single- and multiple unit systems.

1. **Single-Unit Dosage Forms**

In Low-density approach for the globular shells apparently having lower 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 shells24 popcorn, poprice, 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 ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

2. **Multiple-Unit Dosage Forms**

Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. 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. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

CLASSIFICATION OF FDDS

Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and noneffervescent systems.

1. **Effervescent Floating Dosage Forms**

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

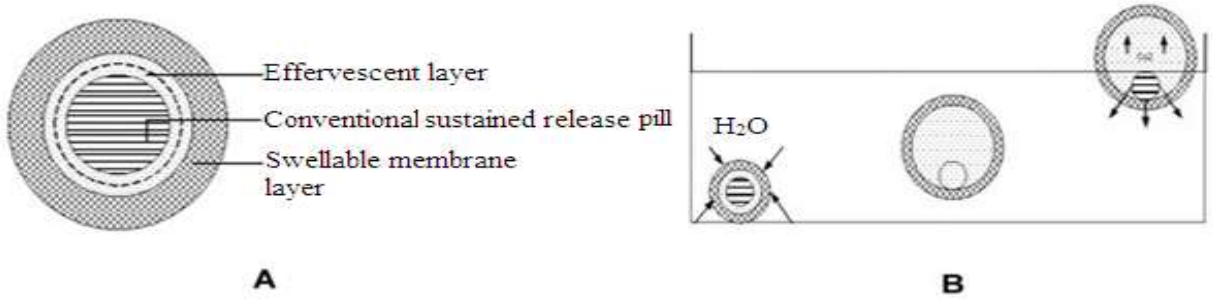


Figure 4. (A) Multiple-unit oral floating drug delivery system.
(B)Working principle of effervescent floating drug delivery system.(Arora et al., 2008)

2. Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of G 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

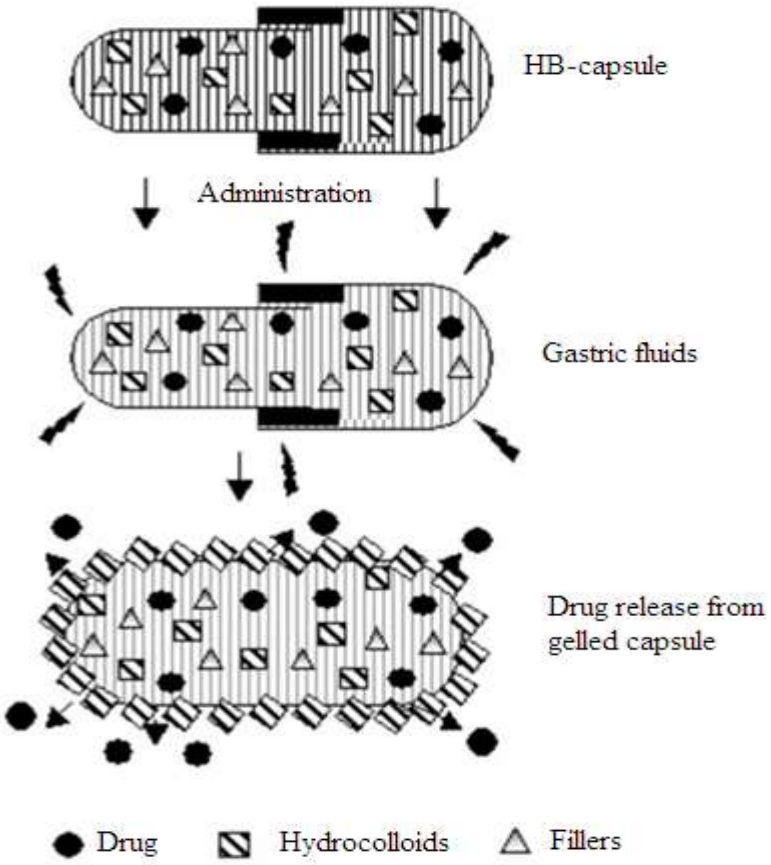
This system can be further divided into four sub-types:

- **i.** Colloidal gel barrier system
- **ii.** Microporous compartment system
- **iii.** Alginate beads
- **iv.** Hollow microspheres / Microballons

Other systems under floating behavior are as follows

a) Hydrodynamically balanced system

This dosage form contains one or more gel-forming hydrophilic polymers. The capsule shell dissolves in the gastric fluid, the outermost hydrophilic colloid hydrates, the hydration and swelling of the surface polymer produces a floating mass which forms an outside gel barrier and substantially retains the shape of the capsule prevents the mass from disintegrating. Drug release is controlled by the formation of hydrated buoyancy at the surface. Continuous erosion of the surface allows water penetration to the inner layer, maintaing surface hydration and buoyancy. Incorporation of fatty excipients gives low density formulations and reduced penetration of water, thereby reducing the erosion. Examples: Verapamil HCl and Paracetamol.



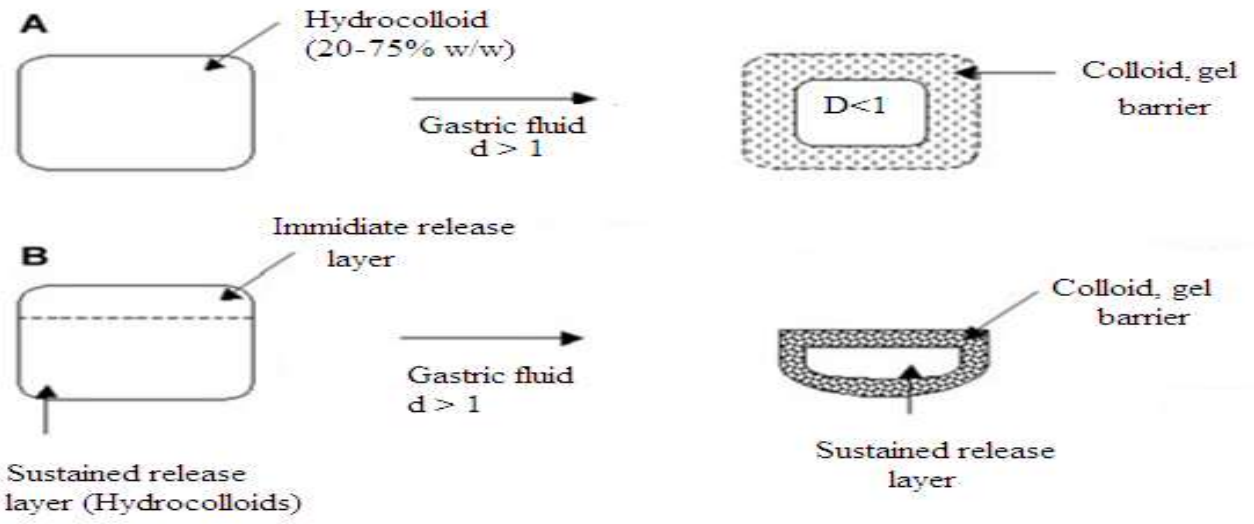


Figure 5. Working principle of hydrodynamically balanced system

b) Low-density systems

They are made of low-density materials (<1mg/cc), entrapping oil or air. Most are multiple unit systems such as hollow microspheres (microballoons), hollow beads, floating pellets etc. At present, hollow microspheres are considered to be one of the most promising buoyant systems due to multiple unit systems and good floating properties.

c) Intragastric osmotically controlled DDS

Intragastric osmotically controlled drug delivery system consist of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. The osmotic pressure-controlled part consists of two components, a drug reservoir having a drug delivery orifice and the osmotic component contains an osmotically active salt, and is enclosed within a semi-permeable housing.

GASTRORETENTIVE DOSAGE FORMS:

Table 3 : Commonly used drugs formulated as gastroretentive dosage form

S. No.	Dosage form	Active ingredient
1.	Microballoons	Riboflavin
2.	Floating granules	Diclofenac sodium, indomethacin and prednisolone
3.	Films	Cinnarizine

4.	Floating capsules	Chlordiazepoxide HCl, diazepam, furosemide, misoprostol, and L-dopa, benserazide, ursodeoxycholic acid and pepstatin
5.	Floating tablets and pills	Acetaminophen, acetylsalicylic acid, ampicillin, amoxycillin trihydrate, fluorouracil, isosorbide mononitrate, atenolol, diltiazem, paminobenzoic acid, theophylline and verapamil
6.	Floating microspheres	Aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and Tranilast

ADVANTAGES OF FDDS (Mayavanshi et al., 2008)

Floating drug delivery systems have numerous advantages listed below:

1) The principle of HBS can be used for any particular medicament or class of medicament.

2) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

3) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

4) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

5) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

6) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, 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. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

LIMITATION OF FDDS

1) There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3) Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

APPLICATION OF FDDS

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. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD 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 capsules (8 hours).

2. Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Eg. 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.

3. Absorption Enhancement

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.

Table 4: Some Marketed Product Of FDDS

S. No.	Brand Name	Drug(dose)	Company, Country	Remarks
1	Madopar	Levodopa(100mg) Benserazide(25mg)	Roch Products, USA	Floating, CR capsule
2	Valrelease	Diazepam(15mg)	Hoffmann-La Roche, USA	Floating Capsule
3	Liquid Gaviscon	Aluminium Hydroxide (95mg) Magnesium carbonate (385mg)	Glaxo Smithkline, India	Effervescent floating liqid alginate
4	Topalcan	Al-Ag antacid	Pierre Fabre Drug, France	Floating liquid alginate
5	Almagate Float coat	Al-Ag antacid	Pierre Fabre Drug, France	Floating liquid form
6	Conviron	Ferrous Sulfate	Ranbaxy, India	Colloidal gel forming FDDS
7	Cifran OD	Ciprofloxacin (1g)	Ranbaxy, India	Gas generating floating
8	Cytotec	Misoprostat (100mcg/200mcg)	Pharmacia, USA	Bilayer floating capsule

Table 5. Example of drug used in literatures with their description

S. No.	Drug	Excipients	Method	References
1.	Nizatidine	PVP-K30, Avicel, HPMC E5, Ethyl cellulose.	Wet granulation	Mahalaxmi et al (2011)
2.	Nifedipine	Ethyl cellulose, Ethanol, Ether	Solvent diffusion-evaporation technique	Zhao et al (2010)
3.	Fenoverine	Anhydrous citric acid, Magnesium stearate, HPMC K4M, HPMC 100LV	Direct compression method	Yamsani et al (2010)
4.	Domperidone	HPMC K4M, Caropol 934P, Sodium alginate, Sodium bicarbonate	Wet granulation method	Prajapati et al (2010)
5.	Captopril	Hydroxypropyl methylcellulose, Sodium bicarbonate	Matrix tablets	Robles et al (2010)
6.	Artesunate clindamycin	HPMCK100M, Povidone	Direct compression method	Strusi et al (2010)
7.	Propranolol HCl	HPMC K4M, HPMC E15 LV,HPC, Guar gum	Direct compression method	Jagdale et al (2009)
8.	Cefodoxime proxetil	Hydroxy propyl methyl cellulose	Precipitation method and dripping method	Gadad et al (2009)
9.	Acyclovir	HPMC K4M,Guar gum , Xanthan gum	Wet granulation method	Patil et al (2009)

10.	Rosiglitazone maleate	Eudragit RS100 granules, Tributyl citrate, Petroleum ether, Heavy liquid paraffin	Emulsification (oil-in-oil type) Solvent evaporation technique	Kamila et al (2009)
11.	Verapamil HCl	Xanthun gum BP, HPMC K4M,HPMC K 15M, poly vinyl pyrrolidone	Wet granulation method	Patel et al (2009)
12.	Ciprofloxacin HCl	HPMC K4M, HPMC K100M Crospovidone	Wet granulation method	Arza et al (2009)
13.	Ranitidine HCl	Glyceryl behenate, Microcrystalline cellulose, HPMC, Triethyl citrate	Direct compression method	Shahiwala et al (2009)
14.	Nifedipine	Gelatin	Coated microcapsule	Li et al (2009)
15.	Metformin HCl	Ethyl cellulose, Acetone LR, Liquid paraffin	Non-aqueous emulsification solvent evaporation technique	Patel et al (2009)

METHODS FOR PREPARATION OF FLOATING GRANULES

1. WET GRANULATION

- Spray drying granulation
- Fluid bed granulation

2. DRY GRANULATION

- Slugging process
- Roller compaction

3. OTHER GRANULATION TECHNIQUE

- Melt granulation

- Foam granulation

EXCIPIENT SELECTION:

It is based on the following criteria:-

It should be chemically inert and should not show any incompatibilities with the active agent and other excipients.

All the polymers used should be compatible with the gastric environment for the controlled mechanism and can easily swells on contact with the gastric fluid to control buoyancy and release of the active agent.

PREPARATION OF FLOATING GRANULES BY USING DIFFERENT CARRIER-

1. **By using Lipid exicipients**
   Lipids are widely used for the preparation of gastroretentive drug delivery system. Due to the hydrophobic nature they can be considered as an effective carrier for the design of a Multi-unit floating drug delivery system of a highly soluble drug like Diltiazem HCl (Shimpi et al 2004).
   e.g. – Gelucire 54/02, 50/13,43/01,Compritol and Precirol.

2. **By using Microporus Carriers**
   Floating has been achieved with the preparation of low density solid system by inclusion of high porous system. Jain et al, (2007) has prepared floating granules of Repaglinide using calcium silicate as porous carriers. **e.g.-** Sodium borosilicate, Calcium Silicate, Polyvinyl floride, Polypropylene foam powder.
3. **By using Chitosan-**

   Miyakazi et al, (1988) has prepared granules of Indomethacin using chitosan and found that the drug release for more than the drug release for more than 6 h, with longer residence time in stomach. **e.g.** Chitosan high viscous, Chitosan middle viscous, Chitosan low viscous.

PREPARATION OF FLOATING GRANULES

The floating granules may be prepared by two techniques-

1. Melt granulation technique-

In this technique the carrier will be melted at 50-60 ^{0}C, and the drug is added, mixed well and cooled at room temperature. The mass is passed through a 710- µm sieve to obtained uniform sized granules.

2. Melt solidification technique-

The drug and polymer is melt on a water bath maintained at 100-110 ^{0}C, stirred it for molten mass, and cooled at 5 ^{0}C using ice. The mass is passed through a 710 710- µm sieve to obtained uniform sized granules.

CHARACTERISATION OF FLOATING GRANULES

- Particle size determination
- Surface topography by SEM
- True density determination
- Granule size analysis (sieving / zeta sizer)
- Hot stage polarizing microscopy (HSPM)

EVALUATION PARAMETERS OF FDDS

- Evaluation of floating ability
- Drug content
- Specific gravity
- Density of formulation
- In vitro drug release

CONCLUSION

FDDS promises to be a potential approach for gastric retention. Floating matrix formulations are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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