Review on gastroretentive drug delivery systems

Parth Chauhan*[1], MS Patel[2] and NM Patel[3]

Department of pharmaceutics, B. M. Shah College of Pharmaceutical Education and Research, Modasa, District- Sabarkantha, Gujarat

*Parthchauhan[39]@gmail.com**

Abstract

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. Incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, and polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recently developments of Stomach Specific FDDS are discussed that helps to overcome physiological adversities like short gastric residence times and unpredictable gastric emptying times

Keywords: Floating drug delivery systems, gastric residence time, effervescent, noneffervescent

1. Introduction

Oral drug delivery is the most desirable and preferred method of administering therapeutics agent for their systemic effect. The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient Compliance, flexibility in formulation and handling of these forms. This system has been of limited success. Oral dosage forms have proved to be successful in achieving a plethora of controlled release objectives ranging from immediate release to site specific delivery (Garg *et al.,* 2003; Patel *et al.,* 2006, Ahmed *et al.,* 2002).

An although tremendous advances have been seen in oral controlled drug delivery system during last two decades.1 Oral formulations are being developed into different types, such as controlled release ,delayed release, fast dissolving and taste masking formulations (Appaji, 2001) and other delivery technologies are being tried to deliver already existing and new drug molecules, oral formulations still control more than 60% of the market in ability to restrain and localize the DDS within the desired regions of the GIT (Rouge *et al.,* 1996; Hajeri & Amiji, 2002).This approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility.

1.1 Need for gastroretentive drug delivery system

Various drugs have their greatest therapeutic effect when released in the stomach,particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example,material passes through the small intestine in as little as 1-3 hours.5 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:

- Drugs acting locally in the stomach
  - E.g. Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach
  - E.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH
  - E.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption
  - Cyclosporine, Methotrexate, Levodopa, etc.

Drugs which are absorbed rapidly from the GI tract.

- E.g. Metonidazole, tetracycline.
- Drugs that degrade in the colon
  - E.g. Ranitidine, Metformin HCl.
- Drugs that disturb normal colonic microbes
  - E.g. antibiotics against Helicobacter pylori

1.2 Factors affecting gastric retention time of the dosage form

1.2.1 Density

GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

1.2.2 Size & Shape of dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric.

1.2.3 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.

1.2.4 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 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.

1.2.5 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.

1.2.6 Caloric content

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

1.3 Approaches to achieve gastric retention floating – a low density approach

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus 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 a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.

Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcelluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy (Garg & Gupta, 2008; Timmermans and Moes, 1990).

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time (Seth & Tossounian, 1984). The Floating drug delivery system (FDDS) can be divided into effervescent and non effervescent systems.

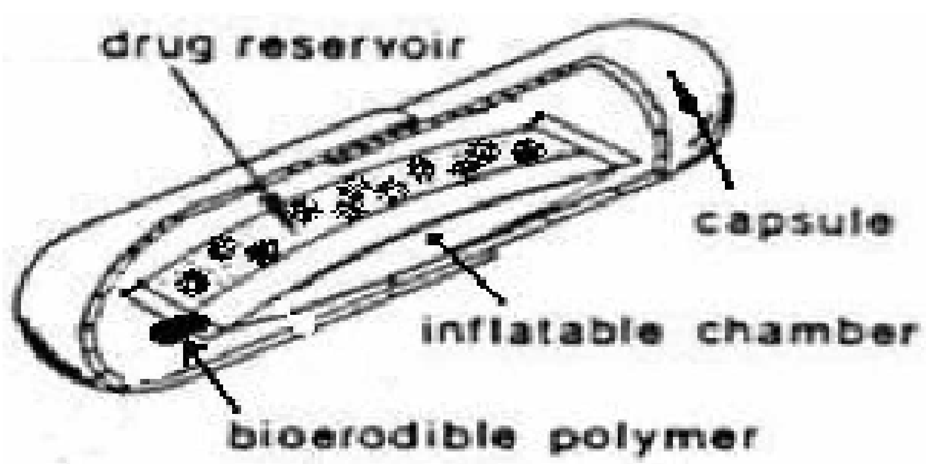
1.3.1 Effervescent systems

These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium Bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO_2 is liberated and gets entrapped in swollen Hydrocolloids, which provides buoyancy to the dosage forms.

1.4 Volatile liquid containing systems

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that Gasifies at body temperature to cause the inflation of the chamber in the stomach.These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

Fig.1. *Inflation chamber*



1.4.1 Gas generating systems

These buoyant systems utilised matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. 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 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 minicapsules 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. (Yeole *et al.,* 2005).

1.4.2 Matrix Tablets

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug.Bilayer tablet can also be prepared by gas generating matrix in one layer and second layer with drug for its SR effect. Floating capsules also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of 2 drugs (Metronidazole and Tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for Triple Therapy of *H. Pylori.*

Fig.2. *Effervescent pill*

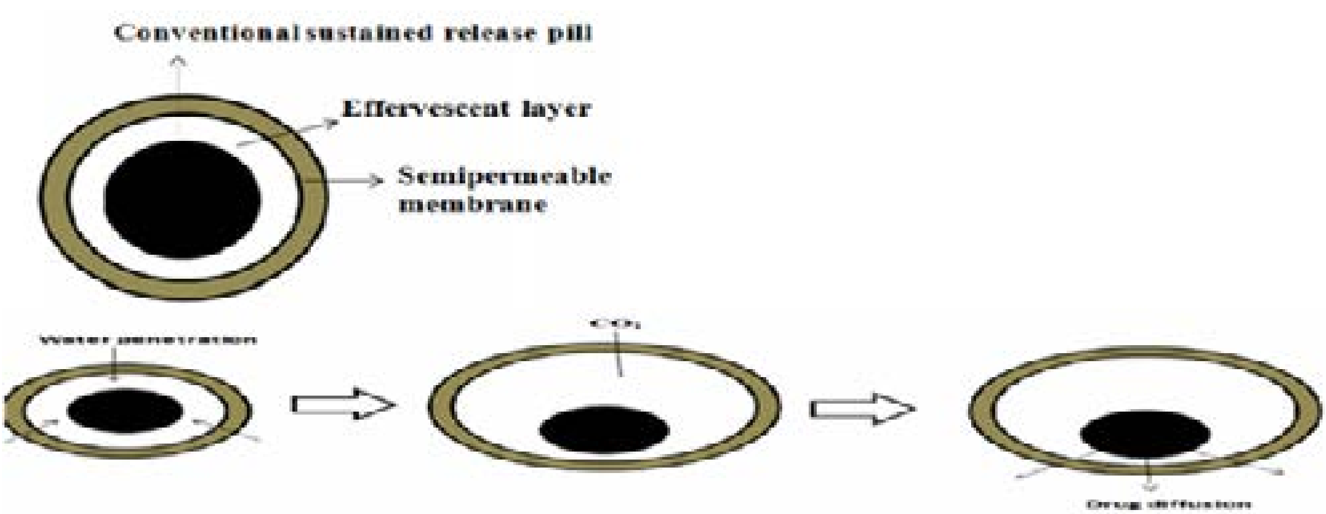
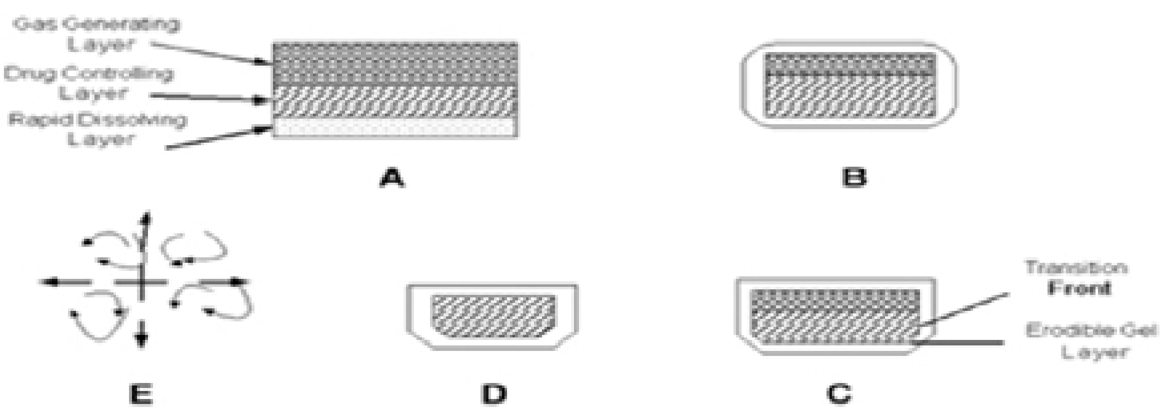


Fig.3. *Triple layer matrix tablet*



1.5 Noneffervescent system

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 <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.

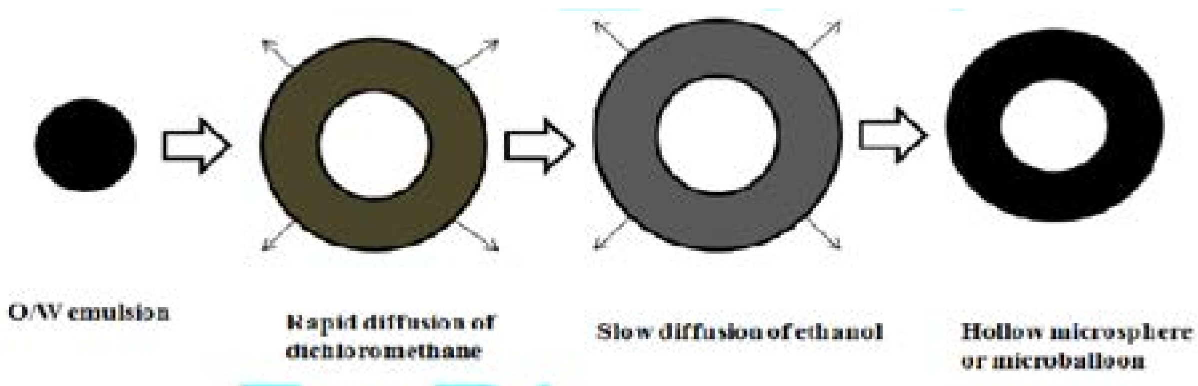
1.6 Hydrodynamically balanced systems

Sheth and Tossounian16 first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems 17,18. The polymer is mixed with drugs and usually administered inhydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form 18. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LPR, based on the system was marketed during the 1980's 19. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile several strategies have been tried and, investigated to improve efficiencies of the floating hydrodynamically balanced systems

1.7 Microballoons / Hollow microspheres

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods (Fig.1.) (Reddy & Murthy, 2002) to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours (Garg & Gupta, 2008). At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

Fig.4. *Formulation of floating hollow microsphere or microballoon*



1.8 Alginate beads

Talukdar & Fassihi (2004) recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate.

These beads are then separated and dried by air convection and freeze drying, leadingto the formulation of a porous system, which can maintain a floating force for over 12hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs (Garg & Gupta ,2008; Whiteland *et al.,*1996).Micro porous compartment system: This approach is based on the principle of the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls (Harrigan, 1977).

The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the Stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid (Vyas & Khar, 2006). Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

1.9 Bioadhesive Systems

Bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS) in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane. A bio/muco-adhesive substance is a natural or synthetic polymer capable of producingan adhesive interaction based on hydration–mediated, bondingmediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosa (Gupta & Robinson, 1992; Park & Robinson, 1984).

Fig.4. *Mucoadhesive system*

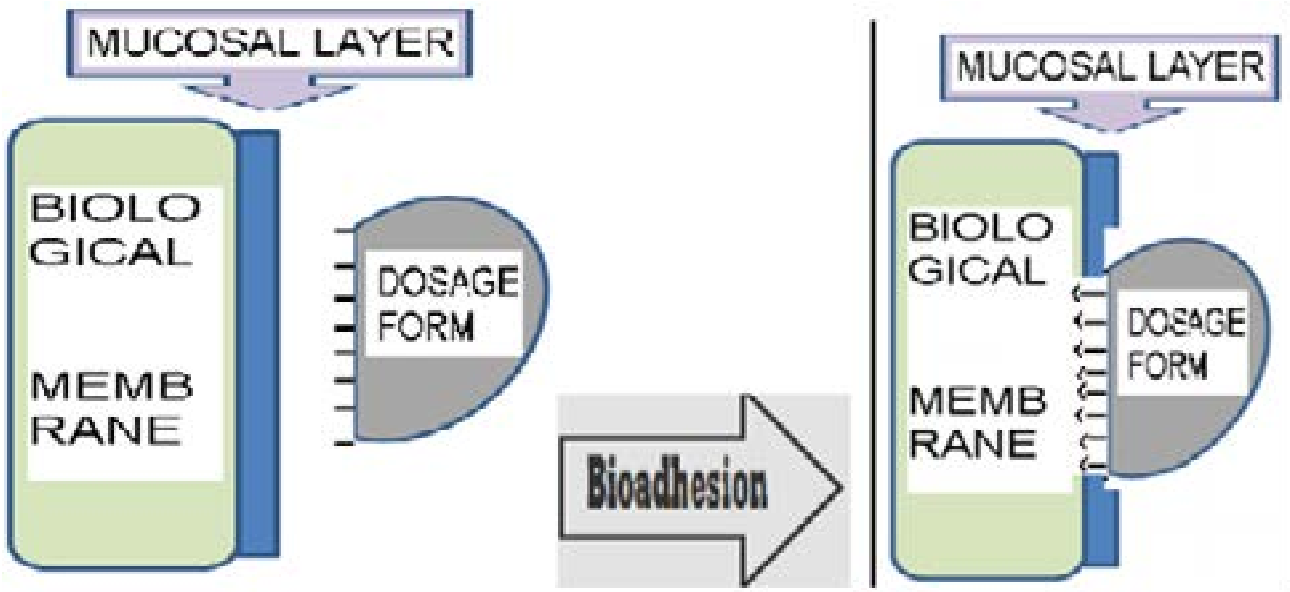


Fig.6. *Swellable system*

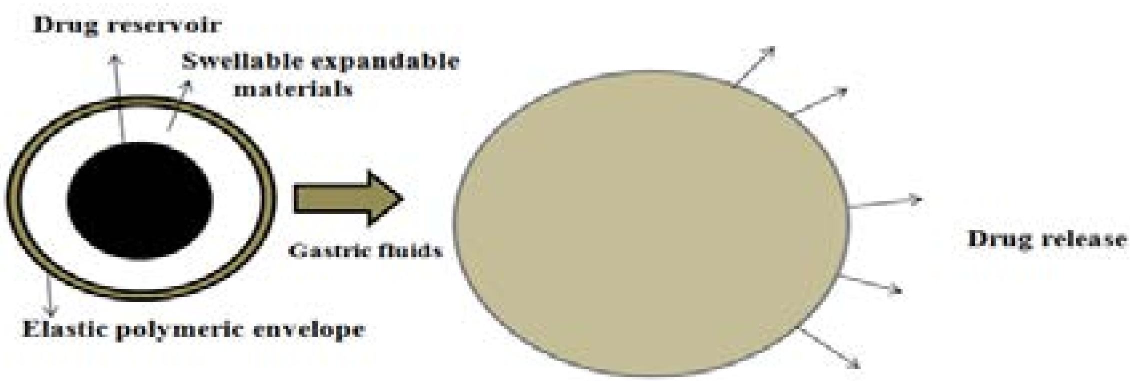
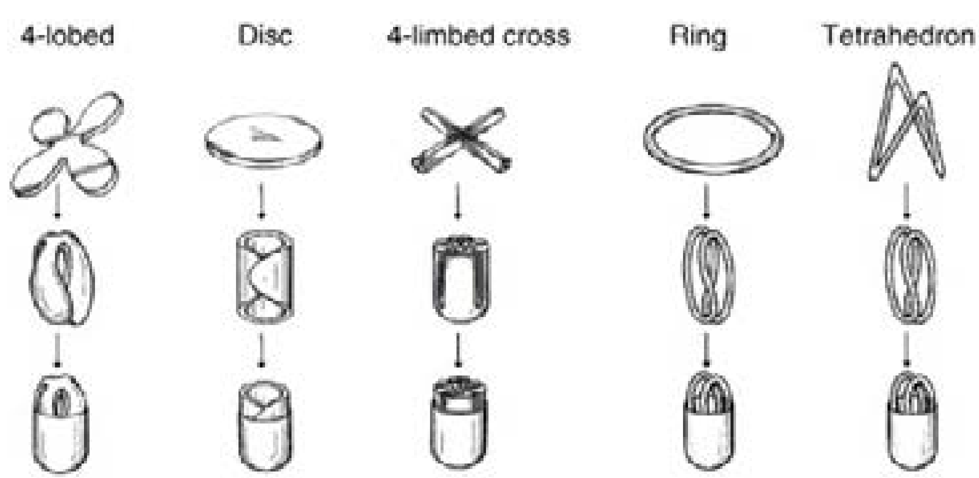


Fig.7. *Various geometric form of unfolding system*



1.10 Swelling system

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems'. Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release on coming in contact with gastric fluid, the polymer imbibes water and swells.

1.11 High density systems

These systems with a density of about 3 g/cm^3 are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8 g/cm^3. It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc. to manufacture such high density formulations. Floating Drug Delivery

Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations (Clarke *et al.,* 1993; Clarke *et al.,*1995).

1.11.1 Raft forming systems

Raft forming systems have received much attention for the delivery of antacids and drugdelivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids.

The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (*H. Pylori*) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float (Caldwell *et al.,* 1988; Gupta *et al.,* 2002; Gupta *et al.,* 2002).

1.11.2 Expandable system

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus (Caldwell *et al.,* 1988). As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state.

Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslink's in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period.

On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer (Gupta *et al.,* 2002). An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion (Deshpande *et al.,* 1997). These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration (Gupta *et al.,* 2002).

- The expandable GRDFs are usually based on three configurations:

- A small collapsed configuration which enables sufficient oral intake
- Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.
- A smaller form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.
- The expansion can be achieved by Swelling system ii) Unfolding system

1.12 Magnetic systems

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach (Ito *et al.,* 1990) used this technique in rabbits with bio adhesives granules containing ultrafine ferrite (g-Fe_2O_3). They guided them to the esophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2hr-10hrs. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

1.13 Evaluation of gastroretentive dosage form

1.14 Invitro evaluation (Desai & Bolton, 1993; Patel *et al.,* 2005)

1.14.1 Floating systems

a) Buoyancy Lag Time (Arrora *et al.,* 2005)

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time (Burns *et al.,* 1995)

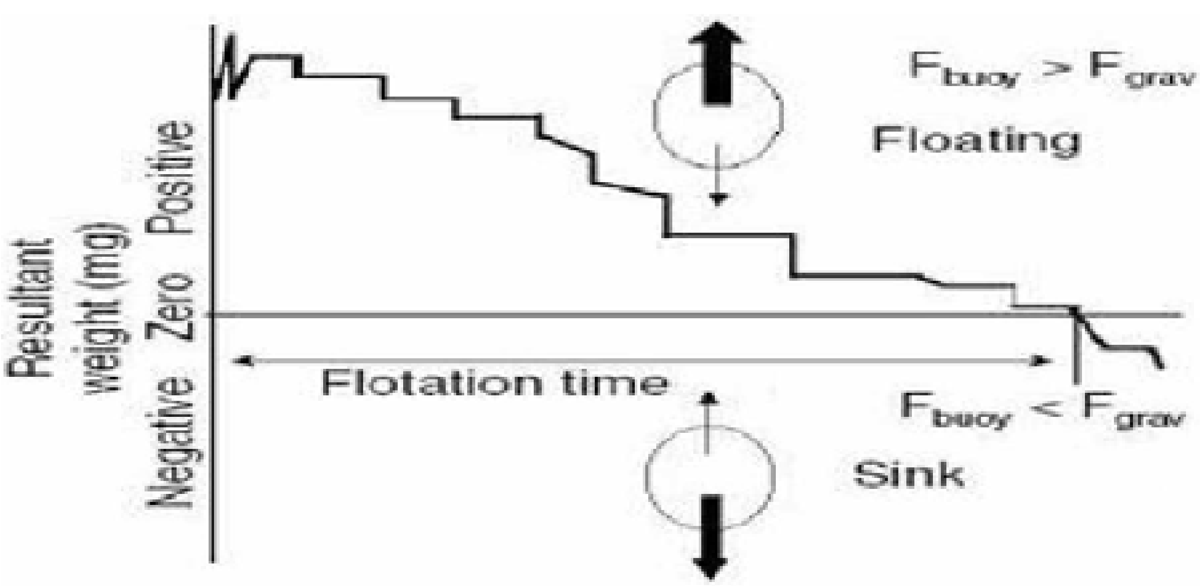
Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

c) Specific Gravity / Density

Density can be determined by the displacement method using benzene as displacement medium.

d) Resultant Weight (Timmermans & Andre, 1994)

Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time.



For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (Fbuoy) and gravity force (Fgrav) acting on dosage form so when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

1.15 Swelling systems

1.15.1 Swelling Index

After immersion of swelling dosage form into SGF at 37^{0}C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

1.15.2 Water Uptake

It is an indirect measurement of swelling property of swellable matrix. Here dosage form isremoved out at regular interval and weight changes are determined with respect to time.So it is also termed asWeight Gain.

Water uptake = WU = (Wt – Wo) * 100 / Wo

Where, Wt = weight of dosage form at time t

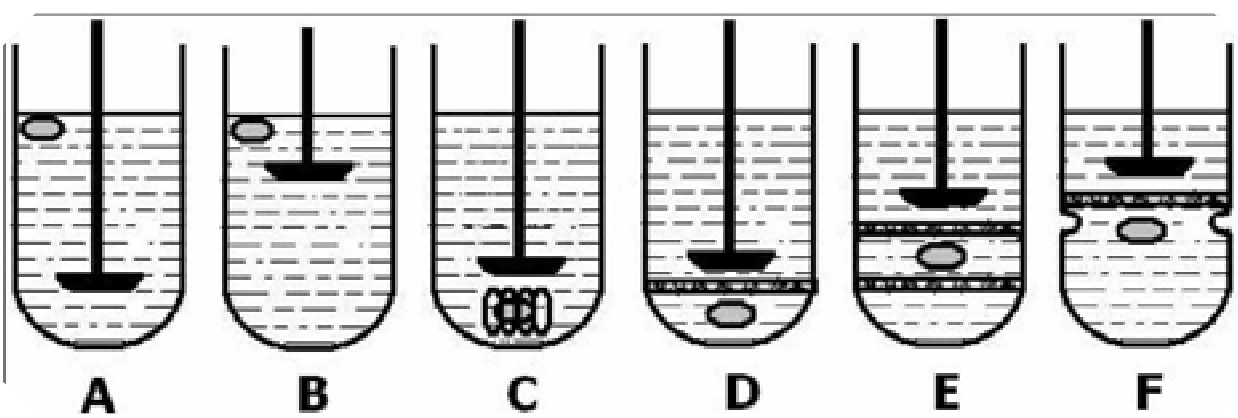
Wo = initial weight of dosage form

1.15.3 Invitro dissolution tests (Burns *et al.,* 1995; Pillay & Fassihi, 1998)

A. In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

B. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

Fig.8. *Dissolution of floating dosage form*



C. Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.

D. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

E. Other method suggests placing dosage form between 2 ring/meshes.

F. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

G. Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the in-vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

1.16 Invivo evaluation

1.16.1 Radiology

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

1.16.2 Scintigraphy

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99 Tc.

1.16.3 Gastroscopy

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

1.16.4 Magnetic Marker Monitoring

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment.Advantage of this method is that it is radiation less and so not hazardous.

1.17 Ultrasonography

Used sometimes, not used generally because it is not traceable at intestine.

1.18 13C Octanoic acid breath test

13C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO_2 is replaced with 13C isotope. So time up to which $^{13}CO_2$ gas isobserved in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO_2 release. So this method is cheaper than other.

1.19 Advantages of gastro retentive delivery systems (Gupta *et al.,* 2002)

1) Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide

2) Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillins and cephalosporins)

3) For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.

4) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

5) Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

6) The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable Effects of side effects.

7) Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

8) Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

9) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

10) The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

1.19.1 Limitations

- Require a higher level of fluids in the stomach.
- Not suitable for Drugs that...
- Have solubility problems in gastric fluid.eg. phenytoin

- Cause G.I irritation. E.g. NSAIDS.
- Are unstable in acidic environment.
- Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and
- corticosteroids etc.
- The floating systems in patients with achlorhydria can be questionable in case of
- swellable system.
- Retention of high density systems in the antrum part under the migrating waves
- of the stomach is questionable.
- The mucus on the walls of the stomach is in a state of constant renewal,
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1.20 Future prospects

While the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called 'once-a-day' formulations may be replaced by novel gastroretentive products with release and absorption phases of approximately 24 hrs.

Table.1. Commercial Gastroretentive Floating Formulations

Product	Content	Manufacturer	Type of formulation
Madopar®	Levodopa(100 mg), Benserazide(25 mg)	Roche products, USA	Floating, CR capsule
Valrelease®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
Liquid Gaviscon®	Al-hydroxide(95 mg), Mg carbonate(358 mg)	GlaxoSmithKline, India.	Effervescent floating
Topalkan®	liquid alginate preparation Al-Mg antacid	Pierre Fabre Drug, France.	FDDS
Almagate FlotCoat®	Al-Mg antacid - Floating dosage form	Ranbaxy, India	Colloidal gel forming

1.21 List of drugs explored in floating dosage forms

Microspheres: Aspirin, Griseofulvin, P-nitro aniline, Ibuprofen, Ketoprofen, Terfenadine, Tranilast.
Granules Diclofenac sodium, Indomethacin, Prednisolone.
Films Cinnarizine, Drug delivery device.
Capsules Chlordiazepoxide HCl, Diazepam, Furocemide, L-Dopa and Benserazide, Misoprostol, Nicardipine, Propranolol HCl, Ursodeoxychoric acid.
Tablets/Pills Acetaminophen, Aspirin, Amoxycillin trihydrate, Ampicillin, Atenolol, Captopril, Ciprofolxacin, Chlorphe-

niramine maleate, Cinnarizine, Furosemide, 5-Fluorouracil, Isosorbide mononitrate, Diltiazem, Isosorbide dinitrate, Nimodipine, Para amino benzoic acid, Prednisolone,Quinidine, Varapamil HCl, Riboflavin, Sotalol.

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