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Glimpse of Comprehensive Review on Floating Drug delivery System: A Global perception

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Abstract

Floating Drug delivery system is designed to prolong the gastric residence time after oral administration, at a particular site and improving bioavailability. The idea of gastric retention comes from the need to localize drugs at a specific region of gastrointestinal tract (GIT) such as stomach in the body. The drugs which are poorly soluble in intestine due to alkaline pH; gastric retention may increase solubility before they are emptied. Floating dosage form can be prepared as tablets, capsules by adding suitable ingredients as well as by adding gas generating agents. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDs), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. This review also summarizes the in-vitro techniques, in vivo studies to evaluate the performance and application of floating systems.

Keywords: Floating Drug Delivery System, Floating Systems, Effervescent Systems, and Non-Effervescent

Contents

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1. Introduction

The oral route is considered as the most promising route of drug delivery, this route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration which lead to high levels of patient compliance and still the preferred route of drug administration. More than 50% of the drug delivery systems available in the market are oral drug delivery systems[1].Drugs that are easily absorbed from the gastrointestinal tract but eliminated quickly from the blood circulation, an incomplete release of the drug and shorter residence time of the dosage form, will lead to lower bioavailability[2].To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug

concentration levels for longer durations (Hirtz J. et al. 1985)[3]. Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The under lying principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieve floating. These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. FDDS continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Different approaches are currently used to prolong the gastric retention time, like hydro dynamically balanced systems, swelling and expanding systems, polymeric bio-adhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

2. Experimental

Physiology of Basic Gastrointestinal Tract:

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made 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.et al.1984)[4]

Physiology of Stomach:

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae[5] (shown in fig. 1)

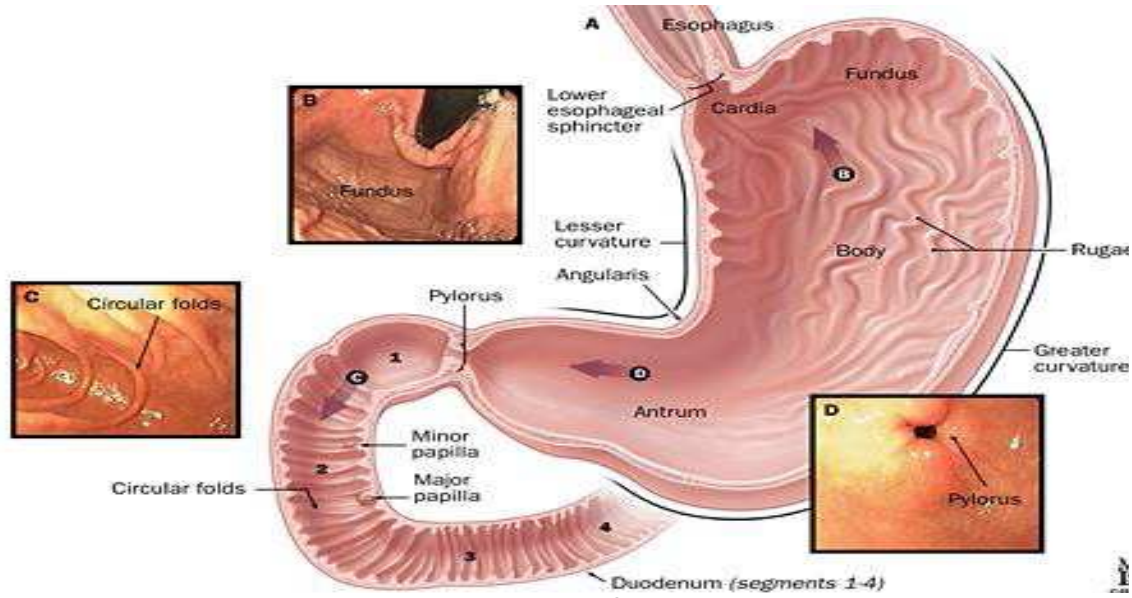

Fig. 1: Physiology of stomach

There are four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands:

Mucous cells: secrete alkaline mucus that protects the epithelium against shear stress and acid.

Parietal cells: secrete hydrochloric acid.

Chief cells: secrete pepsin, a proteolytic enzyme.

G cells: secrete the hormone gastrin.

The contraction of gastric smooth muscle serves two basic functions:

- Ingested food is crushed, ground, mixed and liquefying to form Chyme.
- Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.

Different Features of Stomach:

Gastric pH**:** Fasted healthy subject 1.1 ± 0.15; Fed healthy subjects 3.6 ± 0.4

Volume**:** Resting volume is about 25-50 ml.

Gastric secretion**:** Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mol of hydrogen ions per hour. Effect of food on Gastric secretion**:** About 3 liters of secretions are added to the food in Gastro intestinal transit time.

Salient Features of Upper Gastrointestinal Tract:

Section	Length (m)	Transit time(h)	pH	Microbial count	Absorbing surface area (m^2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I,

P – Passive diffusion; C – Aqueous channel transport; A – Active transport; F – Facilitated transport;
I – Ion-pair transport;

Gastric motility:

Spontaneous movements of the stomach that aid in digestion by moving food through the stomach and into the small intestines. Contractions of gastric smooth muscle serve two basic functions. First, it allows the stomach to grind, crush and mix ingested food, liquefying it to form what is called chyme. Second, it forces the chyme into the small intestine, a process called gastric emptying (Regina Bailey, 2009)[6]. Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems Liquid readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing pyloric gatekeeper. The gastric volume is important for dissolution of the dosage form in vivo. The resting volume of the stomach is 25-50 ml. There is a large difference in gastric secretion of normal and achlorhydric individuals. Gastric pH also has pronounced effect of absorption of drug from delivery system. The pH of fasting stomach is 1.2-.2.0 and in fed conditions 2.0-6.0.8(Hoffmann A et al.1998)[7]

Gastric empty rate

Gastric emptying occurs during fasting as well as fed states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours (Stanley SD et al.1998)[8] This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases (fig 3 as described by Wilson and Washington. (Vyas SP et al.2002)[9]

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

2. Phase II (Preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 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.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles

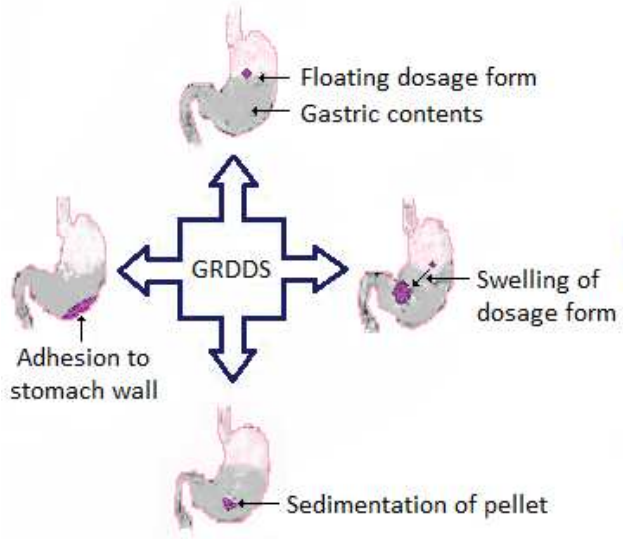

Fig. 2: Different approaches of gastric retention

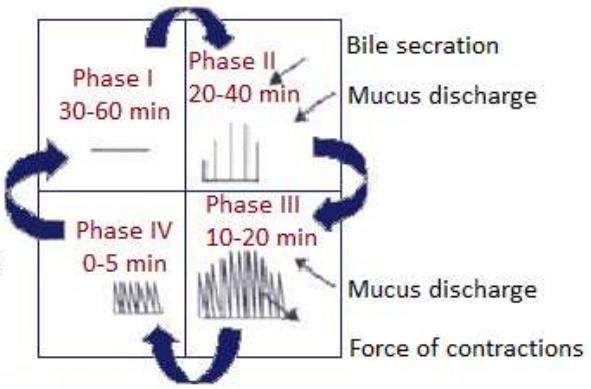

Fig. 3: Motility pattern in GIT

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 slowdown of gastric emptying rate[10] .Scintigraphic 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.

Factors Affecting Gastric Etention

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. Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients also increase gastric retention of drug[11.]These efforts resulted in GRDFs that were designed, in large part, based on the following approaches. (Shown in figure 2)

1. Low density (dosage form) DF that causes buoyancy in gastric fluid[12, 13]
2. High density DF that is retained in the bottom of the stomach[14, 15]
3. Bioadhesion to stomach mucosa[16]
4. Expansion by swelling or unfolding to a large size which limits passage of dosage form through the pyloric sphincter[17]

Oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). Dosage form with prolonged GRT or gastro-retentive dosage form (GRDF) provides an important therapeutic option[18]. Various approaches for preparation of gastroretentive drug delivery system include floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension system and sachet systems[19, 20].

Factors Affecting Gastric Retention

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastroretentive system.

Density: GRT is a function of dosage form buoyancy that is dependent on the density[21.] Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT[22.]

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. (Shown in fig 12)

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, the GI motility is characterized by periods of strong motor activity or the migrating myloelectric complex (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.

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[23]

Caloric content – GRT can be increased by four 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.

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 – Elderly people, especially those over 70, have a significantly longer GRT.

Posture – GRT can vary between supine and upright ambulatory states of the patient[24]

i) Upright position

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements[25].

ii) Supine position

This position offers no reliable protection against early and erratic emptying. 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[26].

Concomitant drug administration–Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride may affect the
Performance of FDDS. The coadministration of GI motility decreasing drugs can increase gastric emptying time.

Biological factors: Diabetes and Crohn's disease can affect floating time.

Feeding regimen: Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4 to10 h has been reported after a meal of fats and proteins[27.]

Types of Floating Drug Delivery Systems (FDDS)

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

A. Effervescent System,

B. Non- Effervescent System.

A. Effervescent System:-

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce Carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the Gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

I. Gas generating systems

II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems:

1. Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS): These systems are formulated by intimately mixing the CO_2 generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration (shown in fig.4).

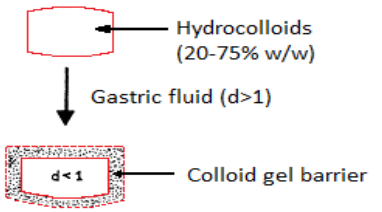

Fig 4: Intra Gastric Single Layer Floating Tablet

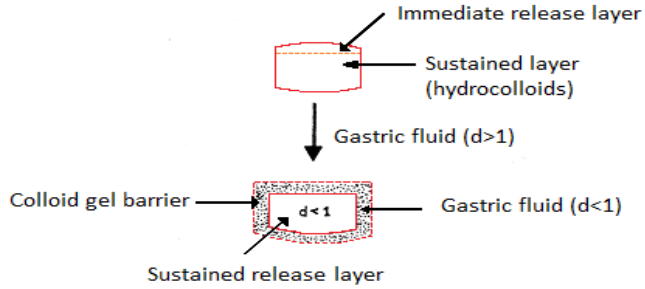

Fig. 5: Intra Gastric Bilayer Floating Tablet.

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet and containing two layers (shown in fig 5)

i. Immediate release layer

ii. Sustained release layer.

3. Multiple Unit type floating pills: These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system (fig 6).

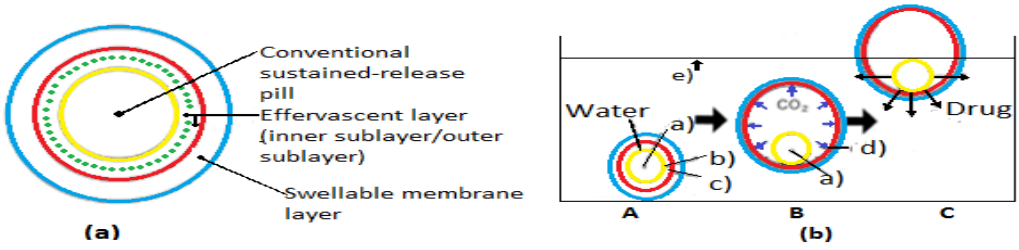

Fig. 6: (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) Penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) Conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable Membrane layer; (e) surface of water in the beaker (37^0C).

II. Volatile Liquid / Vacuum Containing Systems [28] :

The GRT of a drug delivery system can be sustained by incorporating a 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 PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the Inflatable systems from the stomach.

Vacuum Containing Systems consists of

1. Intragastric Floating Gastrointestinal Drug Delivery System
2. Inflatable Gastrointestinal Delivery Systems.
3. Intragastric Osmotically Controlled Drug Delivery System:

1. Intragastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a Vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, (as shown in fig.7).

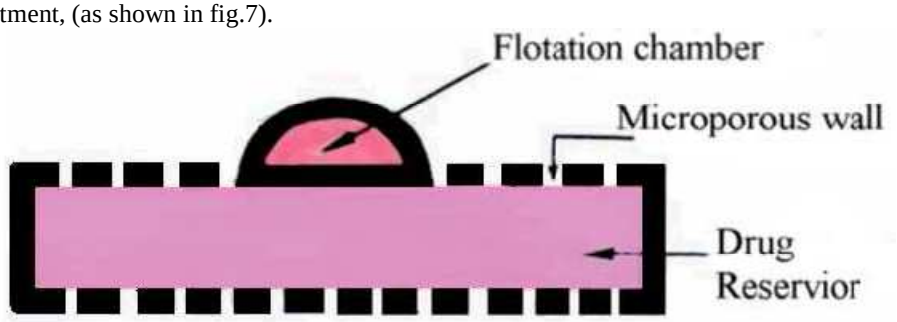

Fig.7: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated Polymeric matrix, then 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 compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. (This system is shown in fig.8)

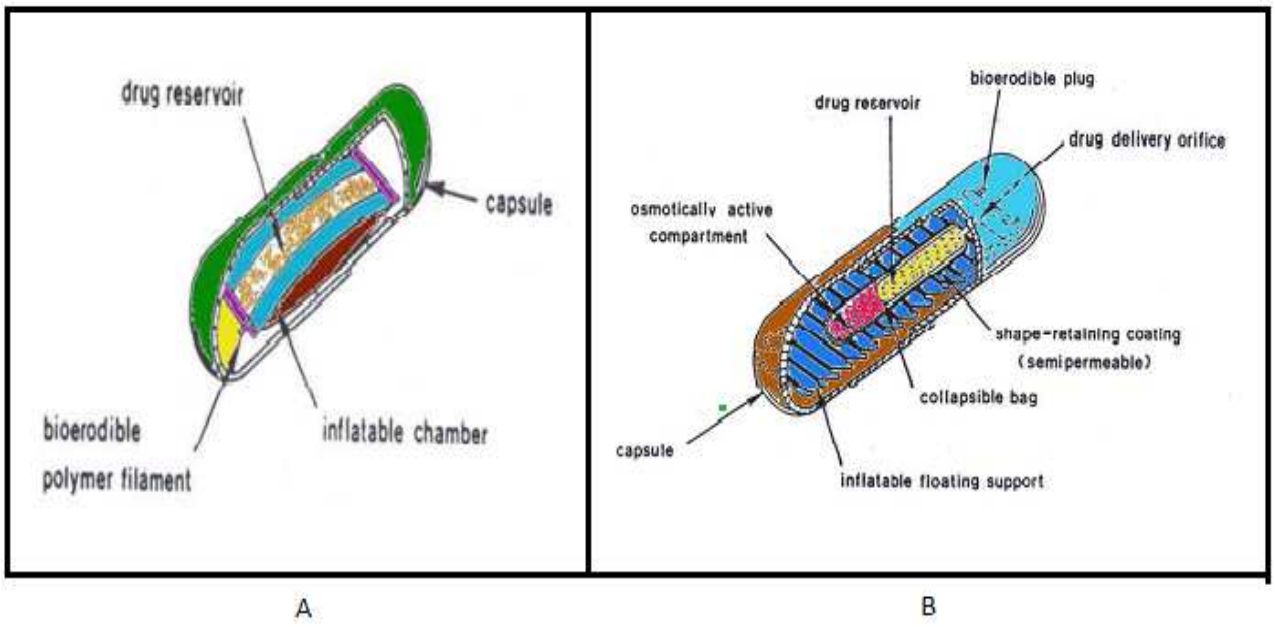

Fig. 8: Inflatable Gastrointestinal Delivery System

Fig .9: Intragastric Osmotically Controlled Drug Delivery System

3. Intragastric 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 Intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. (This system is shown in fig.9).

B. Non effervescent systems:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Bilayer Floating Tablets:

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

3. Alignate Beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hour[29,30].

4. Hollow Microspheres:

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0 C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro. (This system is shown in fig. 10)

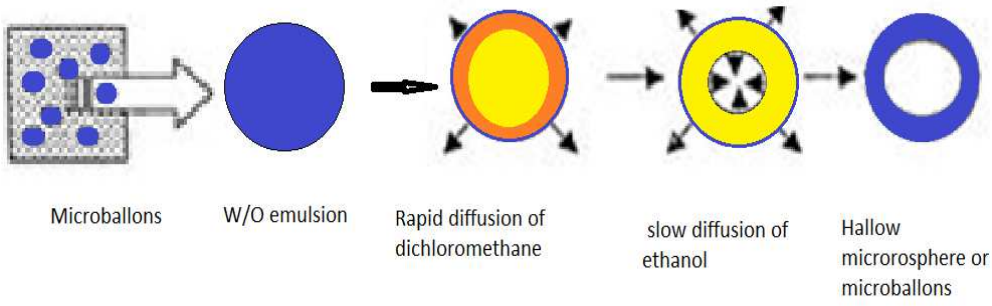

Fig 10: Formulation of floating hollow microsphere or microballons

Especial Types Of Floating Drug Delivery Systems (FDDS)

Floating System Based On Ion Exchange Resin

The resin beads were loaded with bicarbonate and theophylline which were bound to the resin. The loaded resin beads were coated with a semi permeable membrane to overcome rapid loss of CO_2. After exposure to gastric

media, exchange of bicarbonate and chloride ions took place and lead to the formation of CO_2, which was trapped within the membrane, causing the particles to float. Gastric residence time was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of sustaining the drug release[31].

Floating Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [32] .Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.

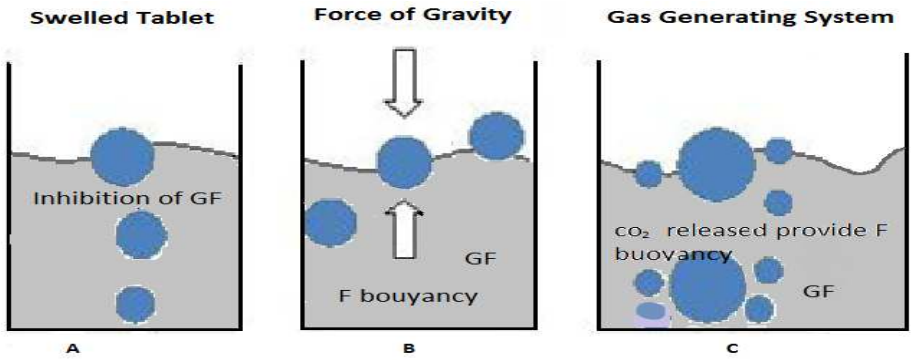

Fig 11: Mechanism of floating systems, GF= Gastric fluid

Programmable drug delivery

A programmable, controlled release drug delivery system has been developed in the form of a non-digestible oral capsule (containing drug in a slowly eroding matrix for controlled release) was designed to utilize an automatically operated geometric obstruction that keeps the device floating in the stomach and prevents it from passing through the remainder of the GIT. Different viscosity grades of hydroxypropyl-methyl-cellulose were employed as model eroding matrices. The duration during which the device could maintain its geometric obstruction (caused by a built in triggering ballooning system) was dependent on the erosion rates of the incorporated polymers (the capsule in hosed core matrix). After complete core matrix erosion, the ballooning system is automatically flattened off so that the device retains its normal capsule size to be eliminated by passing through the GIT[33].

Bioadhesive or Mucoadhesive drug delivery systems

Bio adhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bio adhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc[34, 35]

Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT) [36, 37]:

1) A small configuration for oral intake,
2) An expanded gastro retentive form,
3) A final small form enabling evacuation following drug release from the device.

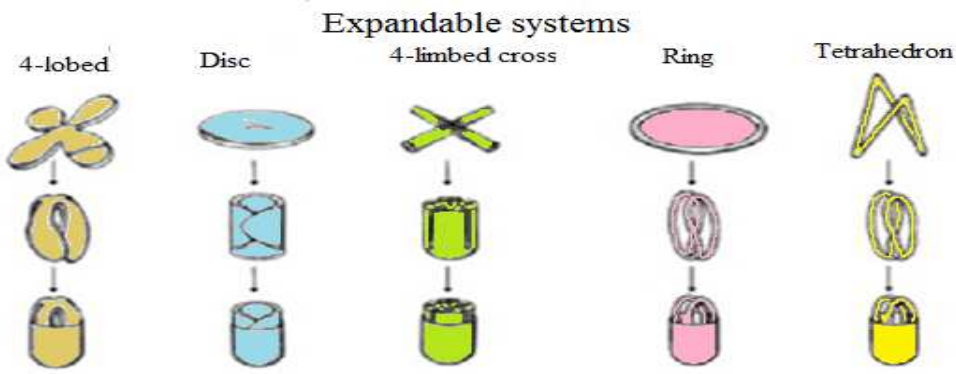

Fig 12: Different geometric forms unfolded systems

Thus, gastroretentive is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldableand swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach [38, 39]. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. (This system is shown in fig. 12). Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective[40] Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy[41].

Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to wok, the external magnet must be positioned with a degree of precision that might compromise patient compliance[42]

Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO_2 and act as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids[43].

High density systems

These systems, which have a density of ~3g/cm^3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements[44, 45]. The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%)
and achieve required density of 2.4-2.8g/cm^3. Diluents such as barium sulphate (density=4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high density formulation[46] (fig 13).

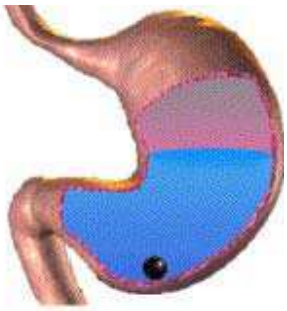

Fig.13: High density systems

Modified systems

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device[47].

Practical approaches in designing FDDS

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm**3**, so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system (Moya Nakagawa et al. 2006)[48].

Formulation 0f Floating Dosage Form

The following types of the ingredients can be incorporated in to FDDS[49]

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

Hydrocolloids: Suitable hydrocolloids are synthetics, anionic or non ionic like as hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having Ph 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

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. Like as Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used.

Release rate accelerant:

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 retardant: Insoluble substances such as dicalcium phosphate, talc magnesium strearete decresesd 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.

Selection of Polymeres [50, 51; 52]

A. Gas Generating Agents

Alkalinizing agents and acidulent: Sodium bicarbonate, Calcium carbonates, Citric acid, Tartaric acid, Adipic acid

Rational behind the selection Effervescent compound generally use for this purpose. Sodium bicarbonate, calcium carbonate with citric acid and tartaric acid. When these compounds come in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swelled hydrocolloids, which provide buoyancy to the dosage forms. Sodium bicarbonate induced CO_2 generation in the presence of dissolution medium (0.1 N HCL). The gas generated trapped and protected within the gel, formed by the hydration of polymer, thus decreasing the density of the tablet as the density of the tablet falls below 1, the tablet become buoyant.

Acidulent is used; since the pH of the stomach is elevated under fed condition (~3.5). Acidulent (Citric acid, Tartaric acid, Adipic acid) was incorporate in the formulation to provide an acidic medium for sodium bicarbonate.

B. Viscolyzing agent: Sodium alginate, Carbopol 934

Rational behind the selection

They used to increase the viscosity in the system. Carbopol is being used in the controlled release solid dosage formulations since last four decades. The numbers of manufacturers commercializing controlled release tablets using carbomers are increasing considerably in recent period of development. Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%). Still they show extremely rapid and efficient swelling characteristics in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The Carbopol polymers produce tablets of excellent hardness and low friability. These polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics. Carbomers show larger dissolution times at lower concentrations than other excipients. Because of these factors

Carbopol polymers have greater extent in formulating dosage forms. Because Carbopol polymers swell rapidly in water and absorb great quantities, to avoid the use of flammable solvents, roller compaction is being used as the method to prepare a new form of Carbopol polymer 71G NF. Carbopol polymer 71G NF is a useful and versatile controlled-release additive for tablet formulations in direct compression.

C. Swelling agent/Gel forming polymer: Hydroxypropylmethylcellulose (HPMC)

Rational behind the selection

Hypermellose powder is stable material, although it is hygroscopic after drying. Solution is stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypermellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point 50-90°C, depending upon grade and concentration of material. Grades which are generally used in floating tablet, which are highly viscous in nature like HPMC K 100, HPMC K 4, HPMC K 15.

D. Disintegrating agent Povidone, Polyplasdone XL and XL-10

Rational behind the selection

PVP belongs to a class of compounds known as super disintegrantes. When they comes in contact with the fluid media they provide the swelling properties to the system they used as highly active explosive agent and as an accelerating agent for disintegration of solid medications. In tabletting, povidone solutions are used as binder in the wet granulation processes

Evaluation Parameters of Stomach Specific FDDS

There are 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. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

1. Hardness, friability, assay, content uniformity (Tablets) these tests are performed as per described in specified monographs.

2. 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 mole.lit-1 HCl maintained at 37o C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium[53].

3. Drug release: The test for in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37^0 C. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replaced with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms.

4. Drug loading, drug entrapment efficiency, particle size analysis, surface characterization, micromeritics studies and percentage yield (for floating microspheres and beads)

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM). The measured weight of prepared microspheres was divided by total amount of all non-volatile components used for the preparation of microspheres, which will give the total percentage yield of floating microspheres[54, 55]

5. Content uniformity

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of solvent, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically in UV.

6. Weight gain and water uptake (WU): Weight gain or water uptake 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 37oC 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.

7. X-Ray/ Gamma scintigraphy: For *in vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. In each experiment, the animals are allowed to fast overnight with free access to water, and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 mL of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine. Gamma scintigraphy is a technique whereby the transit of a dosage form through its intended site of delivery can be non-invasively imaged *in vivo* via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The inclusion of a γ-emitting radionucleide in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ-scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of Radiopharmaceutical[56, 57]

8. Specific Gravity: Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium[58]

9. Pharmacokinetic studies are the integral part of the in vivo studies and several works has been on that. The pharmacokinetics studies of verapamil, from the loading pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The t_{max} and AUC (0-infinity) values (3.75h and 364.65 ng/mlh, respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets (t_{max} value 1.21h, and AUC value 224.22ng/mlh) (Sawicki, 2002)[59]. No much difference was found between the C_{max} values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

Drugs used in the formulations of stomach specific floating dosage forms:

-Floating microspheres – Aspirin, Griseofulvin, pnitroaniline, Ibuprofen, Ketoprofen[60], Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast[61]and Terfinadine[62]

-Floating granules - Diclofenac sodium, Indomethacin and Prednisolone

-Films – Cinnarizine[63], Albendazole

-Floating tablets and Pills - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate[64], Paraaminobenzoic acid, Piretanide[65], Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol [66], pentoxyfilline and Diltiazem HCl.

ADVANTAGES OF FDDS (Natasha Sharma., 2013)[67]

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

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

Disadvantages Of Floating Drug Delivery Systems (Vedha hari b.n.et al 2010, Sasa Baumgartner et al.2000)[68]

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
4. These systems also require the presence of food to delay their gastric emptying.
5. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
6. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
7. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Drugs those are unsuitable for gastroretentive drug delivery Systems[69]

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc

Application of Floating Drug Delivery System[70, 71, 72]

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 follow:

Enhanced Bioavailability: The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Sustained Drug Delivery: Oral control release (CR) formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach

for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

Site-Specific Drug Delivery Systems: These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin.

Absorption Enhancement: Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

Minimized Adverse Activity at the Colon: Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Reduced Fluctuations of Drug Concentration: Continuous input of the drug following CR- GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

Pharmaceutical Aspects: In designing of FDDS, following characteristics should be sought:

i) Retention in the stomach according to the clinical demand;

ii) Convenient intake;

iii) Ability to load substantial amount of drug with different physicochemical properties and release them in a controlled manners;

iv) Complete matrix integrity of the SR formulation in the stomach, inexpensive industrial manufacture, optimization between the buoyancy time and release rate (Buoyancy time increases by increasing drug: polymer ratio but release retards by increasing polymer level), lag time i.e. the time taken by the dosage form to float should be low (Wong P S Let al.2000)[73]. Most of the floating systems reported in literature are single-unit systems; these systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered, owing to their fortuitous ('all-or-nothing') emptying process. On the other hand, multiple-unit dosage forms appear to be better option since they reduce the inter subject variability in absorption and lower the probability of dose dumping (El-Kamel A Het al.2001)[74.]

Future Perspectives in Floating Drug Delivery Systems[75]

Among the drugs currently in clinical use are several narrow absorption window drugs that may benefit from compounding into a FDDS. Replacing parentarl administration of drugs to oral pharmacotherapy would substantially improve treatment. It is anticipated that FDDS may enhance this possibility. Moreover, it is expected that the FDDS approach may be used for many potentially active agents with narrow absorption window, whose development has been halted due to lack of appropriate pharmaceutical FDDS technologies. Combination therapy to treat H.Pylori infections in a single FDDS need to be developed. Further investigation may concentrate on the following concept:

Identification of a minimal cut-off size above those DFs retained in the human stomach for prolonged period of time. This would permit a more specific control to be achieved in gastroretentivity.

1. Design of array of FDDS, each having a narrow GRT for use according to the clinical need e.g. dosage and state of disease. This may be achieved by compounding polymeric matrices with various biodegradation properties. Study of the effect of various geometric shapes, in a more excessive manner than previous studies, extended dimensions with high rigidity, on gastroretentivity.
2. Design of novel polymers according to clinical and pharmaceutical need.

3. Conclusion

Floating drug delivery system can provide sufficient gastric retention which may help to sustained release dosage form with enhanced absorption. This article gives an overview of parameters affecting gastric emptying in humans as well as on the main concepts used to design pharmaceutical dosages form with prolonged gastric retention time. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. 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. Based on the literature surveyed, it may be concluded that gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due to their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability.

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