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## FLOATING DRUG DELIVERY SYSTEMS: A NOVEL APPROACH

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### ABSTRACT

During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exists today. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, superporous hydrogels and magnetic systems. The current review focuses briefly about the FDDS that is one of the most leading methodologies in gastroretentive drug formulations.

**Keywords:** Floating drug delivery systems, Gastric residence time, Advantages.

### INTRODUCTION

The ultimate goal of any drug delivery system is effective disease/disorder management, minimum side effects and greater patient compliance in the cost effective manner. The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in body in a well-defined controlled manner. This would eliminate the haphazard and uncontrolled blood plasma profiles of drugs usually associated with conventional dosage forms Gastro retentive dosage forms, i.e. those designed to exhibit a prolonged gastric residence time (GRT) have been a topic of interest in terms of their potential for controlled drug delivery [1].

FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine. It is also useful for drugs that act locally in the proximal part of gastrointestinal (GI) tract such as antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer and for drugs that are poorly soluble or unstable in the intestinal fluid [2]. Most of the floating systems previously reported are single unit systems such as tablets and capsules. A drawback of these systems is the high variability of the GI transit time due to their all-or-nothing emptying processes. On the other hand, the multiple-unit dosage forms may be an attractive alternative since they have been shown to reduce the inter- and intra - subject variabilities in drug

absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating systems have been developed in different forms and principles such as air compartment multiple-unit system [3], hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low-density foam powder, beads prepared by emulsion– gelation method [4]. Use of swellable polymers and effervescent compounds is another approach for preparing multiple-unit FDDS [5].

Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres [6].

## FACTORS AFFECTING THE GASTRIC EMPTYING

- Density, size and shape of the dosage form
- Concomitant ingestion of the food and its nature, caloric content and frequency of intake.
- Administration of drugs acting as anticholinergic agent (e.g. Atropine, Propentheline), opoids (e.g. Codeine) and prokinetic agents (e.g Metoclopramide, Isapride)
- Biological factor such as gender, posture, age, sleep, body weight, physical activity and disease states (e.g. diabetes, crohn's disease) [7,8].

## CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems are classified depending up on the two formulations variables Effervescent and Noneffervescent systems.

### a) Effervescent floating dosage forms

These are the matrix types of systems which are prepared by using swellable like methyl cellulose, HPMC and chitosan based polymers as well as various effervescent compounds like Sodium carbonate, Calcium carbonate, Tartaric acid and Citric acid [9]. They are formulated in such a way that when in contact with the acidic gastric contents liberation of CO<sub>2</sub> takes place and gets entrapped in to the swollen hydrocolloids which provides buoyancy to the dosage forms such as Famotidine, Amlodipine besylate which is shown in figure no 1 (a).

### b) Non effervescent floating dosage form

These dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonates, polymetha acrylate and polystyrene<sup>25</sup>. The formulation is done by mixing the drug and the gel-forming hydrocolloid, after oral administration of this dosage form swells while in contact with gastric fluids attains bulk density of <1 [10]. The buoyancy of dosage form was attained due to the air entrapment in to the swollen gel like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass Drugs such as Famotidine, Levodopa which is shown in figure 1 (b).

## METHODS OF PREPARATION OF FLOATING MULTIPARTICULATE SYSTEM

### 1) Solvent evaporation method

Floating multiparticulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing Polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity

and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide and Polycarbonates [11].

Furthermore, a novel multi-particulate gastroretentive drug delivery system based on low-density foam powder has been proposed and its performance demonstrated *invitro*. Floating microparticles consisting of Polypropylene foam powder, Verapamil HCl (as the model drug) and Eudragit RS, Ethylcellulose or Poly (methyl methacrylate) (PMMA) were prepared with an oil-in-water solvent extraction/evaporation method (Figure 2a). The drug and release-rate-controlling polymer were dissolved in Methylene chloride. Polypropylene foam powder was then dispersed within this organic phase. The resulting suspension was subsequently emulsified into an external aqueous Poly (vinyl alcohol) solution and agitated with a stirrer to allow microparticle formation. The microparticles were separated by being sieved, washed with water and dried in a desiccator; they were irregular in shape and highly porous. Importantly, the drug encapsulation efficiency was high and almost independent of the theoretical loading of the system. In all cases, good *in-vitro* floating behavior was observed. Interestingly, a broad spectrum of release patterns could be obtained with the investigated formulations.

Further studies focused on the development of an improved preparation method for this type of lowdensity, foam-based, floating microparticle and also on the demonstration of the system's performances *invitro*. Major advantages of the suggested novel preparation technique include short processing times, no exposure of the ingredients to high temperatures, the ability to avoid toxic organic solvents and high encapsulation efficiencies (close to 100%). Floating microparticles consisting of Polypropylene foam powder, model drug (Chlorpheniramine maleate, Diltiazem HCl, Theophylline or Verapamil HCl) and a second polymer [Eudragit RS or Poly(methyl methacrylate)] were prepared by soaking microporous foam particles with an organic solution of the drug and polymer and subsequent drying (Figure 2b). Good *in-vitro* floating behavior was observed in most cases and a broad variety of drug release patterns could be achieved by varying the drug loading and type of second polymer. In addition, the lowdensity microparticles could be compressed into rapidly disintegrating tablets, providing an easily administrable oral dosage form [12].

### 2) Ionotropic gelation method

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. Since, the use of Alginates, Gellan gum, Chitosan and Carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural

polyelectrolytes in spite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. Biomolecules can also be loaded into these beads under mild conditions to retain their three dimensional structure [13]. The schematic representation of ionotropic gelation method is shown in figure 3.

Talukder, R. et al developed floatable multiparticulate system with potential for intra gastric sustained drug delivery. Cross-linked beads were made by using calcium and low methoxylated pectin (LMP), which are an anionic polysaccharide, Calcium, LMP and Sodium alginate. Beads were dried separately in an air convection type oven at 40°C for 6 hours and in freeze dryer to evaluate the changes in bead characteristics due to process variability. Riboflavin (B-2), Tetracycline (TCN) and Methotrexate (MTX) were used as model drugs for encapsulation. Ionic and nonionic excipients were added to study their effects on the release profiles of the beads [14].

### 3) Emulsion solvent diffusion method

Kawashima and colleagues proposed hollow microspheres (so-called 'microballoons') with drug in their outer polymer shell prepared by novel emulsion solvent diffusion method. Based on Eudragit-S (an enteric polymer), containing the drug in the polymeric shell. The preparation procedure and mechanism of microballoon formation is schematically illustrated in Figure 4. A solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles [15,16].

### FLOATING MICROSPHERES: DEVELOPMENT AND CHARACTERIZATION

Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents, low cost of therapy and ease of administration leads to higher levels of patient compliance. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution

of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres [15].

Over the last three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time. High-density systems having density of ~3 g/cm<sup>3</sup>, are retained in the rugae of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm. Swelling systems are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells [16].

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems. Floating systems first described by Davis (1968), are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period.

While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. The floating drug delivery system can be divided into gas generating and non-effervescent systems. Floatation of drug delivery system in stomach can be achieved by effervescent systems, incorporating a floating chamber filled with vacuum, air or carbon dioxide produced as a result of effervescent reaction between organic acids and carbonates incorporated. These buoyant systems utilize matrices prepared with swellable polymers (e.g. methocel), polysaccharides (e.g. chitosan), effervescent components containing sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. Non-effervescent systems incorporate a high level (20–75% w/w) of one or more gel forming, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, polystyrene) into hollow microspheres, tablets or capsules [17].

Development of Floating Microspheres Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres

are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs [18].

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. Hollow microspheres of Acrylic resins, Eudragit, PMAA, Polyethylene oxide, and Cellulose acetate; Polystyrene floatable shells; Polycarbonate floating balloons and Gelucire floating granules are the recent developments [19].

### Evaluation of the multiparticulate FDDS

#### Friability

Friability of all formulations was determined by using USP friability test apparatus. Friability of the pellet formulations was evaluated over 5 gm of samples in Roche Friabilator at 25 rpm for 4 minutes. Prior to and following the test, the weights of the formulation were accurately recorded and the friability ratios were calculated with following equation.

Percent friability (% F) was calculated as follows,

A loss of less than 1 % in weight is generally considered acceptable for functional coating.

#### Bulk Density and Tapped Density:

A quantity of 5 gm of each formulation was previously lightly shaken to break any pellet agglomerates formed. This quantity was introduced into a 10 ml measuring cylinder. The pellets were carefully leveled without compacting it, and the apparent volume was measured (V<sub>0</sub>). Then cylinder containing sample was tapped using Tap density tester (Veego) for 500 times and the tapped volume was measured to nearest graduated unit. LBD and TBD were calculated using the following formula:  
 LBD = Weight of the pellets / Volume of packing  
 TBD = Weight of the pellets / Tapped Volume of the packing.

#### Hausner ratio:

It provides an indication of the degree of densification which could result from vibration of the feed hopper.

Hausner ratio = Tapped density/ Bulk Density

Lower the Hausner ratio better is the flow property.

#### Compressibility index:

The compressibility of the granules was determined by Carr's Compressibility Index:

Carr's compressibility index (%) = [(TBD-LBD) X 100] / TBD

Where, TBD (Tapped Bulk Density or Tapped Density), LBD (Loose Bulk Density or bulk Density)

#### Content uniformity of coated pellets

Drug content of different formulations was estimated in triplicate. 50 mg of the coated pellets were weighed and crushed in mortar and was transferred to 100 ml volumetric flask. To it, 100 ml methanol was added. The solution was stirred for 1 hr. and filtered through Whatman filter paper no.41, after suitable dilution the drug content was determined spectrophotometrically at 243 nm.

#### Scanning Electron Microscopy (SEM)

The shape and surface characteristics of the pellets were investigated and photographed with help of scanning electron microscopy (JEOL and Tokyo, Japan JSM-6360, Department of Physics, University Pune). Pellets Surface was evaluated before and after coating, at 40X, 45X, 100X & 350 X magnifications.

#### Floating ability

The floating abilities of the coated effervescent-layered pellets, were determined using 250ml beaker containing 50ml 0.1N HCl. Twenty pellets were placed in the medium; the time required to float and duration for how long they remain floating (floating time) were measured by visual observation. The percentage of floating pellets was calculated by the following equation:

Floating pellets (FT %) = number of floating pellets at the measure time / Initial number of the pellets × 100

#### Dissolution study

The USP type-I (rotating basket) dissolution test apparatus (Veego scientific DT 6D). was used to study the drug release from the multiparticulate FDDS at 37.0±0.5 °C, 50 rpm using 900 ml of

0.1N HCl. 20 mg equivalent weight of drug pellets was used for dissolution study. 5 ml aliquot of the dissolution medium was withdrawn at predetermined time intervals of 0.5 hrs and was replaced by equivalent amount of fresh medium kept at same temperature, aliquot solutions were filtered through Whatman filter paper no.-41. The filtrates were analyzed by UV- visible spectrophotometer at 241 nm. Percent drug released in the sample was determined from the standard calibration curve and cumulative percent drug dissolved was calculated using PCP Disso v2.08 software.

The study was performed in triplicate for each formulation [20].

#### **Advantages of Floating drug delivery system**

- The gastroretentive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result 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 floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- The gastroretentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
- When there is a vigorous intestinal movement and a short 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 [21-23].

#### **Application of Floating Drug Delivery Systems**

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. 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. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability. 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.

Hollow microspheres can greatly improve the 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.

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.

Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers. 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. 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 quite beneficial for rheumatic patients.

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 [24].

These are Floating drug delivery other applications summarized as follows.

#### **1. Sustained Drug Delivery:**

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of  $<1$  as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Eg. Sustained release floating capsules of nifedipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

#### **2. Site-Specific Drug Delivery:**

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

**3. Absorption Enhancement:**

Drugs that have poor bioavailability because of sitespecific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption [25,26].

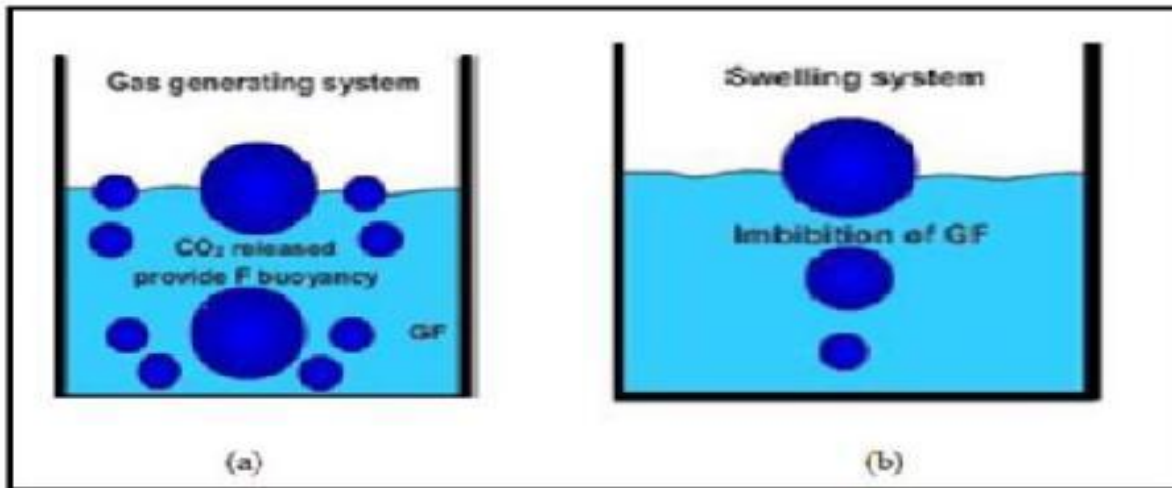
**FUTURE PROSPECTS**

Gastro retentive floating multiparticulate have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. The control of gastro

intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patient.

The market for drug delivery system has come a long way and will continue to grow at an impressive rate. Today’s drug delivery technologies enable the incorporation of drug molecules into a new delivery system, thus providing numerous therapeutic and commercial advantages. Multiparticulate drug delivery systems provide several all the advantages including greater flexibility and adaptability of microparticulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. It is little wonder therefore, that such systems are growing rapidly in popularity.

**Figure 1.** (a) Effervescent Systems (b) Swelling Floating System



**Figure 2:** Schematic presentation of the preparation of floating microparticles based on low-density foam powder, using (a) The solvent evaporation method or (b) The soaking method.

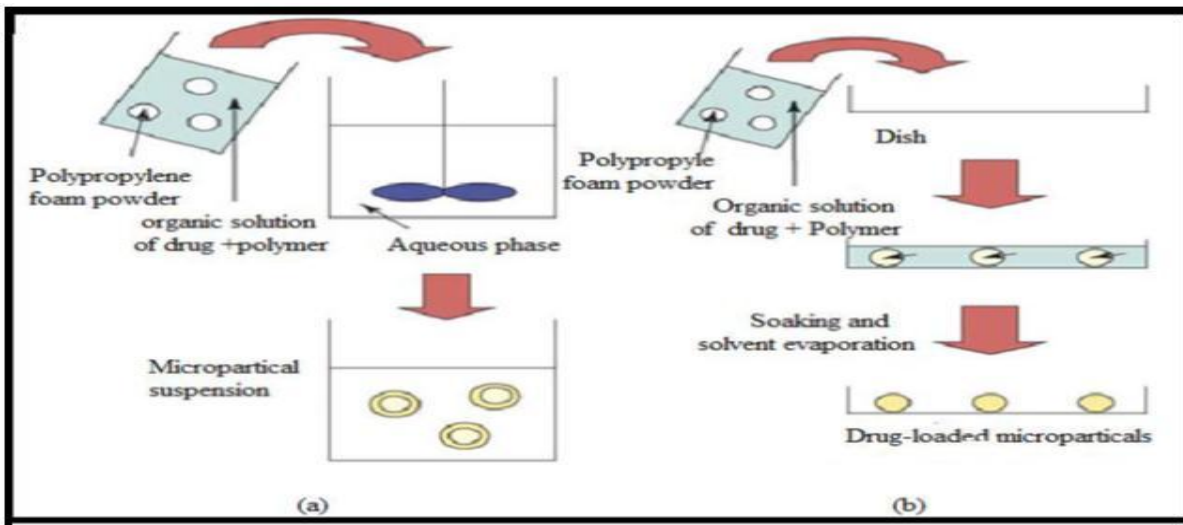


Figure 3. Ionotropic gelation method

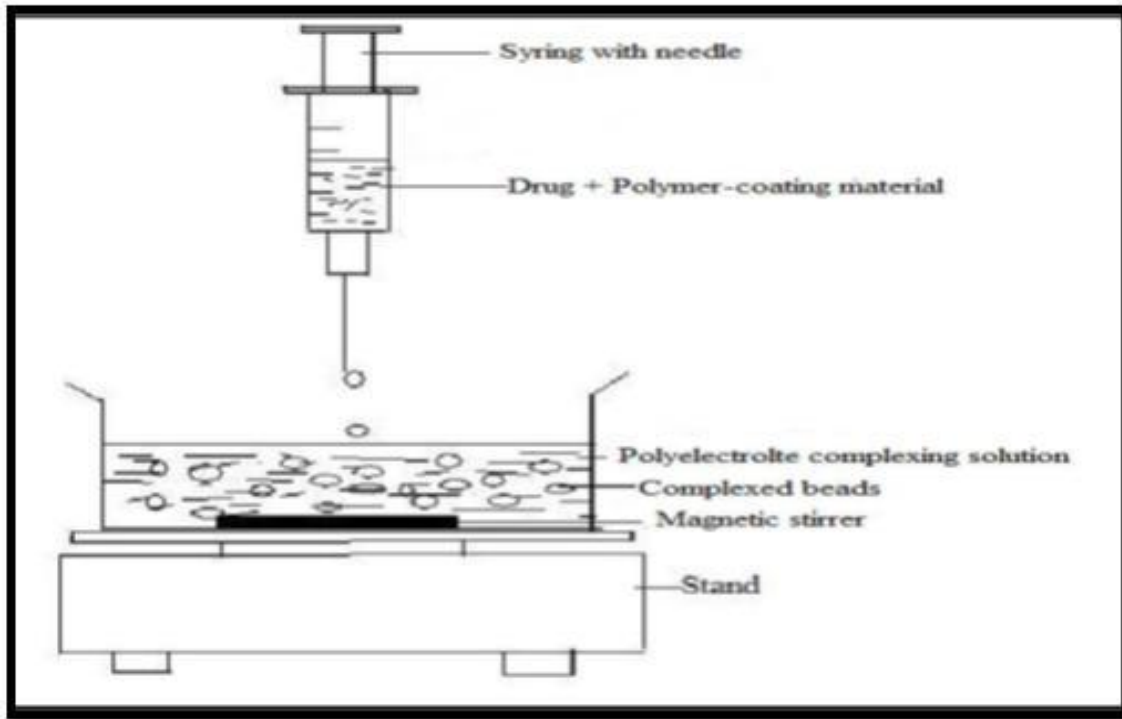
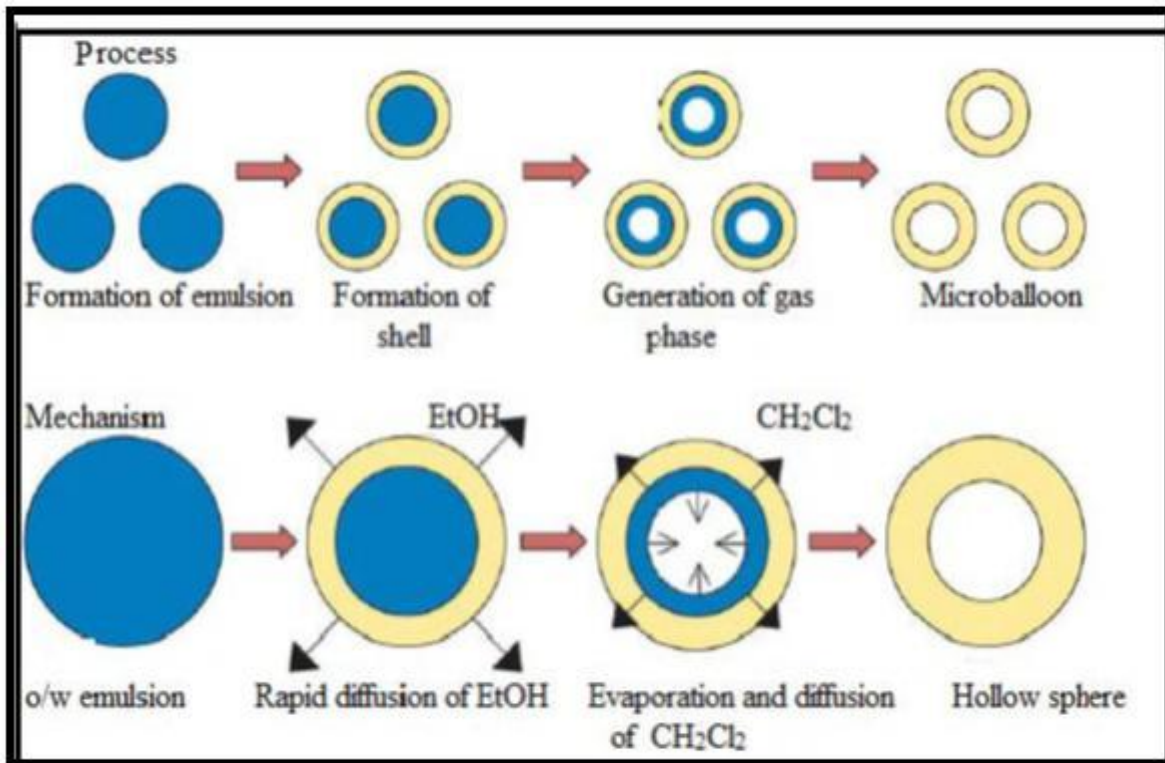


Figure 4. Preparation technique (emulsion-solvent diffusion method) and mechanism of 'microballoon' formation.





## REFERENCES

1. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. *AAPS Pharm. Sci. Technol.*, 2005, 47.
2. Jain SK, Awasthi AM, Jain NK, Agrawal GP. *J. Contr. Release.*, 107, 2005, 300–309.
3. Iannucelli V, Coppi G, Bernabei MT, Cameroni R. *Int. J. Pharm.*, 174, 1998, 47–54.
4. Streubel A, Siepmann J, Bodmeier R. *Int. J. Pharm.*, 241, 2002, 279–292.
5. Ichigawa M, Watanabe S, Miyake Y. *J. Pharm. Sci.*, 80, 1991, 1062–1066.
6. Garg, R. and Gupta GD. Progress in controlled gastroretentive delivery systems. *Trop J Pharm Res.*, 7(3), 2008, 1055- 1066.
7. Kaus LC, Fell JT, Sharma H, Taylor DC. Gastric emptying and intestinal transit of non disintegrating capsules-the influence of metoclopramide. *Int. J. Pharm*, 22, 1984, 99- 103.
8. Bennett CE, Hardy JG, Wilson CG. The influence of posture on the gastric emptying of antacids. *Int. J. Pharm.* 21, 1984, 341-347.
9. Kumar R, Patil MB, Sachin R. Formulation and evaluation of effervescent floating tablet of famotidine. *Int. J. Pharm. Tech. Res.* 1(3), 2009, 754-763.
10. Goole J, Vanderbist F. Amighi. Development and evaluation of new multiple unit levodopa sustained-release floating dosage forms. *Int. J. of Pharmaceutics*, 334, 2007, 35–41.
11. Muthuamy K, Govindarajan G, Ravi TK. Preparation and evaluation of lansoprazole floating micropellets. *Indian J. Pharm. Sci.*, 67(1), 2005, 75-79.
12. Streubel A, Siepmann J, Bodmeier R. Multiple unit gastroretentive drug delivery systems: A new preparation method for low density microparticles. *J. Microencapsul.* 20, 2003, 329-347.
13. Lim F, Sun AM. Microencapsulated islets as bioartificial endocrine pancreas. *Science* 210, 1980, 908–910.
14. Talukder R, Fassih R. Gastro retentive delivery systems: Hollow beads. *Drug Dev. Ind. Pharm*, 30(4), 2004, 405-12.
15. Kawashima Y, Niwa T, Takeuchi H, Hino T. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (*in-vitro*) and floating behaviour (*in-vivo*). *J. Con. Rel.* 16, 1991, 279-290.
16. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J. Pharm. Sci.*, 81, 1992, 135-140.
17. Carstensen JT. *Pharmaceutics of solids and solid dosage forms*, New York 1976, 136, 230.
18. Umamaheshwari RB, Jain S, Bhadra D, Jain NK. Floating microspheres bearing acetohydroxamic acid for the treatment of *Helicobacter pylori*. *Int. J. Pharm*, 55(12), 2003, 1607-1613.
19. Jain NK. *Advances in controlled and novel drug delivery*, CBS Publishers and distributors, New Delhi, 3rd Edition, 71. Chen GL, Hao WH, Factors affecting zero order release kinetics of porous gelatin capsules. *Drug Dev. Ind. Pharm*, 24, 1998, 557-562.
20. Gholap SB, Banarjee SK, Gaikwad DD, Jadhav SL, Thorat RM. Hollow microspher: A review. 1(1), 2010.
21. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. *J. Con. Rel.*, 64, 2000, 39-51.
22. Menon A, Ritschel WA. Development and evaluation of a monolithic floating dosage form for furosemide. *J. Pharm. Sci.*, 83, 1994, 239-245.
23. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith A. *In-vivo* study demonstrating prolonged gastric retention. *J. Con. Rel.*, 55, 1998, 312.
24. Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: Preparation and release characteristics. *Drug Dev, Ind. Pharm*, 27, 2001, 507-515.
25. Fell JT, Whitehead L, Collet H. Prolonged gastric retention using floating dosage forms. *Pharm. Technology*, 24(3), 2000, 82-90.
26. Moursy NM, Afifi NH, Gholap DM, El-Ashtray Y. Formulation and evaluation of sustained release of chitosan microspheres. *Int. J. Pharm*, 249, 2002, 7-21.
27. Yen MK, Jenkins PG, Davis SS, Combs GA. Improvement of delivery capabilities of microparticle systems using blend of poly (D, L-Lactate co-glycoside) poly (ethylene glycol). *J. Cont. Rel*, 37, 1995, 1-9.
28. Lee JH, Park TG, Choi HK. Development of oral drug delivery system using floating microspheres. *J. of Microencapsulation*, 16 (6), 1999, 715-29.
29. Muthusamy K, Govindrajagan G, Ravi TK. Preparation and evaluation of lansoprazole floating micropellets. *Ind. J. Pharm. Sci.* 67(1), 2005, 75-79.