FLOATING MICROSPHERE: AN APPROACH TO ORAL CONTROLLED DRUG DELIVERY VIA GASTRIC RETENTION

Jaiswal Vicky D.*, Gujarathi Nayan A., Rane Bhushan R., Bakliwal Sunil R., Pawar S.P.
Department of Pharmaceutics, P.S.G.V.P.Mandal’s, College of Pharmacy, Shahada, Maharashtra.

ABSTRACT
Although marvelous advancement in drug delivery, oral route remains the preferred route for the administration due to higher levels of patient compliance. But conventional oral dosage forms not suggest control over drug delivery, leading to fluctuations in plasma drug level. A controlled drug delivery system provides not only prolonged residence time in the stomach but also great practical importance for drugs with an absorption window in the upper small intestine. Gastric emptying is a complex process, which is highly variable and makes in vivo performance of the drug-delivery systems doubtful. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 h. The floating or hydrodynamically controlled drug-delivery systems are useful in such applications. The various buoyant preparations include hollow microspheres, granules, powders, tablets, capsules, pills and laminated films. For the targeting of drugs to stomach specially floating microsphere are widely utilized. These floating microspheres have the advantage that they remain buoyant and distributed uniformly over the gastric fluid to avoid the gastric emptying and release the drug for prolonged period of time. The present review addresses briefly the physiology of the gastric emptying process with respect to floating microspheres as drug-delivery systems.

Key words: Floating Microsphere, Gastric Emptying, Floating drug delivery system.

INTRODUCTION
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. The novel design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs [1]. However, the development process is unacceptable by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be expected that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can
last from a few minutes to 12 h. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine \[^{[4-6]}\]. Furthermore, the relatively brief GET in humans, which normally averages 2–3 h through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the friendly contact of DDS with the absorbing membrane not only maximizes drug absorption but also influence the rate of drug absorption \[^{[3, 5]}\]. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities \[^{[2]}\].

High-density systems having density of \(\sim 3 \text{ g/cm}^3\) are retained in the rogue 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\(^3\). 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 \[^{[3, 5]}\]. Bio/Mucoadhesive systems 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 \[^{[7]}\]. Floating system 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 \[^{[10, 11]}\].
Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent and 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\(^7,9\).

Floating drug delivery systems offer a good protection against early and random gastric emptying of non-digestible forms\(^16\). These systems remain buoyant on the gastric content for extended periods of time because of their low densities compared to that of the gastric fluid\(^12\). Floating dosage forms can be classified as single- and multiple-unit system. For conventional oral sustained or prolonged-release dosage forms, multiple units are more advantageous than single units because they disperse widely and uniformly along the gastrointestinal tract and could less intra- and inter-subject variability. For gastric-retentive systems, multiple units may have the advantage of avoiding all-or-nothing emptying, and increase the probability that some of the dosage form will remain in the stomach\(^20,22\).

**Gastrointestinal retention**

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention reduces drug waste, improves bioavailability, 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\(^25,29\).

To profitably modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) for maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. These are outlined and briefly discussed\(^11\).
Need of Gastroretention $^{[10, 11, 64]}$

- Drugs that are absorbed from proximal part of GIT.
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to stomach and proximal small intestine to treat certain conditions.
- Particularly used for the treatment of peptic ulcers caused by $H. pylori$ infections.

Stomach anatomy

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. It has been reported that the mean value of pH in fasted healthy subjects is $1.1 \pm 0.15$. But when food comes into the stomach, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basal gastric secretion in women is slightly lower than that of men $^{[58]}$.

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 myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (Basal phase) lasts from 30 to 60 minutes with unusual contractions.
2. Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles\textsuperscript{[43]}. 

![Figure 1: Motility pattern in GIT](image)

**FACTORS AFFECTING THE GASTRIC EMPTYING**

1. Density, size and shape of the dosage form\textsuperscript{[12-14]}.
2. Concomitant ingestion of the food and its nature, caloric content and frequency of intake\textsuperscript{[15,16]}.
3. (Simultaneous) administration of drugs acting as anticholinergic agent (e.g., Atropine, Propentheline), opioids (e.g., Codeine) and prokinetic agents (e.g., Metoclopramide, Isapride)\textsuperscript{[57]}.
4. Biological factor such as gender, posture, age, sleep, body weight, physical activity and disease states (e.g., diabetes, crohn’s disease)\textsuperscript{[48]}.

**SUITEABLE DRUG CANDIDATES FOR FLOATING GASTRORETENTION**\textsuperscript{[27, 31, 32]}

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. 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.

1. Narrow absorption window in GI tract, e.g., Riboflavin in a vitamin Deficiency and Levodopa.
2. Primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.
3. Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
4. Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
5. Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.

APPROACHES TO GASTRORETENTION

Several techniques are reported in the literature to increase the gastric retention of drugs [16, 19].

1. High density systems

These systems, which have a density of ~3g/cm³, are retained in the rugae of stomach and capable of withstanding its peristaltic movements. The only major drawback with
these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.42.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation[16].

2) Swelling and expanding systems

These systems are also called as “Plug type system”, since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state[21].

By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon 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 cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer [22].

3) Incorporating delaying excipients
Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system [2].

4) Modified systems
Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device [36].

5) Mucoadhesive & bioadhesive systems
Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a sitespecific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most exceptional excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc [25, 26].

6) Floating systems
Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach
can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas [46,34].

**Figure 5**
The mechanism of floating systems

**Mechanism of floating systems**
Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. 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 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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain
the submerge object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations \(^{[62, 63]}\).

Figure 6

Mechanism of floating systems, GF= Gastric fluid

**CLASSIFICATION OF FDDS BASED ON MECHANISM OF BUOYANCY**

A) Single unit

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract \(^{[65, 66]}\).

Noneffervescent systems

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules \(^{[1, 29]}\). For the preparation of these types of systems, the drug and the gelforming hydrocolloid are mixed thoroughly. 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 \[^{19, 66}\].

**Effervescent systems or gas generating systems**

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, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 \[^{56, 66}\].

**B) Multiple unit**

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the ‘all-or-none’ gastric emptying nature of single unit systems. It reduces the intersubject variability in absorption and the probability for dose dumping is lower \[^{2, 64}\].

**Noneffervescent systems**

A little or no much report was found in the literature on noneffervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

**Effervescent systems**
A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radiolabeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 hr32 [2, 9, 47].

Floating microspheres
A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, Eudragit® S and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymerplasticizer ratio [47].

**TABLE 1: LIST OF FLOATING MICROSPHERE’S MARKETED PREPARATIONS**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Brand name</th>
<th>Drug (dose)</th>
<th>Company (Country)</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Conviron</td>
<td>Ferrous Sulfate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>2.</td>
<td>Cytotee</td>
<td>Misoprostol (100/200 mcg)</td>
<td>Pharmacia</td>
<td>Bilayer capsule floating</td>
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<td></td>
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<td></td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>3.</td>
<td>Topalkan</td>
<td>Al-Mg Antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid alginate preparation</td>
</tr>
<tr>
<td>4.</td>
<td>MODAPAR</td>
<td>Levodopa (100mg) Benserzide (25mg)</td>
<td>Roche products (USA)</td>
<td>Floating CR Capsules</td>
</tr>
<tr>
<td>5.</td>
<td>Liquid Gavison</td>
<td>Al Hydroxide (95mg) Mg carbonate (358mg)</td>
<td>Glaxo SmithKline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>6.</td>
<td>Valrelease</td>
<td>Diazepam (15mg)</td>
<td>Hoffmann-la Roche (USA)</td>
<td>Floating capsules</td>
</tr>
</tbody>
</table>

Mechanism of gastroretention
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 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 is needed to allow proper achievement of buoyancy \[49\].

**MATERIALS AND METHODS FOR PREPARATION OF FLOATING MICROSPHERES**

**A) MATERIALS**

Polymers and other ingredients
Following types of ingredients can be incorporated for preparation of floating microsphere in addition to the drugs \[5, 37\].

1. Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, Chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC.

2. Inert fatty materials (5%-75%): Edible, inert fatty materials having a specific gravity of less than 1 can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
3. Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine)).
4. Release rate accelerants (5%-60%): eg lactose, mannitol
5. Release rate retardants (5%-60%): eg Dicalcium phosphate, talc, magnesium stearate
6. Buoyancy increasing agents (upto 80%): eg Ethyl cellulose
7. Low density material: Polypropylene foam powder (Accurel MP 1000®).

B) METHODS

Solvent Evaporation

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The solvent Evaporation technique is shown in Figure 6. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made [41, 42, 65].
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 \cite{57, 65}. The natural polyelectrolytes inspite, 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 \cite{64, 65}. The schematic representation of ionotropic gelation method is shown in figure 8.
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 no. 8. 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 floating microsphere \(^{42,43}\).
Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. a number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction \([51, 55, 59]\).
PROCESS VARIABLES AFFECTING PHYSICOCHEMICAL PROPERTIES OF FLOATING MICROSPHERES

Stirring rate

To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying agitation speeds; 300 rpm, 500 rpm, 1000 rpm. The size of the resulting microspheres decreased with increasing agitation, but the increase was not statistically significant. It may be inferred that the agitation speed in the study range was not able to break up the bulk of the polymer into finer droplets \[45\].

Temperature of preparation

Optimum preparation temperature is required to microsphere cavity formation. To observe the effect of temperature on microsphere, the solution drug and polymer were poured into an aqueous solution of polyvinyl alcohol at various temperatures, i.e., 20, 30, 40 and 50 °C. It concluded that preparation at 20 or 30°C provided porous microspheres having higher porosity with a surface so rough as to crumble upon touching. Although the respective apparent particle densities of the resulting hollow microspheres were low, both buoyancies were low, probably due to easy penetration of the dissolution medium through the porous surface. The roundness of hollow microspheres prepared at 40 °C was
close to 1; moreover, surfaces were less rough than those of hollow microspheres prepared at 20 or 30 °C. Hollow microspheres prepared at 50 °C exhibited no hollow nature; however, a single large depression occurred on the surface. The hollow microspheres possessed high apparent particle density and low buoyancy due to the absence of a cavity. Few traces of evaporation were observed on the surface, which was attributable to the rapid evaporation of dichloromethane at temperatures beyond the boiling point (40.2 °C). At 40 °C, polymers and the drug were co precipitated, and the shell was formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane. In contrast, hollow microspheres prepared at 50 °C demonstrated a single large depression on the surface, which was a consequence of the rapid evaporation of dichloromethane

Plasticizers

The effect of plasticizer concentration on the surface of microspheres and on the release of the drug was reported that the addition of plasticizer made the wall of material more elastic and flexible, so that it never got brittle or ruptured under pressure. It was also observed that the release of the drug increased significantly with the increase of plasticizer concentration.

Volume of aqueous phase

Jain has studied the effect of various volumes on the formation of hollow microspheres. Volumes of aqueous phase used were 200, 300, 400 and 500 ml they observed that the potential advantage of using large volumes of the external aqueous phase was the reduction of the required stirring times. The solubility of dichloromethane in water is 1% w/v. Using a larger volume (400 to 500 ml), the diffusion of dichloromethane into the aqueous phase, and hence the solidification of particles, occurred faster, when compared to a volume of 200 ml.

Solvent ratio

The bridging liquid plays a key role in microsphere preparation. When a good solvent diffuses into the poor solvent, which causes the precipitation of the drug and the polymer,
a bridge liquid must be present in order to maintain the spherical shape of the microsphere. Too small a volume of the bridging liquid can lead to irregularly shaped microspheres while too large a volume of bridging liquid could prevent the emulsion droplets from solidifying. Therefore, the amount of dichloromethane needs to be carefully controlled.\cite{33}

The ratio of dichloromethane with ethanol also affected the morphology of the microspheres and the best results with spherical shape were obtained when the ratio of ethanol to dichloromethane was 2:1 \cite{26}.

Amount of polymer and viscosity

It was reported that the effect of polymer concentration on in vitro release of aceclofenac from floating microspheres. If increased in density of the polymer matrix at higher concentrations results in increased diffusion path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release \cite{52}.

Srivastava, Ridhurkar and Wadhwa prepared microspheres using a gradually increasing ethyl cellulose concentration in combination with a fixed concentration of hydroxy propyl methyl cellulose (HPMC) to assess the effect of polymer concentration on the size of microspheres. Mean particle size of the microspheres significantly increased with increasing ethyl cellulose. The viscosity of the medium increases at a higher polymer concentration, resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles \cite{23}. When viscosity is increased, the yield of hollow microspheres is decreased, and mean diameter and drug loading amount are increased.

Effect of solvents

Various organic solvents used in the formation of microspheres by the solvent evaporation method. Dichloromethane was employed as polar internal organic solvent phase for preparation of microspheres because it is a good solvent for most of polymers
and drugs. However, it was observed that the microspheres obtained were not at all spherical in shape. To solve this problem, methanol was used, along with dichloromethane, in the preparation of microspheres. The microspheres so obtained were spherical, but lacked smooth texture. To avoid this problem, various solvents were critically screened on the basis of the boiling points, such as dichloromethane (39.75 ºC), acetone (56.5 ºC), methanol (64.7 ºC) and ethanol (78.4 ºC). It was observed that the boiling point increased from DCM to ethanol and so instead of DCM/methanol, ethanol was tried. Ethanol is a good solvent for most water-soluble drugs and water-insoluble polymers, and it is non-toxic. It remained dispersed as droplets in the oily phase, leading to the formation of a stable emulsion. Ethanol may have worked because it has a high boiling point in relation to other organic solvents (dichloromethane, acetone, methanol etc.), which prevented immediate polymer precipitation. The researchers observed that the microspheres so obtained were completely spherical, with a smooth surface \[38, 64\].

Emulsifier concentration

Effect of emulsifier concentration on particle size reported that the particle size and size distribution were increased when the surfactant concentration was reduced from 1% to 0.25% (w/w). The role of the surfactant is to decrease the interfacial tension between the dispersed droplets and the continuous phase, as well as to protect the droplets from collision and coalescence. Low emulsifier concentrations may be insufficient to shield the entire droplet surface; droplets are more susceptible to collision and fusion. Also, at higher concentration of emulsifier, lower encapsulation efficiency and larger particle size were obtained, which suggests that the critical micelle concentration had been exceeded, which directly affected emulsion stability. Hence, the optimum concentration of the emulsifier should be identified \[32, 46\].

Release modifiers

Many drugs are not released in significant amount from this type of floating microsphere at the pH of gastric fluids. So, there is a need for some hydrophilic polymers to be added into the formulation. Various agents, such as HPMC, citric acid, PVP, PEG, etc.,
depending upon their properties, can be used to modify the drug release. These are also called as channeling agents.

It was studied the effect of different viscosity grades of HPMC on the drug release profile by using three different grades of HPMC in combination with various ratios of ethyl cellulose-to-HPMC. The various grades used were HPMC 15cp, HPMC K4M, and HPMC 100LV. The best release was found to be with the lowest viscosity grade of HPMC (HPMC 15cp) when compared to the other two viscosities (HPMC 100LV and HPMC K4M) [26].

CHARACTERIZATION OF THE FLOATING MICROSPHERE

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior show prolonged gastric residence in vivo. Although, in vitro floating behavior alone is not sufficient to proof for efficient gastric retention so in vivo studies can provide definite proof that prolonged gastric residence is obtained [10].

1) Particle size and shape

Size is measured using an optical microscope, and mean particle size is calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer.

Different sizes of microspheres and their distribution in each batch are measured by sieving in a mechanical shaker, using a nest of standard sieves (ASTM) and the shaking period of 15 minutes. Particle size distribution is determined and the mean particle size of microspheres is calculated by using the following formula [42].

\[
\text{Mean particle size} = \frac{\sum (\text{mean particle size of the fraction} \times \text{weight fraction})}{\sum (\text{weight fraction})}
\]

(1)

2) Tapped density and compressibility index

The tapping method is used to determine the tapped density and percentage compressibility index, as follows [23].
3) Surface morphology

The external and internal morphology of the microspheres is studied by scanning electron microscopy (SEM).

The % Yield was calculated from the following equation \[^{[30]}\].

\[
\text{% Yield} = \left( \frac{\text{weight of hollow microspheres}}{\text{weight of drug taken} + \text{total polymer weight}} \right) \times 100
\]

4) Percentage of drug content / drug loading amount (%)

A fixed amount of microspheres containing a drug are dissolved in a suitable solvent such as ethanol, methanol, etc. by ultrasonication. The solution is then filtered through a 5 µm membrane filter. Finally, drug concentration is determined by the UV, spectrophotometrically. Drug content is calculated according to following equation \[^{[48]}\].

\[
\text{% drug content} = \left( \frac{\text{weight of drug in microspheres}}{\text{weight of microspheres recovered}} \right) \times 100
\]

5) Percentage of drug entrapment

The percentage of drug entrapment can be calculated by the following equation.

\[
\text{% drug entrapment} = \left( \frac{\text{calculated drug concentration}}{\text{theoretical drug content}} \right) \times 100
\]

6) Floating behavior

The floating test on the microspheres is carried out using the dissolution method II apparatus, specified in the USP XXII. The microspheres are spread over the surface of the dispersing medium (900 ml), which is agitated by a paddle rotated at 100 rpm. Disintegration test solution No. 1 (pH 1.2), containing Tween 20 (0.02%, w/v), was used as a dispersing medium to simulate gastric fluid. After agitation for a previously determined interval, the hollow microspheres that floated over the surface of medium and those that settled to the bottom of the flask were recovered separately. After drying, each
fraction of the hollow microspheres was weighed. The buoyancy of the hollow microspheres was represented by the following equation \[^{[50]}\].

\[
\text{buoyancy} (\%) = \frac{Q_f}{Q_f + Q_s} \times 100
\]

Where \(Q_f\) and \(Q_s\) are the weights of the floating and settled hollow microspheres, respectively.

7) In-vitro release studies

The release rate of floating microsphere was determined in dissolution apparatus. A weighed amount of floating microspheres equivalent to Dose of drug is taken and placed in the basket of dissolution rate apparatus. The dissolution fluid was maintained at 37 ±1°C at a rotation speed. Perfect sink conditions prevailed during the drug release study \[^{[52, 53]}\].

8) In-vivo studies

The in-vivo floating behavior can be investigated by X-ray photography of hollow microparticulate loaded with barium sulphate in the stomach of beagle dogs. The invitro drug release studies are performed in a dissolution test in a dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models \[^{[17]}\].

ADVANTAGES OF FLOATING MICROSPHERE \[^{[54, 65]}\]

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
3. Better therapeutic effect of short half-life drugs can be achieved.
4. Gastric retention time is increased because of buoyancy.
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Enhanced absorption of drugs which solubilise only in stomach.
8. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
9. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through floating microsphere system.

LIMITATION \[^{[2,66]}\]

Some of the disadvantages were found to be as follows

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.
3. Differences in the release rate from one dose to another.
4. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed

APPLICATIONS OF FLOATING MICROSPHERES \[^{[2,17,47]}\]

1. 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. Hollow microspheres of non-steroidal anti-inflammatory drugs are very effective for controlled release, and reduce the major side effect of gastric irritation. For example, floating microspheres of indomethacin are quite beneficial for rheumatic patients.
3. Floating microspheres are especially effective in the 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 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 the risk of solubility becoming the rate-limiting step in release, by restricting such drugs to the stomach. Positioned gastric release is useful for drugs efficiently absorbed
through the stomach, such as verapamil hydrochloride. The gastroretentive floating microspheres will beneficially alter the absorption profile of the active agent, thus enhancing its bioavailability.

4. 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.

**FUTURE SCOPE OF FLOATING MICROSPHERES DRUG DELIVERY SYSTEMS**

Floating microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate *Helicobacter pylori* from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. This system allows administration of non-systemic, controlled release antacid formulation containing Calcium carbonate and also locally acting anti-ulcer drugs (such as Lansoprazole) [42, 65]. In stomach buoyant floating microsphere are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

Floating microspheres may be used as a carrier for the drugs having narrow absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are absorbed only from very specific regions of GI tract. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin, low molecular weight Heparin and LHRH. Floating microsphere of NSAIDs is very effective for reducing their major side effect, gastric irritation as well as for controlled release; for example floating microspheres of Indomethacin are quite beneficial for rheumatic patient [29, 65].
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. Floating controlled drug delivery systems are employed to solve this problem. Floating microspheres have been showing high potential for gastro retention and provide an efficient means of enhancing bioavailability and controlling the release 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.

REFERENCES


For Correspondence:
Mr. Jaiswal Vicky D.
Email: jaisvicky300688@gmail.com