



A REVIEW ON HERBAL EXCIPIENTS IN NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Due to advances in drug delivery technology, currently, excipients are included in novel dosage forms to fulfil specific functions and in some cases, they directly or indirectly influence the extent and/or rate of drug release and drug absorption. Recent trends towards use of plant based and natural products demand the replacement of synthetic additives with natural ones. Today, the whole world is increasingly interested in natural drugs and excipients. These natural materials have many advantages over synthetic ones as they are chemically inert, nontoxic, less expensive, biodegradable, improve the shelf life of product and widely available. This article gives an overview of natural excipients which are used in conventional dosage forms as well as novel drug delivery systems.

KEYWORDS:- *Natural excipients, gums, mucilage, polysaccharides, starch, volatile oil*

INTRODUCTION

The term excipient was derived from Latin word, excipients, which means to receive, to gather, to take out. The quality of formulation depends on active pharmaceutical ingredient (API), production processes and the excipients used. These excipients contribute in a great way to the performance of the API and maintain the safety, efficacy of the product[1].

Excipients are primarily used as diluents, binders, disintegrants, adhesives, glidants and sweeteners in conventional dosage forms like tablets and capsules[2]. As the establishment of toxicity and approval from regulatory authorities poses a problem with synthetic excipients, of late more interest is being shown by researchers in herbal excipients. The drawback posed by heavy metal contamination often associated with herbal excipients is superseded by their lack of toxicity, easy availability, and economic considerations in pharmaceutical industry as compared to their synthetic counterparts.

Present day consumers look for natural ingredients in food, drugs, and cosmetics as they believe that anything natural will be more safe and devoid of side effects.

The traditional view that excipients are inert and do not exert any therapeutic or biological action or modify the biological action of the drug substance has changed and it is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug. As herbal excipients are non-toxic and compatible, they have a major role to play in pharmaceutical formulation. Hence, this article gives an overview of natural excipients which are used in conventional dosage forms as well as novel drug delivery systems[1-3].

Pharmaceutical Excipients

Pharmaceutical excipients can be defined as nonactive ingredients that are mixed with therapeutically active compound(s) to form medicines. The ingredient which is not an active compound is regarded as an excipient. Excipients affect the behavior and effectiveness of the drug product more and more functionality and significantly. The variability of active compounds, excipients and process are obvious components for the product variability [4].

Classification of Excipients

Excipients are commonly classified according to their application and function in the drug products:

- Binders, Diluents
- Lubricants, Glidants, Disintegrants
- Polishing Film formers and coatings agents



- Plasticizers, Colorings
- Suspending agents Preservatives, antioxidants
- Flavorings, Sweeteners, Taste improving agents
- Printing inks, Dispersing agents Gums [4]

Advantage of Herbal Excipients

- Biodegradable – Naturally occurring polymers produced by all living organisms. They show no adverse effects on the environment or human being.
- Biocompatible and non-toxic – Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence, they are non-toxic.
- Economic - They are cheaper and their production cost is less than synthetic material.
- Safe and devoid of side effects – They are from a natural source and hence, safe and without side effects.
- Easy availability – In many countries, they are produced due to their application in many industries[5].

Disadvantages of Herbal Excipients

- Microbial contamination – During production, they are exposed to external environment and hence, there are chances of microbial contamination.
- Variation – Synthetic manufacturing is controlled procedure with fixed quantities of ingredients while production of natural polymers is dependent on environment and various physical factors.
- The uncontrolled rate of hydration- due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary.
- Slow Process – As the production rate is depends upon the environment and many other factors, it can't be changed. So, natural polymers have a slow rate of production.
- Heavy metal contamination – There are chances of Heavy metal contamination often associated with herbal excipients [5, 6].

Gums and Mucilage

Gums are pathological products formed following injury to the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extra cellular formation; gummosis). Mucilage's are generally normal products of metabolism, formed within the cell (intracellular formation) and/or are produced without injury to the plant. Gums readily dissolve in water, whereas, mucilage form slimy masses. Mucilage's are physiological products[7].

Classification is based on source

(a) Marine origin/algae (seaweed) gums: agar, carrageenans, alginic acid, and laminarin;

(b) Plant origin:

i. shrubs/tree exudates: gum arabic, gum ghatti, gum karaya, gum tragacanth, and khaya and albizia gums;

ii. Seed gums: guar gum, locust bean gum, starch, amylose, and cellulose;

iii. Extracts: pectin, larch gum;

iv. Tuber and roots: potato starch;

(c) Animal origin: chitin and chitosan, chondroitin sulfate, and hyaluronic acid;

(d) Microbial origin (bacterial and fungal): xanthan, dextran, curdian, pullulan, zanflo, emulsan, Baker's yeast glycan, schizophyllan, lentinan, krestin, and scleroglucan.

Guar Gum

Guar gum derived from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae) is a naturally occurring galactomannan polysaccharide. It is made up of a linear chain of β -D-mannopyranose joined by β -(1-4) linkage with α -D-galactopyranosyl units attached by 1, 6- links in the ratio of 1:22 .

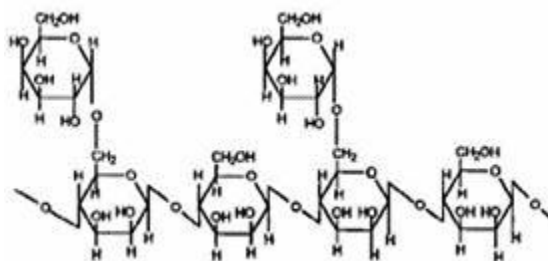


Fig. 1: Structure of guar gum

Guar gum is used in colon-delivery systems due to its drug release retarding property and susceptibility to microbial degradation in the large intestine. Selective delivery of 5-ASA to the colon can be achieved using guar gum as a carrier in the form of a compression coating over the drug core[8].

Further, guar gum-based matrix tablets of rofecoxib were prepared for their intended use in the chemoprevention of colorectal cancer. In vivo studies showed delayed T_{max} , prolonged absorption time and decreased C_{max} indicating that rofecoxib was not released significantly in stomach and small intestine, but was delivered to colon resulting in a slow absorption of the drug and making it available for local action in human colon[9].

Guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as trimetazidine dihydrochloride [10].

Gum Acacia

Gum acacia or gum arabic is the dried gummy exudate obtained from the stem and branches of *Acacia senegal* (Linn.) Willdenow and other related species of acacia (Family Leguminosae). The gum has been recognized as an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid. Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges and as a tablet binder[11].

Sustained release of ferrous sulfate was achieved for 7 h by preparing gum Arabic pellets. Release was further sustained for more than 12 h by coating the pellets with polyvinyl acetate and ethylene vinyl acetate, respectively. The gel layer acts as a barrier and retards the rate of diffusion of $FeSO_4$ through the pellet[12].

Gum arabic was used as an osmotic, suspending and expanding agent in the preparation of a monolithic osmotic tablet system (MOTS) with two orifices on both side surfaces. Water-insoluble naproxen was selected as the model drug. The optimal MOTS were found to be able to deliver naproxen at a rate of approximately zero order up to 12 h in pH 6.8. Cumulative release at 12 h is 81%, and is independent of environment media and stirring rate. Therefore, these MOTS can be used in the oral drug-controlled delivery field, especially for water-insoluble drugs[13].

Karaya Gum

Karaya gum is obtained from *Sterculia urens* (Family sterculiaceae) is a partially acetylated polymer of galactose, rhamnose, and glucuronic acid [11]. Swellable hydrophilic natural gums like xanthan gum and karaya gum were used as release-controlling agents in producing directly compressed matrices. Drug release from xanthan and karaya gum matrices depended on agitation speed, solubility and proportion of drug. Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices [14]. Park et al., [15] showed that mucoadhesive tablets prepared by karaya gum for buccal delivery, had superior adhesive properties as compared to guar gum and was able to provide zero-order drug release, but concentrations greater than 50% w/w may be required to provide suitable sustained release.

Xanthan Gum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β -D-glucose residues) and a trisaccharide side chain of β -D-mannose- β -D-glucuronic acid- α -D-mannose attached with

alternate glucose residues of the main chain. The terminal D-mannose residue may carry a pyruvate function, the distribution of which is dependent on the bacterial strain and the fermentation conditions. The non-terminal D-mannose unit in the side chain contains an acetyl function. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain[11](fig. 2)

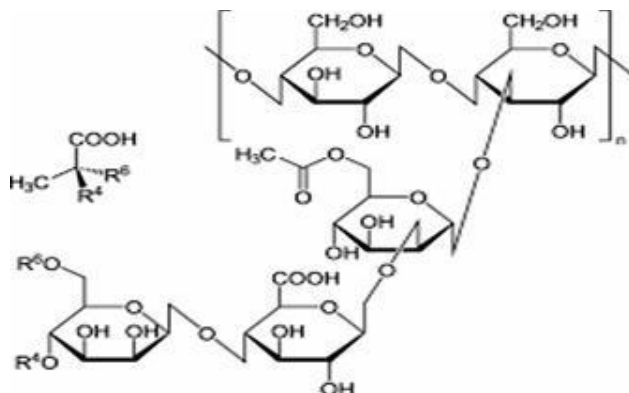


Fig. 2: Structure of xanthan gum

In one of the trials, xanthan gum showed a higher ability to retard the drug release than synthetic hydroxypropylmethylcellulose [16].

Compaction and compression properties of xanthan gum pellets were evaluated and drug release from tablets made of pellets was characterized. Two types of pellets were prepared by extrusion- spheronization. Formulations included xanthan gum, at 16% (w/w) and diclofenac sodium or ibuprofen, at 10% (w/w) among other excipients. Physical properties of pellets and tablets were analyzed. Pellets showed close compressibility degrees (49.9% for pellets comprising diclofenac sodium and 48.5% for pellets comprising ibuprofen). The release of the model drug from both type of tablets revealed different behaviors. Tablets made of pellets comprising ibuprofen released the model drug in a bimodal fashion and the release behavior was characterized as Case II transport mechanism (release exponent of 0.93). On the other hand, the release behavior of diclofenac sodium from tablets made of pellets was anomalous (release exponent of 0.70).

For the latter case, drug diffusion and erosion were competing mechanisms of drug release[17].

Tragacanth: This gum is obtained from the branches of *Astragalus gummifer*, Family Leguminosae. Tragacanth when used as the carrier in the formulation of 1- and 3-layer matrices produced satisfactory release prolongation either alone or in combination with other polymers [18].

Table 1:Some Recently Investigated Natural Gums and Mucilage

Common name	Botanical name	Family	Pharmaceutical applications
Agar	<i>Gelidiumamansii</i>	Gelidaceae	Suspending agent, emulsifying agent, gelling agent in suppositories, surgical lubricant, tablet disintegrates, medium for bacterial culture, laxative [19]
Albizia gum	<i>Albizia zygia</i>	Leguminosae	Tablet binder, coating materials in compression-coated tablets[20]
Abelmoschus gum (Orka gum)	<i>Abelmoschus esculentus</i>	Malvaceae	Suspending agent, disintegrant in low concentrations (4%) [21], poor floating capacity in sustained release tablet but with HPMC shows better results. Okra polysaccharide as a microbially triggered material for colon targeted tablet formulation [22]



Tamarind Seed Polysaccharide	<i>Tamarindus indica</i>	Fabaceae	Microspheres preparation (size range of 230-460µm). In another study, Diclofenac sodium matrix tablets containing TSP[23]
Locust Bean Gum (Carob gum)	<i>Ceratonia siliqua</i>	Leguminosae	Controlled release agent[24]
Fenugreek mucilage	<i>Trigonella foenum-graceum</i>	Leguminosae	Better release retardant[25]
Hibiscus mucilage	<i>Hibiscus rosasinensis</i>	Malvaceae	Sustained release[26]
Almond gum	<i>Prunus amygdalus</i>	Rosaceae	emulsifying, thickening, suspending, adhesive, glazing, and stabilizing properties. Drug release increased[27]
Neem gum	<i>Azadirachta indica</i>	Meliaceae	Controlled release agent[28]
Aloe Mucilage	<i>Aloe barbadensis</i>	Liliaceae	Controlled release agent[29]
Cashew Gum	<i>Anacardium occidentale</i>	Anacardiaceae	Gelling property, Controlled release agent[30]
<i>Moringaoleifera</i> gum agent.	<i>Moringa oleifera</i>	Moringaceae	Gelling property, Binding agent, Controlled release
Acacia	<i>Acacia Senegal</i>	Combretaceae	Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient in cosmetics Osmotic drug delivery[31]
Bhara gum	<i>Terminalia bellerica roxb</i>	Combretaceae	Microencapsulation[32]
Cactus mucilage	<i>Opuntia</i>	----	Gelling agent in sustained drug delivery [33]
Gellan gum		----	Ophthalmic drug delivery, sustaining agent, beads, hydrogels, floating in-situ gelling, controlled release

Polysaccharides in Pharmaceuticals

Natural polysaccharides are extensively used for the development of solid dosage forms. These polymers of monosaccharides (sugars) are inexpensive and available in a variety of structures with a variety of properties. They are highly stable, safe, non-toxic, and hydrophilic and gel forming in nature. Pectins, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in dosage forms. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon which make them potentially useful in targeted delivery systems to the colon[40].

Pectins

Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. They are predominantly linear polymers of mainly (1-4)-linked D-galacturonic acid residues interrupted by 1,2- linked L-rhamnose residues with a few hundred to about one thousand

building blocks per molecule, corresponding to an average molecular weight of about 50,000 to about 1,80 00040. Being soluble in water, pectin is not able to shield its drug load effectively during its passage through the stomach and small intestine.

Focus was shifted to the development of less soluble derivatives of pectin which get degraded by the colonic microflora. To overcome the drawback of high solubility of pectin, mixed films of pectin with ethyl cellulose were investigated as a coating material for colon-specific drug delivery. Polymeric hydrogels are widely used as controlled-release matrix tablets. Sungthongjeen et al.,[41] investigated the high-methoxy pectin for its potential value in controlled-release matrix formulations.

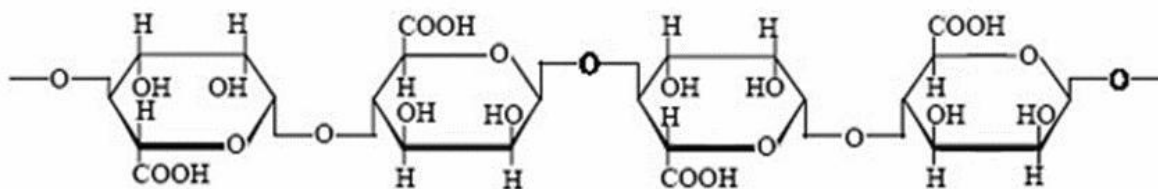
A very low solubility pectin-derivative (pectinic acid, degree of methoxylation (4%) was found to be well suited as an excipient for pelletization by extrusion/spheronization.

Musabayaneet al., [42] investigated the suitability of amidated pectin as a matrix patch for transdermal chloroquine delivery to mask the bitter taste when orally administered. In relation to the food industry, folic acid incorporated microcapsules were prepared using alginate and combinations of alginate and pectin polymers to improve stability of folic acid[43].

In relation to cosmetics, using citronellal as a model compound, pectin gel formulations were evaluated for controlled fragrance release by kinetic and static methods. Pectin/calcium microparticles are promising materials for controlled fragrance release[44].

Alginates

Alginates are natural polysaccharide polymers isolated from the brown seaweed (Phaeophyceae). Alginate acid can be converted into its salts, of which sodium alginate is the major form currently used. A linear polymer consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in the polymer chain, these homogeneous blocks (composed of either acid residue alone) are separated by blocks made of random or alternating units of mannuronic and guluronic acids. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications[45] (fig. 3)



Alginate Acid

Fig. 3: Structure of Alginate acid

Bioadhesive sodium alginate microspheres of metoprolol tartrate for intranasal systemic delivery were prepared to avoid the first-pass effect, as an alternative therapy to injection, and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris.

A new insert, basically consisting of alginates with different hydroxyethylcellulose content was developed to maintain a constant drug level over a certain period in the eye, which cannot be achieved by conventional eye drop application [46]. To achieve 24 h release profile of water soluble drugs, sodium alginate formulation matrices containing xanthan gum or zinc acetate or both were investigated.

The helical structure and high viscosity of xanthan gum possibly prevent zinc ions from diffusing out of the ranitidine HCl sodium alginate-xanthan gum-zinc acetate matrix so that zinc ions react with sodium alginate to form zinc alginate precipitate with a cross-linking structure. The cross-linking structure might control a highly water-soluble drug release for 24 h[47].

In a comparative study, alginate formulation appeared to be better than the polylactide-co-glycolide (PLG) formulation in improving the bioavailability of two clinically important antifungal drugs-clotrimazole and econazole. The nanoparticles were prepared by the emulsion-solvent-evaporation technique in case of PLG and by the cation-induced controlled gelification in case of alginate[48].

Volatile Oils

Volatile oils are generally mixtures of hydrocarbons and oxygenated compounds derived from these hydrocarbons. Many oils are terpenoid in origin; some of them are aromatic derivatives mixed with terpenes (e.g. cinnamon and clove). A few compounds (e.g. thymol and carvacrol) although aromatic in structure, are terpenoid in origin [49].

Starches

It is the principal form of carbohydrate reserve in green plants and especially present in seeds and underground organs. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species, as is also the ratio of the content of the principal constituents, amylose and amylopectin [50]. Many starches are recognized for pharmaceutical use (fig. 4). These include maize (*Zea mays*), rice (*Oryza sativa*), wheat (*Triticum aestivum*), and potato (*Solanum tuberosum*) [51].

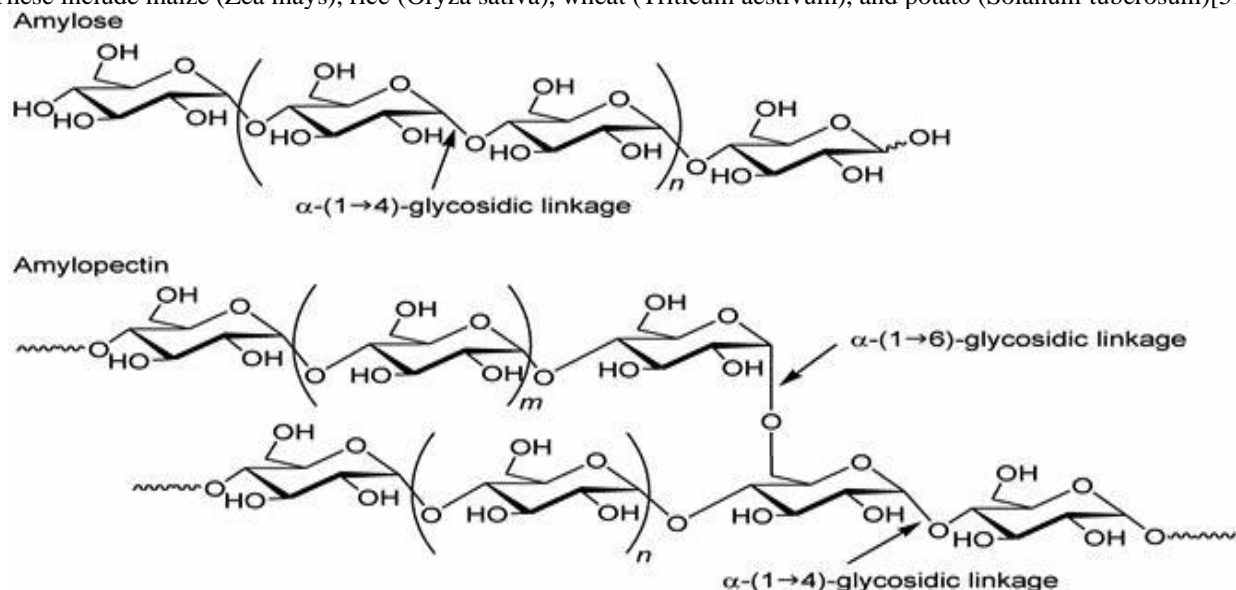


Fig. 4: Structures of (A) amylopectin or α - amylose and (B) β -amylose

Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible tablet controlled-release matrix systems. To deliver proteins or peptidic drugs orally, microcapsules containing a protein and a proteinase inhibitor were prepared [52].

Acetylating of starch considerably decreases its swelling and enzymatic degradation. Thus, starch-acetate (SA) based delivery systems were tested for controlled drug delivery [53].

Menthol

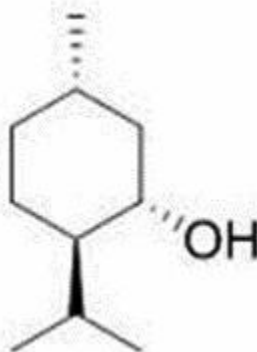


Fig. 5: Menthol

Menthol is obtained by steam distillation of the flowering tops of *Mentha piperita* belonging to the family Labiatae. A membrane - moderated transdermal therapeutic system (TTS) of nimodipine [54] using 2% w/w hydroxypropyl methylcellulose (HPMC) gel as a reservoir system containing menthol as penetration enhancer and 60% v/v ethanol-water as solvent system was prepared.

Menthol was tested for improving the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer [55]. Terpenes such as menthol, cineole and propylene glycol (PG) were tested as chemical enhancers to improve the skin penetration of propranolol. Release and skin permeation kinetics of propranolol from film preparations were examined in in vitro studies using a Franz-type diffusion cell. In vitro skin permeation studies showed that cineole was the most promising enhancer among the enhancers examined [56].

Caraway

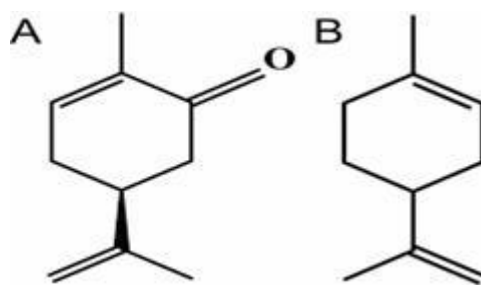


Fig. 6: a) Carvone b) Limonene

Caraway fruit consists of the dried, ripe fruits of *Carum carvi* (Umbelliferae). The volatile oil consists of the ketone carvone (fig. 6) and the terpene limonene [49]. In another attempt, it was concluded that the limonene-based TTS of nicorandil provided the desired plasma concentration of the drug for the predetermined period with minimal fluctuations and improved bioavailability.

CONCLUSION

Today the stress is on patient compliance and to achieve this objective there is a spurt in the development of NDDS. As the herbal excipients are promising biodegradable materials, these can be chemically compatible with the excipients in drug delivery systems. In addition, herbal excipients are non-toxic, freely available, and less expensive compared to their synthetic counterparts. They have a major role to play in pharmaceutical industry. Therefore, in the years to come, there is going to be continued interest in the natural excipients to have better materials for drug delivery systems.

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