

## Review on Floating Microsponges: An Updated

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**Abstract**

Floating microsponges are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several essential drugs. Floating microsphere greatly improves the therapy of stomach by releasing the drug locally and thus used for drug targeting at particular organ. This can be sustained over a longer duration of time. Floating drug delivery (FDDs) permit prolonged and continuous release of the drug to the upper part of Gastro intestinal tract (GIT) and this expressively extend the duration of drug release and improve bioavailability of drugs that have narrow therapeutic window, by this technique dosing frequency and patient compliance is increased. The purpose of this paper is to briefly describe the floating microsphere drug delivery (FMDD), factors related to Floating Drug Delivery, its advantages disadvantages, and emphasis is given over its significance over conventional form of drug deliveries.

**Keywords:** GRDFs, FMDD, GIT.

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**Introduction****Floating Drug Delivery System (FDDS)**

Oral route is most preferable route of drug delivery due to easy administration, flexibility in formulation, low cost and patient compliance. Oral controlled release drug delivery system shows some limitation associated with gastric emptying time. Too rapid and variable gastric emptying could results in incomplete drug release from dosage form into absorption window leading to low efficacy of administered dose[1]. Controlled release drug delivery system (CRDDS) provide drug release at a predictable, predetermined and controlled rate. CDDS is capable to maintain optimum drug concentration in the body for extended time period, increase activity of duration for short half-life drugs, reduced dosing frequency, reduced side effects and drug wastage and better patient compliance[2]. Prolong gastric retention improves solubility of drug (that are less soluble in a high pH environment), reduces drug wastage and improves bioavailability. Floating drug delivery system has application for local drug delivery to the stomach[3].

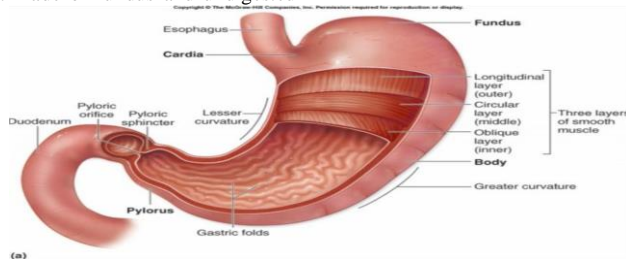
**Basic Gastrointestinal Tract Physiology**

For the development of Gastroretentive drug delivery system must have knowledge of physiology of gastrointestinal tract. Anatomically the stomach is divided into 3 parts- (1) fundus, (2) body and (3) antrum (pylorus) The proximal part made of fundus and undigested

material store in body so body acts as reservoir, and antrum (pylorus) is the responsible site for mixing motion and acts as a pump, cause gastric emptying[4].

**Stomach Physiology**

The main function of stomach is to process and transport the food. It act as a short-term storage reservoir, enzymatic digestion started in stomach where various juices mix with food which are produced by gastric smooth muscles and resulting in liquefaction of food and it is released for small intestine for further process[2]. Stomach is part of digestive system which is located between oesophagus and small intestine. Structurally the wall of stomach is similar to the other parts of the digestive tube but stomach has an extra oblique layer of smooth muscle inside the circular layer which facilitates the motion inside the stomach. When stomach is empty, it is contracted and its mucosa and sub mucosa are thrown up into distinct folds known as rugae[4]. Gastric emptying occurs during both fasting as well as fed states. The pattern of motility is differing in both states. Interdigestive series of electrical events take place during fasting state, which cycle both through stomach and intestine every 2 to 3 hours. This is known as interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into 4 phases which are following-

**Fig-1 Anatomy of gastrointestinal tract[4]**

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Table 1: Various phases of activity in migrating myoelectric cycle

Phase no.	Phase name	Activity
Phase 1	Basal phase	This phase is lasting from 30 to 60 minutes with rare or no contractions.
Phase 2	Preburst phase	This phase consist intermittent action potential and contractions. That gradually increases intensity and frequency as phase progress and it lasts for 20 to 40 minutes.
Phase 3	Burst phase	This phase have short period of intense and regular contractions and these waves are responsible for swept out of undigested material from stomach to the small intestine. And these waves are also known as the housekeeper wave. Burst phase lasts for 10 to 20 minutes.
Phase 4		This phase occurs between phases III and I of 2 consecutive cycles and last for 0 to 5 minutes[4].

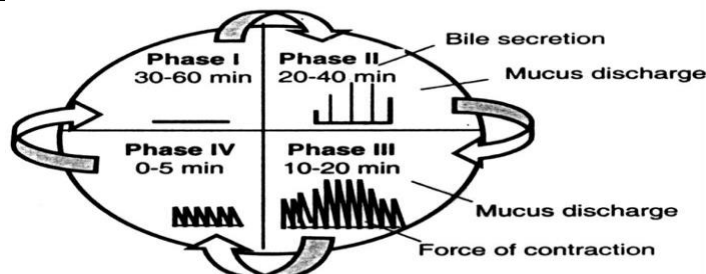


Fig.1: Four connective phases of activity in migrating myoelectric complex[4]

**Factors Affecting Gastric Residence Time of FDDS[4]****(A) Formulation factor**

- **Density:** Floating dosage forms have density less than gastric fluid, i.e. less than 1.0g/ml and this property cause distance between pyloric sphincter and dosage form and the dosage unit is retained in the stomach for a longer time. For describing its floating capabilities the bulk density of a dosage form is not the most appropriate parameter, floating force kinetics of such dosage form has shown that.
- **Shape:** The shape of dosage form is also important factors that affect its gastric residence time. Ring, tetrahedron, cloverleaf, string, pellet, and disk these are six shapes were screened *in vivo* for their gastric retention potential.
- **Viscosity grade of polymer:** Floating properties and drug release of FDDS is greatly affected by viscosity of polymers which are used in formulation, polymers interaction also affect floating property of formulation. Instead of high viscosity polymers (e.g. HPMC K4M) low viscosity polymers (e.g. HPMC K100 LV) were found to be more beneficial in improving floating property. Increase in polymer viscosity cause decreased drug release.

**(B) Idiosyncratic factors**

- **Age:** Gastric emptying time is changed according to age of subject. Elderly subjects gastric emptying is lower than younger subjects. Other variation is also observed like Intrasubject and intersubject variations in gastric and intestinal transit time. Elderly people those over 70 years have longer GRT.
- **Gender:** Gastric emptying time is slower in female than male.
- **Posture Upright position:** This position protects floating against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements while the floating dosage forms show prolonged and more reproducible GRTs.
- **Supine position:** In supine position both conventional and floating dosage form retained prolong. The gastric retention of floating forms appears to remain floated anywhere between the lower and higher curvature part of the stomach. These units may be swept away by the peristaltic movements, on moving distally and that move the gastric contents towards the pylorus.
- **Concomitant intake of drugs:** Drugs such as anti Cholinergics (e.g., atropine) prokinetic agents (e.g., metoclopramide and cisapride), opiates (e.g., codeine) may affect the properties of floating drug delivery system. Sometime administration of GI-

motility decreasing drugs with other drugs can increase gastric emptying time.

- **Feeding regimen:** Gastric residence time is increase in presence of food, while the empty stomach decreases gastric residence time. A GRT is increasing 4 to 10 hours after taking fats and proteins in meal.

**Drugs Suitable For Gastroretention [5]**

Appropriate candidates for controlled release gastroretentive dosage forms are those which have poor colonic absorption but having better absorption properties at the upper part of the GIT. Sustained release in the stomach is better technique for drugs which are not readily absorb in stomach or upper part of small intestine, sense sustained release formulation increase contact time of drug in stomach and also enhance drug absorption.

- Drugs having Narrow absorption window in GI tract, like riboflavin and levodopa.
- Drugs which are locally acting the stomach, like antacids.
- Drugs degrade in the colon, like ranitidine HCl and metronidazole.
- Drugs absorbed from upper part of GIT and stomach, like hlordiazepoxide and Cinnarazine.
- Drugs disturb normal colonic bacteria, like amoxicillin, Trihydrate.

**APPROACHES TO GASTRORETENTION[5,6]**

There is following approaches to get gastroretention

- High density system
- Swelling and expanding systems
- Incorporating delaying excipients
- Modified systems
- Mucoadhesive & bioadhesive systems
- Floating systems

**High density system:** This type of gastro retentive formulation were prepared by using high density polymers. And having density ~3g/ml are retained in stomach and capable of withstanding its peristaltic movements.

**Swelling and expanding systems:** Also known plug type system, since they show tendency to remain logged in the pyloric sphincters. Controlled and sustained drug release can be achieved by selection of polymer with the proper swelling properties and molecular weight. Once it coming in contact with gastric fluid the polymer suck water and swells. This ability of polymers cause gastroretention and controlled release of drug.

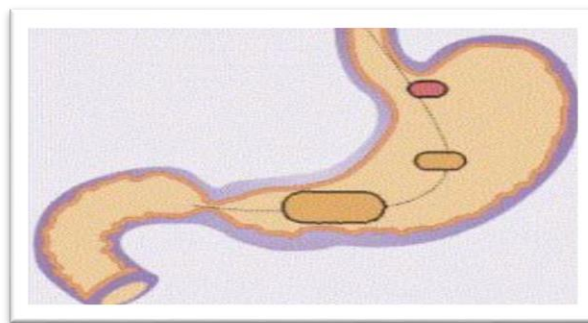
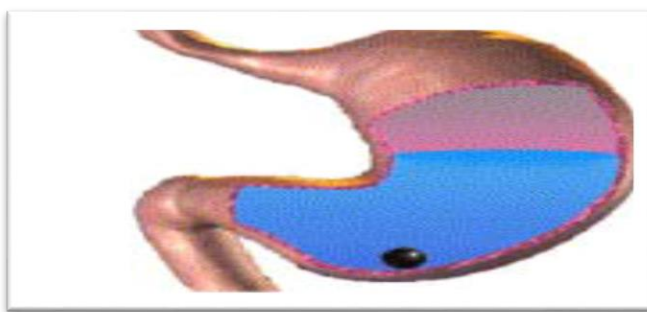


Fig. 2: High density systems Fig. 3: Swellable tablet in stomach[2]

**Incorporating delaying excipients:** It is also an important approach for gastroretention. It include feeding of digestible polymers or fatty acid salts that changes the motility pattern and increase gastric retention, also incorporating delaying excipients like trietanolamine myristate in a delivery system.

**Modified systems:** This system consists non disintegrating geometric shape molded from silastic elastomers. Which increase the GRT depends on shape, size and flexural modules of drug delivery device.

**Mucoadhesive & bio adhesive systems:** Mucoadhesive approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some example of mucoadhesive polymers are polycarbophil, carbopol, lectins, chitosan, CMC and gliadin. This approach is used for localised action in stomach.

**Floating systems:** Density of floating drug delivery system is less than gastric fluid so remain floated in stomach for longer time without affecting gastric emptying rate. Drug is released slowly at the desired rate from the system. After release of drug residual system were emptied from the stomach. Floation of a drug delivery system in the stomach can be achieved by incorporating low density polymers, floating chamber filled with vacuum, air or inert gas.

#### Advantages of Floating Dosage Form[5]

- This system is especially advantageous for those drugs which are absorbed from stomach or the proximal part of the small intestine, e.g., furosemide and riboflavin.
- The fluctuations in plasma drug concentration are minimized and side effect associates with concentration are also minimized.
- Complete absorption of drug from the floating formulation is expected even at alkaline pH of intestine. The dissolution occurs in gastric fluid and after emptying of the stomach contents the dissolved drug is available for absorption in small intestine.
- Because of site-specific absorption from the upper part of the GIT, Drugs that have poor bioavailability are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.
- FDDS improves patient's compliance by reducing dosing frequency.
- Better therapeutic effect achieved from short half-life drugs.
- Because of buoyancy gastric retention time is increased.

- Increase absorption of drugs which are only solubilize in stomach.
- Because of sustained release effect, floatability and uniform release of drug through multi particulate system avoiding gastric irritation.

#### Limitations of Floating Drug Delivery Systems[5]

- Drugs which have poor solubility and unstable in acidic medium are poor candidates for FDDS.
- FDDS required high level of fluid in stomach for floating of dosage form.
- Drugs which are irritant to Gastric mucosa are also not suitable for FDDS.
- Drugs which under goes first pass metabolism may not be desirable for the preparation of these types of systems, e.g.- nifedipine.

#### Classification of Floating Drug Delivery System (FDDS)[7,8]

Based on formulation variables FDDS is classified into two types:

- Effervescent floating dosage forms.
- Non-effervescent floating dosage forms.

**Effervescent systems:** This type of system is also known gas generating system, 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. , CO<sub>2</sub> is liberated and gets entrapped in swollen hydrocolloids when formulation comes in the contact of gastric fluid, which provides buoyancy to the dosage forms. The best stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

**Non-effervescent systems:** This type of system is prepared by mixing drug and gel forming hydrocolloids. After oral administration when dosage form comes in the contact of gastric fluid it will swell and attains a bulk density of <1 g/ml. The air entrapped within the swollen matrix cause buoyancy of formulation. And it is act as a sustained release reservoir. These system use gel forming, swellable cellulose type hydrocolloids and matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. e.g.- hollow microspheres or micro balloons.

Table 2: Difference Between Conventional and Gastroretentive Drug Delivery[9]

S. No.		Conventional DDs	GRDDs
1	Drug which have Narrow absorption window in Small intestine	Not suitable	Good candidates for GRDDs
2	Drugs with Rapid absorption through GIT	Not much Beneficial	Very much beneficial
3	Drug having	Not much	Very much

	degradation in colon	Beneficial	beneficial
4	Drugs which acting locally in the stomach	Not much Beneficial	Very much beneficial
5	Drugs having poor Solubility at an alkaline pH	Not much Beneficial	Very much beneficial
6	Dose dumping	There is High risk of dose dumping	But there is no risk of dose dumping
7	Toxicity	High possibility of Toxicity	Low possibility of Toxicity
8	Patient compliance	Less	Increases Patient compliance

### Microsponge

Microsponges are tiny sponge like micron size spherical particles and contain active pharmaceutical ingredient. Microsponges consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface[10]. Microsponges drug delivery system provide controlled release of active ingredients, it provides various advantages over other technology like improved product stability, reduced side effects, increased elegance and increased formulation flexibility. Microsponges are mostly used for topical administration and recently for oral administration also. They can be incorporated in to conventional dosages forms like ointments, creams, lotions, gels, tablets and powder and provide broad package of benefits and thus provide formulation flexibility. Microsponges are ranging from 5-150  $\mu\text{m}$ [11].

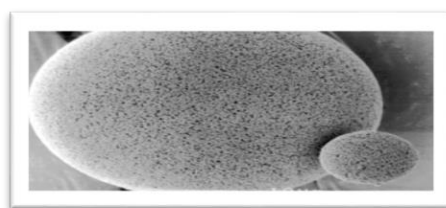


Fig.4: View of microsponge [12]

### Advantages of Microsponges[11,12]

When microsponges are applied to the skin, it releases its active ingredients slowly to the skin on a time mode and also it is activated such as rubbing, temperature and pH effect etc. with excellent efficacy and minimized irritation. Advantages of microsponges are as follow:

- pH stability- these formulations are stable over a range of pH 1-11.
- Temperature stability- these are stable at the temperature up to 130°C.
- Compatibility- these are compatible with most vehicles and ingredients.
- Self-sterilising- because their average pore size is 0.25 $\mu\text{m}$  where bacteria cannot penetrate.
- Higher payload- these have higher payload (50% to 60%).
- Microsponges are free flowing.
- Microsponges provide continuous action up to 12 hours i.e. extended release.
- Microsponges are cost effective.
- It can absorb oil up to 6 times its weight without drying.
- Microsponge drug delivery system improves bioavailability.

### Limitation of Microsponges[13]

- Absorption of traces of residual monomers may cause toxic effect in the body.
- The preparation methods mostly use Organic solvents as porogens, which cause an environmental hazard, as some may be highly inflammable, causing a safety hazard.

### Advantages of Microsponges Over Other Technologies and Delivery Systems[11]

#### Advantages over microencapsulation and liposomes

Microcapsules and liposomes cannot control drug release because once the wall of liposome is burst the API within microcapsule will be released. Liposomes have lower payload, tough in formulation, chances of microbial growth and limited chemical stability. While microsponges drug delivery system (MDDS) have several benefits in contrast of above system. Such as,

- MDDS has pH stability between the range of 1 to 11 and temperature up to 130°C.
- Better compatibility with maximum vehicles and ingredients.
- It has self-sterilizing property because average pore size is 0.25 $\mu\text{m}$ , where bacteria can't penetrate.
- MDDS has high payload
- And formulation of microsponge is cost effective.

**Advantages over conventional formulation:** Conventional formulation of topical drugs are planned to work on outer layer of skin. Such product will release their API after application of high concentration of API. In compare to conventional system MDDS avoid accumulation of API with in epidermis and dermis. Potentially the MDDS can decrease significantly the irritation of active drug throughout decreasing the efficacy.

**Advantages over ointment:** Ointments are aesthetically unattractive, greasy, and sticky that often results in lack of patient compliance. Efficacy of this delivery system is low hence requiring high concentration of API for effective therapy.

Some other drawbacks of topical formulation which are uncontrolled like evaporation of API, disagreeable odour and potential incompatibility of drug with vehicle. Whereas microsponges system maximize contact time of API with epidermis and reducing its transdermal penetration into the body.

### Properties of Drugs That is Entrapped into Microsponges[12]

Certain considerations are taken while selecting excipients for formulation of microsponges in order to achieve desired product characteristics:

- The drug should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- Drug should be either fully miscible in monomer as well as having ability to be miscible by addition of small amount of a water immiscible solvent.
- Spherical structure of the microsponges should not be collapse.
- Drug should be water immiscible or slightly soluble.
- The solubility is also an important factor it should be limited, if not the vehicle will empty the microsponges before the application.
- Polymerization catalyst should not affect the stability of drug.



- For release control payload and polymer design of the microsponges for the active must be optimized.

#### Method of Preparation[33,41]

Microsponges preparation takes place in one or two step process based on physiochemical properties of drug to be incorporated in microsponges. If the drug is porogens i.e inert non-polar substance which will generate the porous structure, it should not stop the polymerization process or become activated by it. So microsponges from porogens drug can be prepared by one step process (liquid-liquid suspension polymerization)

There are two methods for preparation of microsponges:

- Quasi-emulsion solvent diffusion
- Liquid-liquid suspension polymerization

#### Quasi-emulsion solvent diffusion[39,41]

This method is most widely used for preparation of microsponges. Quasi-emulsion solvent diffusion method includes two phases as internal and external phase, an internal phase containing polymer such as eudragit S 100 dissolved in dichloromethane (organic solvent). Then with the help of ultrasonication process drug dissolve in polymer solution. External phase was prepared with continuous stirring of distilled water and polyvinyl alcohol for adequate period of time. After that internal phase poured in to external phase and stirred for 3 hrs. Microsponges are then separated by filtration. Finally, the microsponges are washed and dried in an air heated oven at 40°C for 12 h.[13,14]

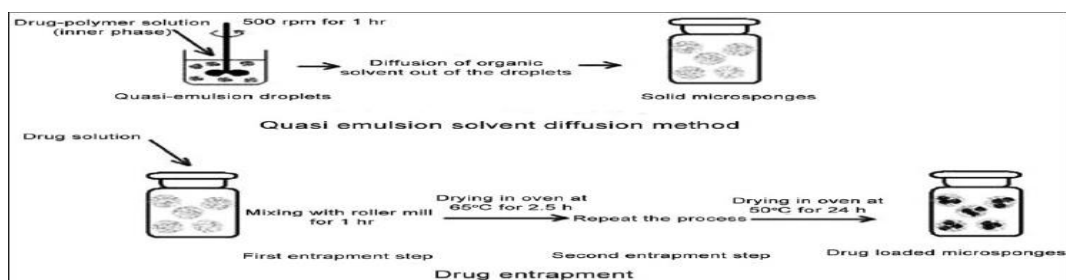


Fig.5: Preparation of microsponges by the quasi-emulsion solvent diffusion method[12]

Table 3: List of Marketed Products Based on Microsponges [15,16,49-56]

Manufacturer	Therapeutics Uses	Product name
Dermik Laboratories, Inc.	Actinic keratoses	Carac Cream
AMCOL Health & Beauty Solution	Soothing, Anti-Wrinkles	Glycolic Acid Moisturizer w/SPF 15
Intendis Inc. Morristown NJ07962 USA	Microwash provide gradual release of active ingredient into skin and absorb natural skin oils. Benzoyl peroxide is an oxidizing agent that posses	NeoBenz@Micro, Neo@MicroSD NeoBenz@ antibacterial properties.
Avon	Anti-wrinkle Line	Eliminator Dual Retinol Facial Treatment
Ortho-McNeil Pharmaceutical, Inc	Micro Acne	Retin A vulgaris
Sothys	Anti-wrinkles Retinol 15	Night cream
SkinMedica Inc	Hyper pigmentation	EpiQuin Micro
Biomedic	Helps maintain healthy skin	Retinol cream
John and Ginger Dermalogica Skin Care Products	Lotion Skin protectant	Dermalogica Oil Control
Dermalogica	20 Sunscreen	Oil free matte block SPF
Biophora	20 Excellent exfoliation	Salicylic Peel
SDR Pharmaceuticals, Inc	Moisturizing Cream Moisturizer	Lactrex™ 12%
Scott Paper Company	Protects baby's skin	Ultra-Guard

**Evaluations of Floating Microsponges** [16,17,18,19,26,45-49]

- ❖ Angle of repose
  - ❖ Bulk density
  - ❖ Tapped density
  - ❖ Compressibility index
  - ❖ Hausner's ratio
  - ❖ Particle size analysis
  - ❖ Encapsulation efficiency
  - ❖ *In-vitro* dissolution study
  - ❖ Scanning electron microscopy (SEM)
  - ❖ *In-vitro* buoyancy.
- **Angle of Repose:** This evaluation parameter has been performed by allowing the powder to fall over the graph sheet placed on horizontal surface through a funnel kept certain conventional height (about 2 cm). The height of heap has been measured and then perimeter of the base of the heap has been drawn on a graph sheet with the help of pencil. Then radius of circle has been calculated. The angle of repose is given as:  

$$\Theta = \tan^{-1}(h/r)$$
  - **Bulk Density:** It has been measured by pouring the pre-weighted powder into a measuring cylinder and initial volume was noted as bulk volume. The powder has been tapped 3 times till a constant volume called bulk density has been obtained. From this, the bulk density is calculated according to formula given below. The unit of bulk density is gm./ml.  

$$P_i = M/V_i$$
  - **Tapped Density:** After determining the poured bulk density weighed quantity of microsponges has been taken into a graduated cylinder. Volume occupied by microsponges has been noted down. Then the cylinder has been subjected to 500, 750 & 1250 taps. % volume variation has been calculated and subjected for additional 750 taps, % variation is calculated.  

$$P_t = M/V_t$$
  - **Compressibility Index:** Weighed microsponges has been transferred to 100 ml graduated measuring cylinder and subjected to 500, 750, and 1250 taps in tap density tester. Less than 2% difference should be observed between two taps. It is calculated by following formula-  

$$I = V_o - V_t / V_o \times 100$$
 Where  $V_o$  is bulk volume and  $V_t$  is tapped volume
  - **Particle size analysis:** Optical microscope is used to perform particle size analysis on microsponges formulation. Initially stage micrometer and eye piece micrometer were adjusted properly and then calibration factor has been determined. Then microsponges were taken on a slide and size has been observed and noted.  
 Calibration factor = eye piece micrometer division/ stage micrometer division  $\times 100$
  - **Encapsulation efficiency:** Take 10mg of microsphere formulation and dissolve in 10 ml 0.1 HCl and subjected to ultrasonication for 20 min at 25°C then the sample was filtered and analysed.  

$$\% \text{ Encapsulation efficiency} = (A/T) \times 100$$
 A = Actual amount of drug present in pre weighted quantity of microsponges.  
 T = Theoretical amount of drug present in microsphere.
  - **Scanning Electron Microscopy (SEM):** Surface characteristics of API and micro-sphere formulation has been checked by SEM. Samples have been fixed on a brass tube using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 Kev accelerating voltage.
  - ***In-vitro* Buoyancy:** The buoyancy of microsponges increased with decrease in density of microsponges. So microsponges formed with high quantity of eudragit have been more buoyant than those formed with less.

**Conclusion**

After study of many literatures, it may be concluded that floating drug delivery offers various potential advantages for drug with poor bioavailability due to their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered competently thereby maximizing their absorption and enhancing absolute bioavailability. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the inflection of controlled oral drug delivery. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life.

Microsphere system offers the potential to hold API in a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract. In oral application, the microspheres system has been shown to increase the rate of solubilisation of poorly water soluble drug by entrapping such drug in the microsphere system's pores. Because these pores are very small, the drug in effect reduced to microscopic particles with resultant increases in surface area and thus greatly increases the rate of solubilizing. An added benefit is that floating microsphere increase gastric retention time thus bioavailability of drug is increased.

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