

REVIEWS

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Natural polymers, gums and mucilages as excipients in drug delivery

Naturalne polimery, żywice i kleje roślinne jako substancje pomocnicze w podawaniu leku

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Summary

Use of natural polymers, gums and mucilages in drug delivery systems has been weighed down by the synthetic materials. Natural based excipients offered advantages such as non-toxicity, less cost and abundantly availability. Aqueous solubility of natural excipients plays an important role in their selection for designing immediate, controlled or sustained release formulations. This review article provide an overview of natural gum, polymers and mucilages as excipients in dosage forms as well as novel drug delivery systems (**Polim. Med. 2012, 42, 191–197**).

Key words: natural polymers, excipients, drug delivery, gums, mucilages, controlled release, sustained release

Streszczenie

Wykorzystanie naturalnych polimerów, żywic i klejów roślinnych w systemach podawania leków, zostało zdominowane przez użycie materiałów syntetycznych. Substancje pomocnicze pochodzenia naturalnego oferują takie zalety, jak nietoksyczność, mniejsze koszty i szeroką dostępność. Rozpuszczalność w wodzie naturalnych substancji pomocniczych odgrywa ważną rolę w ich wyborze w projektowaniu preparatów o natychmiastowym, kontrolowanym i przedłużonym uwalnianiu. Artykuł ten dostarcza informacji na temat naturalnych żywic, polimerów i klejów roślinnych, jako substancji pomocniczych w postaciach leku oraz w nowych systemach podawania leku (**Polim. Med. 2012, 42, 3-4, 191–197**).

Słowa kluczowe: naturalne polimery, substancje pomocnicze, podawanie leku, żywice, kleje roślinne, kontrolowane uwalnianie, przedłużone uwalnianie

Introduction

Natural polymers and their semi-synthetic derivatives gained popularity in development of novel drug delivery systems. They are degradable, compatible with bioactive agents, readily available, and possess ability for chemical modifications. Synthetic excipients suffer with the problem of their unwanted harm to body, that's why researchers take more interest in development of natural excipients. In recent years, patients seek the pharmaceutical products containing natural herbal ingredients. Herbal based formulations are more safe and cause no side effects.

Natural polymers, gums and mucilages modify the drug release from formulation. As suggested by a study

that the release behavior of drug from formulation containing natural polymers depends on the physicochemical properties of both the drug and polymer. Release pattern of polymer, morphology, particle size, size and shape of dosage form are also some of factors that influence the release of drug [1].

Research performed on natural polymers

For many studies, the objective was to predict characteristics and uses of various natural polymers as described below:

Chitosan. Invertebrates, insects and yeast are the main source of chitin. Chitin have antimicrobial activity, which make its wide use in packaging material. Chitosan is a derivative of chitin. Biocompatibility of chitosan allows its use in various biomedical applications. Tapola et al. [2] investigated the safety aspects of chitosan tablets. The result of their study suggested that chitosan tablets was safe for human use. Sahasathian et al. [3] prepared sustained release tablets of amoxicillin by using chitosan as release retarding agent. The obtained results revealed that chitosan having particle size less than 75 micron showed best sustained release behavior. Chitosan was found to provide the release of drug with first order kinetics. Recently, Sogias et al. [4] studied chitosan and its half-acetylated derivative as excipient in mucoadhesive tablets.

In an attempted chitosan and its mixtures with carboxymethylcellulose sodium showed ability to retard prednisolone release from tablet matrix. It was concluded by Inouye et al. [5] that by using a suitable blend of chitosan and carboxymethylcellulose sodium desired sustained release could be achieved. Chitosan and sodium alginate-based mucoadhesive vaginal tablets were developed by El-Kamel et al. [6]. Chitosan and sodium alginate were used as matrixing agents for preparing metronidazole bioadhesive vaginal tablets. According to them formulation containing chitosan (6%), sodium alginate (24%), sodium carboxymethyl cellulose (30%), and microcrystalline cellulose (20%) showed good mucoadhesive properties. Inouye et al. [7] prepared sustained release intragastric 'floating' tablets composed of chitosan. They employed two types of chitosan (chitosan H and L). They concluded that preparation containing chitosan L showed slower drug release than preparation composed of chitosan H.

Goel et al. [8] evaluated interpolymers chitosan-alginate complex and chitin as superdisintegrants. They formulated fast disintegrating tablets of ondansetron HCl using chitosan-alginate (1:1) complex. Prepared tablet showed good mechanical strength and less disintegration time. They proposed that chitosan-alginate complex swelled up due to uptake of water and ultimately lead breakage of tablet matrix within seconds.

Xanthan gum. It is hydrophilic, anionic-bacterial heteropolysaccharide, derived from fermentation of gram-negative bacteria *Xanthomonas campestris*. For many studies, the goal was to evaluate sustained release action of xanthan gum [9, 10]. A modification in release profile of drugs is also observed on combination of polymers. Rasul et al. [11] prepared sustained release tablets of metoprolol tartrate using xanthan gum and tragacanth in different proportions. Tablets were prepared by direct compression using microcrystalline cellulose as diluents. Results showed that increase in xanthan gum amount in tablets showed increase sustained release of drug. All the formulations followed Higuchi or zero order kinetics. In a study, use of xanthan gum

in mucoadhesive formulations has been reported [12]. Phaechamud et al. [13] fabricated sustained-release matrix tablets containing chitosan combined with xanthan gum which prolonged the drug release more extensive as compared to that containing single polymer. By utilizing release retarding properties of xanthan gum, controlled release profile was achieved in delivery of pentoxifylline [14]. Patel et al. [15] evaluate xanthan gum and guar gum for formulation of floating dosage form for dipyridamole. The prepared tablets had desired buoyancy characteristics. Hence xanthan gum could be use in floating drug delivery formulations. Gohel et al. [16] explored the use of blend containing xanthan gum and hydroxypropylmethyl cellulose for development of modified release drug delivery system of diltiazem HCl. The drug release kinetics for tablets followed Hixson-Crowell equation and showed drug release for 12 h.

Tamarind seed polysaccharide. It is a galactoxyl-glucan. Sumathi et al. [17] isolated tamarind seed polysaccharide from tamarind kernel powder and studied the sustained release behavior of both water-soluble and water-insoluble drugs from tamarind seed polysaccharide. Acetaminophen, caffeine, and theophylline were used as water-soluble drug whereas salicylic acid and indomethacin as water-insoluble drug. It was founded that the mechanism of release of soluble drugs was anomalous whereas water-insoluble drug showed zero order release behavior.

Gellan gum. It is an exocellular polysaccharide secreted by *Pseudomonas elodea*. This gum had been investigated for pharmaceutical applications such as tablet disintegrant, binder, gelling agent and controlled release polymer [18]. Smith et al. [19] prepared enteric coated dosage form by utilizing gellan gum, sodium alginate and hypromellose. The dosage form remained intact for about two hours in HCl (pH 1.2) but when placed in buffer (pH 6.8) it was ruptured. Thus, it was concluded that these natural polymers can be used in the formulation of delayed release dosage forms. Babu et al. [18] evaluated the suitability of gellan gum macrobeads for development of gastroretentive controlled delivery of amoxicillin. They prepared gellan gum beads by using ionotropic gelation with calcium ions. The macrobeads provided release which was fitted to diffusion model. Hence, gellan gum could be used in controlled drug delivery formulation.

Emeje et al. [20] prepared matrix tablets of metronidazole using gellan gum in different concentrations and studied its release profile. It was concluded from the study that optimum concentration of gum (0.2% w/w) showed most effective as a disintegrant. The use of gellan gum as a controlled release carrier in the formulation of gastro-floating matrix tablets has been done by Elmowafy et al. [21]. In a study, an attempt to design bi-layer tablet of metoclopramide HCl and ibuprofen, the use of gellan gum as disintegrant was

done [22]. Narkar et al. [23] used gellan gum in preparation of stomach-specific controlled release mucoadhesive drug delivery system. They employed amoxicillin trihydrate as model drug. The *in vitro* dissolution study showed that drug release upto 7 h in a controlled manner and following the Peppas model. From the results of both *in vitro* and *in vivo* mucoadhesivity study, it was revealed that gellan gum beads possess good mucoadhesivity even after 7 h. Singh et al. [24] investigated the suitability of gellan beads for the development of colon specific controlled drug delivery system. Gellan beads to deliver azathioprine were prepared as a potential colonic delivery system by ionotropic gelation and were coated with Eudragit S-100. Gum releases drug in controlled manner. Thus, it was suggested the use of gellan gum as a carrier for controlled colonic specific drug delivery systems.

Rosin. It is a clear, pale yellow to dark amber thermoplastic resin that present in oleoresins of tree *Pinus soxburghi* and *Pinus toeda* belong to family Pinaceae. Nande et al. [25] prepared diclofenac sodium loaded microspheres using PEGylated rosin derivative. Microspheres were formulated by emulsion solvent evaporation method. *In vitro* dissolution study showed that the release follows Higuchi equation. It was reported that fickian diffusion was the mechanism of drug release. They suggested that PEGylated derivatives of rosin could be used for preparing microspheres to obtain sustained release of drug. In another study, Nande et al. [26] evaluate potential use of PEGylated derivatives of rosin as film formers, which showed sustained release. Fulzele et al. [27] prepared sustained release microcapsules of diclofenac sodium by employing polymerized rosin. They use polymerized rosin as wall-forming agent. Formulated microcapsules showed sustained release of drug for about 10 hr. *In vitro* dissolution study showed that drug release from microcapsules follow Higuchi-order release pattern. Pathak et al. [28] prepared tablets of aspirin using rosin and its esters as hydrophobic matrix materials for controlled drug delivery. The tablets were formulated by wet granulation technique. Formulations had good mechanical strength and showed hardness greater than 6 kg/cm². Disintegration time for tablets was greater than 150 min. Thus, rosin act as a hydrophobic matrix forming agent for development of controlled drug delivery systems.

Grewia gum. Grewia gum is a biodegradable hydrophilic gum obtained from *Grewia mollis*. It is mainly used in formulations of controlled release dosage forms. As gum is hydrophilic so when it comes in contact with aqueous medium it swells and forms a viscous dispersion. Ogaji et al. [29] evaluated grewia gum as a suspending agent in liquid oral preparations. They formulated suspension of ibuprofen using grewia gum. They found that grewia gum showed minimal changes in viscosity on storage. Hence, grewia gum could be utilized as suspending agent in suspension formulations.

Carrageenan. It is obtained from seaweeds of class Rhodophyceae. Red seaweeds including *Iradaea aminariodes*, *Chondrus crispus*, *Euchema spinosum* are the major sources. Picker et al. [30] and Hariharan et al. [31] suggested carrageenan use as excipient in controlled-release tablets. Bonferoni et al. [32] prepared carrageenan-diltiazem complex and evaluate it as a excipient used in controlled-release formulations. In their study they found that there was the highest crushing strength and the slowest drug release, when the finest sieve fraction of complex was employed. They also suggested that drug release mechanism was surface dissolution or erosion. Picker et al. [30] evaluate carrageenans (Gelcarin GP-812 NF, Gelcarin GP-911 NF and Gelcarin GP-379 NF) as excipients for controlled-release solid dosage forms. The prepared tablets had high crushing strength. They suggested that the studied carrageenans showed good compactibility and controlled release behavior.

Picker et al. [33] studied the drug release from ternary mixture composed of kappa-carrageenan, microcrystalline cellulose and theophylline monohydrate. The results showed different drug release mechanisms from ternary mixture based on the concentration of kappa-carrageenan used. When proportion of kappa-carrageenan about 20% v/v was used, there was fast release of drug whereas when 30% v/v was used, it showed zero-order kinetics. This was due to swelling of tablets made of ternary mixture. Bani-Jaber et al. [34] prepared interpolymeric complex of carrageenan and chitosan and evaluated its influence on drug release. It was concluded that this complex was able to sustain drug release from polymeric matrix. Ghanam et al. [35] proposed the use of carrageenan pellets for the preparation of multiparticulate tablets which showed modified drug release. In another study evaluation of carrageenans (Gelcarin GP-379 and Viscarin GP-209) as a carrier for the preparation of controlled-release drug delivery system was carried out. Tablets containing both carrageenans in equal proportion showed zero-order release profile [31].

Terminalia catappa gum. Kumar et al. [36] examined terminalia catappa gum as vehicle for oral sustained release tablets. Dextromethorphan hydrobromide was selected as a model drug for their study. Dextromethorphan hydrobromide tablet composed of terminalia catappa gum prepared by direct compression method. Sustained release of drug was demonstrated in phosphate buffer (pH 6.8). Formulation showed sustained release of more than 8 hr. Hence, terminalia catappa gum is a promising basis in the design of controlled drug delivery system.

Mimosa pudica seed mucilage. Singh et al. [37] examined the sustained-release properties of mimosa pudica seed mucilage on diclofenac sodium. Tablets were prepared by wet granulation method. Results showed that as the increase concentration of mucilage in formu-

lation, decreases the release of drug from tablets. Higuchi square root release kinetics was followed by formulations and showing diffusion release mechanism when high amount of mucilage was utilized whereas showed both matrix erosion and diffusion mechanisms for formulations composed of less amount of mucilage. Ahuja et al. [38] prepared buccal discs of fluconazole by using mimosa pudica seed mucilage as bucoadhesive. The discs were prepared by employing direct compression method. The results revealed that polymer showed bioadhesion time of 10 h and more than 85% release of drug in 10 h.

Pectin. It is methoxyester of pectic acid. Plant cell walls are the major source of pectin. The different sources of pectin include sunflower, orange, lemon, carrot, mango, guava and papaya. It has more stability in acidic media. In one study, it has been suggested that pectin in combination with gelatine can be used as an encapsulating excipient to provide sustained release. Turkoglu et al. [39] used pectin-hydroxypropylmethylcellulose compression coat on 5-aminosalicylic acid core tablets for colonic delivery. The study confirmed that selective delivery of 5-aminosalicylic acid to colon could be achieved utilizing pectin-hydroxypropylmethyl cellulose as a carrier in the form of a compression coating.

Rao et al. [40] evaluated use of pectin in combination with hydroxypropylmethyl cellulose and hydroxyethyl cellulose for colon drug delivery. Naproxen tablet matrices prepared by using different proportion of polymers. Tablet coating was done by ethyl cellulose and cellulose acetate phthalate. Results showed that pectin-hydroxyethyl cellulose base coat could be used as carrier to deliver naproxen to colon. Mura et al. [41] investigated a new colonic drug delivery system using pectin matrix system with Eudragit S100 coating.

Alginate. Sodium alginate is a natural polysaccharide isolated from the brown seaweed. Alginates offer utilizations in dosage forms including microspheres, beads, liposomes, tablets, buccal films. Sodium alginate act as thickening agent and hence, use in preparation of pastes and creams. It is also employed as disintegrating agent and binder in tablet formulations. Miyazaki et al. [42] prepared bioadhesive tablets of ketoprofen using mixture of chitosan and sodium alginate in different ratios (4:1, 1:1 and 1:4). It was found from the study that 1:4 ratio of chitosan and alginate served to be the optimized oral sustained release tablet of ketoprofen. Liew et al. [43] studied the release behavior of drug from sodium alginate based formulations. According to them, alginate particle size affect the extent of burst release and also sodium alginate based matrices sustained the drug release upto 8 hr.

Gum acacia. It is obtained from stems of tree *Acacia Arabica*. It is water soluble and form viscous gel in water. In studies it was showed that gum acacia could be used as binder in tablets. In combination with gelatin, gum acacia can be used as encapsulating agent in preparation

of microspheres. Dash et al. [44] prepared microspheres and microcapsules of tolinaftate by using gelatine-acacia coacervation method. Stability study of formulation was performed and found that the drug was stable in microspheres and microcapsules formulation for about 6 months. Lu et al. [45] suggested the use of gum arabic in preparation of oral controlled drug delivery. They prepared naproxen osmotic tablets. In their tablets they use gum arabic as osmotic agent. The effect of gum arabic on drug release was studied. The optimal formulation deliver drug by following zero order for 12 hr.

Locust bean gum. Malik et al. [46] evaluated locust bean gum as superdisintegrants. They fabricated orodispersible tablets of nimesulide, by using locust bean gum. Results of their study concluded that tablet formulation containing 10% locust bean gum showed 13 seconds disintegration time. Vijayaraghavan et al. [47] evaluated combination of locust bean gum with chitosan as a mucoadhesive excipient for buccal tablets. Propranolol hydrochloride was selected as model drug. Force of detachment for buccal tablets was found between 11.71 and 14.61. Thus it was suggested that the excipient give sufficient mucoadhesive applications.

Khaya gum. It is naturally occurring hydrophilic polysaccharide obtained from tree, *Khaya grandifolia* belonging to family Meliaceae. In studies khaya gum used as binding agent in tablets, for drug targeting and controlled release has been reported. Odeku et al. [48] evaluated khaya gum as a controlled release agent in tablet formulations. Paracetamol tablets were formulated by employing direct compression method. From their studies, it was found that khaya gum provide controlled release of drug for 5 hr. Also combination of khaya gum and hydroxypropylmethylcellulose showed zero-order time independent release kinetics. Thus, tablets matrices composed of khaya gum could be utilized to obtain sustain release. In another study Odeku et al. [49] studied khaya and albizia gum coating for drug targeting to the colon. Odeku et al. [50] evaluated khaya gum as binder in tablets. Paracetamol was used as model drug. All fabricated tablets possess friability value less than 1%. Tablet formulations containing khaya gum as binder had lower tensile strength values.

Tragacanth gum. Iqbal et al. [51] evaluated combination of polyvinylpyrrolidone K90 with gum tragacanth for sustained release by using diclofenac sodium as model drug. They carried out *in vitro* and *in vivo* release study. Both these studies showed that gum tragacanth could be used for sustain release of drug.

Okra gum. Kalu et al. [52] evaluated hibiscus esculentus gum (okra gum) as excipient for controlled release tablet. It was suggested that this okra gum could be utilized in the formulation of sustained-release tablets for upto 6 hr.

Hibiscus rosasinesis mucilage. Jani et al. [53] evaluate Hibiscus rosasinesis mucilage as an excipient for sustained release tablet. It was suggested that this mu-

cilage could be utilized as release-retarding excipient to get sustained release for upto 12 hr, when 1:1.5 ratio of drug:mucilage was used. Ameena et al. [54] examined suitability of hibiscus rosasinesis mucilage as a binding agent in the formulation of tablet dosage form. From the results of studies it was revealed that hibiscus rosasinesis mucilage had good binding efficacy and could be used as release-retarding agent.

Guar gum. Altaf et al. [55] evaluated the use of guar gum as carrier in the formulation of sustained release systems. They formulated tablets using diltiazem as model drug. Results revealed that guar gum-based tablets could be economical alternative to diltiazem sustained release tablets. In a study performed by Al-Saidan et al. [56], results confirmed that guar gum based matrix tablet provide controlled drug delivery.

Karaya gum. It is naturally occurring hydrophilic gum obtained from *Sterculia urens*. Foster et al. [57] prepared gastric retentive gel composed of sodium alginate and karaya gum. The *in vivo* study was carried out in rats. The time for gastric residence for gel was found 1 to 8 hr. They suggested that sodium alginate-karaya gum gels can be utilized for designing gastric retentive dosage forms. Babu et al. [58] studied solid

dispersion of nimodipine prepared with modified gum karaya. Solid dispersions were formulated by cogrinding method. The dissolution rate of drug from solid dispersions was significantly higher than that of physical mixtures and pure drug.

Leucaena leucocephala seed polysaccharide. This seed polysaccharide is isolated from seed kernel of *Leucaena leucocephala*. Jeevanandham et al. [59] suggested the use of leucaena leucocephala seed polysaccharide for sustain-release of drug. This studied the sustained release behavior of leucaena leucocephala seed gum on both water-soluble and water-insoluble drug. Deodhar et al. [60] use leucaena leucocephala gum as a tablet binder. Pendyala et al. [61] suggested that leucaena gum have potential for its use in tablet formulation as a disintegrant.

Conclusion

The present review of the literature shows the release behavior of natural polymers, gums and mucilages. Therefore, in the years to come, these act as herbal excipients in drug delivery systems.

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