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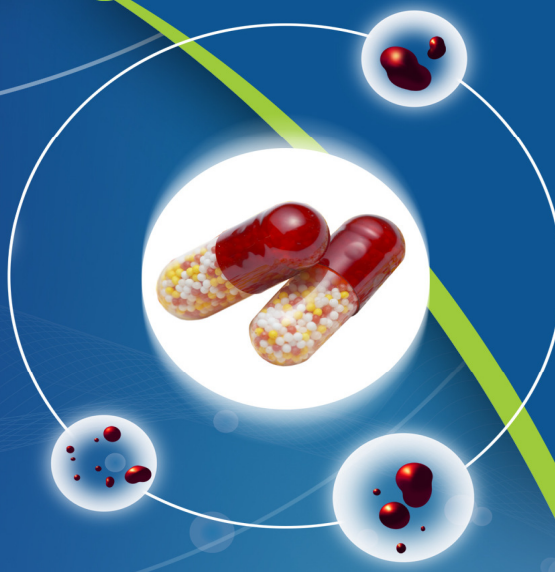

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Review Article

MICROBALLOONS FOR DRUG DELIVERY: A REVIEW

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ABSTRACT

The purpose of this review on micro balloons is to accumulate the recent literature with special focus on the recent development on floatation to achieve gastric retention. Hollow microsphere promises to be a potential approach for gastric retention. The recent developments of floating drug delivery systems including approaches to design effervescent systems and non-effervescent systems, micro balloons and recent developments and future potential. The advantages, limitation application, list of polymers used in hollow microspheres, characterization of hollow microspheres and formulation aspects are covered in detail.

Keyword: *Hollow microspheres (microballons), Floating Drug Delivery Systems, Polymers, Gastro-retentive drug delivery systems.*

INTRODUCTION

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two systems: [1, 2]

Effervescent systems

- *Volatile liquid containing systems*
- *Gas-generating Systems*

Non-Effervescent Systems

- *Colloidalgel barrier systems*
- *Microporous Compartment System*
- *Alginate beads*
- *Hollow microspheres*

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

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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. [3]

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. [4]

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 core[4] (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. [5, 6]

At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

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. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. [7]

Mechanism

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments. [2]

Advantages

a. Reduces the dosing frequency and thereby improve the patient compliance.

b. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects and despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

c. Hollow microspheres are used to decrease material density and Gastric retention time is increased because of buoyancy.

d. Enhanced absorption of drugs which solubilise only in stomach

e. Drug releases in controlled manner for prolonged period.

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

g. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.

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

i. Better therapeutic effect of short half-life drugs can be achieved.[1, 2]

Limitation

Some of the disadvantages were found to be as follows

a. The modified release from the formulations.

b. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.

c. Differences in the release rate from one dose to another.

d. 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.

e. Dosage forms of this kind should not be crushed or chewed.[8]

Applications

a. Solid and hollow microspheres 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.

b. 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.[5, 9]

c. 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.[5, 9]

d. The drugs recently reported to be entrapped in hollow microspheres include Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, Ibuprofen, Terfenadine. [5, 9]

e. Floating microspheres can greatly improve the pharmacotherapy of stomach through local drug release. Thus, eradicating Helicobacter pylori from sub-mucosal tissue of the stomach are useful in the treatment of peptic ulcers, chronic gastritis, gastro esophageal reflux diseases etc. Floating bio adhesive microspheres of aceto hydroxamic acid are formulated for treatment *of Helicobacter pylori* infection. Hollow microspheres of ranitidine HCl are also developed for the treatment of gastric ulcer. [5, 9]

f. 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.

g. 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 gastroretentive controlled-elease 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.[10]

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

i. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients.

Materials and Methodologies

Materials

***Drugs*:** Drugs with narrow absorption window in GI tract, primarily absorbed from stomach and upper part of GIT, locally act in the stomach, degrade in the colon, disturb normal colonic bacteria. E.g. Aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin, Para aminobenzoic acid, furosemide, Calcium supplements, Chlordiazepoxide and Scinnarazine riboflavin, Levodopa, Antacids and Misoprostol, Ranitidine HCl and Metronidazole, Amoxicillin trihydrate.

***Polymers*:** Cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide. [5, 11, 12]

Solvents: It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres. e.g. ethanol, dichloromethane (DCM), acetonitrile, acetone, isopropyl alcohol (IPA), dimethylformamide (DMF).[13]

***Processing medium*:** It is used to harden the drugpolymer emulsified droplets when the drug-polymer solution is poured into it, should not interact with the former; mainly used are liquid paraffin, polyvinyl alcohol and water.

***Surfactant*:** They are stabilizers or emulsifiers, play the role of hardening the microspheres as well. e.g. tween 80, span 80 and SLS.

***Cross linking agent*:** Chemical cross-linking of microspheres can be achieved using cross linking agents such as formaldehyde, glutaraldehyde or by using diacid chlorides such as terephthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent. [14]

***Hardening agent*:** This helps to harden the microspheres formed in the processing medium. e.g. n-hexane, petroleum ether (in case the processing medium is liquid paraffin).

Methods of Preparation

a. ***Solvent Evaporation Method*:** Floating multiparticulate dosage form can be prepared by solvent diffusion and evaporation methods to create the hollow

inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants / polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonate.

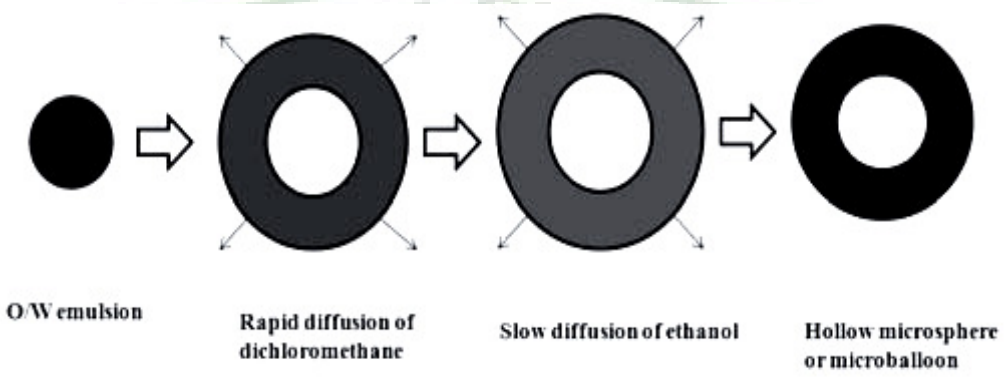

Figure1: Formulation of floating hollow microsphere or microballoon

b. ***Emulsion Solvent Diffusion Method*****:** 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 (Figure 3). 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 [3]

Characterization

a. Percentage yield

The percentage yield of the floating microspheres was determined for drug and was calculated using the following equation [21, 22, 23]

$$\text{Yield} = \frac{M}{M_o} \times 100$$

Where M = weight of beads

Mo = total expected weight of drug and polymer.

b. Micromeritic properties

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties.[24] Particle size is measured using an optical microscopy and mean particle size was calculated by measuring 200 to 300 particles with the help of calibrated ocular micrometer. 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.

$$Tapped\ density = \frac{Mass\ of\ microspheres}{Volume\ of\ microspheres\ after\ tapping}$$

The compressibility index was calculated using following formula:

$$I = V_b - V_t / V_b \times 100$$

Where, V_b is the bulk volume and V_t is the tapped volume. The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

True density was determined using a Helium densitometer. Porosity (e) was calculated using the following equation:

$$e = \{1- (tapped\ density/true\ density)\} \times 100$$

Angle of repose (θ) of the micro balloons was determined by the fixed funnel method.

***c. In vitro buoyancy*:** Fifty milligrams of the floating microspheres were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. 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. [25]

$$Buoyancy\ (\%) = \{W_f / (W_f + W_s)\} \times 100$$

Where, W_f and W_s are the weights of the floating and settled microparticles

c. Scanning electron microscopy

Dry microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then picture of microsphere were taken by spectro random scanning of the stub.

The microspheres are viewed at an accelerating voltage of 20KV. [26]

d. In-Vitro Release Studies

The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to required amount of drug was filled into a hard gelatin capsule and placed in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid was maintained at 37 ± 1° and rotation speed at a specific rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each time 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.

f. *Data analysis of release studies*

Five kinetic models including the zero order (Equation 1), first order (Equation 2), Higuchi matrix (Equation 3), Peppas-Korsmeyer (Equation 4) and Hixon-Crowell (Equation 5) release equations were applied to process the *in-vitro* release data to find the equation with the best fit using PCP Disso v3 software.[27,28]

$$R = k_1 t \qquad (1)$$

$$\log UR = K\ 2t / 2.303 \qquad (2)$$

$R = k_3 t^{0.5}$ (3)

$R = k4tn$ or $\log R = \log k4 + n \log t$ (4)

$(UR)^{1/3} = k5t$ (5)

g. *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, 3]

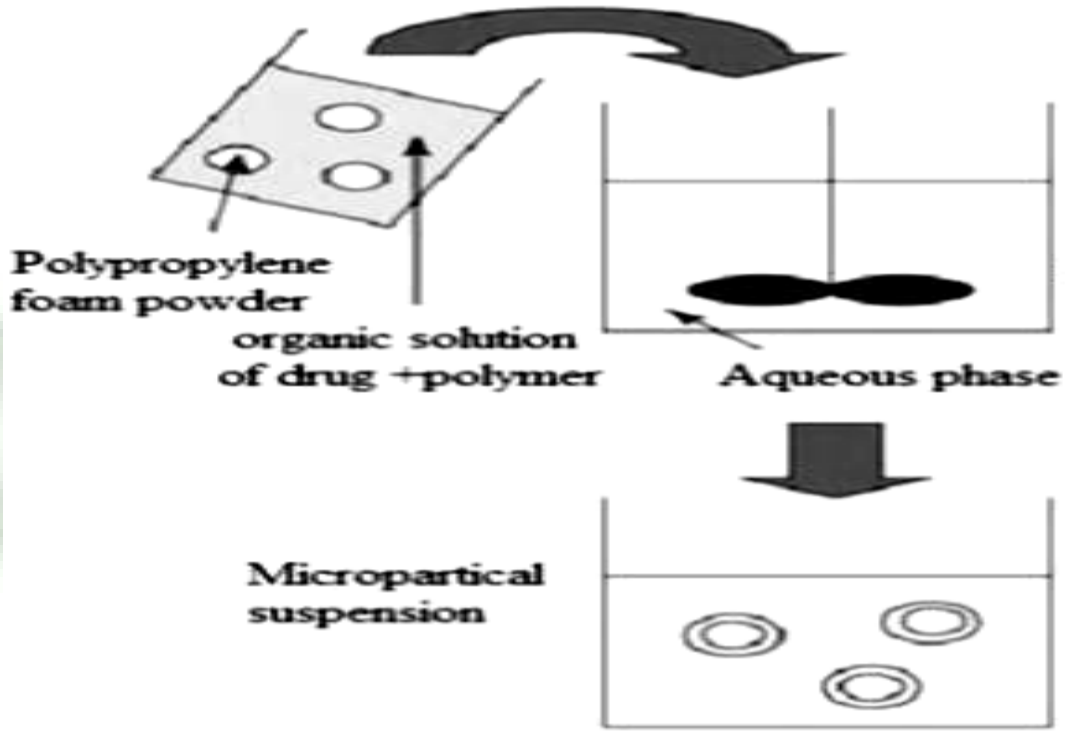

Figure 2: The solvent evaporation method

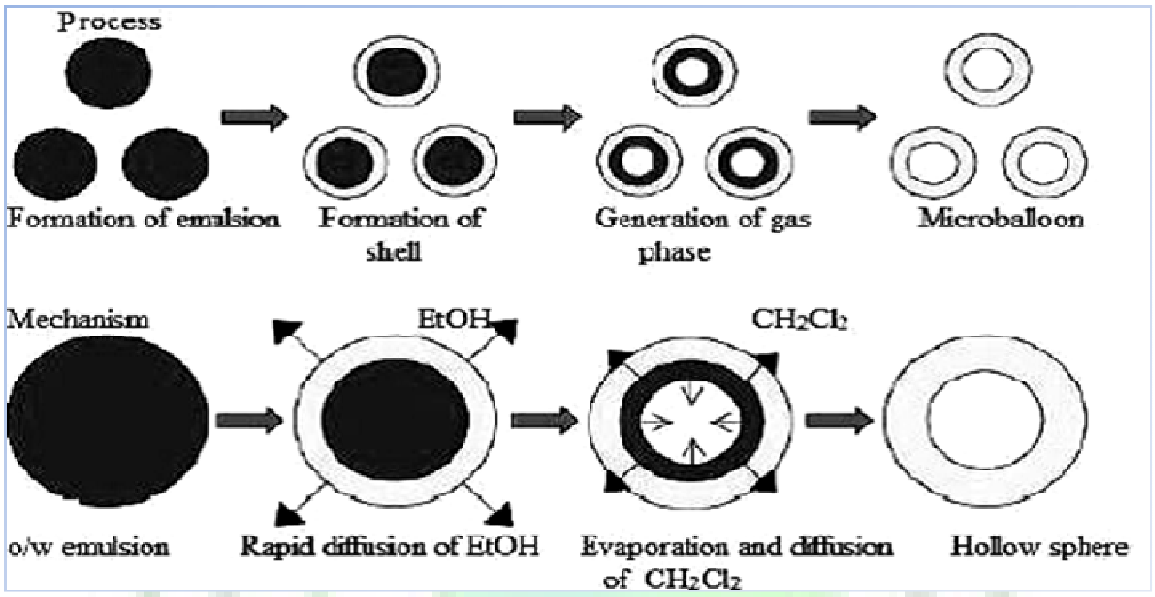

Figure 3: Preparation technique (emulsion-solvent diffusion method) and mechanism of microballoon

RECENT ADVANCE

Recently development in hollow microspheres as hollow magnetite microspheres and it use as drugs carriers. Francisco Márquez *et al* [29] have developed synthesized monodisperse hollow magnetite microspheres by a one step process through a template-free hydrothermal approach.

Yuning Huo *et al* have developed developed hollow CdS-TiO_2 microspheres with enhanced visible light photocatalytic activity. [30]

Fabrication of hollow carbonate apatite microspheres as bone substitutes have developed by Kazuhiro S *et al* using calcite microspheres as a precursor. [31]

Changchun Wang *et al* have recent developed in uniform double shell hollow microspheres from new polymer backbone transition method as effective acoustic echo imaging contrast agents. [32]

- The quantitative efficiency of gastro retentive drug delivery systems in the fasted and fed states.

Recently however, with the advances in technology, Kapil Kumar and AK Rai [33] have been opened a new doors for the development of hollow microspheres of curcumin as herbal drug delivery systems.

FUTURE POTENTIAL

The control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. It is anticipated that various novel products using gastroretentive drug delivery technologies may enhance this possibility. Further investigations may concentrate on the microballoons concepts:

- Design of an array of gastro retentive drug delivery systems, each having narrow GRT for use according to the clinical need, e.g., dosage and state of diseases.
- Determination of minimal cut-off size above that dosage forms retained in the GIT for prolonged period of time.

- Design and development of gastroretentive drug delivery systems as a beneficial strategy for the treatment of gastric, duodenal cancers and treat Parkinson's disease.
- Development of various anti-reflux formulation utilizing gastroretentive technologies.
- Exploring the eradication of Helicobacter pylori by using various antibiotics.
- Design and synthesis of novel polymers according to their clinical and pharmaceutical need.
- Design and synthesis of novel mucoadhesive agents to develop bioadhesive drug delivery systems for improved gastroretention.

Design of novel mucoadhesive delivery using various natural mucoadhesive agents according to their clinical and pharmaceutical need.

Table I: Formulations of Microballoons (Hollow microspheres)

Dosage form	Drug	Polymer	Method	Reference
Hollow microspheres	Ranitidine HCl	Eudragit RLPO	Solvent evaporation method	[15]
Micro balloons	Propranolol hydrochloride	Eudragit S	modified emulsion solvent diffusion technique	[16, 19]
Hollow microspheres	Repaglinide	Eudragit S	modified emulsion solvent diffusion technique	[17]
Hollow microspheres	Famotidine	Eudragit-S-100	solvent diffusion evaporation method	[18]
Hollow microspheres	Glipizide	Eudragit RS100	Emulsion solvent evaporation technique	[20]

CONCLUSION

In recent review we concluded that the floating hollow microcapsules showed gastroretentive controlled release delivery system, promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

Hollow microspheres are low-density, 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. Floating hollow microcapsules of melatonin showed gastroretentive controlled release delivery system.

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