Role of excipients and polymeric advancements in preparation of floating drug delivery systems

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Abstract

Since decade or two, the development of floating drug delivery systems becomes a significant and novel tool as having low density than gastric content. There are various advanced polymers including chitosan, eudragit, etc., and excipients such as; pore forming agent, surfactants, etc. All of them are discussed briefly, and results are concluded from various reputed researches. We have discussed all natural and synthetic systems with their effect on the release and other parameters which are essential for the floating formulation development.

Key words: Controlled delivery, floating, gas generation, polymers

INTRODUCTION

Gastroretentive systems are dosage forms having ability to retain itself in the stomach to increase absorption of released drug from acidic medium in a controlled manner. Gastroretention is achieved by four types of modifications such as High density systems, modified shape systems, mucoadhesive systems, and floating systems.

Floating drug delivery system is a gastroretentive drug delivery system, has bulk density less than gastric fluids and so remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

First of all, Davis et al. investigated the floating systems to utilize the problem of swelling of dosage forms and have given an advanced gastroretentive system to the pharmaceutical field which is now-a-days one of the most effective controlled release dosage form.

In spite of fewer limitations such as gastric motility, pH, and presence of food the floating delivery system still have advantages such as improved bioavailability of the drug, prolonged release, and local action which contribute in therapeutics of any disease significantly.

DOSAGE FORMS BASED ON FLOATING SYSTEMS

Single- and multi-unit dosage forms are two types of approaches available to formulate floating dosage forms.

A number of approaches has been used to increase floating time of the dosage form in the stomach such as hydrodynamically balanced systems, gas-generating systems, raft-forming systems, low-density systems etc. They are basically classified into two types such as; effervescent and noneffervescent systems. In the case of effervescent system, gas-generating agents are used for the effervescence in dosage form and case of noneffervescent system only swellable polymers or hydrocolloids are used (e.g., hydroxy propyl methyl cellulose [HPMC], Eudragit) are used. These systems can be formulated in both types of dosage forms; single and multiple units.

EXCIPIENTS USED IN DIFFERENT FLOATING DOSAGE FORMS

On the basis of the role in dosage form.

Hydrocolloids

Hydrocolloids are gel-forming agent, which swells in contact with gastric fluid and maintains a relative integrity of shape and bulk density less than the gastric content.
c.g., Acacia, pectin, agar, alginites, gelatin, casein, bentonite, veegum, methylcellulose (MC), HPMC, ethylcellulose (EC), HPC, hydroxyethyl cellulose, and carboxy methylcellulose sodium (Na CMC).

**Inert fatty materials**
Edible, pharmaceutical inert fatty material, having a specific gravity <1 can be added to the formulation to decrease the hydrophilic property of formulation and hence, increases the buoyancy. E.g., purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils.

**Release rate accelerants**
The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5% to 60% by weight. E.g., lactose, mannitol, etc.

**Release rate retardants**
Insoluble substances such as calcium phosphate, talc, and magnesium stearate decreased the solubility and hence, retard the release of medicaments. E.g., dicalcium phosphate, talc, magnesium stearate, etc.

**Buoyancy increasing agents**
Materials like EC, which has bulk density <1, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80% by weight. E.g., polypropylene foam powder, etc.

**Effervescent agents**
These are the agents which generate carbon dioxide after reacting with gastric acidic medium.

E.g., sodium bicarbonate, citric acid, tartaric acid, di-sodium glycine carbonate, citroglycine, etc.[15,16]

On the basis of origin, the polymers are categorized in three types:
1. Natural polymers like, chitosan, sodium alginate, etc.
2. Semi-synthetic polymers like, EC, HPMC, etc.
3. Synthetic polymers like, acrylic acid derivatives, lactic acid derivatives, etc.

**CHITOSAN**
Chitosan (obtained by alkaline deacetylation of chitin) is a swellable, natural linear biopolyaminosaccharide. Chitin is a straight homopolymer composed of -(1,4)-linked N-acetyl-glucosamine units, while chitosan comprises of copolymers of glucosamine and N-acetyl-glucosamine. The emulsion cross-linking and the ionotropic gelation are most preferred and widely used methods for the preparation of floating microspheres. In both methods, cross-linking is required due to its ionic nature. Different grades of chitosan are available on the basis of their degree of deacetylation and molecular weight, and their solubility can also vary between slightly acidic medium to the aqueous medium.[17-19]

Degree of deacetylation and molecular weight also affects the formulation of microspheres. Honary et al. demonstrated that the high molecular weight chitosan produces smaller and more uniform microparticles which give higher release rate and high viscosity, where reverse in case of low molecular weight chitosan. It has been shown by researchers that the amount of chitosan adsorbed on the tissue increased with a decrease in cross-linking. The mucoadhesion property of the microparticles was dependent on the molecular weight of chitosan means microparticles prepared from high molecular weight chitosan were significantly more mucoadhesive than the lower molecular weight chitosan.[20]

The degree of deacetylation fundamentally determines the polymer properties including solubility, hydrophobicity, and the ability to interact electrostatically with polyanions by affecting the number of protonatable amine groups. As per the study, the researchers observed that the low degree of deacetylation will not increase the absorption, and high degree of deacetylation can cause cellular toxicity so a medium range can be used in case of degree of deacetylation.[21-23]

Chitosan is used in 0.5-8% concentration for the microsphere preparation. Basically, acetic acid in the concentration of 0.5-3% is used as a solvent for the preparation of the formulation. In some cases, dichloromethane and ethanol in 1:1 ratio are also utilized.[24-27]

El-Nahas and Hosny (2011) prepared and characterized floating microspheres using trimetazidin dihydrochloride as a model drug to increase the residence time in the stomach without contact with the mucosa by the capillary extrusion technique using chitosan as polymer and sodium lauryl sulfate as cross-linking agent. The prepared microspheres exhibited prolonged drug release and remained buoyant for more than 11 h. The microspheres were found to be regular in shape and highly porous. The trimetazidin dihydrochloride release rate was higher in the case of microspheres prepared at a higher agitation speed and decreased with increase in concentration of the polymer and crosslinking agent. The drug entrapment increased with increasing polymer to drug ratio.[28]

El-Gibaly et al. prepared floating microcapsules of melatonin by the ionic interaction of chitosan and a negatively charged surfactant, sodium dioctyl sulfo succinate and compared with conventional nonfloating systems. The use of sodium dioctyl sulfo succinate solution in coagulation of chitosan produced well-formed microcapsules with round hollow core and good incorporation efficiencies. Moreover, release of the drug from these microcapsules was greatly retarded with release lasting for several hours compared with nonfloating microspheres where drug release was almost instant. Most of the hollow microcapsules developed tended to float over-simulated biofluids for more than 12 h. Swelling studies indicated that sodium dioctyl sulfo succinate/chitosan microcapsules showed less swelling whereas, nonfloating microspheres were markedly swollen and lost their integrity in simulated gastric fluid within 5 h.[29]
Sheth et al. prepared and evaluated chitosan-based floating microspheres using levetiracetam, a biopharmaceutics classification system class-I drug having the half-life of 6-7 h by the simple emulsification phase separation technique by varying concentration of crosslinking agent (glutaraldehyde). The prepared microspheres exhibited prolonged drug release and remained buoyant for >8 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. In vitro studies demonstrated diffusion-controlled drug release from the microspheres.\textsuperscript{[30]}

Crosslinking is a major part of microspheres formulation. It can be done by heating or chemical application.

Thakkar and Murthy describe the effect of heating and effect of glutaraldehyde or formaldehyde on crosslinking of chitosan, in which chemical reaction of chitosan with formaldehyde or glutaraldehyde leading to a stronger and more rigid matrix with high-entrapment efficiency than the heat cross-linked microspheres. The glutaraldehyde cross-linked microspheres release the drug slowly compared to the formaldehyde cross-linked microspheres while fastest drug release was observed in heat cross-linked microspheres.\textsuperscript{[31]}

Gonçalves et al. compared the two systems epichlorohydrin and glutaraldehyde in which epichlorohydrin has lower porosity, leading to the drug being impregnated more superficially. Moreover, their higher degree of swelling, facilitating the solvent access to the drug incorporated in the polymeric matrix, increases contact with it, and consequently, allows greater release. For glutaraldehyde, in spite of its high porosity and higher drug loading, the drug release was lower, since the degree of polymer swelling was lower, making solvent access difficult.\textsuperscript{[32]}

In spite of the retarding effect reported by citric acid in chitosan, if mild temperature is used in crosslinking reaction of chitosan with citric acid, it accelerates release rate from chitosan microspheres.\textsuperscript{[33]} Citric acid also prolongs gastro-retention, in the fasted state, when solution is used as an administering vehicle. However, prolonged gastro-retention is not achieved to the same extent when the gastric emptying times are compared to those obtained in the fed state.\textsuperscript{[34]}

Pieróg et al. prepared the membrane of chitosan uncrosslinked and crosslinked swollen in acidic media underwent disintegration. It has been observed that the time needed to membrane disintegration in acidic media increased in the following order: Chitosan ≈ chitosan/sulfate ≈ chitosan/citric acid < chitosan/alginate << chitosan/tripolyphosphate. Degree of swelling at equilibrium state decreased in the following order: Chitosan > chitosan/sulphate > chitosan/citric acid > chitosan/alginate > chitosan/tripolyphosphate. The hydrophilicity of low molecular chemicals used in chitosan crosslinking processes increase in order: Tripolyphosphate < citric acid < sulfate.\textsuperscript{[35]}

Chitosan has also some pharmacological activities such as; hypcholesterolemic, antimicrobial, immunostimulating, antitumor and anticancer effects, accelerating calcium and iron absorption, anti-inflammatory, antioxidant, and angiotensin-I-converting enzyme inhibitory activities. In addition, chitosan and its oligosaccharides have other bio-logical functions such as excluding toxins from the intestines, reducing heavy-metal poisoning in humans, radio-protective properties, and preventing tooth decay and tooth diseases.\textsuperscript{[36]}

Sarojini et al. developed albumin-chitosan-based floating mucoadhesive microsphere of clarithromycin by heat stabilization method in the presence of span 80 to provide prolonged contact time of antibiotics to treat stomach ulcers, increase the gastric residence time, decrease the diffusional distance, and also act locally at the infectious site. Drug release from the microsphere was found to be first-order release, which shows high-percentage drug release.\textsuperscript{[37]}

Raj et al. prepared prazosin loaded chitosan polyelectrolyte complex hydrogel beads via ionotropic gelation by crosslinking with sodium tripolyphosphate. A combination of eudragit polymer was studied with chitosan having prazosin dispersed within them. Thus, prazosin dispersed in 2% glacial acetic acid and having chitosan and polymer dispersed within. It was a cross linked with 2% sodium tripolyphosphate solution adjusted to pH of 4.5-6. These beads were able to sustain the release of prazosin from the beads. The in vitro dissolution rate profile showed a sustained release of the drug from the beads over a 7 h study period. Prazosin release decreased with increasing concentration of chitosan.\textsuperscript{[38]}

Yassin et al. designed a new extended release floating multiparticulate delivery system for verapamil by incorporation into hydrogel beads made up of chitosan. The beads were formed by dropping solutions of verapamil and chitosan in a solution of tripolyphosphate using a syringe pump with adjustable constant rate and further crosslinked using glutaraldehyde. The produced beads from all batches showed a very good spherical geometry with a mean diameter in the range of 1.3-2.0 mm. The drug loading efficiency was around 42% for all batches. The % friabilities were <1% indicating that the beads surfaces are highly resistant to attrition. Batches prepared using medium molecular weight chitosan showed both the slowest release rate among all the prepared batches and showed good floating characteristics comprising short onset (around 5 min) and the long duration of buoyancy (more than 6 h). This technique would provide a simple and commercially viable method of preparation of chitosan beads for controlling the release of some drugs.\textsuperscript{[39]}

**SODIUM ALGINATE**

Alginate is a polysaccharide that is abundant in nature, as it is synthesized by brown seaweeds and soil bacteria.\textsuperscript{[40]} It is widely employed in the food processing industry, often as a thickener.
or emulsification stabilizer and in the pharmaceutical industry since it is the first byproduct of algal purification. Sodium alginate consists of α-L-guluronic acid residues (G blocks) and β-D-mannuronic acid residues (M blocks), as well as segments of alternating guluronic and mannuronic acids (GM blocks). The guluronate residue blocks allow alginate fibres to form gels by binding Ca$^{2+}$ ions and stomach H$^{+}$ ions, which cross-link the fibres into a viscous polymer matrix.

It has very valuable properties such as the biocompatibility, bioadhesiveness, pH sensitivity, and nonimmunogenic. The gelation of alginate can be achieved under the extremely mild environment with the help of nontoxic reagents. The gels formed (with reaction of alginate and Ca$^{2+}$, Sr$^{2+}$, Ba$^{2+}$ ions) have reticulated structure which can entrap the drugs and able to release the drugs in the sustained manner. The plain beads have limitation like drug loss due to leaching and so now the recent trend is to form polyelectrolyte complexes of alginate with other polymers to have influence on network complexity, which will check drug leaching and release.

Alginate beads are prepared by ionotropic gelation method. Beads having approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated and frozen in liquid nitrogen, and freeze dried at $-40^\circ$C for 24 h, leading to the formation of the porous system, which can maintain a floating force over 12 h.

Sahasathanith et al. developed mucoadhesive and floating chitosan-coated alginate beads as a gastroretentive delivery vehicle for amoxicillin, toward the effective eradication of Helicobacter pylori, a major causative agent of peptic ulcers. Amoxicillin-loaded alginate beads coated with 0.5% (w/v) chitosan exhibited excellent floating ability, high-encapsulation efficiency, high-drug loading capacity, and a strong in vitro mucoadhesion to the gastric mucosal layer. In vitro, amoxicillin was released faster in simulated gastric fluid than in simulated intestinal fluid. Alginate-chitosan complex could be prepared with a $>90\%$ drug encapsulation efficiency and exhibited more than $90\%$ muco-adhesiveness, 100% floating ability, and achieved sustained release of amoxicillin for over 6 h in simulated gastric fluid.

Yotsuyanagi et al. reported that alginate gel particles show a pH-sensitive swelling property, that is, the particles remain unchanged in distilled water or acidic medium but swell rapidly in pH 7.0 phosphate buffers to a size greater than the original size. This property of alginate can be useful for drugs, which are acid-sensitive because they can be shielded from attack of gastric juices and can be release at desirable rates in the intestine due to reswelling of xerogels in the intestine.

Gadad et al. prepared sodium alginate floating beads containing cefpodoxime proxetil, a third-generation cephalosporin antibiotic by precipitation method using calcium carbonate as gas generating agent, which form pores. The size of the beads was in the range of 700-1000 μm which can be increased as increase in the concentration of the gas-forming agent and decreases with an increase in the concentration sodium alginate. The porosity depends on the concentration of the gas-forming agent. All the formulations showed good floating time. The in vitro dissolution study reveals that the concentration of the gas generating agent and sodium alginate affects the release rate.

Murata et al. prepared two types of alginate beads of metronidazole in which one had vegetable oil and second one was with chitosan. The release rate being inversely related to the percentage of oil and was not affected by the kind of chitosan. These release properties of alginate gels are applicable not only for sustained release of drugs but also for targeting the gastric mucosa.

Choudhury and Kar developed oil entrapped alginate floating beads of metformine hydrochloride (Hcl) by emulsion gelation method. Without homogenization, oil started being separated out, and uneven sized beads were formed. On increasing the homogenization time, the size of the beads formed decreased and size uniformity was obtained. The results were shown that the amount of oil affected the morphology of beads. The increase in concentration of oil caused an increase in size and sphericity of the beads, which could be due to their density and volatility. The higher the density of the oil used, the larger was the size and better the spherical nature. As the density of oil decreased, the volatility increased. Oil-filled pores were visible on the surface. The uneven size of the pores could be due to the coalescence of the oil droplets during the gelling process. The release profile indicates that the sustaining action was more pronounced with liquid paraffin followed by groundnut oil > castor oil > mentha oil > conventional alginate beads.

Adel and Elkasabgy extended drotaverine Hcl residence in the stomach by forming calcium alginate floating beads using sodium alginate, isopropylmyristate (oil), and Gelucire® 43/01 (lipid) adopting emulsion gelation technique. Incorporation of Gelucire® 43/01 to oil-based beads enhanced the in vitro performance of the beads. Coated beads prepared using drug: Sodium alginate ratio of 1:3 w/w, 20% w/v, isopropylmyristate 20% w/v, and Gelucire® 43/01 showed promising in vitro performance. The beads floated for 12 h in the dogs’ stomach and produced three-fold increase of the total amount of drotaverine Hcl absorbed within 24 h compared to that of drotaverine Hcl powder. In a study where potassium bicarbonate as a pore...
forming agent, sodium alginate as polymer, and calcium chloride in acetic acid as crosslinking agent utilized for the formulation of valsartan floating beads. The prepared formulation with 5.2% sodium alginate and 0.625% potassium bicarbonate having porosity 21-28% and bulk density < 1 was in the optimum zone.\footnote{68}

Sodium alginate has several biological activities such as; it enhances the biological activity of vascular endothelial growth factor,\footnote{69} immunomodulator,\footnote{70} antitumor activity,\footnote{71} anticoagulant activity.\footnote{72}

**CALCIUM PECTINATE**

Pectin is an inexpensive, nontoxic polysaccharide extracted from citrus peels or apple pomasces, and has been used as a food additive, a thickening agent and a gelling agent. It also has bioadhesive properties toward other gastrointestinal tissues, which can be used as a drug delivery device on a specific site for targeted release and optimal drug delivery due to intimacy and duration of contact. Pectin has a very complex structure, which depends on both its source and the extraction process. Numerous studies contributed to elucidate the structure of pectin. Basically, it is a polymer of a-D-galacturonic acid with 1-4 linkages.\footnote{73-75}

Calcium pectinate hydrogels are stable in low pH solution, and are being investigated as a carrier material for different controlled release systems. Various approaches to induce buoyancy in crosslinked gel beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, have been used.\footnote{76-78}

Calcium pectinate is used in concentration about 1-5%.\footnote{79,80} It is basically used for the preparation of beads.\footnote{81,82}

Sriamornsak and Nunthanid prepared the conventional calcium pectinate beads by ionotropic gelation method. Briefly, pectin was dissolved in water with agitation. The solutions were extruded using a nozzle of 0.80-mm inner diameter into calcium chloride solution containing acetic acid and gas generating agent with gentle agitation at room temperature. The gel beads formed were allowed to stand in the solution for 20 min, separated and washed with distilled water. The beads were air-dried at 37°C for 12 h or freeze-dried.\footnote{83,84}

Sriamornsak et al. developed floating emulsion gel beads of calcium pectinate using an emulsion-gelation method to modify the drug release by applying some additives into the starting solution prior to bead formation, by hardening with glutaraldehyde, and by coating with polymer. The additives (PEG10000, glyceryl monostearate, and Eudragit L) had a slight, insignificant, effect on the drug release. Using 2% glutaraldehyde as a hardening agent prolonged the drug release. Coating the beads with Eudragit RL significantly sustained the drug release while the beads remained buoyant. The results suggest that beads are suitable as a carrier for intragastric floating drug delivery and that their release behavior could be modified by hardening with glutaraldehyde or by coating with Eudragit RL.\footnote{85}

Badve et al. developed floating hollow calcium pectinate beads of diclofenac sodium intended to overcome limitations of various approaches for imparting buoyancy by simple process of acid-base reaction during ionotropic crosslinking. The floating beads obtained were porous, hollow with bulk density <1. In vivo studies by gamma the-scintigraphy determined on rabbits showed gastroretention of beads up to 5 h. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer which suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system for site- and time-specific release of drugs acting as per chronotherapy of diseases.\footnote{86}

Sriamornsak et al. prepared wax-incorporated pectin-based emulsion gel beads of metronidazole using a modified emulsion-gelation method. The drug-loaded gel beads were found to float on simulated gastric fluid if the sufficient amount of oil was used. Incorporation of wax into the emulsion gel beads affected the drug release. Water-soluble wax (i.e., polyethylene glycol) increased the drug release while other water-insoluble waxes (i.e., glyceryl monostearate, stearyl alcohol, carnauba wax, spermaceti wax, and white wax) significantly retarded the drug release. However, the increased amount of incorporated wax in the formulations significantly sustained the drug release while the beads remained floating.\footnote{87}

Gadad et al. designed porous floating beads of captopril by ionotropic gelation method with low-methoxy pectin and gellan gum as polymer and sodium bicarbonate as pore forming agent. Formulation containing low-methoxy pectin and gellan gum in ratio of 3:1 and 250 mg sodium bicarbonate has porosity of 38.41%, bulk density <1, entrapment efficiency 83.10% and particle size 1.124 mm. It showed two-phase release pattern; lag phase and rapid pulsatile phase. In vivo gamma-scintigraphical study indicated that it has 6 h of retention time.\footnote{88}

**GUAR GUM**

Guar gum is a natural nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (family Leguminosae). In pharmaceuticals, guar gum is used in solid dosage forms as a binder, disintegrant, and as a polymer in the floating drug delivery system.\footnote{89} Guar gum mainly consisting of polysaccharides of high molecular weight (50,000-8,000,000) composed of galactomannans, mannose: Galactose ratio is about 2.1. It consists of linear chains of (1-4)-b-D-mannopyranosyl units with a-D-galactopyranosyl units attached by (1-6) linkages.\footnote{90}

It is soluble in hot and cold water but insoluble in most organic solvents. It has excellent thickening, emulsion, stabilizing, and film forming properties. It has an excellent ability to control
rheology by water phase management. The viscosity of guar gum is influenced by temperature, pH, presence of salts, and other solids.\[^{83-85}\]

Thahera et al. (2012) developed floating system of norfloxacin with guar gum, sodium CMC, HPMC15 KM with other excipients such as povidone (PVP) K30 (binder), sodium bicarbonate, and microcrystalline cellulose in different concentrations. The formulations were found to extend the drug release over a period of 7-12 h and the drug release decreased with decrease in polymer concentration. A formulation which exhibited 99.87% of drug release in 12 h, and floating lag time of 130 s with a floating time of 24 h was considered as ideal formulation and no drug-excipient interaction in the prepared formulations was confirmed by fourier transform infrared spectroscopy studies.\[^{96}\]

Hajare and Patil designed floating tablet of metformin Hcl, an anti-diabetic biguanid with poor bioavailability and absorption window at the upper part of gastrointestinal tract prepared by wet granulation method incorporating natural polymers guar gum and k-carrageen and a polymer HPMC either alone or in combination. Formulation prepared with a combination of 6% w/w k-carrageen, and 11%w/w guar gum showed good gel strength, stable, and persistent buoyancy for 12 h, least floating lag time of 58 s with good matrix integrity throughout dissolution period. Comparison study with Glutamet\[^{8}\] showed that the optimized formulation has better and complete release than the marketed product. Studies revealed usefulness of natural polymers over synthetic.\[^{97}\]

**XANTHAN GUM**

Xanthan (a well-known biopolymer) is an extracellular heteropolysaccharide produced from bacterium Xanthomonas campestris which is a natural, biosynthetic, edible gum, and an extracellular anionic polysaccharide. Xanthan gum consists of glucose, mannose, and gluconic acid, and is used in different foods as thickener and stabilizer.\[^{98}\]

Xanthan is a long-chained polysaccharide with a large number of trisaccharide side chains (composed of two mannose units and one gluconic acid unit) and consists of a b-(1, 4)-D-glucose backbone. This gum develops a weak structure in water, which creates high-viscosity solutions at low concentration. Viscosity remains fairly constant from 0°C to 100°C.\[^{99}\]

It hydrates rapidly in cold water without lumping to give a reliable viscosity, encouraging its use as thickener, stabilizer, emulsifier, and foaming agent. Xanthan solutions are highly viscous, even at low concentrations. This property is useful in many industrial applications, especially in the food and cosmetic industries.\[^{99,101}\]

Nagesh et al. also developed floating tablet of carvedilol with HPMC and natural gums such as; guar gum, xanthan gum, and gum ghatti. The result indicated that the release of drug from xanthan gum and guar gum was more controlled manner than xanthan gum and guar gum alone. The drug release mechanism was nonFickians diffusion.\[^{102}\]

Patel et al. prepared floating delivery system with xanthan and guar gum of dipyridamole using factorial design, and it was concluded that the ratio of xanthan to guar gum had equal or dominant role as controlling factor on kinetics of drug release compared to content of polymer blends.\[^{103}\]

**ETHYLCELLULOSE AND HYDROXY PROPYL METHYL CELLULOSE**

Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined together by acetal linkages. Coating agent; a flavoring agent; tablet binder; tablet filler; viscosity increasing agent are some other properties of EC. EC, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films.\[^{94}\]

Hydroxy propyl methyl cellulose (a semi-synthetic polymer) is dominant hydrophillic vehicle which is used in the preparation of oral controlled drug delivery systems. It belongs to the family of hydrophilic polymers which in contact with liquid (water or body fluid) swell and makes a gel layer around dry core of the polymer matrix. Its drug-releasing factors are very complex due to micro and macrostructures of HPMC exposed to water are strongly time dependent. It is an odorless and tasteless, white to slightly off-white color, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer and cellulose. The kinetics of the gel layer formation depends on the external parameters such as temperature, molecular weight of the polymer, and pH of the solution. It is a modification of alkali cellulose, which is produced when purified wood pulp is treated with 18% sodium hydroxide solution. Methyl and hydroxypropyl ether groups are introduced into the molecule by reacting the alkali cellulose with methyl chloride and propylene oxide, respectively.\[^{95-97}\]

There are several grades of HPMC like, K4M, K100M, K15M etc., which are used in the preparation of floating microspheres and floating tablets.\[^{98-100}\]

Karthikeyan et al. developed floating microspheres of cefpodoxime proxetil by nonaqueous solvent evaporation method using different grades of HPMC such as HPMC K15M (15 cps), HPMC K4M (4000 cps), HPMC100 LV (100 cps) and EC in order to demonstrate the effect of different viscosities on drug release profile. The prepared floating microspheres were found to produce the percentage yield of 50.5-72.21%, drug entrapment efficiency of 14.1-28.2%, buoyancy percentage of 70.1-88.25% and drug release of microspheres of 65.09-101.88%. The better drug release profile was found to be with formulation having drug: Polymer ratio of 1:2. HPMC 15cps showed much significant increase in the drug release while comparing with the other two grades of HPMC.\[^{101}\]
Shakya et al. developed a hydrophilic matrix, HPMC-based floating tablet of oxofluracin using cross-PVP as swelling agent, sodium bicarbonate as gas generating agent and citric acid to provide sufficient acidic medium to gas generating agent. Maximum cumulative percentage drug release at 12 h is around 100% and maximum floating duration is around 16 h. Serum drug level monitoring in human subjects for 24 h showed extended drug release for sufficiently longer duration making its once daily administration sufficient. The optimized formulation, when compared to the conventional immediate release preparation, seems to be promising for improving bioavailability of oxofluracin for enhancing its therapeutic efficacy along with improving patient convenience due to less frequent dosing requirement.[102] Singh et al. prepared a floating drug delivery system of famotidine by solvent evaporation technique using EC and HPMC as rate controlling polymer. Results showed that the polymer ratio and stirring speed affected the size, incorporation efficiency, and drug release of microspheres, and the best results were obtained at the ratio of HPMC:EC (1:6). The mean particle size of prepared floating microspheres increased, but the drug release rate from the microspheres decreased as the polymer concentration increased. The developed floating microspheres of famotidine may be used in the clinic for prolonged drug release in the stomach for at least 12 h, thereby improving the bioavailability and patient compliance.[107]

Patel et al. designed floating dosage forms of verapamil Hcl by incorporating HPMC, carbopol, and xanthan gum to provide gel forming property. HPMC and xanthan gum ratio 3:2 exhibited maximum release in 24 h with a good floating duration of more than 2 h. X-ray studies on dogs also showed no significant change in in vivo floating ability.[103]

Ethylcellulose is one of the most used polymers for the preparation of microspheres. It is also used in concentration up to 20% for better results.[109]

Vaghani et al. developed a multiple-unit-type oral floating dosage form of 5-fluorouracil to prolong gastric residence time for the treatment of stomach cancer by solvent evaporation method using EC as a polymer. The yields of preparation were very high, and low-entrainment efficiencies were noticed with larger particle size for all the formulations. Mean particle size, entrainment efficiency, and production yield were highly influenced by polymer concentration. Porous EC microspheres are promising controlled release as well as stomach targeted carriers for 5-fluorouracil.[104]

Saravanan and Anupama prepared ranitidine Hcl loaded floating microspheres by novel solvent evaporation-matrix erosion method using EC and polyethylene glycol (as pore forming agent to induce buoyancy) blend. Fourier-transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction studies indicated intact, and amorphous nature of entrapped drug in the microspheres. The drug-loaded microspheres could float 10 h and sustain the drug release over 4-6 h.[105]

Tejaswi et al. developed floating microspheres of clarithromycin and were successfully incorporated into the polymer, EC by solvent evaporation method. The obtained microspheres were spherical in shape and the size ranging from 3 μm to 5 μm. The entrainment efficiency results showed that the drug is encapsulated up to 69%. The buoyancy studies showed that all the formulations were floating more than 12 h. In vitro release profile showed that the drug was released in a sustained manner up to 12 h. Stabilities studies showed that the formulation can be stored at 40°C, 28°C, and 4°C temperatures without affecting drug loading.[106]

Kumar and Rai prepared and evaluated floating microspheres of curcumin for prolonged gastric residence time and increased drug bioavailability by emulsion solvent diffusion method, using HPMC, EC, Eudragit S 100 polymer in varying ratios. Ethanol/dichloromethane blend was used as a solvent in a ratio of 1:1. The floating microspheres showed particle size, buoyancy, drug entrapment efficiency, and yield in the ranges of 251-387 μm, 74.6-90.6%, and 72.6-83.5%, and 45.5-82.0%, respectively. Maximum drug release after 20 h was 81.3% by the best formulation.[108]

In an in vivo study on EC-based floating microspheres of ranitidine Hcl with dose of 35 mg/kg, results showed around 2.4 times increase in bioavailability.[109]

As per the literature it has been confirmed that HPMC can be used with other polymers but it may cause less entrapment efficiency and high-particle size of microspheres.[110]

**ACRYLIC ACID DERIVATIVES**

There are several derivatives which are used as polymers for the preparation of floating microspheres. Eudragit and carbopol are the mostly used derivatives in preparation of floating microspheres.

Eudragit is a derivative of acrylic and methacrylic acids. There are several grades of eudragit which were utilized for the preparation of floating microspheres. Eudragit RL, E, and RS grade are used for the preparation of floating microspheres.[111] In those grades, RL 100 and RS 100 are in granular forms and used widely than any other polymer which are pH independent swelling polymer with mucoadhesive properties.[112]

Lee et al. prepared floating acrylic resin microspheres with an internal hollow structure by a solvent diffusion and evaporation method. The yield of microspheres depended on the diffusion rate of ethanol and/or isopropanol in the organic phase. They were successfully produced when a mixture of ethanol and isopropanol was used instead of ethanol alone. The mixing ratio of components in the organic phase affected the size, and the yield of microspheres, and the best results were obtained at the volume...
ratio of ethanol:isopropanol:dichloromethane (8:2:5). Direct introduction of the organic phase into the aqueous phase through a glass tube also significantly improved the yield by avoiding the contact of the organic phase with the surface of water. The optimum rotation speed and temperature were 250 rpm and 25°C, respectively. When a drug had low solubility in dichloromethane and high solubility in both water and a mixture of ethanol/isopropanol, the loading efficiency was the lowest. The release profiles were significantly different depending on the solubility of the drug in the release medium and the physico-chemical properties of an encapsulated drug.[113]

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres by the emulsion solvent diffusion technique consisting of calcium silicate (as porous carrier) repaglinide (an oral hypoglycemic agent) and Eudragit S (as polymer). The microparticles were found to be regular in shape and highly porous. The formulation demonstrated favorable in vitro floating and release characteristics. The drug encapsulation efficiency was high. Incorporation of calcium silicate in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. The designed system, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of repaglinide.[114]

Kawashima et al. (2006) prepared hollow microspheres by a novel emulsion-solvent diffusion method using ethanol:dichloromethane solution of drug (tranilast or ibuprofen) and an enteric acrylic polymer which were poured into an agitated aqueous solution of polyvinyl alcohol thermally controlled at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug. The drugs incorporated in the solidified shell of the polymer were found to be partially or completely amorphous. The flowability and packability of the resultant microballoons were much improved compared with the raw crystals of the drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for >12 h. The drug release rates were drastically reduced depending on the polymer concentration at pH 6.8.[115]

Carbopol is also an acrylic acid derivative and frequently used in floating drug delivery due to its high mucoadhesive property and high swelling property. The floating tablets prepared using carbopol with combination of other polymers cause decrease in floating lag time which also gives a better result with eudragit.[116,117]

Floating microspheres were also prepared by emulsification solvent evaporation method using different grades of HPMC, carbopol 934, carbopol 940, and EC. Floating have been accepted as a process to achieve controlled drug delivery by prolonging the residence time of the dosage form at the site of absorption, thereby improving and enhancing the bioavailability of the drug.[118,119]

In a study on hollow microsphere of rosiglitazone maleate prepared from ethyl cellulose, HPMC and eudragit in different concentrations and ratios, Gangdharappa et al. showed that floating microspheres of rosiglitazone maleate had better glycemic control than conventional dosage form.[120]

Wang et al. also developed amultiunit floating dosage form of nitrendipine using EC and eudragit as polymers and compared with the nonfloating polymers having same polymers in which best results are observed in floating dosage forms. When this floating dosage form is compared with conventional dosage form the resultant relative bioavailability was found to be 166.01%.[121]

DIFFERENT OTHER EXCIPIENTS USED IN FLOATING DELIVERY SYSTEM

There are various excipients such as surfactants (sodium lauryl sulfate, poly vinyl alcohol, arlacel-60, tweens, spans etc.), gas generating agents (sodium bicarbonate, calcium carbonate), and pore forming agents (citric acid, silicates) are used in the formulation of floating drug delivery system.

Remya et al. prepared floating tablets of furosemide and studied the effect of two surfactants such as; sodium lauryl sulfate and arlacel-60 in different concentrations. The formulation containing 5% concentration of aracel-60 has low floating lag time and gives a better result in comparison to others. Formulation without surfactant has higher floating lag time and inefficient release profile than any of the formulation having surfactant.[112]

El-Nahas and Hosny developed chitosan-based floating microspheres and used sodium lauryl sulfate in concentration from 1% to 3% as crosslinking agent for chitosan and provides better results.[128] El-Gibaly et al. utilized sodium dioctyl sulfosuccinate, a negative charge surfactant to provide ionic interaction.[29]

Poly vinyl alcohol is also used in concentration from 0.25% to 4%.[123] Semalty et al. prepared floating microspheres of ofloxacin and used poly vinyl alcohol in 1% concentration, and this concentration provides better results than other.[124]

Kharia et al. developed floating tablet of acyclovir and used sodium bicarbonate and tartaric acid as gas generating agents. In some cases, citric acid is also used in place of tartaric acid but with an increase in citric acid concentration floating lag time was increased. When sodium bicarbonate and calcium carbonate is compared but preparing floating beads, the results indicate that the calcium carbonate is superior to sodium bicarbonate as a gas forming agent in alginate bead preparations.[31,125,126]
CONCLUSION AND FUTURE PROSPECTIVE

As per our discussion, we have seen that recently chitosan is in trend for the development of novel multi-particulate systems and has great results in improvement of bioavailability through other dosage forms. We can utilize these efforts in the development of floating drug delivery systems. There are still very few evidences of floating ability of chitosan microspheres. EC, HPMC, and Eudragit are most widely and commonly used polymers. There are various expensive polymers also which are synthetic in nature, but chitosan can be the best alternative for this. With proper polymer and surfactant ratio, we can formulate a better floating dosage form having controlled release ability.

In spite of various benefit till date, there is very few utilization of this drug delivery system on an industrial level. This delivery system can play a beneficial role in the absorption of acidic active pharmaceutical ingredients with decrease in dosing frequency.

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