NATURAL MUCILAGE BASED ENGINEERED MICRON SIZED PARTICLES: A NOVEL CARRIER SYSTEM FOR DRUG DELIVERY

Abstract

Novel drug delivery is growing area of drug delivery nowadays. Novel drug delivery systems offers many advantages such as controlled, site specific drug delivery at desired predetermined rate. Gastroretentive drug delivery improve gastric residence time of drug and deliver drug in gastric region and upper part of small intestine. Many scientific experts have utilized various approaches for retention of drug delivery system in stomach region of gastro intestinal tract. The mucoadhesive gastroretentive drug delivery is best suitable approach for prolonging gastric residence time of drug. The use of natural mucilage for mucoadhesive potential is recently explored area. Thus present book chapter highlights the outcomes of mucilage based microspheres in effective drug delivery.

Keywords: Natural mucilage, Microspheres, Novel drug delivery, Gastroretentive drug delivery

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I. CONTROLLED DRUG DELIVERY SYSTEMS

The oral route is most common, safe and convenient route of drug administration. The solid oral dosage form like tablet is most popular oral dosage form because of ease of handling, large scale production and stability [1]. About 80% oral dosage forms are available in the form of tablet. However, these dosage forms suffer with number of limitations like:

- The daily administration of dosage form is required which is difficult to monitor and greater chance of missing dose.

- The dosage form like tablet is available with fixed strength thus careful calculation is required to prevent overdosing. It is difficult to calculate exact dose of drug required for a child and geriatric patients.

- After oral administration the drug absorbs in systemic circulation and undergoes non-specific distribution in target site as well as off target site. Thus, majority of administered drug undergoes wastage and more amount of drug need to be administered to produce desired pharmacological effect which may precipitates dose dependent side effects.

After oral administration of a drug, the drug is absorbed in systemic circulation and concentration of drug in blood plasma increases gradually with time as represented in figure. This phase is known as absorption phase where rate of drug absorption is more than rate of elimination. The therapeutic action of drug starts when concentration of drug in blood plasma reaches in therapeutic window. Once the concentration reaches up to peak level, the descending phase begin. In this phase, the concentration declined due to metabolism and excretion thus generally known as elimination phase. During this phase the rate drug elimination is more than its rate of absorption. The therapeutic action of drug is observed until the concentration remains in therapeutic window. The time period during which concentration of drug remains above the MEC is known as duration of action. Once concentration of drug fall below the MEC, the second dose of drug need to be administered to produce desired pharmacological effect. Thus, fluctuations in plasma drug concentration are observed with conventional drug delivery systems. Extensive researches have been conducted to minimize the limitations associated with conventional drug delivery systems. The fruitful outcome of these researches is developed modified drug release systems.

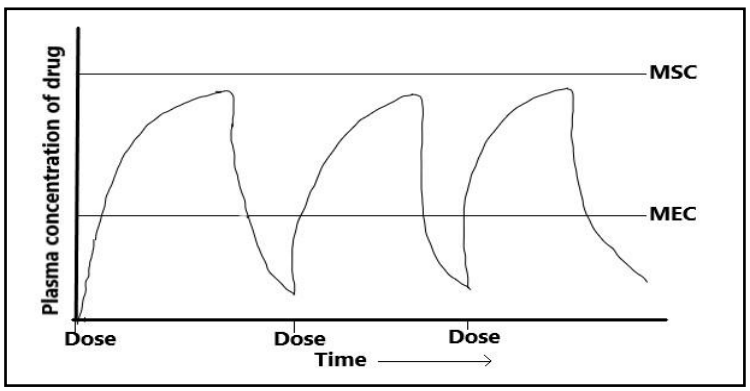

Figure 1: Typical plasma level time profile of conventional oral drug delivery system.

1. **Rationale:** As mentioned earlier, controlled release drug delivery system was investigated to minimize limitations associated with conventional systems [2]. The controlled release system is defined as the system which releases an encapsulated drug at a predetermined rate so that a constant plasma drug concentration is maintained for extended period of time with minimum side effects. The basic concept behind formulation of controlled release formulations is to alter pharmacokinetics and pharmacodynamics of drugs either by modifying molecular structure or using novel drug delivery principles and physiological parameters. Thus, in depth understanding of pharmacokinetics and pharmacodynamics parameters of drugs is necessary before designing of system. The desirable characteristic of such system is the duration of drug action. The controlled release system should provide therapeutic drug concentration for prolonged period of time. This can be achieved by controlled release of drug from system. The controlled release is possibly achieved by combining drug with the release modifying polymer. The polymer is used to control release of drug from system. This could possibly prolong the duration of drug action. The objective behind formulation of such system is to improve patient compliance by ensuring safety and enhanced efficacy of drug. This could be ensured by controlling plasma drug concentration and reducing dosing frequency.

   The rationales of controlled release system are highlighted below:
   - To provide controlled release of medicament for prolonged duration of drug action.
   - To increase the bioavailability of drug.
   - To provide a location-specific action of drug within the GIT.
   - To reduce dosing frequency and to improve patient compliance.

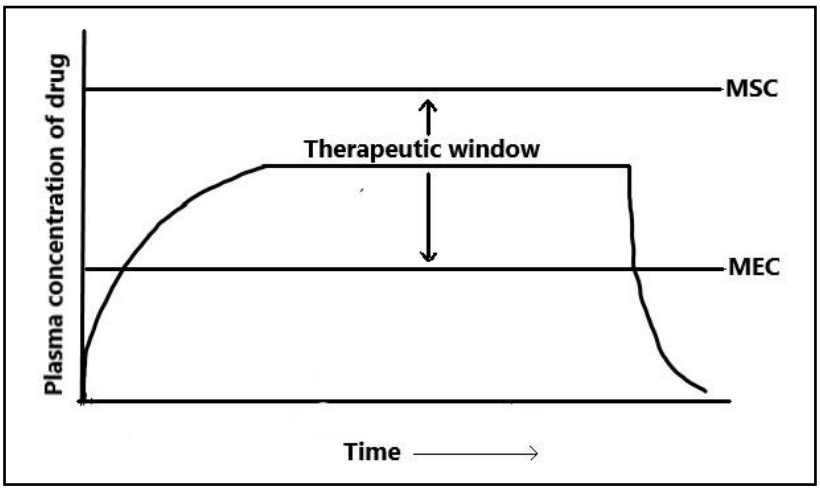

Figure 2: Typical Plasma Level - time profile of controlled release system.

2. **Advantages:** The desirable therapeutic advantages can be achieved by prescribing controlled release formulation

   - The controlled release dosage form releases the drug in controlled manner, thus frequency of drug administration can be reduced which improve patient compliance and convenience.

- The concentration of drug in blood plasma is maintained in therapeutic window for prolonged period of time and fluctuations in plasma drug concentration due to repeated administration can be minimized.
- The total amount of drug administration can be reduced by utilizing controlled release concept thus availability of drug can be maximizing with a minimum dose.
- The release of drug from dosage form is controlled which eventually control absorption of drug in systemic circulation.
- As fluctuations in plasma drug concentration is minimize, the safety margin of highly potent drugs can be increased, and the incidence of both local and systemic adverse effects can be reduced.

3. Disadvantages

- Administration of sustained/controlled release formulation does not permit prompt termination of therapy. Immediate changes in dose strength during therapy are not possible.
- Unpredictable *in vitro-in vivo* correlation is observed with controlled release formulations.
- In controlled release systems, the polymers are included to control the drug release. Thus, accidental release of drug (dose dumping) may be observed; specially with reservoir system, where defects/rupture in polymeric coat is responsible for dose dumping.
- The cost of these systems is high due to use of expensive equipment and processes are involved in manufacturing of such systems.
- The controlled release approach is not applicable to all drug candidates. The characteristics of drugs need to be study while selection of suitable drug candidate.

II. APPROACHES TO DESIGN CONTROLLED RELEASE SYSTEM

Basically, controlled release of drug from system is achieved by either modification of drug molecule or by modification of dosage form or by utilizing novel nanocarriers [2]. The various approaches were investigated for controlled release of drug. The modification of existing conventional oral dosage with drug release retarding polymer is widely investigated technique for controlled delivery of drug [3]. The use of nanocarriers involves encapsulation of drug in nanocarriers like liposomes [4], nanoparticles [5], niosomes [6] and solid lipid nanoparticles [7], nanostructured lipid carriers [8]. The encapsulated drug in nanocarriers releases in controlled manner. The use of nanocarriers for controlled delivery of through various routes have been investigated widely for effective management of various disease conditions [9].

Based on the mechanism of drug release control the controlled release system can be classified into following;

- Diffusion controlled systems
- Dissolution controlled systems

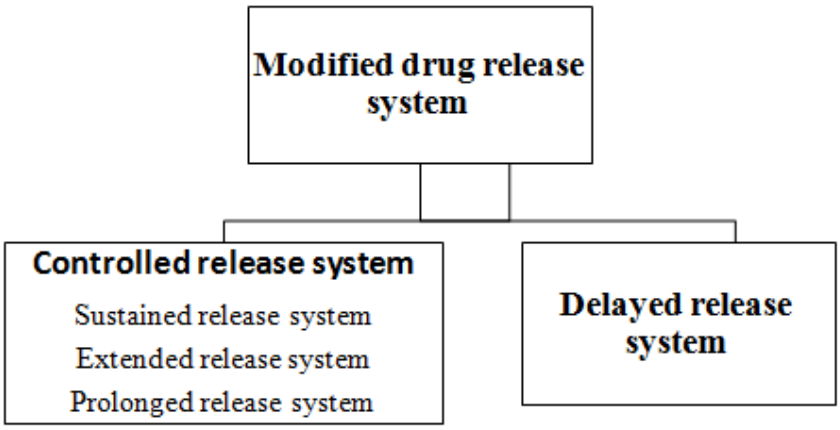

Figure 3: Classification of Modified Release System

1. **Diffusion Controlled Systems:** In these systems, the drug release rate from drug delivery systems has been preprogrammed at specific rate. As name suggests, the drug release rate is controlled by diffusion of drug from system. The controlled diffusion of drug from system has been accomplished by system design i.e. by effective use of polymeric drug releasing barrier. These systems have divided into three types: reservoir system, matrix system and matrix reservoir hybrid system.

    - **Reservoir System:** In this type of controlled drug delivery systems, a drug formulation/drug is totally/partially encapsulated with thin polymeric membrane. The encapsulated drug is released in surrounding environment by diffusion through polymeric membrane. The diffusion of drug through polymeric membrane is rate controlling/slow step. The drug reservoir consists of either solid drug, suspension of drug in viscous polymer or concentrated drug solution. The polymeric membrane may be porous, nonporous or microporous designed for specific release rate of drug. The encapsulation of drug in polymeric membrane is accomplished by spray coating, air suspension, microencapsulation, capsulation or injection molding. This system can be fabricated in different shape or size i.e. for suitability of administration. Since, the thickness of polymeric coating is uniform, the rate of drug diffusion is constant throughout the lifetime of product. The drug release rate from this system is controlled by controlling partition coefficient and diffusivity of drug and thickness of polymeric membrane.

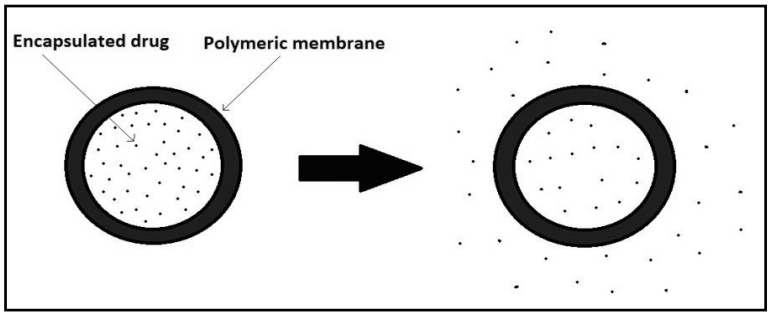

Figure 4: Reservoir type controlled drug delivery system

- **Matrix System:** The drug reservoir in this system consists of homogeneous dispersion of drug in polymer matrix. The polymer matrix is formed by crosslinking of either lipophilic or hydrophilic polymer. The dispersion of drug of drug in polymer matrix is accomplished by two methods:

  - Mixing of therapeutic dose of fine drug particles with liquid/viscous polymer, followed by crosslinking of polymer chains.
  - Mixing of powdered drug particles with rubbery polymer at elevated temperature.
  - The resulting medicated polymer matrix is then molded/ extruded to desired shape device for specific application. Another simple technique for fabrication of this system is dissolution of drug and polymer in common volatile organic solvent, followed by evaporation of organic solvent [10].

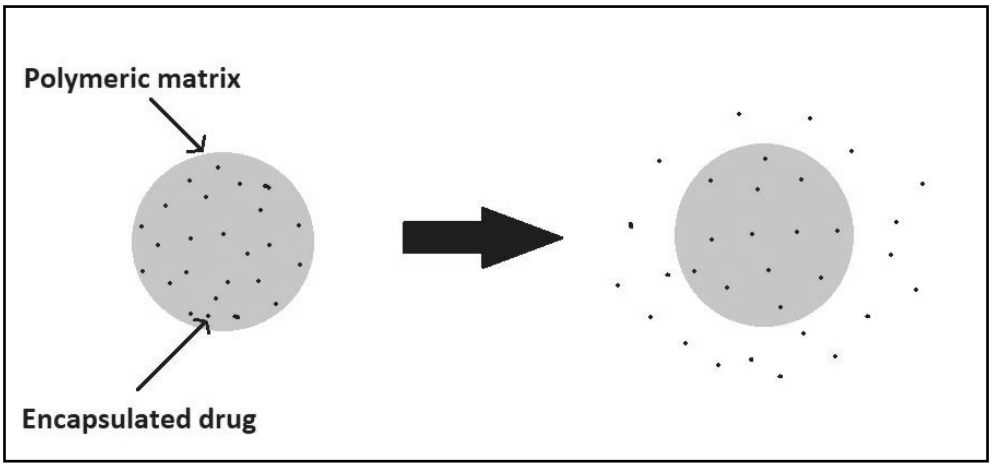

Figure 5: Matrix type controlled drug delivery system

2. **Dissolution Controlled Systems :**This system releases the drug in controlled manner where dissolution is rate limiting step in drug release. When drug dissolution rate is high, it is mixed with a carrier having a slow dissolution rate. According to diffusion layer theory, the dissolution process is diffusion layer controlled. In such case, rate of diffusion of drug from solid surface to bulk medium thorough stagnant layer is rate limiting step.
   There are two ways to fabricate dissolution-controlled system i.e. reservoir system and matrix system.

   - **Reservoir system :**In this approach, the drug particles or granules are coated with slowly dissolving polymeric material. The coated particles are then compressed into a tablet or filled in capsules for oral administration.
   - **Matrix system :**In this approach, the solid drug is encapsulated in polymer matrix. The drug solid is homogeneously mixed with polymer and compressed into desired shape for administration. The rate of availability of drug is controlled by permeation of dissolution medium into the polymer matrix. The permeation of medium is controlled by porosity of the matrix, the wettability of the tablet and surface area.

III. GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Oral route of drug administration is the most preferred convenient and safer route of systemic drug delivery. However, drugs which have short half-lives are eliminated quickly from the systemic circulation, thus frequent dosing of these drugs is required to maintain its concentration within therapeutic window [11]. To avoid these drawbacks, oral sustained-controlled release formulations has been investigated to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. These modified release oral drug delivery have recently gained interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance. After oral administration, such a drug delivery systems releases the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT. These drug delivery systems suffer from mainly two limitations: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release at absorption zone (stomach or upper part of small intestine) leading to incomplete drug absorption.

The design of oral modified release dosage form with prolonged gastric retention can possibly overcome these limitations. These dosage forms can possibly retain in stomach for prolonged period of time and releases the drug in sustained manner. Prolonged gastric retention improves bioavailability, increases the duration of drug release, and reduces drug waste [12].

Gastro-retentive drug delivery system is a novel approach to prolong gastric residence time, these dosage forms can retain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs [13].

Drug targeting to the stomach can also be attractive for several other reasons:

- To produce a prolonged local action on to the gastroduodenal wall for e.g., drugs used in treatment of *H. pylori* infection e.g., Amoxicillin, Misoprostol.
- For drugs which have poor stability in the colon e.g., Ranitidine, Metformin HCl.
- For drugs which have a narrow absorption window e.g., Cyclosporine, Methotrexate, Levodopa.
- For the drugs which have primarily absorption site is the stomach e.g., Amoxicillin.

1. **Gastrointestinal tract physiology:**The stomach is situated in the left upper part of the abdominal cavity. Anatomically stomach is divided into three parts: fundus, body and antrum (or pylorus). The proximal stomach, made up of fundus and body regions, which serves as a reservoir for the ingested materials, while the distal region (antrum) is the major site of mixing motions. Antrum also acts as a pump to force the content from stomach to intestine [14].

   Gastric emptying is process, where content in the stomach transfer into small intestine. Gastric emptying occurs in both fasted as well as fed state. The pattern of gastrointestinal motility is different in fasted and fed states. The bioavailability of orally administered drugs will depend on the state of feeding. In the fasted state, a series of electrical events occurs in both stomach and small intestine after every 2–3h. This cyclic

event is called the interdigestive myoelectric cycle or Migrating motor complex (MMC). MMC is often divided into four phases: basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals.

- Phase I (basal phase): lasts from 40–60 min with rare contractions of gastroduodenal walls.
- Phase II (pre-burst phase) lasts for 40–60 min with intermittent contraction action potential. As the phase progresses the intensity and frequency of contraction also increases gradually.
- Phase III (burst phase): lasts for 4–6 min. It includes intense and regular contractions for short periods. Due to this contraction all the undigested material pass from the stomach to the small intestine.
- Phase IV: lasts for 0–5 min and occurs between phases III and I for two consecutive cycles.

In feed state, the gastric emptying rate is slow than in fasting state since the onset of MMC is delayed. To achieve prolonged gastric retention, the dosage form must resist gastric emptying. For this, the dosage form must be able to withstand in the stomach against the force caused by peristaltic waves. Thus, it is necessary to understand the factors affecting gastric retention of dosage form.

2. **Mucoadhesive or bioadhesive gastroretentive systems :**Another important approach to prolonged gastric residence time of drug delivery system is the use of bioadhesive/mucoadhesive polymers [15].

The surface epithelium of stomach constantly exposes to gastric fluid which contains highly concentrated hydrochloric acid (approximately 0.16 N) and protein digesting enzyme, pepsin. Thus, in order to maintain integrity, the surface epithelium has self-protective mechanism i.e. mucus. Mucus contains mucin i.e. oligosaccharides with sialic acid (pKa=2.6) and glycoproteins which are capable to neutralize HCl thus protects the epithelium.

The adhesive properties of mucus layer have been recognized and used for development of gastroretentive system. The drug delivery system consists of drug core coated with mucoadhesive polymer as shown in figure 1.6 Thus after ingestion of such system, the mucoadhesive polymer hydrates and bind/adhere to mucin molecules in mucus lining of stomach. This enables the device to retain in stomach for extended period of time by resisting gastric emptying. The drug molecules contained in core are constantly released in stomach for absorption. A bio/mucoadhesive polymer is a natural or synthetic polymer capable of adhere to biological membrane, which is then called a bioadhesive polymer or with the mucus lining of the GIT, which is then called a mucoadhesive polymer.

Several approaches have been utilized for incorporation of drug in mucoadhesive polymer for preparation of gastroretentive system. For water soluble polymer it is possible to use polymer to coat the surface of microsized capsule shape drug core. The

duration of gastric retention of such system is controlled by dissolution of mucoadhesive polymer.

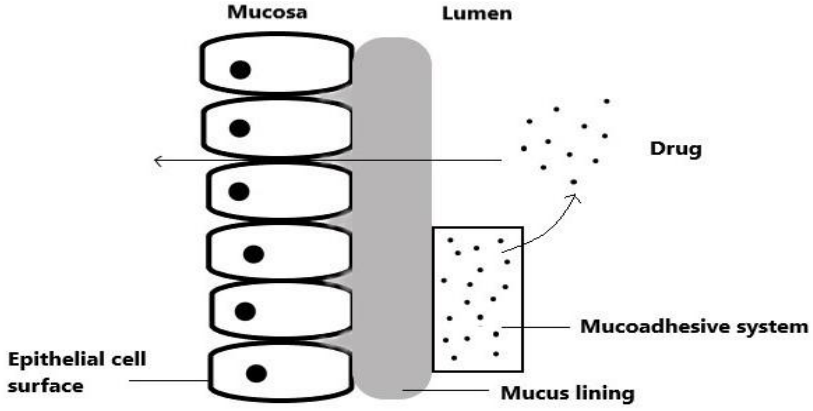

Figure 6: Mucoadhesive system: Interaction of system with mucus lining of stomach

IV. NATURAL POLYSACCHARIDES: A PROMISING CARRIER FOR ORAL DRUG DELIVERY

The use of natural excipients as carriers in drug delivery systems is recent trend of oral drug delivery. At present, socio-economic condition of the modern world has elevated the interest of natural polymers. Environmental concerns are also playing considerable role and contributing to the growing interest in natural polymers due to their biocompatibility, biodegradability and low processing cost [16].

Naturally obtaining polymers are diverse class of macromolecules with a wide range of pharmaceutical applications. Various natural polymers can be classified as proteins-based natural polymers like collagen [17], gelatin, silk fibroin, fibrin and natural polysaccharides like chitosan, starch, alginate, gellan gum, pectin, gum acacia, gum tragacanth, guar gum. These polysaccharides have some excellent water solubility as well as swelling potential, which eventually are useful for oral controlled drug delivery.

1. **Natural gums:** Natural gums are obtained from different parts of the plant. Chemically, these are polysaccharides containing monosaccharides blocks joined in linear as well as branched fashion. Thus, hydrolysis of gums results in formation of various sugar units. Gum acacia and tragacanth are most common gums used in pharmaceutical formulations since long period of time. These gums are produced by the plant as part of protection mechanisms on injury to the plant. The process of formation of gum is termed as gummosis, which indicates breakdown of cell walls [16].

   Many scientific experts have investigated use of natural gums in various drug delivery systems. The gums are commonly used as suspending agent, thickening agent, emulsifying agent, binder, drug release retardant, mucoadhesive agent, gelling agent etc. The commonly used gums and their pharmaceutical applications are represented in below mentioned table.

Table 1: Common Natural Polysaccharides and their use in Drug Delivery

Name of gum	**Botanical name**	**Constituent**	**Applications in drug delivery**	**Reference**
Gum acacia	*Cyamopsis tetragonoloba (Fabaceae)*	Galactose, Mannose	Suspending agent, emulsifier, tablet binder, demulcent and emollient	[18]
Gum tragacanth	*Astragalus brachycalyx (Fabaceae)*	Arabino galactans, Pectinaceous	Suspending agent, emulsifier, demulcent and emollient	[19]
Almond Gum	*Prunus dulcis (Rosaceae)*	L-arabinose, L-galactose	Adhesive and suspending agent	[20]
Tamarind gum	Tamarindus indica *(Fabaceae)*	Glucosyl: Xylosyl: Galactosyl	Drug release retardant	[21]
Grewia gum	*Grewia mollis (Malvaceae)*	Galacturonic acid, Rhamnose	Drug release retardant	[22]
Khaya gum	*Khaya grandifoliola (*Meliaceae)	L-arabinose, L-galactose	Drug release retardant	[23]
Terminalia catappa gum	*Terminalia catappa (Combretaceae)*	Cyanidin 3-glucoside, Gallic acid	Drug release retardant	[24]
Okra gum	*Abelmoschus esculentus (Malvaceae)*	Rhamnose, Glucose	Suspending agent, drug release retardant	[25]
Albizia gum	*Albizia zygia (Fabaceae)*	Mannose, Arabinose	Emulsifier	[26]
Cashew gum	*Anacardium occidentale (Anacardiaceae)*	Galactose, Rhamnose	Suspending agent, drug release retardant	[27]
Bhara gum	*Terminalia bellirica (Combretaceae)*	Gallic acid, Ellagic acid	Drug release retardant	[28]

Name of gum	**Botanical name**	**Constituent**	**Applications in drug delivery**	**Reference**
Cordia gum	*Cordia myxa (Boraginaceae)*	Galactose, Mannose, Rhamnose	Drug release retardant	[29]
Honey Locust Gum	*Gleditsia triacanthos (Fabaceae)*	Carbohydrates, Fats, Fibers	Drug release retardant	[30]
Tara Gum	*Caesalpinia spinosa (Fabaceae)*	Galactomannans	Drug release retardant	[31]
Neem Gum Azadirachta indica	*Azadirachta indica (Meliaceae)*	Galactose, Fucose	Binder	[32]
Moringa oleifera Gum	*Moringa oleifera (Moringaceae)*	Glucuronic acid, Galactose	Binder, gelling agent	[33]
Gum Damar	*Shorea javanica (Dipterocarpaceae)*	Resins	Drug release retardant	[34]
Hakea Gum	*Hakea gibbose (Proteaceae)*	Arabinose, Galactose	Binder, drug release retardant	[35]
Olibanum Gum	*Boswellia serrata (Burseraceae)*	Resins, Carbohydrates	Binder, drug release retardant	[36]
Alginate	*Laminaria species (Laminariaceae)*	Alginic acid	Stabilizer, suspending agent, emulsifier, gelling agent, tablet coating, tablet binder, matrix in controlled release, bioadhesive enhancer	[37]
Xanthan gum	*Xanthomonas campestris*	D-mannosyl, D-glucosyl, as well as D-glucosyluronic acid	Stabilizer, suspending agent, emulsifier, gelling agent, tablet binder, matrix in controlled release, bioadhesive enhancer	[38]

Name of gum	Botanical name	Constituent	Applications in drug delivery	Reference
Guar gum	*Cyamopsis tetragonoloba (Leguminosae)*	Galactomannans	Suspending agent, emulsifier, gelling agent, thickener, tablet binder, matrix in controlled release, bioadhesive enhancer	[39]
Karaya gum	*Firmiana simplex (Malvaceae)*	α-d-galacturonic	Suspending agent, emulsifier, sustained release agent, bioadhesive enhancer	[40]
Gum ghatti	*Anogeissus latifolia (Combretaceae)*		Binder and emulsifier	[41]
Gellan gum	*Sphingomonas elodea*	Rhamnose, glucuronic acid and glucose	Stabilizer, suspending agent, emulsifier, matrix in controlled release	[42]
Locust bean gum	*Ceratonia siliqua (Fabaceae)*	Galacto-mannopyranosyl amine units	Mucoadhesive, colon targeting of drugs	[43]
Konjac	*Amorphophallus konjac (Araceae)*	Galactose, Mannose	Gelling agent, drug release retardant	[44]

2. **Plant Derived Gums in Nanomedicine:** The biodegradability, non-toxicity, non-reactivity, adequate availability are few characteristics of natural gums. These characteristics play key role in use of natural gums as excipient in novel drug delivery systems. The study of physical and chemical properties of the gums are essential in selection of suitable gum in development of drug delivery systems. The structural modification of natural gum can result in formation of new class of polymers [16].

Gums act as stabilizer in many nanocarrier based systems. The nanoparticles like gold and silver nanoparticles can be stabilized using gum. Gums can prevent aggregation of nanoparticles, thus aids in stabilization of nanoparticles. Gums can adsorb over the surface of nanoparticles and forms protective layer around the nanoparticle surface which can possibly prevent aggregation of nanoparticles and enhance stability of nanosystem. Gum can also increase viscosity of dispersion medium which can minimize Brownian motion of nanoparticles.

3. **Plant Derived Mucilage:** The term mucilage indicates substances which have high water absorbing and swelling capability on contact with water. Several species of

mucilaginous species of plants have been used in traditional system of medicine in the world since last 4000 year. Mucilage is metabolic product of the plant formed by various cells. It plays key role in food storage, germination of seeds as well as serve as important component of water storage in plants. Mucilage found in seed endosperms, roots and rhizomes may act primarily as energy reserves [16].

Chemically these are high molecular weight (approx. 200,000 Da) compounds consisting of sugar and uronic acid units. These are generally sulphuric acid esters and have a complex structure of polysaccharide. The high-water absorbing capability of mucilage is due to presence of hydroxyl groups in sugar structure of mucilages. However, upon addition of alcohol, mucilages are precipitated in the form of amorphous or granular mass [45].

Some important plants and their parts yielding mucilages are presented below:

- Intra cell mucilages: Rhizome of *Agropyrum repens L.*, Bulb of *Urginea maritime L*. (squill); Bulb of *Allium sp.* (onion, garlic), Flower stalks of *Hagenia abyssinica*, Pulp of *Musa paradisiacal*, etc.
- Cell-membrane mucilages (secondary wall mucilages): Bark of Cinnamomum species, Bark of *Rhamnus frangula L.*, Root bark of *Sassafras variifolium* (Salisbury), Inner bark of *Ulmus fulva*, Seed-coat of *Linium usitatissimum L.*, Seed-coat of *Cydonia vulgaris L*., etc.
- Metamorphosis of cell-wall: Pith and medullary ray cells: Gum Tragacanth. Parenchyma cells of wood and bark: Cherry gum. Various cells of the bark: Gum Arabic. Primary wall as intercellular substances: Thallus of *Chondrus cripus*.
- Secreting hairs (Driizenzotten): Leaves of *Viola tricolor L*. and *Coffea arabica L*.

Table 2: Botanical sources, constituents and pharmaceutical applications of common mucilages.

Common name	Botanical name	Constituent	Applications in drug delivery	Reference
Mimosa mucilage	***Mimosa pudica*** *(Fabaceae)*	D-glucuronic acid, D-xylose	Drug release retardant	[46]
Hibiscus rosa-sinensis	*Hibiscus rosa-sinensis (Malvaceae)*	D-glucuronic acid, Rhamnose	Binder and drug release retardant	[47]
Asario Mucilage	*Lepidium sativum (Brassicaceae)*	Galactose, Mannose	Emulsifier and suspending agent	[47]
Fenugreek Mucilage	*Trigonella foenum-graecum (Fabaceae)*	Galactose, Mannose	Drug release retardant	[47]
Aloe Mucilage	*Aloe vera (Xanthorrhoeaceae)*	Galactan, Arabinan, D-glucuronic acid	Drug release retardant	[47]

Phoenix Mucilage	*Phoenix dactylifera (Arecaceae)*	Cellulose, Mannose, Pectin	Binder	[47]
Cassia tora Mucilage	*Senna tora (Fabaceae)*	Tannins, Cinnamaldehyde	Binder and suspending agent	[47]
Cocculus Mucilage	*Cocculus hirsutus (Menispermaceae)*	Carbohydrates	Gelling agent	[47]
Cordia Mucilage	*Cordia dichotoma (Boraginaceae)*	Carbohydrates	Binder and emulsifier	[47]
Ocimum Mucilage	*Ocimum americanum (Lamiaceae)*	Galacturonic acids, Rhamnose	Disintegrating agent	[47]

4. **Plant derived mucilage in nanomedicine :**Some mucilages have been reported to show antihypertensive, antibacterial, antioxidant, antiasthmatic and hypoglycemic activities. The promising application of mucilage is drug delivery. Mucilages are widely investigated for development of drug delivery systems. The less toxicity, biocompatibility and biodegradability are ideal properties of mucilage which are useful in development of drug delivery systems. Many scientific investigators have utilized plant derived mucilage for development of nano and microcarrier based systems.

Mucilage obtained from Quince seeds mainly contains glucuronic acid [48]. The mucilage act as an emulsifier as well as foaming agent [49]. It also acts as thickening agent because of its high molecular weight. Akram et al. 2022 [50] formulated cefixime loaded Quince seeds mucilage- sodium alginate microspheres for sustained oral drug delivery. Formulated microcarrier based systems showed sustained drug release behavior with non-Fickian type of drug release pattern. In addition to this, the formulated microspheres showed enhanced antibacterial potential with minimum toxicity. The slow drug release is due to controlled release of cefixime across gum-alginate matrix.

Kurra et al. 2022 [51] formulated jackfruit and Okra mucilage based oral controlled drug delivery system for colon targeted drug delivery of curcumin. Jack Fruit Mucilage obtained from fruit pulp of *Artocarpus heterophyllus* (Moraceae) fruits. Okra Mucilage obtained from the pods of *Abelmoschus esculentus* (Malvaceae). The formulated drug delivery system, showed mucoadhesive behavior of system as well as controlled delivery of curcumin at colon region of gastrointestinal tract.

Ghumman et al. 2019 utilized [52] Taro corn mucilage for fabrication of alginate beads. Taro corn is *Colocasia esculenta,* which is normally cultivated in Asia. Taro corn contains rich percentage of mucilage which is generally used as binder in tablets and emulsifier. In addition to this, it has good swelling ability in aqueous medium and mucoadhesive potential. The pregabalin loaded Taro corn-alginate microspheres were formulated using ionic gelation technique. The formulated microspheres showed acceptable particle size and surface characteristics. The drug release pattern was sustained following Korsmeyer-Peppas model. In addition to this, the microspheres showed better

bioavailability of drug compared to free drug. Thus, natural mucilages are viable mucoadhesive agent for sustained delivery of drug.

Nayak et al. 2013 [53] utilized *Plantago ovata* mucilage for controlled delivery of glibenclamide. The ionotropic gelation technique was successfully utilized for formulation of glibenclamide loaded mucilage-alginate beads. The formulated beads showed good mucoadhesive property as well as controlled drug release behavior.

5. **Gum-alginate based microspheres for controlled drug delivery:** Microspheres are spherical, micron sized biocompatible carriers utilize for controlled delivery of encapsulated drugs. The drug loaded in matrix of microspheres is released in controlled manner. Microspheres can be prepared using polymers, proteins and lipids. Recently, natural gum and alginate combination has been explored for fabrication of biocompatible matrix of microspheres. Numerous scientific experts working in pharmaceutical field have investigated various natural gums for formulation of biocompatible microspheres.
Noureen et al. 2022 [54] utilized *Prunus armeniaca* gum-alginate combination to enhance bioavailability of tramadol. The tramadol loaded microspheres containing *Prunus armeniaca* gum-alginate was fabricated using ionic gelation method. Infrared spectroscopy was used to confirm drug and excipient compatibility. The microspheres showed sustained delivery of drug following Korsmeyer-Peppas model. In addition to this, formulated microspheres were found to be non-toxic in mice model.

Sharma et al. 2022 [55] fabricated *Acacia nilotica* gum-alginate microspheres for sustained delivery of naringin. The microspheres showed slow drug delivery up to 6 hours. Das et al. 2022 [56] used gellan gum and alginate combination for entrapment of metronidazole. The gellan gum-alginate microspheres were crosslinked in present investigation using maleic anhydride. The formulated microsphere released the loaded drug in controlled manner.

Mady et al. 2021 [42] successfully utilized two gums i.e., Okra and gellan gums for formulation of metformin hydrochloride loaded microspheres. The drug loaded microspheres containing gums and alginate were fabricated using ionic gelation technique. Fabricated microspheres showed enhanced mucoadhesive potential tested using goat intestinal mucosa. The formulated microcarrier showed acceptable encapsulation efficiency of metformin and sustained drug release behavior for 10 hours. The mucoadhesive potential of natural gums was investigated in present investigation. Thus, natural gums could be viable alternative to synthetic mucoadhesive for sustained gastrointestinal drug delivery.

Reddy et al. 2021 [57] formulated Karaya gum-alginate microbeads for sustained release of D-penicillamine. The drug loaded microbeads showed better swelling index and sustained drug release up to 35 hours.

Abrar et al. 2020 [58] formulated famotidine loaded *Acacia nilotica* gum microspheres for controlled gastrointestinal drug delivery. The formulated microspheres showed acceptable physicochemical properties and controlled famotidine delivery in simulated gastric fluid.

Ozoude et al. 2020 [23] utilized Khaya gum extracted from *Khaya senegalensis* for sustained delivery of metformin. The Khaya gum-alginate microspheres formulated using ionic gelation technique. The formulated metformin loaded microspheres showed sustained drug release behavior following Korsmeyer-Peppas model.

Figure 7: Overview of preparation and outcomes of natural gum-based microspheres

Mohamed et al. 2017 [59] successfully utilized gum Arabic-alginate microbeads for controlled delivery of protein. The ion induced gelation of calcium alginate was used as technique for encapsulation of bovine serum albumin in Arabic gum microbeads. The formulated microbeads showed acceptable encapsulation efficiency, particle diameter and surface characteristics. In addition to this, the swelling index of microbeads was also better. The protein release followed controlled release behavior.

Shwetha et al. 2018 [60] utilized Okra gum and alginate combination for controlled delivery of metformin. The microspheres showed acceptable particle size, entrapment efficiency and better swelling index.

Kahima et al. 2017 [61] successfully used acacia gum for controlled oral delivery of diclofenac sodium through acacia-alginate beads. Gum acacia-alginate beads were formulated using ionic gelation technique by addition of calcium chloride solution. The formulated beads showed pH dependent swelling ability. The swelling of beads was more at intestinal pH compared to stomach pH because of presence of carboxylic functional groups in gum. The formulated beads showed controlled release of diclofenac sodium by following Hixson- Crowell pattern.

Jana et al. 2015 [62] used locust bean gum for formulation for aceclofenac loaded microspheres. The gum-alginate microspheres were formulated using ionic gelation method. The microspheres showed acceptable physicochemical properties and surface characteristics. The drug release pattern followed Korsmeyer–Peppas model. In addition to this, the microspheres showed better reduction of rat hind pow edema induced by carrageenan compared to free drug. Thus gum-alginate could be viable combination for encapsulation of anti-inflammatory drug.

Mamun et al. 2014 [63] used guar gum and xanthan gum for sustained delivery of glipizide. Microspheres containing guar gum and xanthan gum were formulated in combination with alginate using ionic gelation technique. Microspheres showed acceptable particle diameter and good mucoadhesive potential.

Mazumder et al. 2010 [64] fabricated metronidazole loaded microspheres using guar gum and alginate. Metronidazole is anti-amoebic drug with low solubility in aqueous medium, which limits is use for oral drug delivery. The drug loaded microspheres were prepared using ionic gelation technique. The gum-alginate microspheres showed high encapsulation efficiency of drug. In addition to this, the encapsulate drug release from polymer matrix in sustained manner for 12 hours. Thus gum-alginate microspheres could be vital formulation strategy for delivery of minimum water soluble drug.

Table 3: Overview of natural gum-based microspheres

Gum	Drug	Microcarrier	Outcome
Prunus armeniaca	Tramadol	Microspheres	Sustained drug release and non-toxicity in animal model
Acacia nilotica	Naringin	Microspheres	Sustained drug release
Gellan gum	Metronidazole	Microspheres	Controlled drug release
Okra and gellan gums	Metformin	Microspheres	Better mucoadhesive potential to goat intestinal mucosa
Karaya gum	Penicillamine	Microbeads	Better swelling index and sustained drug release
Acacia nilotica	Famotidine	Microspheres	Controlled drug release
Khaya gum	Metformin	Microspheres	Sustained drug release
Gum Arabic	Bovine serum albumin	Microbeads	Better swelling index
Okra gum	Metformin	Microspheres	Better swelling index
Acacia gum	Diclofenac sodium	Microbeads	Controlled drug release
Locust bean gum	Aceclofenac	Microspheres	Controlled drug release and better reduction of rat hind pow edema induced by carrageenan
Guar gum and xanthan gum	Glipizide	Microspheres	Good mucoadhesive potential
Guar gum	Metronidazole	Microspheres	Sustained drug release

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