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# Microballoons: A Review

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**ABSTRACT:** The purpose of this review is to accumulate the recent study on floating drug delivery system with special emphasis on microballoons as drug delivery. Microballoons are emerging as the most promising drug delivery as it overcome many limitations of conventional drug delivery system. As micro balloons delivery system provides longer retention in gastric pH, hence longer is the residence time and therefore enhance the solubility of drugs that are less soluble in high pH environment. The formation of cavity inside the microsphere depends upon the preparation temperature and the surface smoothness determines the floatability and the drug release rate of the microballoons. The review includes the classification, advantages, disadvantages, method of preparation and future aspects of microballoons,basic anatomy and physiology of stomach also studied

**KEY WORDS**: microballoons, gastroretentive, gastrictime, buoyancy

## I. INTRODUCTION

Microballoons are the gastro retentive drug delivery system and it is based on the non-effervescent approach. Generally microballoons are in spherical shape without core. These microballoons are free flowing powder which consists of protein and synthetic polymers and these microballoons size ranges from 200 µm. These microballoons are low density system which have sufficient buoyancy to float over the gastric fluid for prolonged period of time without any irritation to gastro intestinal tract.1Microballoons are prepared by using different techniques such as simple solvent evaporation method, double emulsion method, phase separation coacervation method, polymerization method, spray drying method, spray congealing method and hot melt encapsulation method.[1]

### Gastroretentive drug delivery systems (GRDDS)

Dosage forms that can be retained in stomach for longer periods of time are called gastroretentive drug delivery systems (GRDDS). GRDDS are suitable and beneficial for such drugs by improving their absolute bioavailability, therapeutics efficiency, increase gastric residence time (GRT), possible reduction of the doses reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.[2]

### Floating drug delivery system:

Many floating systems have been generated based on granules, powders, capsules, tablets, laminated films, beads and hollow microspheres [3, 4] . It can be classified into two systems.

### Effervescent System:

Volatile liquid containing systems (Intragastric floating GRDDS) Gas-generating Systems (Intra gastric single layer and bilayered floating tablets, Multiple unit type floating pills)

### Non-Effervescent Systems:

Hydro colloidal gel barrier systems Micro porous compartment Hollow Microspheres: Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (micro-balloons) are in strict sense, spherical empty particles without core.[6] These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle F

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**Hollow Microspheres:**

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (micro-balloons) 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 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. [6] Hollow microspheres are considered as one of the most promising buoyant systems , as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general 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 were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. [7] Hollow microspheres / microballoons loaded with drug in their outer polymer shelf were prepared by a novel solvent evaporation or solvent diffusion/ evaporation method to create a hollow inner core4(fig 1). The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution edia containing surfactant for more than 12 hours. [8,9]At present hollow microspheres are considered to be one of the most promising buoyant systemssystem Alginate and pectin beadsHollow Microspheres: Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (micro-balloons) 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 200µm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle

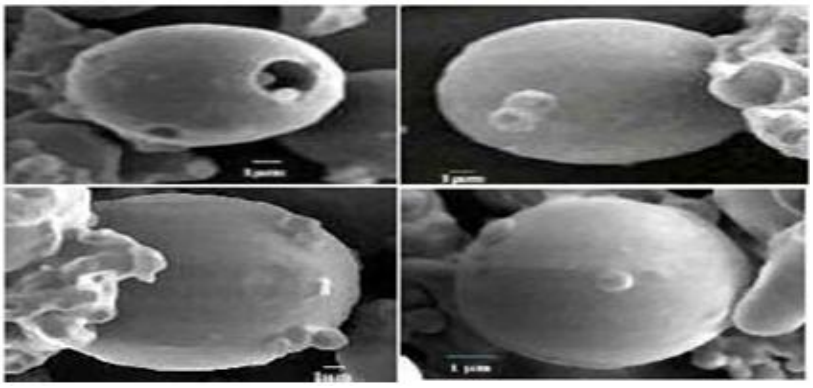

Figure 1 : Hallow microballoons

## II. ADVANTAGES OF MICROBALLOONS

1. Improves patient compliance by decreasing dosing frequency.

2. Gastric retention time is increased because of buoyancy.

3. Enhanced absorption of drugs which solubilise only in stomach

4. Drug releases in controlled manner for prolonged period.

5. Site-specific drug delivery to stomach can be achieved.

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Vol. 7, Issue 1 , January 2020

6. Superior to single unit floating dosage forms as such microspheres releases drug uniformly

and there is no risk of dose dumping.

7. Avoidance of gastric irritation, because of sustained release effect.

8. Better therapeutic effect of short half-life drugs can be achieved.

## III. MECHANISM of FLOATING MICROBALLOONS

When microballoons come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy.[10]

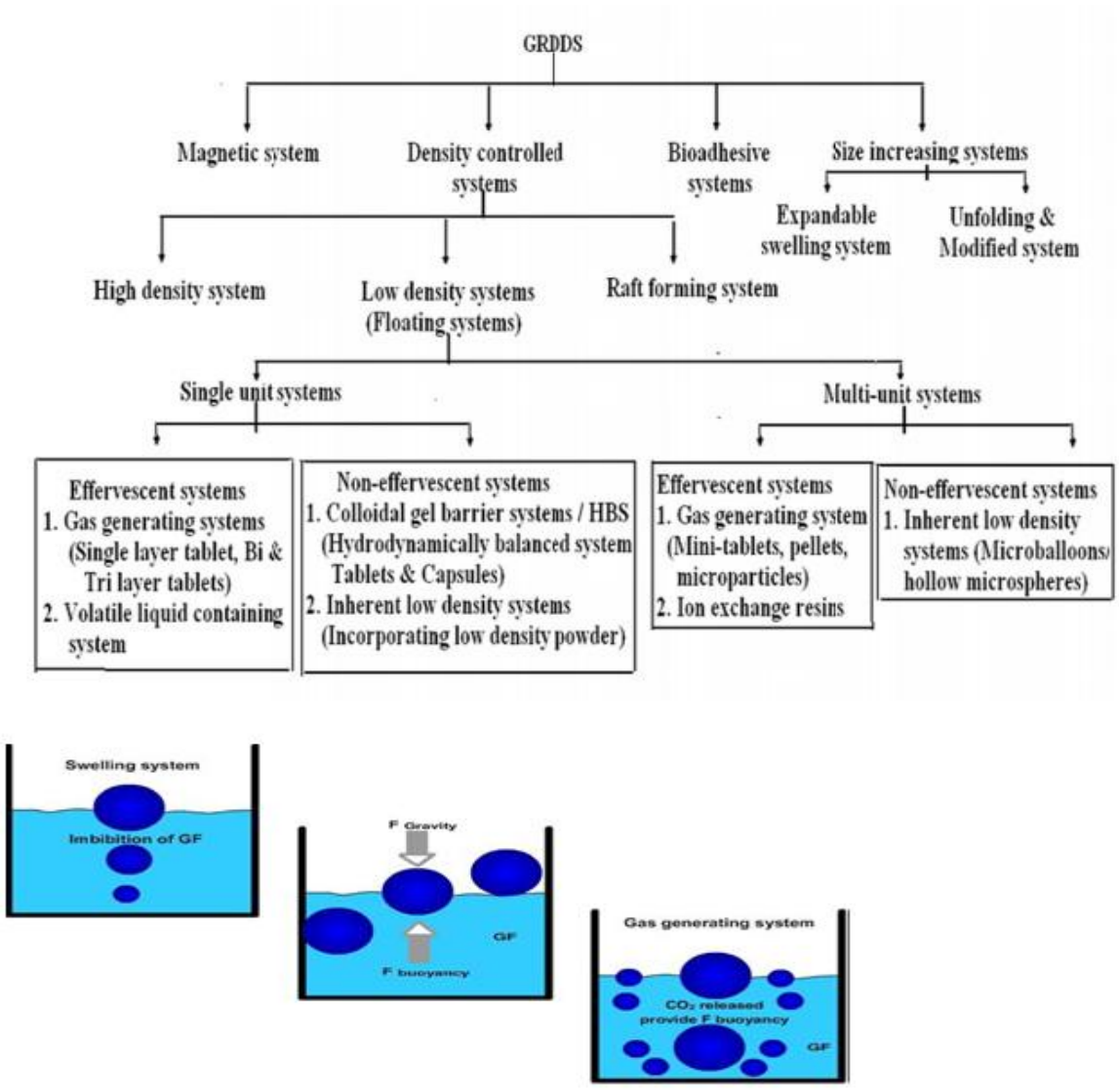


Figure no:2 Mechanism of floating systems, GF= Gastric fluid

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Vol. 7, Issue 1 , January 2020

**Development:**

Floating microspheres are gastro retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer.[11] Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs.

## IV.PREPARATION OF MICROBALLOONS

These micro-balloons are exclusively free flowing powders comprising of proteins or non-biodegradable polymers, usually having a size less than 200 microns. Solid biodegradable microspheres include a drug dissolved or dispersed uniformly through the matrix of particles having the prospective for prolonged drug release. Micro-balloons are manufactured by the method of solvent diffusion and evaporation methods to fabricate the empty or hollow inner core. The polymer is usually dissolved in an organic vehicle and the drug is preferably dissolved or dispersed in the polymer solution.[12,13] The solution having the drug is then subjected to emulsification into an aqueous phase containing polyvinyl alcohol to make oil in water emulsion. After the initiation of a stable emulsion, the organic solvent is now evaporated by increasing the temperature under pressure or by stirring continuously. The removal of solvent leads to precipitation of polymer at the o/w interface of droplets, constructing a cavity and thereby making them hollow to convey the floating propertiesThe polymers analysed for the development of these systems comprises chitosan, cellulose acetate, eudragit, methocel, polyacrylates, polyvinyl acetate, agar, carbopol, polyethylene oxide and polycarbonates.[14]

## V.METHOD OF PREPARATION

### A. Solvent evaporation method

The polymers for the development of such systems include Eudragit, HPMC KM4 and ethyl cellulose etc. Polymers are mixed with drug and further this mixture is dissolved in the solution of ethanol, acetone or dichloromethane either alone or in combination to get homogenous polymer solution. The resulting solution is poured into 100 mL of liquid paraffin rotating at 1500 rpm. The emulsion is formed and heated at 35oC temperature for 3hr. After the formation of a stable emulsion, the acetone or dichloromethane is completely evaporated and resulting solidified microspheres is filtered using whattman filter paper. This hollow microspheres imparts the floating and sustained properties.[15]

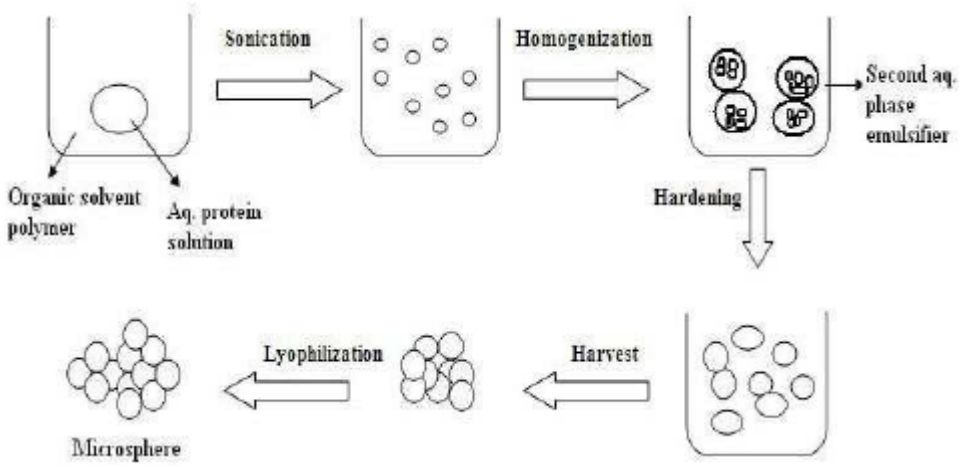


Figure 3: Solvent evaporation method

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Vol. 7, Issue 1 , January 2020

**B. Emulsion solvent diffusion method**

The mixture of drug polymer is dissolved in the solution of ethanol: dichloromethane and this mixture is adding drop wise to polyvinyl alcohol solution. This solution is stirred at 1500 rpm for 1 hour and at different temperature ranges. 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 International Journal of Research in Pharmacy and Pharmaceutical Sciences in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse into the droplets by which drug crystallizes.[17,18]

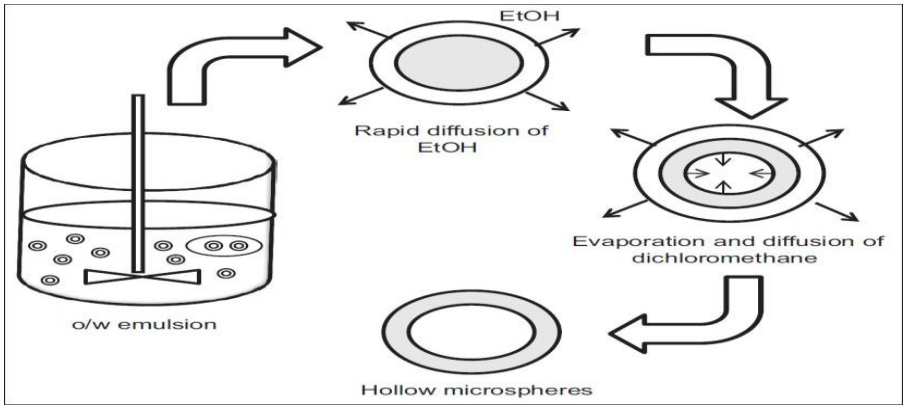


Figure 4: emulsion solvent diffusion method

**C. Solvent diffusion-evaporation technique:**

This technique is with slight modification of both emulsion solvent evaporation method and emulsion solvent diffusion method. Drug, polymers and 0.1% of surfactant such as PEG are mixed in the solution of ethanol: dichloromethane (1:1) at room temperature. This solution is slowly introduced into 80 ml of 0.46% w/w of polyvinyl alcohol as emulsifier. This is stirrer using propeller agitator for 1 hour for evaporation of organic solution and then filtered it.[19] The best formulation is selected on the basis of optimized result of various process variables such as polymer ratio, drug: polymer ratio, stirring speed and concentration of emulsifier.[20]

**D. Spray drying:**

Spray drying is the most widely employed industrial process for particle formation and drying. It is an ideal process where the required particle size distribution, bulk density and particle shape can be obtained in a single step. First of all, polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. to form a slurry. The slurry is then sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This is because the time of the solute diffusion is longer than that of the solvent in the droplets evaporating during the drying process. Subsequently, a solid shell appears leading toward formation of microspheres. Separation of the solid products from the gases is usually accomplished by means of a cyclone separator while the traces of solvent are removed by vacuum drying and the products are saved for later use.[21]

ISSN: 2350-0328
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Vol. 7, Issue 1 , January 2020

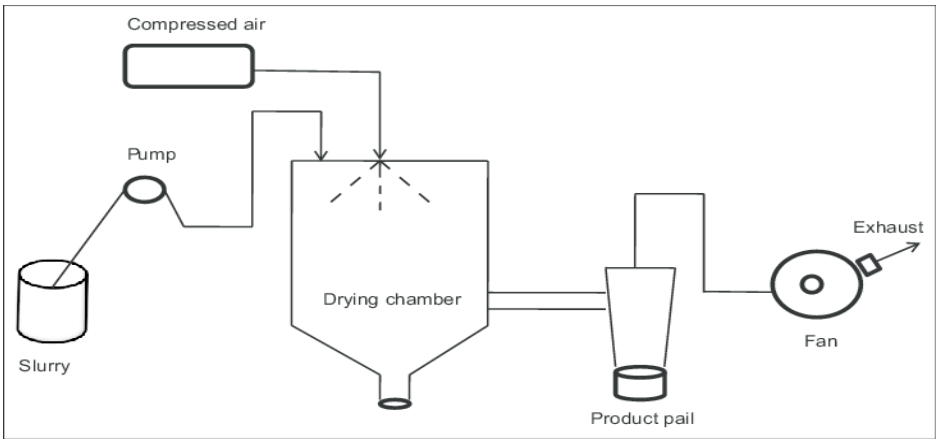


Figure 5: Spry drying method

## VI. CHARACTERIZATION OF THE OPTIMIZED MICROBALLOONS

### A) Determination of bulk density, tapped density and particle density

Different fractions of the optimized formulation (1 g) were taken into a 10ml graduated measuring cylinder separately and the volume was noted down. The graduated measuring cylinderwas tapped 50 times using USP bulk density apparatus .The bulk density and tapped densities were determined using the following formula:

Bulk density =Weight of the floating microballoons Initial volume Tapped density = Weight of the floating microballoons Final volume

Aftertapping Particle density of different fractions was determined by the liquid displacement method by suspending the microballoons in a solvent in which the microballoons were insoluble like distilled water .[22]

### B) Particle size analysis

*Particle size analysis was carried out using the optical microscopic method with the help of a calibrated eye piece micrometer. The size of around 100 particles was measured and median diameter was calculated .*[23]

### C) Scanning Electron Microscopy (SEM)[22]

SEM was performed for morphological characterization of microspheres using scanning electron microscope. They were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness,200nm)under reduced pressure(0.001mmHg).[24]

### D) In vitro drug release study

A USP (United State Pharmacopoeia) basket apparatus has been used to study *in vitro* drug release from microballoons. In this, drug release was studied using a USP dissolution apparatus type I at 100 rpm in distilled water and 0.1 N HCl (pH 1.2) as dissolution fluid (900 ml) maintained at 37±0.5°C. Withdrawn samples were analyzed spectrophotometrically. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition .[25]

### E) Buoyancy percentage

Appropriate amount of Microspheres were placed in 900 ml of 0.1 N hydrochloric acid. The mixture was stirred at 100 rpm in a dissolution apparatus for 8 hrs. After 8 hrs, the layer of buoyant microspheres were pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a dessicator until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\% \text{ Buoyancy} = [W_f / W_f + W_s)] \times 100;$$

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International Journal of Advanced Research in Science, Engineering and Technology

Vol. 7, Issue 1 , January 2020

Where $W_f$ and $W_s$ are the weights of the floating and settled microspheres .[26]

**F) Stability Studies**

During the storage if one performs studies at normal temp it will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. Optimized formulation sealed in aluminum packaging coated inside with polyethylene, and various samples were kept in the humidity chamber maintained at 40°C and 75% RH for 2 months. At the end of studies, samples were analyzed for the physical appearance, drug content and drug release .[27]

**G) Release kinetics**

Data obtained from in-vitro release studies were fitted to various kinetic equations to find out the mechanism of drug release from the ethyl cellulose microsphere. The kinetic models used were:

$Q_t=K_0t$ (zero-order equation) $\ln Q_t=\ln Q_0-K_1t$(first-order equation) $Q_t=Kh$ $t_{1/2}$(Higuchi equation)

Where $Q_t$ is the amount of drug release in time t, $Q_0$ is the initial amount of drug in the microsphere, and $K_0$ , $K_1$ , and Kh are rate constants of zero order, first order and Higuchi equations, respectively. Further to confirm the mechanism of drug release, the first 60% of drug release was fitted in Korsemeyer-Peppas model (power law).

$M_t/M_\infty = k_tn$

where $M_t$ is the amount of drug release at time t and $M_\infty$ is the amount release at time $t = \infty$, thus $M_t / M_\infty$ is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent which can be used to characterize both mechanism for both solvent penetration and drug release .[28]

## VII. Applications

Various applications of micro balloons are given below

**1.** Micro balloons 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.

**2.** Floating microspheres can greatly improve the pharmacotherapy of stomach through local drug release. Thus, eradicating Helicobacter pylori from submucosal tissue of the stomach are useful in the treatment of peptic ulcers, chronic gastritis, gastro esophageal reflux diseases etc. Floating bio adhesive microspheres of acetohydroxamic acid are formulated for treatment of Helicobacter pylori infection. Hollow microspheres of ranitidine HCl are also developed for the treatment of gastric ulcer. [29]

**3.** Solid and Microballoons vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are.

**4.** 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 gastroretentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.[30]

**5.** These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system. [31]

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 7, Issue 1 , January 2020

**6.** The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Amino glycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.

**7.** Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and Glipizide loaded Chitosan microspheres.[32]

**8.** Micro balloons of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients .[33]

## VIII. CONCLUSION

Floating drug delivery system (FDDS) provides an additional advantage to release drug at the desirable rate for prolonged time by increasing the gastric retention time of drugs. Among various approaches of FDDS, microballoons as delivery system is emerging as the innovative, most reliable dug delivery for specially those drugs that can't withstand the acidic pH of the stomach. Besides many advantages of microballoons drug delivery, there are few disadvantages too on which work is still going to eradicate or overcome them.

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