Classification, Method of preparation and Characterization of Floating Microspheres.

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ABSTRACT

Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuation in plasma drug concentration. The oral route achieved such popularity due to its ease of administration but has drawback of non-site specificity. GRDDS providing better bioavailability to poorly absorbed drugs, Floating microspheres is to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. These systems are useful in overriding the several problems encountered during the development of a pharmaceutical dosage forms. The purpose of this review is to focus on the recent advances in the field of formulation, characterization, evaluation and applications of floating microspheres in the area of gastro retentive dosage forms. Floating microspheres is one of several approaches to gastro retention, like mucoadhesion flotation, sedimentation, expansion, modified shape system etc. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.

Keywords: Floating Microspheres, preparation methods, GRDDS, Evaluation.

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INTRODUCTION

The development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [9]. The relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. 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 improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment [1-3]. Depending on the proteinoid amino acid composition the size range of the microsphere is 0.1-10mm. Drug is entrapped within the microspheres by inducing phase transition in the drug solution. The microspheres are stable in acidic and enzymatic environment until the pH reaches the titration point, at this point microsphere undergo spontaneous dissociation and thereby release their contents [5]. The most important characteristics of microsphere is the micro phase separation morphology which endows it with a controllable variability in degradation rate and also drug release [6].

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

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. 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 inter digestive 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), which is further divided into following 4 phase:

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

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.

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.

Phase IV lasts for 0-5 minutes and occurs between phases III and I of 2 consecutive cycles. [7]. After the ingestion of a mixed meal, the pattern of contractions change from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slowdown of gastric emptying rate [4].
Mechanism of 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 (given in the Figure 1 (a)), 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 submerged object. The object floats better if F is on the higher positive side (Figure 1(b)). 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 [7].

\[ F = F_{buoyancy} - F_{gravity} = (D_f - D_s) \cdot g \cdot v \]  -- (1)

Where, \( F = \) total vertical force, \( D_f = \) fluid density, \( D_s = \) object density, \( v = \) volume and \( g = \) acceleration due to gravity.

![Figure 1: Mechanism of floating systems (A) Swelling system (C) Gas generating system Conventional v/s Gastro retentive drug delivery system [8]](image)

<table>
<thead>
<tr>
<th>Conventional drug delivery system</th>
<th>Gastro retentive drug delivery system</th>
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<tr>
<td>1. High risk of toxicity</td>
<td>1. Low risk of toxicity</td>
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<tr>
<td>2. Less patient compliance</td>
<td>2. Improve patient compliance</td>
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<tr>
<td>4. Not much advantageous for</td>
<td>4. Very much advantageous for</td>
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<tr>
<td>• Drugs having rapid absorption through GIT</td>
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<td>• Drugs having rapid absorption through GIT</td>
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<td>• Drugs which are poorly soluble at an alkaline pH</td>
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<tr>
<td>5. No risk of dose dumping</td>
<td>5. Risk of dose dumping</td>
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TYPES OF FLOATING DRUG DELIVERY SYSTEM [4]

FDDS can be divided into two systems:

- Effervescent systems
- Non-effervescent systems

Effervescent Systems

Volatile liquid containing systems:

Intragastric floating gastrointestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in (Figure 2).

Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid (Figure 3) [4,24].
Intragastric osmotically controlled drug delivery systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapors and liquid and has a drug delivery orifice. The osmotically active Compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach [4,24].

Figure 4: Intragastric osmotically controlled drug delivery system [24]

Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. These buoyant systems can be prepared by using swellable polymers like ethocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swell able hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and
Polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc [4].

Non-Effervescent Systems: This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the ‘plug type systems’ since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains are relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [4].

Colloidal gel barrier systems: Hydro-dynamically balanced system (HBS) was first design by Sheath and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swell able cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymers such as polycarbophil, polycrylates and polystyrene, incorporated either in tablets or in capsules. 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 to this dosage forms [4].

Micro porous Compartment System: This technology is based on the encapsulation of drug reservoir inside a micro porous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed top regent 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 [23].
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 into aqueous solution so of calcium chloride, causing precipitation of calcium alginate. The beads are then separated, snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of a porous system, which can maintain an floating force over 12 h [23].

Hollow microspheres: The ethanol, dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h in vitro [1].

E.Raft Forming GF System: Raft forming systems have received much attention for drug delivery for gastrointestinal infection and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low density created by the formation of CO₂. Usually, the system ingredients include a gel forming agents and alkaline bicarbonates or carbonates responsible for formation of CO₂ to make the system less dense and float on gastric fluids [7,2].

METHODS OF PREPARATION OF MICROSPHERES

- Emulsion solvent evaporation technique
- Emulsion cross linking method
- Coacervation method
- Spray drying technique
- Emulsion-solvent diffusion technique
Multiple emulsion method
- Ionic gelation method
- Hydroxyl appetite (HAP) microspheres in sphere morphology [17]

**Emulsion solvent evaporation technique:** In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with de mineralized water and desiccated at room temperature for 24 hrs. Aceclofenac microspheres were prepared by this technique [17].

**Emulsion cross linking method:** In order to improve the residence time in colon floating micro particles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a desiccators’ at room temperature. The following micro particles were sieved and collected [17].

**Coacervation method**

**Coacervation thermal change:** Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80°C by heating. Then the drug was finely pulverized and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

**Coacervation non solvent addition:** Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propyl isobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin.14 times with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50°C for 4 hr [17].

![Figure 9: Formation of a coacervate around a core material](image)

**Spray drying technique:** In this technique polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then
dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air, this form small droplets or the fine mist, from which the solvent evaporates instantaneously leading the formation of the microspheres. The size range is 1-100 μm. By using hot air separate of Microparticle by means of the cyclone separator while the traces of solvent are removed by vacuum drying. Advantages of the process are feasibility of operation. This technique is very useful to encapsulate various penicillin’s [21].

**Emulsion-solvent diffusion technique:** In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible (Figure11). The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes.

**Multiple emulsion method:** 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 lipophillic 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 [10,12].

**Ionic gelation method:** Ionotropic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form beads. Since, the use of alginates, gellan gum, chitosan and carboxy methyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural poly electrolytes 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. The schematic representation of ionotropic gelation method is shown in Figure 12 [4].

![Figure 12: Ionotropic gelation method [4]](image)

**Hydroxyl appetite (HAP) microspheres in sphere morphology**

This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w Emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic Phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co-solvencing and helped them to stay individual droplets. While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres [17].

**EVALUATION PARAMETERS OF FLOATING MICROSPHERES**

**Micro-meritic properties:** Floating microspheres are characterized by their micromeritic properties such as angle of repose, tapped density, compressibility index, and true density and flow properties. 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. The hollow nature of microspheres is confirmed by scanning electron microscopy. The compressibility index is calculated using following formula:

\[ I = \frac{V_b - V_t}{V_b} \times 100 \]

Where, \( V_b \) is the bulk volume and \( V_t \) is the tapped volume [4].

**Particle size and shape:** The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of micro particles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled system [10].

**3. Floating behavior:** A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a desiccators’ and weighed. The buoyancy is calculated from the following formula.

\[ \text{Buoyancy (\%)} = \frac{W_f}{W_f + W_s} \times 100 \]

Where \( W_f \) and \( W_s \) are the weights of floating and settled microspheres respectively [7].

**Entrapment efficiency:** The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation [17].

\[ \% \text{Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100 \]

**In-Vitro Release Studies:** The release rate of floating microspheres were 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 in to 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 [1].
**In-Vivo 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-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs) [1].

**ADVANTAGES & DISADVANTAGES OF FLOATING MICROSPHERES** [1,5,20,23]

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<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
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<tbody>
<tr>
<td>1 The gastroretentive systems are advantageous for the drugs that are primarily absorbed through the stomach, e.g. ferrous salts, antacids.</td>
<td>1 Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.</td>
</tr>
<tr>
<td>2 The gastro retentive systems are advantageous for the drugs that are meant for local action in the stomach. E.g. antacids.</td>
<td>2 Floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.</td>
</tr>
<tr>
<td>3 When there is a vigorous intestinal movement and a short transit time such as in certain type of diarrhea, poor absorption is expected. Under such conditions it may is advantageous to retain the drug in stomach to get a relatively better response.</td>
<td>3 Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.</td>
</tr>
<tr>
<td>4 The FDDS are advantageous for drugs absorbed through the stomach e.g.: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.</td>
<td>4 The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo extensive first pass metabolism, may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability.</td>
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<tr>
<td>5 Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.</td>
<td>5 Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.</td>
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**Applications** [11, 12, 16, 21, 22]

**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, e.g., riboflavin and furosemide.

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

**Microspheres in vaccine delivery:** Improved antigenicity by adjuvant action, Modulation of antigen release. Stabilization of antigen.

**Monoclonal antibodies mediated microspheres targeting:** Monoclonal antibodies are extremely specific molecules. Mabs can be directly attached to the microspheres by means of covalent coupling.
Intratumoral and local drug delivery: In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films were fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible.

Reduced fluctuation of drug concentration: The fluctuation in plasma drug concentration is minimized and concentration dependent adverse effect that associated with peak concentration be prevented.

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.

REFERENCES