Research Article

Design of Floating Drug Delivery Systems: An Update on Polymeric Advancements with Special Reference from Natural Origin

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ABSTRACT

The purpose of writing this review on design of floating drug delivery systems is to give an update on polymeric advancements to compile the recent literatures with special focus on the polymers used in floating drug delivery systems mostly from natural origin. Floating drug delivery systems are less dense than gastric fluids; hence remain buoyant in the upper gastrointestinal tract for a prolonged period, releasing the drug at the desired rate. Thus enhances the bioavailability of certain drugs having absorption window nearer to upper gastrointestinal tract. This review article focuses on: the recent technological development in floating drug delivery systems with special emphasis on the principal mechanism of floatation and advantages of achieving gastric retention and its potential for oral controlled drug delivery; polymers used in both single unit and multiunit floating systems; brief collection on various natural polymers employed for floating drug delivery systems etc. Although a variety of polymeric materials are available to serve as release retarding floating matrices but use of natural polymers to prolong the delivery of the drugs is always an area of active research despite the advent of synthetic biodegradable polymers. Natural polymers remains attractive primarily because they are readily available in the nature, relatively inexpensive, products of living organisms, readily undergoes *in-vivo* degradation, non-toxic and capable of chemical modifications

Keywords: Controlled release, Floating lag time, Floating duration, Gastro retentive drug delivery systems, Natural gums.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. The effective oral drug delivery practice depends on various factors like gastric emptying process, gastrointestinal transit time of dosage form, drug release from dosage form and site of absorption of drug. It has been frequently observed that many drugs which are easily absorbed at upper gastrointestinal tract (GIT), eliminated quickly in to lower GIT because of the peristaltic movement. So it leads to incomplete absorption of drugs from upper part of GIT. To overcome this limitation, the development of oral gastro retentive sustained or controlled release formulations is an attempt to release the drug slowly at upper GIT to maintain effective drug concentration in systemic circulation for a prolonged period. Dosage forms that can be retained in the stomach are called as gastroretentive drug delivery systems (GRDDS). Approaches to increase gastric residence time include.[1,2]

- Bio-adhesive drug delivery systems.
- Floating drug delivery systems.

Floating Drug Delivery Systems (FDDS)

These are the low density systems having their density lesser than the gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. FDDS are classified into two major categories:[3-9]

A. Effervescent systems.

B. Non effervescent systems.

A. Effervescent systems: When they come in contact with gastric juices, release carbon dioxide. This carbon dioxide is trapped inside of the swollen hydrocolloids. This provides buoyancy to the dosage form there by making it to float. These systems may also contain volatile liquids that gasify at body temperature. These are classified as follows:

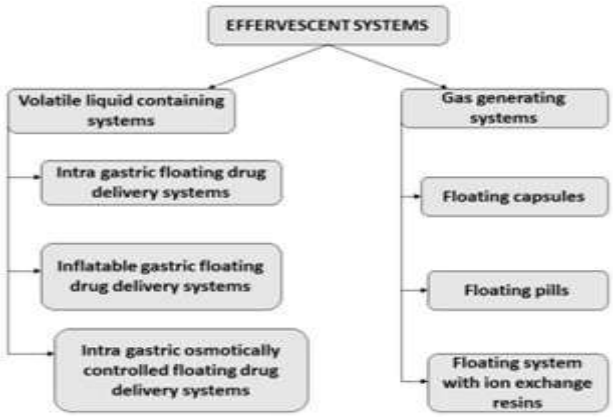

Figure 1: Classification of effervescent systems

B. Non effervescent systems: This type of systems swells after Imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems also known as the "plug type system" since they have a tendency to remain near the pyloric sphincter. One of the formulation methods of such dosage forms involves the

mixing of drug with a gel forming polymers, which swells in contact after oral administration and maintains a relative integrity of shape and a bulk density of less than 1. The most commonly used excipients are gel forming materials such as polycarbonate, polyacrylate, polystyrene etc. this hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of drug release from the dosage form. The various types of this system are as follows:

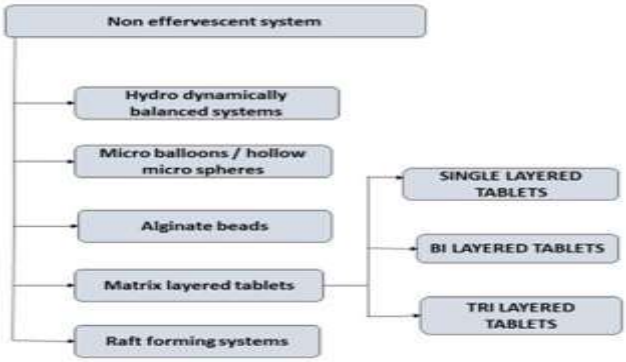

Figure 2: Classification of non-effervescent systems

Hydro dynamically balanced intra gastric delivery systems in either tablet or capsule form are designed to prolong gastro intestinal residence time and to maximize drug reaching to its absorption site. It is prepared by incorporating a high level of one or more gel forming hydrocolloids into formulation and then compressing these granules into tablet. Formulation of this device must comply with following criteria:

- It must have sufficient structure to form a cohesive gel barrier.
- It must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010).

On contact with gastric fluids the hydrocolloid in this floating device starts to become hydrated and forms a colloidal gel barrier around its surface with thickness growing with time.

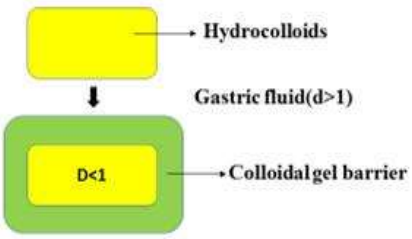

Figure 3: Hydro dynamically balanced intra gastric drug delivery device before and after contact with gastric fluid which activates the formation of the colloidal gel barrier.

This gel barrier controls the rate of solvent penetration into the device and the rate of drug release from the device. It maintains a bulk density <1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6hrs.[10] A gastro intestinal drug delivery system can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum or filled with air or harmless gas. A drug reservoir is encapsulated inside a microporous compartment with aperture along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent direct contact of the stomach mucosal surface with the un dissolved dug. Entrapped air in the floating chamber stimulates the system to float over gastric content. Through the aperture the gastric fluid enters which dissolves the drug for a continuous absorption across the intestine. In inflatable gastro intestinal drug delivery device the residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains a liquid. e.g., ether, that gasifies at body temperature to cause the chamber to inflate in the stomach.

The osmotic pressure controlled drug delivery device consists of 2 compartments

1. A drug reservoir compartment
2. An osmotically active compartment

The reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach the water in the gastric fluid is continuously absorbed through the semi permeable membrane into the osmotically active compartment to dissolve osmotically active salt. An osmotic pressure is thus created, which acts on the collapsible bag and, in turn forces the drug reservoir compartment to reduce its volume and activates the release of drug solution through system containing drug delivery orifice.

In case of vapor pressure activated drug delivery devices, the drug reservoir consisting of drug in solution form is contained inside an infusate chamber, which is physically separated from the vapor chamber containing a vaporizable fluid. e.g., fluorocarbons. This fluid vaporizes at body temperature and creates a vapor pressure. Under the vapor pressure created, the bellows moves upward and forces the drug solution in the infusate chamber to release, through a series of flow regulator and delivery cannula into the blood circulation at a constant flow rate as defined by

$$\frac{dQ}{dt} = \frac{3.1416 d^4 \Delta p}{128 \mu l}$$

d and l are inner diameter and length of delivery cannula. Δp is the pressure difference between the vapor pressure in the vapor chamber and the pressure at the implantation site, and μ is the viscosity of the drug solution. Some of the typical examples are the development of infusaid, an implantable infusion pump of; heparin for anti-coagulation treatment, insulin for

anti-diabetic medication and morphine for patients suffering from the intestinal pain of terminal cancer.[11]

Natural Polymers Used In the Design of Various Floating Drug Delivery Systems

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. For e.g., Acacia, pectin, agar, alginates, gellan gum, guar gum, okra gum, cashew gum, xanthan gum, gelatin, casein.[12]

Xanthan gum (XG): It is a polysaccharide which is heavy molecular weight natural polymer which is obtained from specific species of bacteria. It is obtained by fermentation of glucose using the gram negative bacteria named as *Xanthomonas campestris*. It is nontoxic and non-pathogenic in nature. Xanthan gum is soluble in cold as well as in hot water giving highly viscous solution, which is stable towards heat and change in pH. Xanthan gum is also used as an effective excipient for sustained release of drug and also shows time independent release kinetics. Each xanthan gum repeat unit contains five sugar residues, 2 molecules of glucose, 2 molecules of mannose and one glucuronic acid. The mannose nearest the main chain carries a single group at C-6, This results a stiff polymer chain may exist in solution as a helix form, that interacts with other xanthan gum molecules to form a network. Xanthan gum is anionic in nature so it is not compatible with cationic compounds and xanthan gum is incompatible with oxidizing agents, sodium carboxy methyl cellulose, and dried aluminum hydroxide gel and with some drugs like amitriptyline, tamoxifen. Xanthan gum has also been used with guar gum for the development of floating drug delivery systems. It has also derivatised to sodium carboxymethyl xanthan gum and cross-linked with aluminum ions to prepare microparticles, as a carrier for protein delivery.[13-24]

Venkata S *et al*., prepared non effervescent floating drug delivery systems of poorly soluble drug carvedilol phosphate by using release retarding polymers/swellable polymers such as xanthan gum and poly ethylene oxide by solvent evaporation and melt granulation techniques. Xanthan gum formulation was best with drug retardation up to 12 hrs and floating lag time was lower than 10sec.[25]

Kulkarni A *et al*., prepared a region selective bi layer tablets of atenolol and Lovastatin by direct compression technique using sodium starch glycolate as super disintegrant and HPMC K100M and xanthan gum as the release controlling polymers and sodium bicarbonate as gas generating agent. It was observed that xanthan gum retarded the drug release (>12 hrs) in a better way with improved floating lag time and total floating time than HPMC K100M.[13]

Dey S *et al*., prepared sustained release floating matrix tablet of atenolol using release retardants derived from *xanthomonas campesteris* and *cyamopsis tetragonolobus* to enhance the gastric residence time of tablet in stomach with the aim of enhancing bioavailability. The optimized formulation containing 20% W/W of polymer blend and 50:50 xanthan gum to guar gum ratio was able to float for more than 12hrs.[21]

Mundade S *et al*., prepared controlled release gastro retentive buoyant tablets of Ofloxacin with xanthan gum and polyox WSR 1105 by direct compression technique with other excipients like sodium bicarbonate, citric acid, magnesium stearate etc. The combination of both synthetic and natural polymers had given a better result than individual ones.[18]

Guar gum: It is a poly saccharide, found in the seeds of the plant *Cymopsis tetragonolobus*(family Leguminosae). Researchers have been using guar gum either alone or in combination for fabricating sustained release dosage forms. It swells rapidly in presence of water with a translucent suspension. The contents of guar gum are re divided into water soluble and insoluble parts. The water soluble fraction consists about 85% of gum known as Guaran, which is having high molecular weight hydrocolloid polysaccharide. Guaran on hydrolysis gives 65% galactose and 35% mannose both combined through glycosidic linkages. About 1% mucilage of guar gum poses similar viscosity to that of mucilage of acacia and 3% mucilage similar to mucilage of tragacanth. It has 5-8 times thicker than starch. It acts as protective colloid, binding agent, disintegrant, emulsifying agent etc. Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However, the addition of borate ions to hydrated guar gum produces cohesive structural gels and further hydration is then prevented.[14-17, 22]

Navneeth K *et al*., prepared Atorvastatin calcium floating tablets by using guar gum as the release retardant material. The formulated batches were able to retain themselves in the stomach for approximately 12hrsresulting in enhanced drug solubility and bioavailability as well. The formulations containing natural polymers showed more release retardant effect and controlled drug release profiles in a predictable manner when compared to synthetic polymers.[17]

Chitosan (CHI): Chitosan is commercially obtained by hydrolysis of the amino acyl groups of chitin, a straight chain homo polymer composed of β (1, 4 -2-acetamido-2-deoxy D-glucose) units. Chitosan has one primary amino and 2 free hydroxyl groups or each glucose units. The cationic amino groups react with a number of multivalent anions to form hydrogels. Increased deacetylation enhances the biocompatibility of chitosan. Preparation of hydrogels involved mainly by the modification of chitosan. Various types of modifications are; modification through covalent cross linking, modification through ionic cross linkage, modification through grafting and modification through electrolyte composition.[26-28]

Hascicek C *et al*., prepared gastric floating bi-layer tablets with acetyl salicylic acid by direct compression method. Tablets including HPMC K100M showed the slowest release pattern. The release rate was effectively modified by using combination of HPMC K100M and chitosan for up to 8hrs. The drug release was found to be following Higuchi diffusion mechanism.[26]

Salep: A novel gastro retentive drug delivery system can be achieved by using salep. It is also known as salepi. The flour obtained from grinding of dried palmates of tubers of orchismoriovarmascula of Orchidaceae family. The main polysaccharide content of salep is glucomannan. Highly soluble in hot as well as in cold water which forms a viscous solution. It consists of D-glycopyranosyl and D-mannopyranosyl at ratio of 1:3.3. Its backbone chain containing of b (1→4) linked glycosyl and manosyl residues.[29]

Razavi M *et al*., prepared gastric floating matrix tablets containing1:2.5ratio of famotidine: salep with shortest floating lag time of 35sec and drug release of around 100% within 24hrs.It might be due to the high viscosity of salep used to prepare these formulations resulting in a strong gel matrix, as the air bubbles trapped inside the polymer matrix assisted in floating. Also with increase in the polymer concentration a decrease in drug release rate was noticed from various formulated batches.[29]

Sodium alginate: Another numerously employed release retardant excipient in the design of gastro retentive tablets is sodium alginate. This is a nontoxic biodegradable copolymer composed of L-glucuronic acid and D-mannuronic sea weed species extracted by ion exchange technique. It hydrates and swells in aqueous media. However in acidic medium it swells and remains insoluble which contributes to the buoyancy and controlled release properties.[30-32]

Patel N *et al*., prepared gastro retentive drug delivery system of glipizide tablets by using sodium alginate. From the *invitro* drug release studies it was observed that, the increased concentration of polymer (sodium alginate) in formulation lead to deceased rate of drug release and improved total floating time.[33]

Dios P *et al.*, designed floating matrix tablets incorporating paracetamol as a model drug. High viscosity sodium alginate was used as the swelling excipient as it promotes flotation. Low substituted HPC B1 and 11 were used as disintegrating agents. Sodium bicarbonate was used as gas generating agent, talc, magnesium stearate, micro crystalline cellulose and silicon colloidal anhydrous were used as other excipients for tablet formulation. Higher sodium alginate content resulted in increased floating lag time. It is supposed that sodium alginate in increased concentration leads to formation of the alginic acid layer on tablet surface, leaving the internal space of tablet dry. Due to this effect it takes longer time to float.In lower concentration sodium alginate swells more rapidly enhanced by quick water uptake.[34]

Mina I *et al.*, prepared ciprofloxacin effervescent floating matrix tablets designed by using HPMC K15M and sodium alginate as release retarding polymers and sodium bicarbonate and calcium carbonate as gas generating agents. Formulation F7 containing HPMC K15M (21.42%W/W), sodium alginate (7.14%W/W) and sodium bicarbonate (20%W/W) showed excellent floating properties and sustained action.[32]

Pectin: Pectin is a high-molecular-weight, carbohydrate-like plant constituent consisting primarily of chains of galacturonic acid units linked as 1,4-a-glucosides. The USP 32 describes pectin as a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rindof citrus fruits or from apple pomace. It consists of chiefly partially methoxylated polygalacturonic acids. Pectin gelation characteristics can be divided into two types. They are high-methoxy and low-methoxy gelation. Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in a 1, 4-glucoside chain. Pectin gel beads have shown to be an effective medium for controlling the release of drugs within the gastrointestinal tract. Pectin-based matrices with varying degrees of esterification have been evaluated as oral controlled-release tablets. Low-methoxy pectins were shown to have a release rate more sensitive towards the calcium content of the formulation. Pectin has been used as a component in the preparation of mixed polymer microsphere systems with the intention of producing controlled drug release.[35]

Ela A*et al.*, prepared ketorolac tromethamine floating beads. A solution of ketorolac in water was added to sodium alginate (as copolymers in ratio of 1:1 with other polymers) solution containing methyl cellulose, hydroxyl propyl cellulose, sodium carboxy methyl cellulose and pectin separately and the mix was passed through syringe needle into calcium chloride solution containing glacial acetic acid. Floating lag time and controlled release characteristics of pectin was found to be better than others. The order was in the sequence of: pectin >sodium carboxy methyl cellulose>methyl cellulose>hyroxypropyl cellulose. The order of rate of drug release was: Hydroxy propyl cellulose<sodium carboxy methyl cellulose<methyl cellulose<pectin.[36]

Locust bean gum (LG): It is a natural polysaccharide, translucent white opaque at the edge containing about 88% of D-galacto-D- mannoglycan, 4% pentan, 6% protein, 1% cellulose and 1%ash. The ratio of D- galactose and D-mannose are approximately 20:80.[37, 38]

Salve PS *et al.*, prepared gas generating floating tablets of metformin hydrochloride. The tablet formulation containing metformin hydrochloride: locust bean gum in 1:1 ratio and 10% sodium bicarbonate has shown 90% drug release in 8hrs.Afaster drug release was observed in case of formulation batch containing locust bean gum alone compared to xanthan gumalone due to weak matrix forming tendency of locust bean gum. Hence a

combination of xanthan gum: locust bean gum 2:8 ratio was used to increase the matrix strength.[39]

Swati JC *et al.*, prepared tapentadol (freely water soluble) floating matrix tablets. Xanthan gum and locust bean gum were used as release retarding agents. Other excipients like Sodium bicarbonate, magnesium stearate, citric acid etc. were used. Formulation with 15% and 20% sodium bicarbonate was failed to float. Combination of 20% of sodium bicarbonate with 10% citric acid showed good floatability. For optimized formulations LG (70mg) and XG (50mg) floating lag time was within 5 mins and drug release up to 8 hrs. Results revealed that locust bean gum showed better gelling and matrix forming property compared to xanthan gum.[37]

Olibanum: Olibanum is an oleo gum resin obtained from the incised trunk of the tree *Boswelliaserrata* belonging to the family Burseraceae, commonly known as Sallakiguggul, Salai gum and Indian Olibanum. Different species of *Boswellia* occur in tropical parts of Asia and Africa. Olibanum consist of mainly an acid resin (56-60%), gum (30-36%) and volatile oil (3- 8%). Gum is mainly composed of arabinose with small amount of xylose and galactose. It is an efficient matrix former and micro encapsulating agent for controlled release.[38,40,41]

Devi C*et al.*, prepared sustained release floating matrix tablets of pioglitazone employing Olibanum gum and HPMC. Olibanum was used as matrix former along with sodium bicarbonate as gas generating agent. Bees wax and ethyl alcohol were also employed as floating enhancers. Olibanum was evaluated as a better matrix former for fabrication of floating tablets in comparison to HPMC K15M. In case of optimized batch containing olibanum, floating lag time, total floating duration and drug release were respectively up to 2-6 mins, greater than 44hrs and up to 24hrs.[41]

Okra gum: Okra gum is a natural polymer obtained from the pods of okra plant (*Abelmoschusesculentus*). It has been used as a binder, hydrophilic polymer matrix, suspending and bioadhesive agents. The potential of okra gum, obtained by traditional extraction, as a film coating agent was reported. It remains insoluble at gastric pH. It enormously swells and helps in retarding the drug release.[38]

Rajamma AJ *et al.*, prepared gastro retentive tablets of ziprasidone HCl using natural gums as sustained release carriers. Floating lag time was found to be increased at higher level of okra gum and decreased as level of HPMC K4M increased. This might be because of high swelling property of the later. An increase in viscosity of the swollen gel matrix was observed with increase in the concentration ofokra gum and locust bean gum, which decreases the water diffusion into the core layer. Decrease in hydration of matrix contributed more hindrance for drug diffusion and consequently decreased the drug release rate.[38]

Cashew gum (CG): Cashew gum is the exudate from the stem bark of *Anacardiumoccidentale*Linn (family, Anarcardiaceae).Cashew gum is chemically composed of61% galactose, 14% arabinose, 7% rhamnose, 8% glucose, 5%glucuronic acid and less than 2% other sugar residues. Hydrolysis of the gum yields L-arabinose, L-rhamnose, D-galactose and glucuronic acid. The gum has a highly branched galactan framework comprising of chains of (1→3) -linked β–D-galactopyranosyl units interspersed with β- (1→ 6) linkages. Cashew gum has been studied widely for various pharmaceutical applications as it is inexpensive, non-toxic, biodegradable, and possesses appropriate physicochemical characteristics.[42]

Paula HC *et al.*, prepared a polymeric floating system composed of Alginate (ALG) and CG, loaded with an essential oil (Lippiasidoides-Ls) by ionotropic gelation method, and evaluated their physico-chemical properties along with potential for controlling drug release. Results showed that beads produced with high level of CG exhibit good floatability (up to 5 days) and loading capacity (15.2-23.8%). *In vitro* release data showed a Fickian diffusion profile and *in vivo* experiments showed that ALG-CG floating system presented a superior and prolonged larvicide effect, in comparison with non-floating ones. These results indicate that ALG-CG floating beads loaded with Ls presented enhanced oil entrapment efficiency, excellent floating ability, and suitable larvicide release pattern.[43]

Starch: Starch is a natural poly saccharide which is composed of amylose representing the linear fraction of this macromolecule. Modified starch containing high amount of (70%) amylose has been used successfully in the research and development of swellable hydrophilic matrices. Some properties of high amylose starch can be modified via esterification, etherification and oxidation of its hydroxyl groups or by cross linking with different chemicals such as epichlorohydrin, sodium tri Meta phosphate etc. The lowest drug release rates exhibited by cross linked samples demonstrated that the inter chains ester linkages introduced to the polymer structures by cross linking reactions.[42,44-46]

Saritha M *et al.*, formulated pioglitazone floating matrix tablets with Olibanum, starch acetate and HPMC K15M and comparatively evaluated those with one another. Floating lag time of the formulation containing starch was 4-7 min and floating duration 44-48 hrs. Release retardant characters were as follows: Olibanum>starch acetate>HPMC K15M.[47]

Gellan gum: Gellan gum is a heavy molecular weight polysaccharide, which is obtained from pseudomonas species. It is a fermentation product of the microbe sphingomonas elodea and nontoxic gram negative bacteria. Gellan gum is an anionic deacetylated extra cellular linear polysaccharide comprising glucuronic acid, rhamnose and glucose. Its structure consists of four linked monosaccharides, including one molecule of

glucuronic acid and 2 molecules of glucose. It is available in two forms (high or low acyl content). This gum has an excellent gel strength and outstanding stability, flexibility, high clarity, good film forming ability and thermally reversible gel characteristics. Gellan gum is a water soluble and off white powder. It forms gel when cations added. Thus the thickness and texture of gellan gum in various products can be controlled by manipulating the addition of cationic salts. Gellan gum disperses and hydrates easily in hot or cold water, forming viscous solution. This gum has been considered as a potential carrier for different floating dosage forms by various researchers.[48]

Sterculia gum: Gum sterculia is the dried exudation obtained from the stems and branches of "Sterculia Uren's", belonging to the family Sterculiaceae, a tree native to India. Gum sterculia comes under the group of gums which contain basal chains of galactouronans or galacturonorhamnans with residue of both D-galacturonic acid (in interior chain) and D-glucuronic acid (or its 4-methyl) ether (as terminal units in side chain attached to a variety of different sugar residues). Gum sterculia contains around 43% of D-galacturonic acid, 13% D-galactose and 15% L-rhamnose. Gum Karaya is a negative charged colloid and a high-molecular weight complex acidic polysaccharide. The general utility of Gum sterculia is based on its viscosity. It was successfully evaluated for its suitability in the preparation of hydrophilic matrices, mini-matrices, and microcapsules etc[49,50]

Singh B *et al.*, prepared a gastro-retentive floating drug delivery system of pantoprazole by simultaneous ionotropic gelation of alginate and sterculia gum using $BaCl_2$ as a cross linker. The combination of sterculia gum and alginate enhances the repair of mucosal damage in the GIT. Release of drugs from beads followed a Fickian diffusion mechanism. The drug delivery systems thus designed was found to have a double potential, first due to the therapeutic importance of the sterculia-alginate-based polymer matrix and second, release of pantoprazole in a controlled and sustained manner.[49]

Konjacglucamannan (KGM): Konjacglucomannan is a kind of neutral polysaccharides with excellent biocompatibility and biodegradable activities. The recent studies on the applications of konjacglucomannan and its derivatives are used in pharmaceutical, bio-technical and in fine chemical fields etc.KGM and the polysaccharide of *Bletillastriata* (BSP) have emerged as new sources for development of biomaterials. They have been fabricated into drug delivery vehicles. It demonstrates strong gelling properties and high biocompatibility.[51,52]

Wang K *et al*., prepared Controlled release beads by using alginate (ALG), KGM and chitosan (CHI). Bovine serum albumin and insulin were used as model proteins for *in vitro* assessments. It was observed that KGM shows excellent hydrogen binding and electrostatic interaction characteristics. After treating the beads with 0.1 N HCl for 4hrs and putting them into pH 7.4 buffer, protein release was observed for 1 hr in case of ALG–CHI beads whereas around 3 hrs from ALG–KGM–CHI beads. However, the leaking of protein from ALG–KGM–CHI beads was also increased in 0.1 N HCl. Concentration of gelling ion had great effect on release rate of drug and its gel structure. Studies of water of hydration had shown that swelling of ALG–KGM–CHI beads was greater than that of ALG–CHI beads in acidic solution, but the opposite result was obtained in alkali solution. The result indicated that the diffusion of protein was related to the viscosity and swelling nature of KGM.[53]

Liang H *et al.*, investigated the effect of ball-milling time on the structure, floating and controlled-release properties of konjac flour. After 8 hrs of ball milling, the particle size of konjac flour decreased from 152µm to 19.8µm. The results indicated that longer ball-milling time lead to higher angle of repose, lower molecular weight and coarser surface of konjac flour. Compared with native konjac flour, the 4 hrs ball-milled konjac flour achieved the shortest floating lag time, longest floating duration and the best controlled-release properties when used as excipients in floating drug delivery systems. The water distribution in tablets with different dissolution time was observed by magnetic resonance imagining. For konjac flour with 4hrs of ball milling developed a hydrogelling layer at the surface delaying penetration of moisture into the inner region of the tablet and delaying drug release.[54]

Casein: Casein can enclose bioactive molecules and modify the release and/or improve the bioavailability of the associated molecules. It has ability to modify drug dissolution from compacts. Casein films have high tensile strength, favors its use as an acceptable film-coating for tablets. Naturally occurring genipin and a natural tissue enzyme, transglutaminase, were used as cross linkers to prepare novel casein-based hydrogels for the controlled release of bio actives.[55-56]

Elzoghby AO *et al.*, prepared casein floating beads to enhance the residence time of drugs in the stomach based on its emulsifying and bubble-forming properties. Casein-based micro particles entrapping bioactive molecules were prepared via emulsification-chemical cross linking with glutaraldehyde, enzymatic cross linking by transglutaminase, simple co-acervation and electrostatic complexation. Casein nano-formulations were also prepared to deliver nutraceuticals and synthetic drugs via enzymatic cross linking, graft copolymerization, heat-gelation and polyelectrolyte ionic complexation. It can be concluded that casein-based formulations are promising materials for controlled drug delivery.[55]

Bulgarelli E *et al.*, prepared controlled release beads of casein–gelatin. These have been prepared by emulsification solvent extraction method and cross-linked with d,l-glyceraldehyde in an acetone-water(3:1) mixture (v/v). Casein emulsifying properties cause air bubble incorporation and the formation of large apertures in the beads. It showed increased drug release rate creating high porous matrix, in comparison with beads without

cavities. This may be due to the rapid diffusion of the drug through water filled apertures. The study showed that cavities act as an air reservoir and enable beads to float. Therefore, it was concluded that casein could be suitable and inexpensive for the formation of an air reservoir for floating systems.[56]

CONCLUSION

Natural polymers have been used significantly in designing and synthesis of novel drug delivery systems because of their biodegradable, biocompatible, eco-friendly nature and vast availability. Hence these natural polymers will expand the scope of new drug delivery systems in the future. As per our discussions, we have seen that recently sodium alginate and xanthan gumare in trend for the development of floating drug delivery systems and has great results in improvement of bioavailability. There are various expensive polymers which are synthetic in nature, but sodium alginate and xanthan gum can be the best alternative for those. With proper selection of natural polymers and their blending with other polymers better floating dosage forms with improved floating lag time, floating duration and drug release can be achieved. The use of plant-based polymeric can be a good replacement for synthetic polymers in the development of controlled release floating dosage forms, because plant based materials can be modified to meet the requirements of drug delivery systems. Formulations prepared by such renewable and eco-friendly plant resources can be considered as promising floating matrix forming agents to bring about sustained release action with site specific delivery for improved bioavailability, supported by more elaborated research in this aspect. In spite of various benefits 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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