Review Article

A review on applications of natural polymers in gastroretentive drug delivery system

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ABSTRACT

The objective of this review is to provide the overview of the role of natural polymers in gastroretentive drug delivery system (GRDDS), its characteristics, ongoing research, trend of future developments, and applications in the field. Appropriate articles were searched from Medline database using the search term "Natural Polymer and Gastric," restricted search for the past 5 years and accessed only 21 open access articles to narrate this review. The approach of various natural polymers in industrial applications such as medicine, agriculture, and similar areas is growing rapidly in this era. It was observed biodegradable and non-toxic materials like the natural polymers are evident by the mounting level of its use in the pharmaceutical field. Using various natural polymers have been aiding the drug delivery systems for prolongation of time as the drug transporters with the objective of improving bioavailability and therapeutic efficacy. The use of natural polymers in novel drug delivery like GRDDS to possess floating or mucoadhesive in the gastric system for the benefit of increasing gastric resident time and to improve therapeutic efficacy, particularly those drugs are having narrow therapeutic index such as carvedilol, itopride, and glipizide. The physical characteristics of natural polymers facilitates sustained, swelling, and mucoadhesive nature based on literature reviewed, therefore, natural polymers also suitable to GRDDS as like synthetic or semi-synthetic polymers.

KEY WORDS: Drug delivery, Gastric, Herbal, Mucoadhesive, Polymers

INTRODUCTION

Natural polymers and their derivatives widely used for the development of novel drug delivery system for their compatibility with other ingredients and biodegradability, ready availability, and ability for chemical modification. Natural polymers are given most preference because synthetic excipients cause unwanted side effects in human. More ever herbal products are safer to use so now patients and researchers looking for the natural herbal constituents instead synthetic or semi-synthetic polymers.

Several studies showed that natural polymers containing formulations release activities of drug influenced by the physiochemical properties, morphology, and release pattern of polymer, shape of dosage form and particle size.[1] Natural gums have diverse applications as a binders, suspending agents, disintegrant, swelling nature, emulsifying agents and mucoadhesive [Table 1]. They are also useful in the preparation of sustained release and immediate release formulations.[2] Gastroretentive drug delivery systems (GRDDS) are of many types such as effervescent, non-effervescent, mucoadhesive, raft forming, low-density and high-density system, and without effecting on gastric emptying rate such systems remains floating or adhesion into stomach mucous membrane for longer period time because of system consists of density that is less than gastric fluids (1.004 g/cm^3). When system floats or adhered in the gastric region, the drug is released from this system and entered only the solution form into duodenum (upper part of small intestine) having larger surface area that's providing more absorption of drugs. The best events of these systems are well-regulated fluctuations in plasma drug concentration, particularly those drugs with narrow therapeutic index and increased gastric resident time.[3]

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Advantages of GRDDS

GRDDS is suitable for those drugs which are well absorbed through stomach and local action in it, for example, antacids, etc. Poor drug absorption may occur in diarrhea due to vigorous intestinal movement, it can be prevented using this system to retain drug in stomach and its better response. It increases the patient compliance and lowers the dosing frequency. Therapeutic effect can be improved of drugs having short half-life. Minimizing the mucosal irritation due to drugs releasing slowly at controlled rate. In this system, the continuous drug release from the dosage form at constant rate in prolonged manner provides a desired plasma drug concentration their by prevent drug fluctuations. Drugs which are unstable in intestinal pH can also be used. Dose dumping cannot occur. Sustained and uniform release of drug can prevent the gastric irritation. By the administration of prolonged release, gastroretentive dosage forms dissolution in the gastric fluid can be maintained as well as in alkaline pH of small intestine.[4]

Disadvantages of GRDDS

This system is not suitable for those drug which are acid insoluble or unstable in gastric fluid, for example, phenytoin and erythromycin, respectively. Not suitable for those drugs which produces gastric lesions on slow release, for example, Non-steroidal anti-inflammatory drugs. This system is not compatible with those drugs which absorb specifically in colon, for example, corticosteroids. Drug delivery systems with increased size may contain the high risk of preservation in the stomach for long time and may pose a life-threatening effect on further use of this system. For bioadhesive system, the most difficult for is the high turnover proportion of gastric mucus. For efficient result and effect, this floating system needs high fluid level in the stomach so it can float.[5]

Applications of GRDDS

GRDDS stays in the stomach for longer period to enhance gastroretention time, while sustained drug delivery system shows limited effect due to short retention time in the stomach. Drug cannot pass through pylorus because of increased size due to swelling nature and low density than gastric fluids. Those drugs which metabolized in upper GIT, their bioavailability and absorption can be enhanced using this system. Those drugs that absorbed from the stomach and proximal part of the small intestine have advantage of this system. It provides sufficient therapeutic level and effect and decreases the systemic exposure to the drug and reduced side effects due to slow delivery of drug from this system. It can also reduce the dosing frequency of many drugs due to prolonged gastric availability, for example, Metformin, Itopride, glipizide, and carvedilol.[6] This system can decrease the counteraction of the body may lead to higher efficiency and productivity of drug.[7] Unwanted actions or activities of drug in the colon can be avoided due to retention of drug in gastric retention. Drugs like beta-lactam antibiotics that absorbed from the small intestine and their presence in the colon may cause microorganism's resistance.[1]

Natural Polymers from Plant Origin Suitable to GRDDS

Natural polymers can be produced by plant origin, which are naturally available. They show no adverse reaction on human beings. Most of the natural polymers are non-toxic, non-irritant, and biocompatible because these plant materials are having rich in carbohydrates. Natural polymers are isolated from natural sources using organic solvents and are easily collected in different seasons in large quantities with low cost. Now in developing countries, their productions have been promoted because of its wide use in industries. The percentage yield and constituents in natural materials may vary with different species and also differences in their seasonal collection from different region and at different times. They may have slow rate of production.[8]

Table 1: Applications of natural polymers in GRDDS

Natural polymers	Applications
Colocasia esculenta gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Guar gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Gum karaya	Swelling agent, Binders, Mucoadhesive, Sustained effect
Limonia acidissima gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
LBG	Swelling agent, Binders, Mucoadhesive, Sustained effect
Mimosa pudica gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Okra gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Tamarind gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Tara gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Xanthan gum	Swelling agent, Binders, Mucoadhesive, Sustained effect
Carrageenan	Swelling agent, Binders, Sustained effect
Chitosan	Swelling agent, Binders, Sustained effect
Pectin	Swelling agent, Binders, Sustained effect
Psyllium husk	Swelling agent, Binders, Sustained effect

LBG: Locust bean gum, *L. acidissima: Limonia acidissima, M. pudica: Mimosa pudica, C. esculenta: Colocasia esculenta*, GRDDS: Gastroretentive drug delivery system

Guar gum

Guar gum belongs to family Leguminosae and derived from cyamopsis tetragonolobus kernels. It is also known as Guaran, Cluster bean, Cyamopsis, Calcutta-lucerne, and Guarina.[9] It is a whitish-yellow powder and has taste or odor. It is water soluble and is not soluble in organic solvents. Guar gum has ability to increase viscosity and used in solid dosage forms as a disintegrant and binder in pharmaceutical industries.[10]

Xanthan gum

Bacterium *Xanthomonas campestris* produced xanthan gum naturally. This gum appears as odorless, free-flowing fine powder or cream. Polysaccharide B-1459, Keltrol, Rhodigel, Merezan, and Corn sugar gum are soluble in warm or cold water and are insoluble in ethanol and ether. This gum is stable material and is polysaccharide in nature with D-glucose backbone like cellulose. Their aqueous solutions are durable in existence of enzymes, bases, salts, acids, and stable at pH range 3–12 and temperature between 10–60°C. It is non-toxic and non-irritant and used in cosmetics and food products, in topical and oral pharmaceutical formulations and preparations. It is also used as stabilizing agent, gelling agent, viscosity-increasing agent, suspending agent, emulsifying agent, and thickening agent.[10]

Chitosan

It is composed of glucosamine and N-acetylglucosamine and is linear cationic polysaccharide. Chitosan is prepared by the deacetylation of chitin that is obtained from crustacean shells. It is biodegradable, biocompatible, and non-toxic. It is odorless creamy or white flakes or powder and partially insoluble in 95% ethanol and soluble in water. It is used as viscosity enhancer, mucoadhesive, film-forming agent, tablet binder, coating agent, and disintegrant.[11]

Pectin

Pectin is non-toxic and economic polysaccharide extracted from apple pomaces and citrus peels. On the base of both extraction process and source pectin is a complex structure. Actually, it is a D-galacturonic acid with 1–4 linkages. It is used as a bulking agent, food additive, and a gelling agent due to the pectin ability to form gel based on degree of esterification and molecular size, it is an alluring candidate for pharmaceutical care, for example, as drug carrier for controlled released applications.[12]

Carrageenan

Carrageenan, naturally occurring repeating units of galactose and 3, 6-anhydrogalactose high molecular weight anionic gel-forming polysaccharides, extracted from red seaweeds species such as *Euchema*, *Chondrus crispus*, *Iridaea*, and *Gigartina stellate*. Depending on degree of sulfation, are classified into different types: λ-carrageenan (three-sulfate), κ- carrageenan (di-sulfate), and ι- carrageenan (monosulfate). Highly sulfated λ-carrageenan is a thickener agent and does not form gel while κ- and ι-carrageenan forms gel, which influences their release kinetics.[11] Carrageenans are mostly utilized because of their superb physical functional properties in food industries, such as bulking agent, thickening, stabilizing abilities, and gelling. Because of the high robustness, good compatibility, and persistent viscoelasticity of the tablet during granulation and compression, it proved to be useful as tablet excipient agents. Hence, for sustained release formulations, carrageenans are suitable excipients.[13]

Gum karaya

Gum Karaya is known as Sterculia gum obtained from *Sterculia urens* Roxburgh and other species of Sterculia (Family – Sterculiaceae). After acid hydrolysis, Gum Karaya commonly produces D-galactose, D-galacturonic acid, L-rhamnose, and small proportions of D-glucuronic acid. It is sparingly soluble in water, poorly soluble in 0.1 N HCl and simulated gastric fluid and it is slightly insoluble in ethanol (95%), other similar organic solvents and alkali solutions at pH above 6.5. As the gum Karaya swells in water, thus in different formulations, it is used as release rate controlling polymer. It possessed higher erosion and very low hydration capacity. Under investigation, zero-order drug release is observed along with erosion of matrices.[13]

Okra gum

Okra gum obtained from the pods of *Hibiscus esculentus*, yields high viscosity mucilage at low concentrations. It is polysaccharides having hydrophilic nature, currently used in pharmaceutical industry as a swelling polymer in dosage forms. Okra gum contains different coil polysaccharides consisting of rhamnose, galactose, and galacturonic acid are used as a tablet binding agent and to produce tablets with good friability, hardness and drug release profiles. Due to its chemically inert, safe, biodegradable, non-irritant, eco-friendly, and biocompatible properties, it has advantage over most commercial synthetic polymers because it is widely harvested and do not require toxicology studies. Okra gum is beneficial as a retarding polymer in the formulation of sustained release tablets as extraction in water give highly viscous solution with slimy appearance.[13]

Locust bean gum (LBG)

LBG also known as Carob bean gum and it is derived from the seeds of the leguminous plant *Ceratonia siliqua* Linn., consists basically of neutral galactomannan polymer made up of 1, 4-linked D-mannopyranosyl units with every fourth or fifth chain unit is substituted on C6 with a D-galactopyranosyl unit. There is variation in ratio of D-galactose to D-mannose based on varying origins of the gum source materials and growth effecting conditions of the plant during production. LBG is more effective to use as a gelling, stabilizer, and thickening agent and

shows a wide variety of application in preparation and development of various novel drug delivery systems.[14,15]

Psyllium husk

Psyllium obtained from the plant Plantago psyllium, the husk and seed of Plantago ovata is referred to as psyllium. Psyllium is classified as a mucilaginous fiber due to its powerful gel forming ability in water. Psyllium husk is biocompatible, inert, swellable, biodegradable, inexpensive, and easily available. The seed contains sterols, unsaturated fatty acids ranging 5–10% lipids, traces of cyclopentano pyridine-type alkaloids, proteins (15–18%), aucubi, and trisaccharide, carbohydrates-planteose, and 10–12% mucilage of the heteroxylan type. Psyllium husk serves as reliable means for GRDDS as it shows release retardant properties. Researchers have also focused on prolonged retention of dosage form use in the GIT; stomach.[16]

Tamarind gum

Tamarind is xyloglucan also called as Tamarind Kernel Powder is collected from seed of the tamarind tree under the family of *Tamarindus indica*. Tamarind gum; a polysaccharide composed of galactosyl: xylosyl: glucosyl in the ratio of 1:2:3. Higher plant primary cell walls has major structural polysaccharide called xyloglucan and used as binder, gel-forming agent, stabilizer, and thickener in pharmaceutical and food industries. Tamarind gums used in formulating matrix tablets are evaluated for its drug release characteristics by wet granulation technique. Different concentrations of polymers are used in tablets preparation. Decrease in drug release is observed with increase in polymer content.[17]

Tara gum

Tara gum is obtained from family Leguminosae from the endosperm of seed of Caesalpinia spinosa. Tara gum is odorless and white powder. Like, guar and LBGs, major component is galactomannan polymers consist of a linear main chain of (1-4)-β-D-mannopyranosyl units with α-D-galactopyranose units attached by (1-6) linkages. The ratio of galactose to mannose is 1:3, produce highly viscous thick solutions, at 1% concentration. Tara gum is used in formulation of gastroretentive controlled release tablets and emulsions for drugs in pharmaceutical industries such as glipizide, metformin hydrochloride, carvedilol, clozapine and ciprofloxacin hydrochloride, and itopride has been claimed in patents. Good gastroretentive property is observed using Tara gum in combination increases floating time of the dosage form. Tara gum also used in formulation of emulsions.[17]

Novel Natural Polymers for GRDDS

Mimosa pudica gum

Mimosa pudica (Mimosaceae), commonly known as sensitive plant, is a diffuse undershrub found widely in the tropical and subtropical parts of India. Seeds of gum mucilage containing olysaccharides, which is composed of d-xylose and d-glucuronic acid. Mimosa seed mucilage hydrates and swells rapidly on coming in contact with water. The isolated seed mucilage having sustained release properties employing diclofenac sodium as a model drug and mucilage suitable for various GRDDS as a swelling and mucoadhesive polymer.[18]

Limonia acidissima gum

Limonia acidissima gum (Rutaceae), commonly known as wood apple and elephant apple, found widely in the tropical and subtropical parts of India. Mucilage obtained from trunk of trees composed of carbohydrates. Mucilage hydrates and swells rapidly on coming in contact with water. The isolated stem mucilage having sustained release properties and mucilage suitable for various GRDDS as a swelling polymer.[19]

Colocasia esculenta gum

Colocasia esculenta is a plant of Araceae family widely cultivated in tropical areas of Southeast Asia. Underground tubers (corns and cormels) containing rich in carbohydrates. Colocasia tubers mucilage hydrates and swells rapidly on coming in contact with water. The isolated tubers mucilage having sustained release properties and mucilage suitable for various GRDDS as a swelling polymer.[20]

Evaluation Parameters to Identify Floating or Mucoadhesive Behaviors of Drug in Stomach using Animals or Healthy Volunteers

X-rays are widely employed for internal body examination using radioopaque marker like barium sulfate in dosage forms instead drug and the gastroretentive imaging is done by X-rays at different time intervals (0, 1, 6, 12, and 24 h). Many researchers used X-ray images in gastroretentive dosage forms for assessing various parameters for their availability. One can conclude and correlate the route of dosage form and gastric empting time in the GIT. To identify availability of dosage form in stomach, usually X-ray images are useful tools to conform whether the dosage form available or not.[21]

Gamma scintigraphy γ-camera or scinti scanner is used for the indirect observation of a formulation by the involvement of a γ-emitting radio nucleotide. In γ-scintigraphy, the γ-rays emitted by the nucleotide are directed on a camera, which aids to focus and view to locate the location of the dosage form in the gastrointestinal tract. Peroral endoscopy is also known as gastroscopy used with video systems or fiber optics and used to observe visually the evaluation of GRDDS and effect of prolongation in the stomach to conclude.[1]

In magnetic marker monitoring method, iron powder is magnetically used as marker inside the dosage form and images are resulted by highly sensitive biomagnetic measuring equipment. It is more beneficial as it has no radiations making it safer. Structures are elegantly checked by the help of iron powder and pictures are taken in accurate and delicate bioattractive way.[22]

Ultrasonography is used occasionally as it does not show results in intestine. Imaging of some abdominal organs is obtained in the interface on the reflection of substantially different acoustic impedances. As fine acoustic results on interference with physiological milieu are not achieved by the DFs, therefore, it is not used on regular bases for conclusion of FDDS. The characterization included solvent penetration in the gel, interactions among gastric wall, and GRDDS during peristalsis and assessment of intragastric location of the hydrogels.[21] 13C octanoic acid breath test in GRDDS due to stomach chemical reactions octanic acid releases CO_2 gas through the breath, so 13C octanoic acid is incorporated in it. It was observed in this reaction is the formation of 13C isotope instead of the CO_2 gas. Dosage form gastric retention time is observed with the passage of time in release of 13C isotope instead CO_2 gas. In this method as the dosage form reaches the intestine there is no CO_2 gas is observed.[23]

CONCLUSION

The entire reviewed articles provide the overview of role of natural polymers in GRDDS, its characteristic effects, ongoing research, trend of future developments, and applications in the field. Based on literature reviewed, it was observed due to physical characteristics of natural polymers and physiological acceptability facilitates sustained, floating, or mucoadhesive characters in GRDDS, therefore, it is concluded that natural polymers also behaves as like synthetic and semisynthetic polymers and it is suitable to GRDDS to enhance gastric residence time, bioavailability, and therapeutic efficacy of drugs.

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