

Review Article



Natural Polymers Employed in Designing of Gastro Retentive Drug Delivery Systems

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ABSTRACT

In recent years, various scientists have tried to establish advances in research and development of rate controlled oral drug delivery system to overcome the drawbacks such as short gastric residence time, unpredictable gastric emptying time. To overcome these drawbacks gastro-retentive drug delivery system is developed which has the ability to retain in stomach for longer period of time and there by increases the bioavailability, perhaps providing therapeutically effective plasma drug concentration for longer period of time, which increases gastric retention period and thereby reducing dosing frequency. Several gastro retentive approaches have been currently used to prolong the gastro-retentive time. Prolong residence time of drug in stomach enhances its absorption, dissolution, and eventually bioavailability. This current review is to make provision with brief overview of the main purpose of natural polymers used in the development of gastro retentive drug system as well as their features, current research, future development trends and application in gastro-retentive system. Natural polymer has several advantages like biocompatibilities, nature in origin, safe, nontoxic, cost effective, biodegradable and their uses are increasing in pharmaceutical field. various natural polymers are used to authorize drug delivery system remain further as drug carriers, to obtain boosting therapeutic efficacy. Natural polymers provide gastric retention through various approaches such as low-density system, high density system, mucoadhesive system, swellable system.

Keywords: Gastro retentive, natural polymers, low density system, high density system, mucoadhesive system, swellable system.

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GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

Definition: Dosage form that can be retained in the stomach for prolong period of time are known as gastro retentive drug delivery system¹.

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro-intestinal tract for local as well as systemic effects². GRDDS shows wide range of therapeutic and benefits that are limited in the oral convention systems. They show local drug action, minimises the fluctuation in plasma drug concentration levels and also improves bioavailability and patient compliance³.

Incorporation of drugs in a controlled release gastroretentive forms which can remain in gastric region for several hours would significantly prolong the gastric residence time of drugs and reduce drug waste enhance the solubility of drugs that are less soluble in high pH environment⁴.

GRDDS can improve controlled delivery of drugs that have narrow absorption window by continuously releasing drug for a prolonged period of time before it reaches to

absorption site and perhaps improving the gastric residence time^{5,6,7}.

APPROACHES TO GASTRIC RETENTION

Various approaches have been followed to encourage gastric retention of oral dosage forms.

- 1) Floating drug delivery system
- 2) High density systems
- 3) Bio adhesive systems
- 4) Swellable systems

Floating drug delivery system

Floating drug delivery system is a low-density system or hydrodynamically balanced system. The system has tendency to float on gastric content and remain in stomach for extended period of time. Dosage form should have less density than that of gastric fluid (1.004-1.001gm/cm³) so that the dosage form float on the gastric fluid and slowly release the drug at desired rate from the system. After the drug release from the residual system, it emptied from the stomach. Hence it increases the gastric residence time and control the plasma drug concentration fluctuations^{8,9,10}.

High density system

In high density system the dosage form density should be greater than gastric fluid(1.004gm/cm³). Due to high density of dosage form it settle in lower part of the stomach and withstanding with peristaltic movement. These systems are coated by heavy inert material are used for coating such as barium sulphate, iron powder, zinc



oxide and titanium oxide. To attain longer retention in the stomach^{5,11}.

Bio adhesive system

The system is incorporated with mucoadhesive polymers that attached to the walls of the stomach to avoid gastric emptying. Gastric mucoadhesion does not tend to be strong enough to impart dosage forms the ability to resist the strong propulsion forces of the stomach wall. Most promising excipients are lectins, Carbopol, chitosan, Gildan. The system binds to the mucin and extends gastric residence time by increasing the intimacy and contact between the dosage form and biological membrane. The adhesion of polymers with mucous membrane may be mediated by hydration^{4,12}.

Swelling and expandable system

Swelling system are also referred as plug type system. The presence of polymers in this system promotes the swelling of dosage form is designed in small size enough to administrate through the oral route. But once it reaches to the stomach its imbibition gastric fluid and shows swelling property there by its size is expanded and difficult to move through the pyloric sphincter. Hence it prolongs the gastric residence time in the stomach^{13,14}.

NATURAL POLYMERS

Plant based polymers are naturally available and can be made into natural polymers. Natural gums are hydrophilic carbohydrate polymer of high molecular weight. As these plant elements are rich in carbohydrates most of these natural gums are found to be nontoxic, non-irritable, biocompatible. They are insoluble in organic solvents. Gum either water soluble or absorb water and swell in cold water in order to provide viscous solution^{15,16}.

Table 1: Advantages and Disadvantages of Natural Polymers

S.No	Advantages	Disadvantages
1	Biodegradable.	Microbial contamination
2	Environment friendly	Batch to batch variation
3	Biocompatible and non-toxic	Reduced viscosity and stored
5	Local availability	-

Chitosan

Chitosan is natural polymer prepared by the alkaline deacetylation of chitin that is obtained from crustacean shells. The sources of chitin are the shell wastes of shrimps, lobsters, krill and crab. It is a cationic polysaccharide composed of glucosamine and N-acetylglucosamine^{17,18,19}. It has favour biological properties such as biodegradability and biocompatibility and also have anti -bacterial properties makes it suitable for site specific delivery. when chitosan exposed to acidic pH 1.2 or neutral media it

becomes buoyant and provide control release²⁰. In chitosan film increases in thickness their release rate is decreased²¹. It is good applicant for development of conventional, novel gastrointestinal drugs and gene drug delivery system²². It plays crucial part in stomach specific drug delivery, intestinal drug delivery and colon specific drug delivery. In pharmaceutical field chitosan is used for formulating various dosage forms such as films, beads, intragastric floating tablets, microspheres and nanoparticles^{23,24,25}. Utilization of chitosan in biomedical fields and pharmaceutical fields as viscosity enhancers, mucoadhesive, film forming agent, binder, coating agent, disintegrant²⁶. Krishna SK et.al were develop the verapamil hydrochloride effervescent floating tablets in nine different formulations in different grades of polymers and effervescent agents by employing natural polymer chitosan. Same ratio ratio of chitosan, Carbopol, HPMC-K100M shows slow and complete drug release spread over 12 hrs²⁷.



Figure 1: Powder form of Chitosan

Guar gum

Guar gum is obtained from seeds of *Cyamopsis tetragonolobus* kernels belongs to the family Leguminosae. It is also called as guaran cluster bean, *Cyamopsis*, *Calcutta lucern* and guarina²⁸. It is a natural polysaccharide composed of linear chains of [1-4]-6-D-mannopyranosyl units with D-galactopyranosyl units attached by (1-6) linkages²⁹. It is whitish yellow in colour powder with no odour and taste. It is soluble in water and insoluble in organic solvents. Guar gum has more viscosity and in pharmaceutical industries gum is used as a binder, disintegrant for formulating solid dosage forms in floating drug delivery system³⁰. Efficacy of gum or modified gum used for developing the oral controlled release tablet^{31,32,33}.



Figure 2: Powder Form of Guar Gum

Few scientists revealed that guar gum used as a hydrophilic matrix to formulate the oral controlled release dosage forms, lately highlighted that guar gum act as a flexible carrier for oral extended-release drug delivery³⁴. They switch reference product (Dilacor XRO). In guar

formulation no changes are observed in in-vitro dissolution testing, accelerated stability studies. The results of *in vitro* *in vivo* correlation were successfully established for guar-based system^{35,36}.

Xanthan gum

Xanthan gum was synthesised by the bacteria *Xanthomonas campestris*³⁰. It is well known as biopolymer and anionic polysaccharide whose structure depends on the bacterial strain and fermentation conditions³⁷. It is stable polysaccharides with D-glucose backbone similar to that of cellulose. This comes in fine powder or cream that is odourless with free-flowing properties³⁰. Gum has excellent solubility and stability under acidic and alkaline conditions in presence of salts and resists to common enzymes¹⁶. Gum is utilized as thickening agent, stabilizing agent, gelling agent, viscosity modifier, suspending agent, and emulsifier in formulations³⁰. Xanthan is non-irritant and nontoxic used in cosmetic, food products, topical and oral pharmaceutical formulations and preparations^{26,38}. Xanthan gum is a useful pharmaceutical excipient it is assigned as generally recognised as safe (GRAS) used as a tablet excipient. Rasul et.al prepared sustained release tablet of metoprolol tartrate with combination of xanthan and tragacanth gum in different proportions by direct compression method using microcrystalline cellulose as a diluent. Increasing the amount of gum increases the sustained release of drug³⁹. For designing the modified release drug delivery system of diltiazem HCl is blended with gum and hydroxypropyl methyl cellulose showed drug release for 12hrs and their release rate kinetics followed by Hixson-crowell equation⁴⁰.



Figure 3: Powder Form of Xanthan gum

Okra gum

Okra gum is obtained from the fresh fruits of the plant *Abelmoschus esculentus* belongs to the family Malvaceae. Okra gum contains major polysaccharide component widely in molar ratio of galactose, galacturonic acid, and rhamnose with some fractions of glucose, mannose, arabinose and xylose⁴¹. Gum is used as binding agent, suspending and retarding agent. It is excipient for controlled release tablet. It was found that okra gum could be employed in sustained release upto 6 hrs. Extracted mucilage of okra, tragacanth, sodium CMC were used in formulation of paracetamol suspension. The mucilage was superior suspending agent than tragacanth and finally concluded that suspending efficiency was similar to sodium CMC⁴². In preparation of tablets *abelmoschus*

esculentus mucilage powder was potent as disintegrant in low concentrations (4 %)⁴³. For colon targeted tablet formulation okra polysaccharide was found by a microbially triggered material. Finally, the author concluded that okra polysaccharide has utmost potential to delivery maximum amount of drug to the site of action, in this case it is colon where it undergoes degradation which occurs due to the existence of anaerobic microbes⁴⁴.



Figure 4: Powder Form of Okra gum

Hibiscus mucilage

Mucilage is obtained from fresh leaves of *Hibiscus-rosa-sinensis* belongs to the family Malvaceae. It is composed of L-rhamnose, D-galactose, D-galacturonic acid and D-glucuronic acid⁴⁵. Jani et.al evaluate that sustained release tablet contain 1:5 ratio of drug and hibiscus mucilage is used to formulate a tablet here mucilage is employed as a release retarding agent. It shows their sustained release upto 12hrs⁴⁶. Ameena et. al in her study concluded that hibiscus rosa-sinensis mucilage showed excellent binding efficacy and could be used as release retarding agent in the formulation of tablet dosage forms⁴⁷. Kharwade Rs et.al in his study gastro retentive floating tables of domperidone prepared by direct compression method using *H.rosa-sinensis* mucilage. Finally concluded that tablets prepared by hibiscus rosa-sinensis mucilage, HPMC K100 M, Carbopol and sodium bicarbonate as a gas generating agent, could be more efficient on floating and sustained release of domperidone as compared to the tablets using HPMC K100 M, Carbopol only. Thus, proper selection of the ratio of desired drug release was obtained⁴⁸.



Figure 5: Powder Form of Hibiscus mucilage powder

Tamarind gum

It is also called as tamarind kernel powder (TKP). Tamarind xyloglucan is obtained from endosperm of the tamarind seed belongs to the family Fabaceae. Tamarind seed polysaccharide is composed of 1:2:3 ratio of galactosyl: xylosyl: glucosyl. In formulation of various dosage forms TKP is utilised as a binder, gelling agent, stabilizer, thickening agent, swelling agent, in pharmaceuticals and

food industries. Tamarind gum has various applications as mucoadhesive and shows sustained effect in GRDDS. Tamarind gum is utilised in formulation of matrix tablet by wet granulation technique. This technique is used to test the drug release characteristics of gum. In production of tablets several polymers concentration is used. Increasing the polymer leads to decreases in medication release⁴⁹. Sumathi et.al studied that tamarind kernel powder shows sustained release behaviour with both water soluble and insoluble drugs. Water soluble drugs are acetaminophen, caffeine, theophylline and water insoluble drugs are salicylic acid, indomethacin. Finally conclude that mechanism of release of soluble drugs was anomalous whereas zero order release behaviour is shown by the insoluble drugs⁵⁰.



Figure 6: Powder Form of Tamarind gum

***Colocasia esculenta* gum**

It is obtained from underground tubers (corns and cormels) of *Colocasia esculenta* belongs to the family Araceae. These tubers have high content of glucose. When mucilage of *Colocasia* tubers contact with the water it quickly hydrates and expands. The mucilage is isolated from the tubers has long-term releasing characteristics. It has various applications as swelling agent, mucoadhesive, sustained effect in GRDDS⁵¹. Chukwu KI et.al in their study the effectiveness of a polysaccharide gum obtained from the cornels of *Colocasia esculenta* was evaluated comparatively with acacia and methylcellulose as binders in the formulation of poorly compressible drugs. The granules of these drugs produced by wet massing method using *Colocasia* and acacia gums as binders. The new polysaccharide gum showed better concentration-strength profile than acacia while methylcellulose yielded mechanically more stable tablets than the two binders. At 4% w/w nominal concentration of *Colocasia* gum in metronidazole tablets and 6% w/w in paracetamol, tablets show very long disintegration time and prolonged release profile. The binders used for comparison yielded tablets that show better in vitro release characteristics⁵².



Figure 7: Powder Form of *Colocasia esculenta* gum

Locust bean gum

Locust bean gum is also called as carbo bean gum. It is obtained from refined endosperm seeds of carbo tree *Ceratonia siliqua* linn belongs to the family Leguminosae. LBG is composed of a neutral galactomannan polymer with D-Galactose and D-Mannose. It is made up of of 1,4-linked D-mannopyranosyl units with every fourth and fifth chain unit is substituted on C6 with a D-galactopyranosyl unit^{53,54}. Gum is neutral, slightly soluble in cold water and requires heat to achieve a full hydration, solubilisation, and maximum viscosity. In pharmaceutical applications for development and formulation of newer drug delivery system^{49,53}. LBG is more effective as gelling, stabilising and thickening agents, swelling agent, mucoadhesive, sustained effect⁵⁵. To study the super disintegrant property of the gum oral dispersible tablets are formulated by locust bean gum and evaluated it against to standard super disintegrant that is croscarmellose sodium⁵⁶. controlled delivery of metoprolol tartrate using the synergistic activity of locust bean gum (LBG) and Xanthan gum (X). The XLBG matrices show precise controlled release than the X and LBG matrices because of burst effect and fast release in case of X and LBG alone respectively The XLBG matrices leads to more precise result than X and LBG matrices due the utilization of synergistic interaction between two biopolymers and lower average size of this allowing a uniformity with the tablet hydration in dissolution media.⁵⁷.



Figure 8: Powder Form of Locust bean gum

Carrageenan

It is isolated from the red seaweed species like *Euchema*, *Gigartina stellate*, *Chondrus crispus*, Iridaea. It is an anionic gel forming polysaccharide having high molecular weight. Carrageenan is composed of repeating units of galactose and 3,6-anhydrogalactose. Carrageenan is divided into three forms based on their degree of sulfation are carrageenan (3-sulfate), carrageenan (di-sulfate), carrageenan (non sulfate or monosulfate). Singh et.al studied that carrageenan is mostly used. because of their excellent functional properties in food industries such as bulking agent, thickening agent, stabilizing and gelling agent¹⁷. During granulation and compression of tablet carrageenan is proven to be used as tablet excipient because of their excellent compatibility, viscoelasticity of tablet⁵⁸. Bonferoni et.al prepared a complex containing carrageenan diltiazem and used as non-API agent in controlled release formulation in their study they suggested that when fined sieve fraction complex was employed then there was highest crushing strength and

delayed drug release. They concluded that studied carrageenan provided (or) offered excellent compactibility and controlled release manner⁵⁹.



Figure 9: Powder Form of Carrageena

Mimosa mucilage

Gum is obtained from seeds of *Mimosa pudica* belongs to the family Mimosaceae. Seed mucilage is composed of D-xylose and D-glucuronic acid. When mimosa seed mucilage comes into touch with water it hydrates and expands quickly. In GRDDS mucilage used as a swelling and mucoadhesive polymer. By using diclofenac sodium as a model medication with mimosa mucilage it develops the sustained release capabilities⁶⁰ and it was observed that proportion of mucilage increases there is decrease in release of drug the mechanism of release being diffusion for tablets containing higher portion of mucilage. Combination of matrix erosion and diffusion for tablets containing smaller proportion of mucilage and study showed that proportion of mucilage increases there was increase in increase percent swelling and decreases in percent erosion of the tablet⁶¹. Ahuja et.al prepared buccal discs of fluconazole by using *Mimosa pudica* seed mucilage as bucoadhesive. These buccal discs prepared by direct compression method. It results that the polymer shows that bioadhesion time of 10hrs and shows drug release more than 85%⁶². Seema mahor et.al prepared a float-adhesive famotidine microspheres by ionic gelation method using *Mimosa pudica* seeds mucilage, chitosan, sodium alginate. Invitro drug release test indicate that the microspheres composed of mucilage or chitosan should show sustained release for 12 hrs and they should have mucoadhesive, floating capability, drug release is determined. Therefore, mucilage containing microspheres show excellent buoyancy and adhesive property compared to chitosan. finally concluded that combining the floatation with mucoadhesive properties increases the oral bioavailability and increases the drug retention time in gastric chamber and improves the treatment of gastric diseases⁶³.



Figure 10: Powder Form of *Mimosa pudica*

Gum Karaya

Gum karaya is known as *sterculia* gum. It is obtained from *sterculiaurens* Roxburgh and other species of *sterculia*⁶⁴. It is naturally occurring hydrophilic gum. Upon acid hydrolysis it usually yields D-galactonic acid, D-galactose, L-rhamnos as principal constituent. Jamil QU et.al in their study the characteristics of gum make isoniazid a good candidate for sustained release dosage form. Karaya gum cross linked with trisodium tri metaphosphate was used as release rate retardant for preparing isoniazid cross-linked matrix tablet⁶⁵. It possessed higher erosion & very low hydration capacity under investigation zero order drug release is observed along with erosion of matrices. Application of gum karaya in GRDDS is swelling agent, mucoadhesive, sustained effect⁶⁶.



Figure 11: Powder Form of *Gum karaya*

Pectin

Pectin is a safe & cost-effective polysaccharide found in citrus peels & apple pomaces. Pectin has a tendency to form gel upon esterification; thus, serves as important drug carrier in the design of gastro retentive controlled release formulation⁶⁷ on base of both extraction process and source. pectin is complex structure actually it's a D-galactouronic acid polymer with 1-4-linkages⁶⁸. The different sources of pectin include sunflower, orange, lemon, carrot, mango, papaya. it has more stability in acidic media. In one study it has been suggested that pectin in combination with gelatin can be used as encapsulating agent to provide sustained release. Rao et.al evaluated use of pectin in combination with hydroxypropyl methyl cellulose and hydroxyethyl cellulose for colon drug delivery and coating was done by ethyl cellulose and cellulose acetyl phthalate results showed that pectin with hydroxyl ethyl cellulose basecoat used as a carrier to delivery naproxen to colon⁶⁹.



Figure 12: Powder Form of Pectin

CONCLUSION

The purpose of writing this review is provide the dynamic role of natural polymers in GRDDS their attribute, current research perspective, future development trends in pharmaceutical fields. Literature with special focus on the principle mechanism to achieve gastro retention by using natural polymers. Physical and chemical properties of natural polymers good candidate to use as a carrier in GRDDS. By using these natural polymers provides prolong gastric retention time, gastric emptying time, GI transit time, shows sustained and targeted drug delivery. Natural polymers in gastro-retentive formulations could replace already existed synthetic polymers and launches their gastro-retentive products into the market with enhanced overall effectiveness. It would be helpful for researchers for future development of gastro-retentive systems by using various natural polymers. Gums obtained from plants could be exploited in future as novel natural polymers used as a various application for development newer drug delivery systems in pharma industry.

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