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Hydrodynamically Balanced Systems (HBS): Innovative Approach of Gastroretention: A Review

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Abstract: The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. 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. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.
Keywords: Floating drug delivery systems, single unit, multiple units, and evaluation in vitro and in vivo.

Introduction:

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.

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug

substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract, and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention. In additions, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size.

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. [1, 2, 3]

Basic Gastrointestinal Tract Physiology and Gastric Retention:

Physiological Consideration.

1. Stomach: The site for gastro retention.

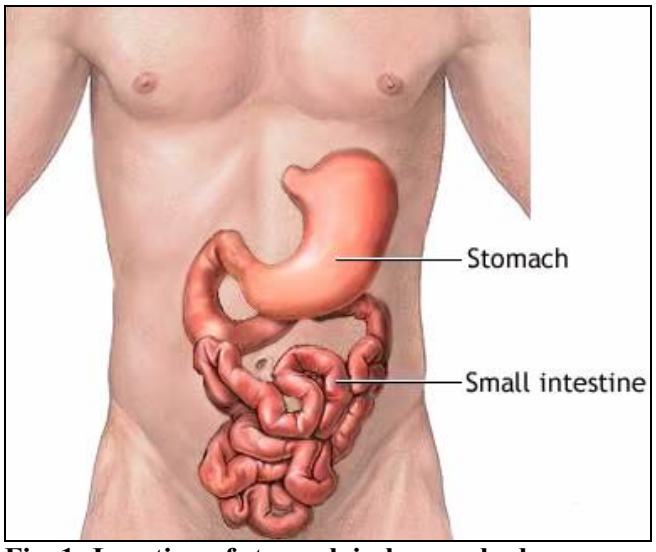

Fig. 1: Location of stomach in human body.

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension: up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of 25-50 ml.

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. [1, 4]

2. Gastrointestinal motility & emptying of food.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 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. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC). This is further divided into following 4 phases.

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.

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 migrating myloelectric cycle (MMC) is delayed resulting in slowdown of gastric emptying rate.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate. [1, 4]

3. Requirements for gastro retention.

The dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms.

It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease. [1, 4, 5]

Why Floating Drug Delivery System?

Hydrodynamically balanced systems (HBS) – Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time. The dosage form must have a bulk density of less than 1. [2, 4, 6]

Factors Affecting Gastric Retention:

Gastric residence time of an oral dosage form is affected by several factors which are follows:-

1. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm.
2. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.
3. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time.
4. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.
5. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.
6. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.
7. Several formulation parameters can affect the gastric residence time. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of food compared with single unit formulation.
8. The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats. The dosage unit is retained in the stomach for a prolonged period. [1, 2, 6]

Floating Drug Delivery Systems:

The concept of FDDS was described in the literature as early as 1962. 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. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

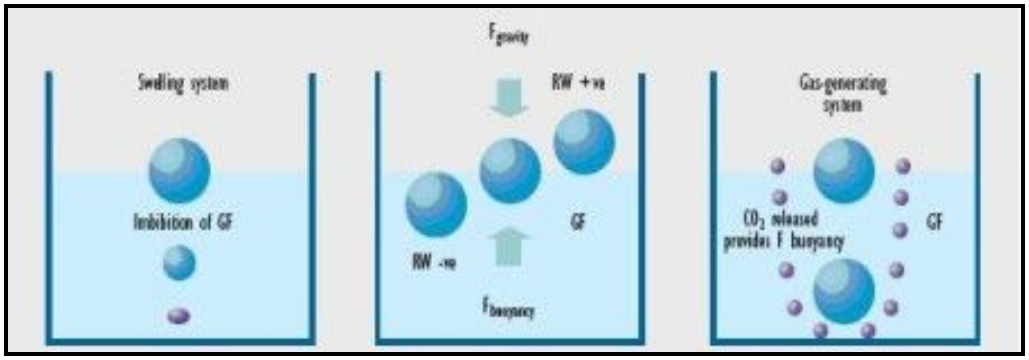

Fig.2: The mechanism of floating systems.

Formulation of this device must comply with the following criteria:

1. It must have sufficient structure to form a cohesive gel barrier.
2. It must maintain an overall specific gravity lower than that of gastric contents (1.004 – 1.010).
3. It should dissolve slowly enough to serve as a drug reservoir. [4, 6]

Applications of Floating Microspheres:

1. The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa
2. Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. 3. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach.
3. pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.
4. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride.
5. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
6. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can also be delivered efficiently thereby maximizing their absorption and improving the bioavailability
7. Hollow microspheres can greatly improve the
8. The development of such systems allow administration of non-systemic, controlled release antacid formulations containing calcium carbonate and also locally acting anti-ulcer drugs in the stomach; e.g. Lansoprazole.
9. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
10. The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms may allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin, low-molecular-weight Heparin, and LHRH.
11. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients.
12. The drugs recently reported to be entrapped in hollow microspheres include Aspirin, Griseofulvin, Ibuprofen, Terfenadine, Diclofenac sodium, Indomethacin, Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin. [7, 8]

Classification of Floating Drug Delivery Systems (FDDS):

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

A. Efervfescent Systems:

1. Volatile liquid containing systems:

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

The device may also consist of a bioerodible plug made up of 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. [8, 9]

Yang et al[10] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients.

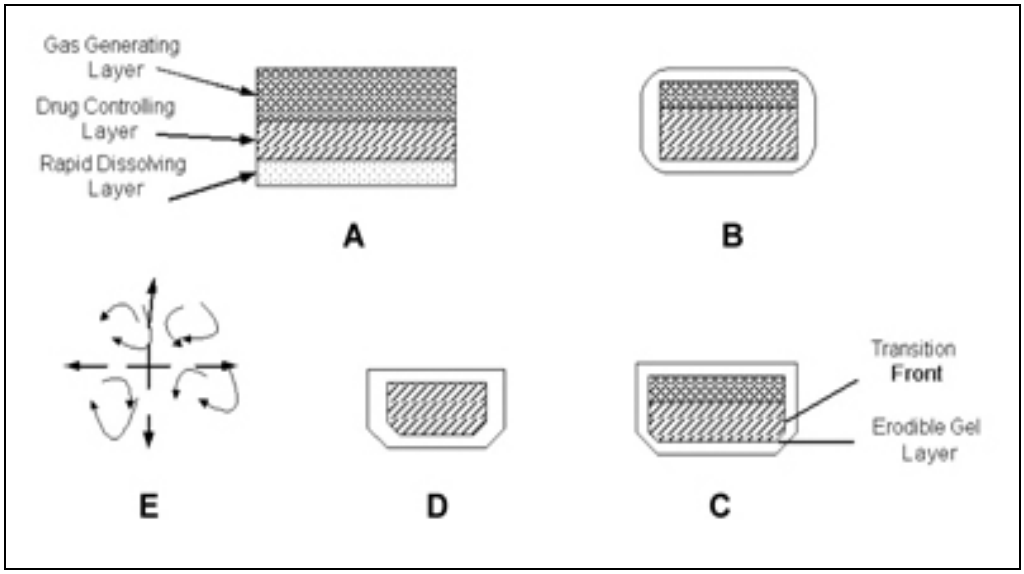

Fig.3: Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.[10]

The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporatinga gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high-localized concentration of tetracycline and metronidazole (Fig.3).

Penners et al [11] developed an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus reside in stomach over an extended period of time. In addition to this, gas-forming agents were incorporated. As the gas formed, the density of the system was reduced and thus the system tended to float on the gastric contents.

2. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

These are matrix types 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 acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Ichikawa et al [12] developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para-amino benzoic acid) released in a sustained manner.

Choi et al [13] prepared floating alginate beads using gas-forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO_2 generation on the physical properties, morphology, and release rates. The study revealed that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less-effective gas-forming agent than sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates. In vitro floating studies revealed that the beads free of gas-forming agents sank uniformly in the media while the beads containing gas-forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%).

Moursy et al[14] developed sustained release floating capsules of nicardipine HCl. For floating, hydrocolloids of high viscosity grades were used and to aid in buoyancy sodium bicarbonate was added to allow evolution of CO_2. In vitro analysis of a commercially available 20-mg capsule of nicardipine HCl (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. The optimized sustained release floating capsule formulation was evaluated in vivo and compared with MICARD capsules using rabbits at a dose equivalent to a human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded that of the MICARD capsules. In the latter case the drug was traced for 8 hours compared with 16 hours in former case.

B. Non-Effervescent Systems:

1. Colloidal gel barrier systems.

Hydrodymamically balance system (HBS) contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. These systems incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. E.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy. [1, 2, 8, 9]

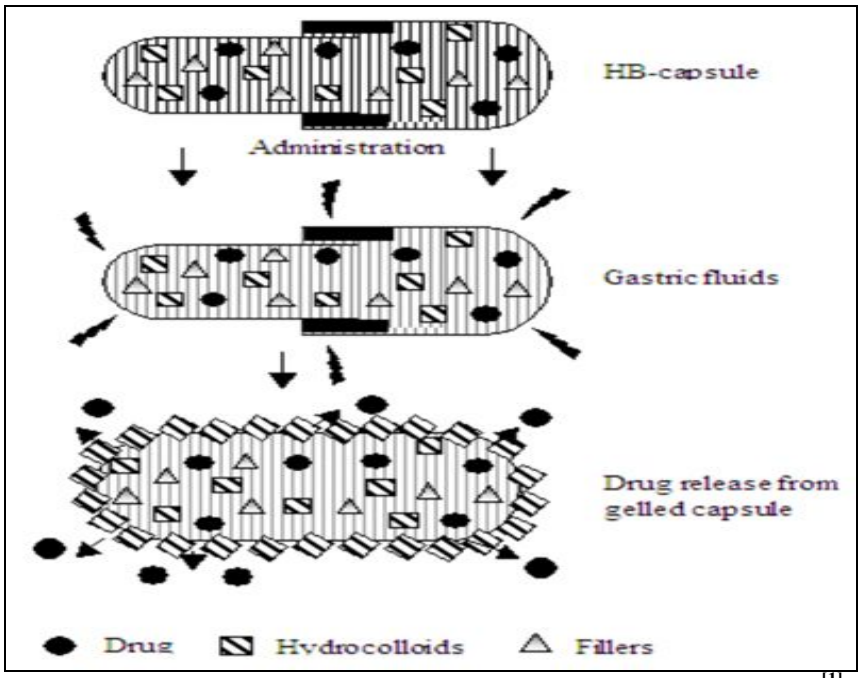

Fig.4: Working principle of hydrodynamically balanced system. [1]

Streubel et al [15] developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethyl metha acrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S. This could be attributed to the different permeabilities of the drug in these polymers and the drug distribution within the system.

Sheth and Tossounian [16, 17] developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids.

2. Microporous Compartment System.

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

Bulgarelli et al [18] studied the effect of matrix composition and process conditions on casein gelatin beads prepared by emulsification extraction method. Casein by virtue of its emulsifying properties causes incorporation of air bubbles and formation of large holes in the beads that act as air reservoirs in floating systems and serve as a simple and inexpensive material used in controlled oral drug delivery systems. It was observed that the percentage of casein in matrix increases the drug loading of both low and high porous matrices, although the loading efficiency of high porous matrices is lower than that of low porous matrices.

3. Alginate beads.

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating force over 12 hours.

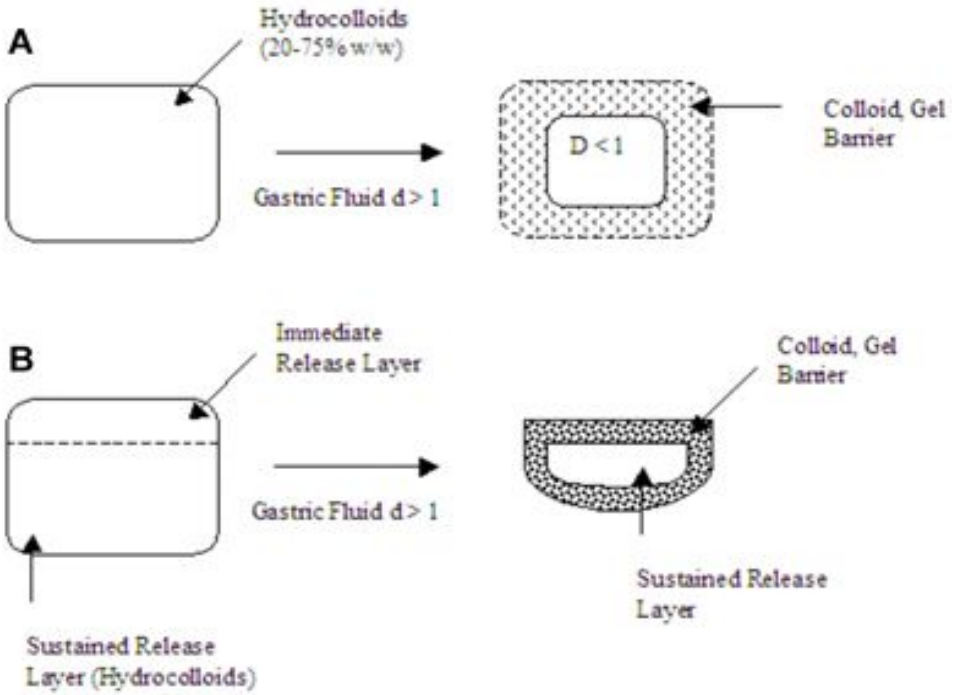

Fig.5 Intragastric floating tablets. [16, 17]

Floating Dosage Forms.

Table: 1-Various floating dosage forms. [3, 21]

Dosage Forms	Drugs
Microspheres	Aspirin, Ibuprofen, Tranilast.
Granules	Diclofenac sodium, Indomethacin, Prednisolone.
Capsules	Diazepam, Furosemide, L-Dopa and Benserazide.
Tablets / pills	Amoxycillin Trihydrate, Ampicillin,Diltiazem,*p*-Aminobenzoicacid, Riboflavin-5'-phosphate, Theophylline, Verapamil HCl.

4. Floating Microspheres.

Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period.

As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release.

As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer.

The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy.

Thanoo et al [19] developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to-polymer ratio increased both their mean particle size and release rate of drug.

Joseph et al [20] developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. In vivo studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration vs time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period.

Characterization Of Floating Microspheres:

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties. Particle size is measured using an optical microscopy and mean particle size was calculated by measuring 200 to 300 particles with the help of calibrated ocular micrometer.]

True density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method.

$$Tapped\ density = \frac{Mass\ of microspheres}{Volume\ of microspheres\ after\ tapping}$$

The compressibility index was calculated using following formula:

$$\mathbf{I = V_b - V_t / V_b \times 100}$$

Where, V_b is the bulk volume and V_t is the tapped volume. The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

The hollow nature of microspheres is confirmed by scanning electron microscopy. [7, 22]

***In-Vitro* Release Studies and *In-Vivo* Release Studies of Floating Microspheres:**

1. *In-Vitro* Release Studies.

The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium.

The dissolution fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 µm membrane filter (Millipore), and analyzed using LC/MS/MS method to determine the concentration present in the dissolution medium.

The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate.

The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. [8]

2. *In-Vivo* Release Studies.

The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs.

The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs). [8]

Methods of Preparetion of Microspheres:

There are following methods used for preparation of microspheres;

1. Simple Emulsion Method.
2. Double Emulsion Method.
3. Polymerization Techniques.
   A) Bulk Normal Polymerization.
   a) Polymerization.
   b) Suspension Polymerization.
   c) Emulsion Polymerization.
   B) Interfacial Polymerization.
4. Phase Separation Coacervation Technique.
5. Solvent Extraction Method.

1. Simple Emulsion Method.

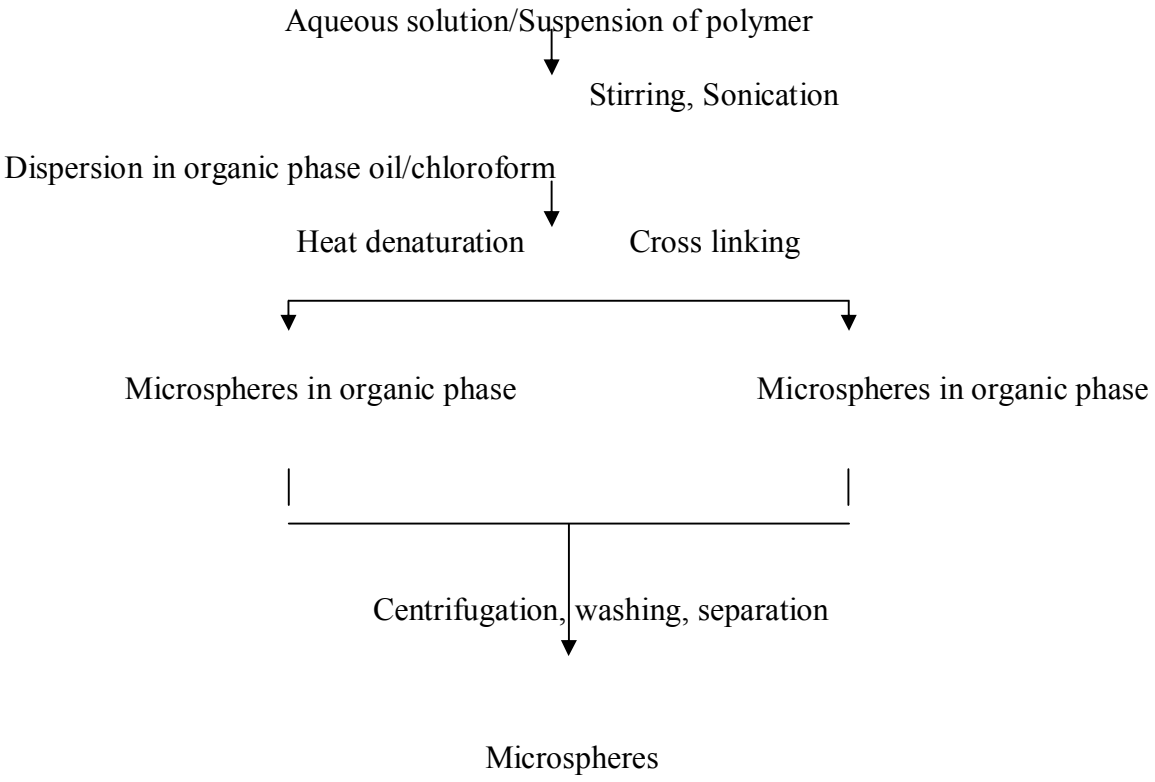

Fig.6 Schematic Representation of Simple Emulsion Method

2. Double Emulsion Method

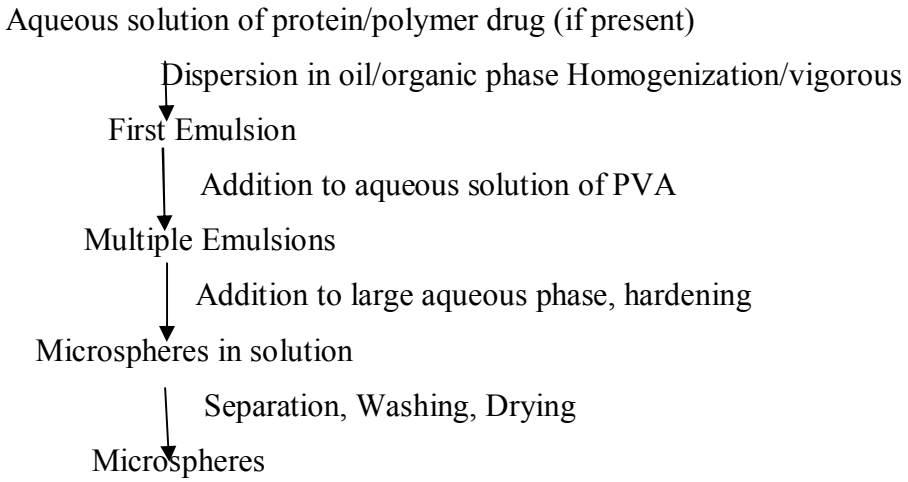

Fig. 7: Schematic Representation of Double Emulsion Method.

3. Polymerisation Technique.

A) Normal Polymerization.

a) Bulk Polymerization.

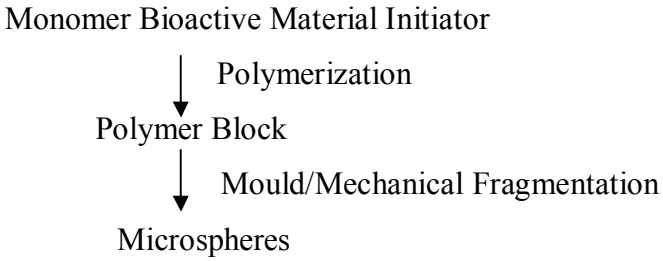

Fig.8: Schematic Representation of Bulk Polymerisation.

b) Suspension Polymerization.

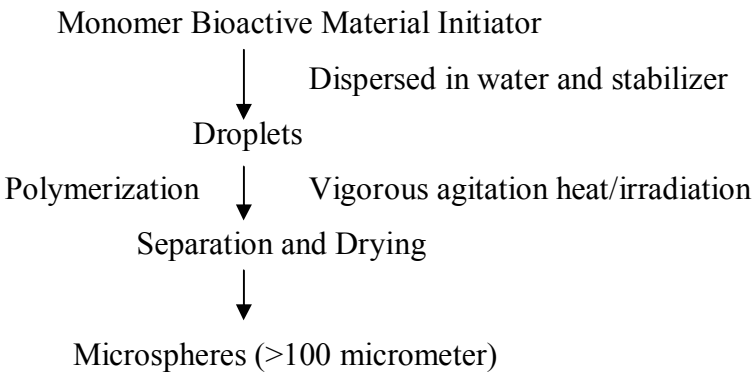

Fig.9: Schematic Representation of Suspension Polymerization.

c) Emulsion Polymerization.

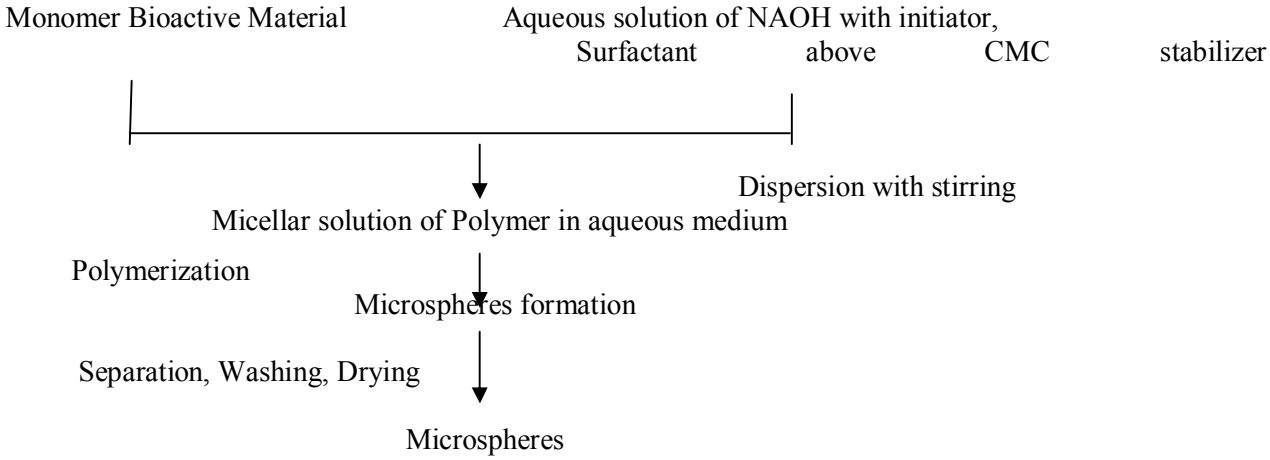

Fig.10 Schematic Representation of Emulsion Polymerization

B) Interfacial Polymerization.

Interfacial polymerization essentially proceeds involving reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelopes the dispersed phase. In this technique two reacting monomers are employed; one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. The continuous phase is generally aqueous in nature throughout which the second monomer is emulsified. The monomers present in either phases diffuse rapidly and polymerize rapidly at the interface.

Two conditions arise depending upon the solubility of formed polymer is the emulsion droplet. If the polymer is soluble in the droplet it will lead to the formation of the monolithic type of the carrier on the other hand if the polymer is insoluble in the monomer droplet, the formed carrier is of capsular(reservoir type).

The degree of polymerization can be controlled by the reactivity of the monomer chosen, their concentration, and the composition of the vehicle of either phases and by the temperature of the system. [23].

4. Phase Separation Coacervation Technique.

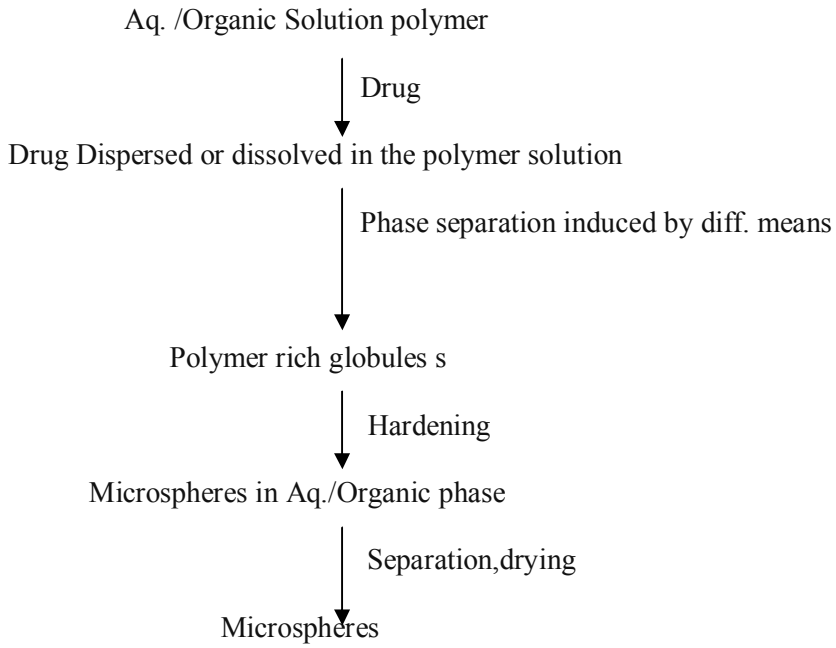

Fig.11: Schematic Representation Phase Separation Coacervation Technique.

5. Solvent Extraction Method.

Solvent extraction method used for the preparation of microparticles,involves removal of the organic phase by extraction of the organic solvent.The method involves water miscible organic solvent such as isopropanol. Ogranic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the water and the solubility profile of the polymer.

Approaches of Design Floating Dosage Forms:

A) Single-Unit Dosage Forms.

In Low-density approach 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 shells 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.

Fluid- filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride.
This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. [22]

B) Multiple Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed.

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.[22]

Advantages Of Floating Drug Delivery System:

1. The Principle of HBS may not limited to any particular medicament or class of medicament The HBS formulations are not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicament, which absorbed from the intestine.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. The HBS are advantageous for drugs absorbed through the stomach.e.g. Ferrous salts, antacids.
4. The efficacy of the medicaments administered utilizing the sustained release principle of HBS formulation has been found to be independent of the site of particular medicaments.

5. 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.
6. Administration of prolongs release floating dosage forms, tablet or capsules, will results in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
7. When there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
8. As sustained release systems, floating dosage forms offer various potential advantages. Drugs that have poor bioavailability because their absorption is limited to upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
9. Floating dosage forms with SR characteristics can also be expected to reduce the variability in transit performance. In addition, it might provide a beneficial strategy for gastric and duodenal cancer treatment.
10. The concept of FDDS has also been utilized in the development of various anti- reflux formulations.[23, 24]

Limitations/Disadvantages Of Floating Drug Delivery System:

1. These systems require a high level of fluid in the stomach for drug delivery tom float and work efficiently-coat, water.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to Gastric mucosa is also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
8. The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm).
9. Floating dosage form should not be given to a patient just before going to bed as the gastric emptying of such a dosage form occurs randomly when the subject is in supine posture. One drawback of hydrodynamically balanced systems is that this system, being a matrix formulation, consists of a blend of drug and low-density polymers. The release kinetics of drug cannot be changed without changing the floating properties of the dosage form and vice versa. [24]

Discussion:

Gestrorertntive systems are vary efficient systems because it can remain in the gastric region for several hours. And hence significantly prolong the gastric residence time of drug. Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Floating Drug Delivery Systems (FDDS) or Hydro dynamically Balanced Systems (HBS) have been developed in order to increase the gastric residence time (GRT).

Conclusion:

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. 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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