FLOATING MICROSPHERE AS A NOVEL TOOL FOR H₂ RECEPTOR BLOCKER

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ABSTRACT
H₂ receptor blockers are amongst the most commonly prescribed medications in the world. Almost all the H₂ blockers available in the market have severe side effects. As awareness of the local treatment in the stomach, it is necessary to develop the dosage forms which give better release in the stomach. A trend in H₂ receptor blocker development has been to improve therapeutic efficacy and reduce the severity of side effects through altering dosage forms by modifying release of the formulations to optimize drug delivery. One such approach is using polymeric microspheres as carriers of drugs. A brief review of the Microsphere, Polymer can be used to formulate microspheres, various methods used to formulate microspheres, in vitro and in vivo evaluation and how H₂ receptor blocker are good candidate for this dosage form are briefly given in this article.

KEYWORD: H₂ Receptor blocker, Floating Microsphere, Polymer

INTRODUCTION
History of H₂ receptor blocker development
Cimetidine was the prototypical histamine H₂-receptor antagonist from which the later members of the class were developed. In 1964 it was known that histamine stimulated the secretion of stomach acid, but also that traditional anti-histamine had no effect on acid production. From these facts the scientists postulated the existence of two histamine receptors. They designated the one acted on by the traditional antihistamines H₁ and the one acted on by histamine to stimulate the secretion of stomach acid H₂. The Scientist team used a Classical design process starting from the structure of histamine. Hundreds of modified compounds were synthesised in an effort to develop a model of the then unknown H₂ receptor. The first breakthrough was N⁵-guanylhistamine, a partial H₂-receptor antagonist. From this lead the receptor model was further refined and eventually led to the development of burimamide a specific competitive antagonist at the H₂ receptor 100-times more potent than N⁵-guanylhistamine, proving the existence of the H₂ receptor. Burimamide was still insufficiently potent for oral administration and further modification of the structure, based on modifying the pKa of the compound, led to the development of metiamide. Metiamide was an effective agent; however, it was associated with unacceptable nephrotoxicity and agranulocytosis. It was proposed that the toxicity arose from the thiourea group, and similar guanidine analogues were investigated until the discovery of cimetidine, which would become the first clinically successful H₂ antagonist. Ranitidine was developed by Glaxo (also now GSK) in an effort to match the success of Smith, Kline & French with cimetidine. Ranitidine was also the result of a rational drug design process utilising the by-then-fairly-refined model of the histamine H₂ receptor and quantitative structure-activity relationships. Glaxo refined the model further by replacing the imidazole-ring of cimetidine with a furan-ring with a nitrogen-containing substituent, and in doing so developed ranitidine. Ranitidine was found to have a far-improved tolerability profile (i.e. fewer adverse drug reactions), longer-lasting action, and ten times the activity of cimetidine. Ranitidine was introduced in 1981 and was the world's biggest-selling prescription drug by 1988

Why new drug delivery?
Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of “old” drugs has been attempted using different methods such as individualizing drug therapy and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, and targeted delivery are other very attractive methods and have been pursued very vigorously. For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory. A trend in H₂ receptor blocker development has been to improve therapeutic efficacy and reduce the severity of side effects through altering dosage forms of H₂ receptor blocker by modifying release of the formulations to optimize drug delivery. These formulations are designed to increase patient compliance through a prolonged effect and reduce adverse effects through lowered peak plasma concentrations. Formulations can affect the safety of preparations by controlling the rate of release of the drug at sensitive sites, by delivering drug to specific sites to minimise systemic exposure, or delivering drug in such a way as to change the rate or extent of the formation of toxic metabolite. The table mentioned below justifies, why there is need of new drug delivery of H₂ receptor blocker.
Although single unit floating dosage forms have been developed, floating microspheres have been incorporated into matrix effervescent reaction between organic acids and carbonates. These buoyant systems utilize matrices having high drug % loading and thus any loss of integrity of the release effect, floatability and uniform release of drug can be avoided, whereas there is no risk of dose dumping. Microspheres releases drug uniformly and there is no risk of dose dumping.

Floating Microspheres

Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres. Over the last three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time. High-density systems having density of ~3 g/cm³, are retained in the rugae of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug >50%) and to achieve the required density of 2.4–2.8 g/cm³. Swelling systems are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems. Floating systems first described by Davis (1968), are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. The floating drug delivery system can be divided into gas generating and non-effervescent systems. Floatation of drug delivery system in stomach can be achieved by effervescent systems, incorporating a floating chamber filled with vacuum, air or carbon dioxide produced as a result of effervescent reaction between organic acids and carbonates incorporated. These buoyant systems utilize matrices prepared with swellable polymers (e.g. methocel), polysaccharides (e.g. chitosan), effervescent components containing sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. Non-effervescent systems incorporate a high level (20–75% w/w) of one or more gel forming, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose), polysaccharides, or matrix-forming polymers (e.g., polycarphill, polycarlylates, polystyrene) into hollow microspheres, tablets or capsules.

The advantages of hollow microspheres include

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

Moreover, the following advantages make them a promising means for the delivery of H₂ receptor antagonist. Microspheres provide constant and prolonged therapeutic effect, which will reduce the dosing frequency and thereby improve the patient compliance. They could be injected into hollow microspheres, tablets or capsules. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects. Microsphere morphology allows a controllable variability in degradation and drug release.

Limitation

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

1. 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. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can also be delivered efficiently thereby maximizing their absorption and improving the bioavailability.

2. 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. The development of such systems allows administration of non-systemic, controlled release antacid formulations containing calcium carbonate and also locally acting anti-ulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

3. 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. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms may allow for more effective oral use of peptide and protein drugs such as Calcitonin, Erythropoietin, Vasopressin, Insulin, low-molecular-weight Heparin, and LHRH.

4. 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.

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

Development of floating microspheres

Micro particulate drug delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human health care. Microencapsulation is a technology devoted to entrapping solids, liquids or gases inside one or more polymeric coatings. The techniques adopted for the preparation should satisfy certain criteria. It should have the ability to incorporate reasonably high concentration of the drug. The particle size should be controlled by altering certain parameters and it should release the active agent with good control over a prolonged time. For parenteral preparations it is desirable to reduce the size of the particles in order to minimize the irritant reaction at the site of injection. The microspheres prepared should be stable and have a good shelf life.

The selection of method depends on the particle size required, route of administration, duration of drug release, etc. All these characteristics will ultimately relate to the other variables like rpm, method of cross linking, duration of cross linking, evaporation time, co-precipitation etc. The microspheres are separated from the reaction mixture by filtration, centrifugation or freeze-drying. Recovery of the prepared microspheres depends up on the size of the particles and the particle characteristics such as composition and swellability. Relatively large and rigid particles are separated by filtration or decantation. Ultracentrifugation is used for separating smaller particles. This step is followed by washing the microspheres in order to remove the residual solvents, surfactant and other additives. The washed microspheres are then air dried, vacuum dried, freeze dried, or reconstituted with an appropriate medium for subsequent use.

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.

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. When microspheres come in contact with gastric fluid the gel former, 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.

Spray drying technique

In Spray Drying the 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. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100μm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions.
this process is rapid and this leads to the formation of porous micro particles shown in Figure 1.

![Spray drying method for preparation of microsphere](image)

**Figure 1** Spray drying method for preparation of microsphere

Yapel. et al. prepare ketoprofen-loaded microspheres with a polymeric blend by a spray drying technique. Solidification is accomplished by rapid evaporation of the solvent in which coating material is solubilized. Organic solutions of two polymers, cellulose acetate butyrate (CAB) an poly (epsilon-caprolactone) (PCL), in different weight ratios, and of ketoprofen were prepared and sprayed, in different experimental conditions, achieving drug loaded microspheres. The process control variables in this technique were feed material properties, feed rate, method of atomization and drying rate. Spray drying method is rapid, reproducible and easy to scale up\(^3\).

**Emulsion cross linking method**

The micro particulate carriers of natural polymers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation\(^3\). The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bio performance of the final multiparticulate product\(^3\).

Kumbar SG et al studied encapsulation of diclofenac sodium into cross linked chitosan microspheres and the effect of cross linking agent. Microspheres of chitosan cross linked with three different cross linking agents viz, glutaraldehyde, sulphuric acid and heat treatment were prepared to encapsulate diclofenac sodium. Chitosan microspheres were produced in a w/o emulsion followed by cross linking in the water phase by one of the cross linking methods. Encapsulation of drug was carried out by soaking the already swollen cross linked microspheres in a saturated solution of diclofenac sodium. The in-vitro release studies were performed in 7.4 pH buffer solution. Microspheres produced were spherical and had smooth surfaces, with sizes ranging between 40-230 microns. The cross linking of chitosan took place at the free amino group in all the cases. Polymer crystallinity increased after cross linking. The percentage of drug loading into the microspheres was found to be up to 28-30% w/w for the sulphuric acid-cross linked microspheres, whereas 23-29 and 15-23% of loadings were obtained with glutaraldehyde (GA)- and heat-cross linked microspheres, respectively\(^2\).

**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 lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction\(^2\).

**Emulsion solvent evaporation**

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is dispersed in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The solvent Evaporation technique is shown in Figure 2. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made\(^6\).
Spray coating

Floating microsphere of antidiabetic drug i.e. metformin HCl

A simple emulsion solvent evaporation method for the prolonged release of highly water-microns and high drug content of microcapsules with a mass median diameter of around 100 microns and high drug content. The microspheres were collected by filtration, washed with deionized water, and dried. The dried spheres were passed through a 60 mesh stainless-steel sieve and stored at room temperature.

Ionic gelation

Floating microsphere of antidiabetic drug i.e. metformin HCl was prepared using Sodium alginate, hydrophobic and hydrophilic polymer, NaHCO₃ and CaCO₃ by Poonam Saluke, Bhusane Rane and evaluated the various properties of microsphere like particle size, % yield, % loading capacity, % entrapment efficiency, in vitro dissolution, floating time and buoyancy time. They found that hydrophobic polymer give longer and better dissolution profile as compare to hydrophilic polymer. More over they also found that particle size as well as floating time of the microsphere containing CaCO₃ is better than microsphere containing NaHCO₃. They also conclude inotropic gelation technique can succefully used for the preparation of microsphere of any drug using different permeability polymer and gas forming agent. Various formulation variables such as concentration of gas forming agents, combination of polymers, cross linking agents were used where influence the various properties of microsphere like particle size, floating time, % entrapment efficiency, % loading capacity, in vitro dissolution. From their project work, they also found that CaCO₃ is more suitable for sustain release dosage form as compare to NaHCO₃.

Spray coating-Wurster process

Prolonged-release microcapsules of diclofenac sodium (DS), applicable as an oral suspension for twice-a-day administration were designed by Hideki Ichikawa. The microcapsules with a mass median diameter of around 100 microns and high drug content exhibited a preferably prolonged release of highly water-soluble DS when prepared by the Wurster process—a spray coating method using a spouted bed assisted with a draft tube. The microcapsule was composed of a calcium carbonate core of 32–44 microns, a drug-layer of DS, hydroxypropyl cellulose and polyethylene glycol 6000, an undercoat of Eudragit L30D and a release-sustaining coat of Eudragit RS30D. Eudragit L30D films were undercoated to decrease the solubility of DS within the environment of the microcapsules and thereby to prolong the drug release. This made it possible to decrease the amount of Eudragit RS30D membrane required to prolong the drug release, leading to decrease in the particle size of products and achievement of high drug content. Thus, prolonged release microcapsules with a mass median diameter of 92 microns and a drug content of 29% were obtained. Wurster process has the advantage that wide variety of coating materials can be used and coating can be applied in the form of solvent solutions, aqueous solutions, emulsions, dispersions and hot melt.

Aqueous dispersion method

Relatively little importance has been given to effect of the rate and method of cooling on properties of drug matrices. R.S. Al-Kassas et al studied effect of the rate and method of cooling on the particle size of ibuprofen microparticules. Ibuprofen microspheres were prepared using an aqueous dispersion method. The method was adopted so that factors like cooling time and stirring rate could be altered. Particle size analysis showed that both the parameters significantly affected the mean particle size although the effects were independent of each other. In vitro release fitted to several models, the Higuchi square root of time model gave the best fit. Chitosan microspheres of indomethacin by an aqueous process were described by Aggarwal A et al. The influence of formulation variables on indomethacin content in the microspheres and time for indomethacin release from the microspheres was investigated. Amongst various variables, the indomethacin:chitosan ratio and amount of cross linking agent were found to be important.

Coacervation method

Controlled-release egg albumin-chitosan microspheres containing indomethacin as a model drug were successfully prepared by coacervation method. This method is simple and...
The formation of three phases:
- Dispersing a core material in a solution of coating polymer
- Immiscible polymer in liquid state. (Coating material phase)

Coating is accomplished by controlled physical mixing of coating solution and core material in liquid manufacturing vehicle phase. Rigidisation could be achieved by thermal, chemical cross linking or desolvation techniques.

The interaction between negatively charged egg albumin molecules in phosphate buffer, pH 7.2, or sodium hydroxide solution and positively charged chitosan molecules dissolved in diluted acetic acid to form an insoluble precipitate was the principle for the formation of the microspheres. Incorporation efficiencies of the microspheres were high and ranged between 63.3 and 92.39, while particle sizes were 435.2 to 693.9 micron for different batches. As the pH of the encapsulation media was increased, from pH 3.77 up to pH 4.91 the incorporation efficiency, particle size, and flowability decreased, along with increase of drug release rate. It was also observed that high concentration of albumin solution and accordingly the increase of albumin-to-chitosan weight ratio were accompanied with increases in incorporation efficiency and particle size with improved microsphere flowability and slow drug release39.

**Hot-melt encapsulation method**

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent like silicone oil, continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. poly anhydrides. Microspheres with diameter of 1-1000 μm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed18.

Lin WJ and Kang WW compared the performance of indomethacin microparticles and their release properties after coating with chitosan and gelatin, respectively. Here the poly (epsilon-caprolactone) (PCL) microparticles were prepared by the hot-melt encapsulation method. This method is having a disadvantage that thermolabile substances cannot be used. But it is reproducible with respect to yield and size distribution. All of the coated microparticles retained their spherical shape irrespective of the type of coating material, and the particle size of coated microparticles was similar to the uncoated ones. The indomethacin encapsulation efficiency was in the range of 8.65 % - 8.81 % for uncoated microparticles and 8.22 % - 8.68 % for coated microparticles.

The release of indomethacin from uncoated microparticles followed a two-exponential release profile, where indomethacin was rapidly released within 4 hour during the first release phase, after that approximately 20% of the drug was continuously and slowly released for up to 24 hour in the second phase. The similar release profile was observed from coated microparticles irrespective of the times of coating and the types of coating material. Both the natural coating materials, chitosan and gelatin, efficiently reduced the initial burst release and the first phase of drug release, but did not alter the second phase of drug release30.

**Emulsion-solvent diffusion technique**

Floating microparticles of ketoprofen were prepared in order to improve the residence time in the colon by A.H. El-Kamel et al using the emulsion-solvent diffusion technique. The drug polymer mixture dissolved in a mixture of ethanol and dichloromethane (1:1) was dropped into 0.2% sodium lauryl sulfate solution. The solution was stirred with a propeller-type agitator at room temperature for 1 hour at 150 rpm. The formed floating microparticles were filtered, washed with water and dried at room temperature in a desiccator. The floating microparticles were sieved and collected31.

**Solvent extraction**

Solvant evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for then microspheres. One variation of the process involve direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer17.

**Characterization of floating microspheres**

Floating microspheres are characterized by their micromeric properties such as particle size, tapped density, compressibility, true density and flow properties including angle of repose. 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,12,31. 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.

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Percentage yield
Percentage yield of floating microspheres is calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula:

\[
\text{Percentage yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100
\]

Drug entrapment efficiency
Estimation of drug content in floating microspheres can be carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl and analysed spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in triplicate manner. The entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of microspheres.

Isoelectric point
The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

Floating Behaviour
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.

Buoyancy (%) = \(\frac{W_f}{W_f + W_s}\)

Where, \(W_f\) and \(W_s\) are the weights of the floating and settled microparticles.

Incorporate Efficiency
To determine the incorporation efficiency, prepared microspheres were taken, thoroughly triturated in pestle mortar equivalent as drug used in formula and suspended in a 5 ml of dichloromethane as dissolving medium. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically.

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 50 mg drug was filled into 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°C 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.

Punitha K. et al prepared floating microsphere of Ranitidine HCl using HPMC 15cps and Eudragit E-100 in various ratio 1:1, 1:2, 1:3. Drug loaded microspheres equivalent to 100 mg of drug was introduced into the 900 ml of 0.1N HCl, containing Tween 80 (0.5%). The medium was maintained at 37±0.5°C at 100 rpm. Aliquots (5ml) were withdrawn at regular intervals for 12 hours and analyzed spectrophotometrically at 315 nm. The dissolution studies were carried out in triplicate in 0.1N HCl (pH 1.2). Sink condition was maintained throughout the study by replacing equal volume of fresh dissolution medium.

In-vivo studies
The in-vivo floating behaviour 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.

CONCLUSION
Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be 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. 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.

\(\text{H}_2\) receptor blocker is found to be good candidate for floating control release dosage forms owing to the local effect in the stomach. Due to the greater stability and wider manufacturing techniques microspheres are preferred over other colloidal drug delivery systems. They are compatible with most of the natural and synthetic polymers and can be used for both parenteral and oral administration. The route of administration, physicochemical properties of drug, toxicity and the site of action are the other factors that determine the method of preparation and drug carrier for \(\text{H}_2\) receptor blocker microspheres. Chitosan is the most widely studied polymer for the preparation of microsphere for oral use and synthetic polymers were used for parenterals use. Studies indicated that the \(\text{H}_2\) receptor blocker microspheres were superior to the conventional formulations with respect to bioavailability and pharmacodynamic properties. The literature revealed that micro-particulate delivery reduces marked fluctuations in plasma between peak and trough levels at the time of next dosages. But the safety profile of these drug delivery systems for \(\text{H}_2\) receptor blockers is not encouraging or not reported extensively so as to conclude that they are the best for this drug class. But most of in vitro/in-vivo
vivo studies shows that they are promising drug delivery systems for H$_2$ receptor antagonist.

REFERENCES