Release Behavior of Drugs from Various Natural Gums and Polymers

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Summary

Polymers are the high molecular weight compounds of natural or synthetic origin, widely used in drug delivery of formulations. These polymers are further classified as hydrophilic or hydrophobic in nature. Depending upon this characteristic, polymers exhibit different release behavior in different media. This property plays an important role in the selection of polymers for controlled, sustained or immediate release formulations. The review highlights the literatures related to the research made on several polymers regarding the release kinetics which made them a novel approach for modifying the action of the particular formulation.

Key words: natural polymer, gum and mucilages, controlled drug delivery, biodegradable polymers

Charakterystyka uwalniania leków z różnych naturalnych gum i polimerów

Streszczenie

Praca jest przeglądem literatury, dotyczącej badań nad różnymi polimerami w odniesieniu do kinetyki uwalniania, które umożliwiają nowe podejście do modyfikowania działania określonych formuł farmakologicznych.

Polimery są związkami pochodzenia naturalnego lub syntetycznego o dużej masie cząsteczkowej, szeroko używanymi w formułach dostarczających leki do organizmu. Polimery te są sklasyfikowane jako hydrofilowe lub hydrofobowe i wykazują różne stopnie rozpuszczalności w zależności od środowiska. Te własności odgrywają ważną rolę w wyborze polimerów do formuł z kontrolowanym, stałym lub natychmiastowym efektem uwalniania.

Słowa kluczowe: polimery, gumy, galaretki, kontrolowane uwalnianie leku, biowchłanialne polimery

INTRODUCTION

Polymers are large chain macromolecules containing a variety of functional groups. Blended with other low- and high-molecular-weight materials, they can be tailored for variety of applications. Polymers are widely used in pharmaceutical dosage forms and food products, which include both synthetic as well as natural polymeric materials. Depending upon the nature of polymers being used in formulations, they play an integral role in different drug delivery technologies. For example, they may be used as agents for controlled drug delivery, sustained drug delivery, targeted drug delivery and various other types of novel drug delivery systems. They may be used in taste masking, stabilization and protection in oral drug delivery systems. Also, they can bind to the particles of solid dos-

age formulations and change the flow characteristics of liquid dosage formulations [1].

The natural polymers are more superior to the synthetic polymers in respect of their highly organized macroscopic and molecular structure. This adds to their strength and biocompatibility. Moreover, their low toxicity and excellent biodegradability have also attracted researchers to pay attention towards the widespread application of natural polymers. The release rate of the drug from natural polymers depends upon several factors such as the physicochemical properties of drugs and the polymers, biodegradation rate of polymers [1], morphology and size of the particles, thermodynamic compatibility that exist between the polymers and the drugs [2–6], and the shape of the delivery devices [7].

The natural polymers widely used in the form of polyelectrolyte complexes in controlled drug delivery systems include three basic types [8–10]:

Neutral polymers: Hydroxypropylmethylcellulose (HPMC).

Cationic polymers: Chitosan.

Anionic polymers: κ-carrageenan, sodium alginate.

Examples of these polyelectrolyte complexes that control drug release from formulations include sodium alginate-chitosan, polyacrylic acid-chitosan, and chitosan-carrageenan. These ionic polyelectrolyte complexes of polymers affect the release of oppositively charged ionic drugs through ion exchange mechanism in dissolution medium [8–10]. Different polymers have different release kinetics depending upon their nature such as their hydrophilicity, hydrophobicity as well as the nature of drug. Hydrophilic polymers does not disintegrate on exposure to an aqueous medium, rather they forms a highly viscous gelatinous layer that controls the drug release from the matrix system. Natural gums such as acacia tragacanth and karaya are more preferred over synthetic materials for controlled drug delivery due to their cost effectiveness, easy availability and nontoxicity. Similarly, natural gums such as agar gum, guar gum and gellan gum have been discovered to be used as polymer for sustained drug delivery. On contact with water, these hydrophilic natural gums hydrate and swell and thus used for single unit dosage formulation. The drug release kinetics from these matrices depends on the relative magnitude of polymer hydration at the moving rubbery/glassy front within the formulation as well as the rate of polymer erosion at the swollen polymer/dissolution medium front. In other words, drug release from hydrophilic matrices is known to be a complex interaction between swelling, diffusion and erosion mechanisms [11].

RESEARCH DONE ON SEVERAL POLYMERS

Some of the investigations done on this area include various polymers as described below:

Chitosan. It is a cationic polysaccharide, linear and composed of copolymers of glucosamine and N-acetylglucosamine. Partial deacetylation of chitin obtained from crustacean shells gives chitosan. It varies with respect of different molecular weights (50–2000 kd), degree of acetylation (40–98%), and viscosity (1% chitosan in 1% acetic acid, <2000 mPa). Chitosan beads, its complexes with drugs and other polymers have been found to be used in various formulations to modify the release profile characteristics. Based on the degree of deacetylation and pH of the buffer, chitosan salts possess solubility in water, pH 9 solution (with 40% deacetylation) and pH 6.5 solution (with 85% deacetylation). It was also found that the polyelectrolyte complex of chitosan with κ-carrageenan leads to the disappearance of the electrostatic linkage between the amino group of chitosan and the sulphonate group of κ-carrageenan in the prepared complex and thus contributes to the swelling of the complex gel. Complexation of chitosan with κ-carrageenan also retards drug release to some extent [12].

Xanthan gum. Xanthan gum, a high molecular weight, water soluble, anionic-bacterial heteropolysaccharide, used as a rheology modifier is derived a result of microbial fermentation of glucose from the bacterial coat of *Xanthomonas campestris*. It is a hydrophilic polymer, biocompatible and inert which along with retarding the drug release provides the time dependent release kinetics. El-Gazayerly *et al.* [13–15] prepared pentoxifylline-controlled release tablets using xanthan gum and found that the drug release rate decreased on increasing the concentration of xanthan gum in the prepared formulation, as reflected from the increase in the mean dissolution time. Mughal *et al.* [16] also prepared propranolol hydrochloride-loaded matrix tablets using guar gum, xanthan gum, and hydroxypropylmethylcellulose (HPMC) as rate-retarding polymers and evaluated drug release in simulated gastric and intestinal media. It was investigated from the study that guar gum alone was not able to control drug release until a 1:3 drug/gum ratio. However, incorporation of HPMC in matrix tablets provided near zero-order release over 12 h where erosion was a major contributing mechanism. Further modification in release profile was observed on combination of highly viscous gel forming polymer HPMC with guar or xanthan gum which resulted in a Higuchi release profile. Xanthan

gum, a single rate-retarding polymer retarded release over 24 h which best confirmed the Higuchi model as depicted from the data. Moreover, 10–20% concentration of xanthan gum when mixed with guar gum was unable to control release. But the formulation prepared with 30% guar gum and 30% xanthan gum behaved as if xanthan gum was the sole rate-retarding gum and drug was released by Fickian diffusion. Syeda *et al.* [17] prepared metoprolol tartrate formulation with the hydrophilic polymer Xanthan gum (XG) and observed that at higher concentration the polymer produced a greater sustaining effect on the release of drug in a first order kinetics. Sachan *et al.* [15] observed that since xanthan gum is water soluble hence it displayed high degree of swelling and small degree of erosion as a result of polymer relaxation. Various studies showed that different ratios of xanthan gum used as a potential excipient for orally controlled release tablets showed dominantly Fickian diffusion during first half of the *in vitro* dissolution period of drug Diclofenac sodium and erosion behavior during the latter half thus, indicating zero-order release. It was also found from the study that xanthan gum matrices showed marked sustained effect on the release of drug propranolol hydrochloride than any other polymer such as locust bean gum alone. The physical mixture of xanthan gum and locust bean gum was found to provide the required release rate, with zero-order release kinetics.

Carrageenan. Carrageenans are naturally occurring high molecular weight anionic gel-forming polysaccharides extracted from certain species of red seaweeds (Rhodophyceae) such as *Chondrus crispus*, *Euchema*, *Gigartina stellata* and *Iridaea*. It is made up of the repeating units of galactose and 3, 6 anhydrogalactose. Depending on the different degree of sulfation, they are classified into various types: ι-(mono-sulfate), κ-(di-sulfate), and λ-carrageenan (three-sulfate). ι- and κ-carrageenan forms gel while highly sulphated λ-carrageenan is a thickener agent and does not form gel, which influence their release kinetics [14, 18, 19]. Liu *et al.* [20] prepared one compartment matrix blend of κ-carrageenan, agar and gelatin with drug theophylline. It was found that the polymer networks showed controlled release of drug thus slowing down the diffusion rate of the drug molecule through the matrices. Release rate of the molecules differs with respect of different hydrophobicity based on selective interaction with κ-carrageenan. Greater the hydrophobicity of the drug, stronger is its adsorption in the chains, which leads to lower diffusion coefficient. Rosario *et al.* [21] prepared directly compressed matrix formulation of theophylline using different concentration of Carrageenan polymer and investigated that the drug release study performed for Carrageenan matrices appears to follow the diffusion model for 90 min., while after 90 min, the drug release follows a zero-order model.

Pectin. Pectin is a complex hydrophilic, heterogeneous polysaccharides consisting mainly of esterified D-galacturonic acid residue and its methyl ester in α (1-4) chain. It is a natural polymer found in the cell walls in most of the higher plants. Certain fruits such as apple, quince, plume, gooseberry, grapes, cherries and oranges contain pectin. It is found to be widely useful in drug delivery due to its easy availability and low production cost. Pectin possesses varying degrees of methyl ester substituents depending on the plant source and preparation which determines its solubility and requirements for gelation. For example, high methoxy pectins (HM) are poorly soluble and forms gel at pH around 3 whereas low methoxy pectin (LM) is more hydrophilic and soluble than HM in pH 7.4 buffer. Chemical modification such as saponification catalysed by mineral acids, bases, salts of weak acids, enzymes, concentrated ammonium systems and primary aliphatic amines also reduces the high solubility of pectin without affecting their biodegradability. Different percentages of chitosan was incorporated in the pectin coat of multilayer tablets of mesalamine to give different coat:core ratio. The effect of this varying coat: core ratio was observed on drug release and found that high Pectin coat: core ratios of compression coated formulations were able to protect the tablet cores from premature drug release. Incorporation of chitosan (3% and 5%) in the Pectin coat offered better protection at a lower coat: core ratio [22, 23]. Tonnesen *et al.* [24] developed a new controlled microcapsular delivery system using pectin differing in its source of origin, molecular weight and the degree of esterification. It was found that the release kinetics of poor water soluble drug prednisolone follows a combination of dissolution and diffusion kinetic parameters in one parameter. High methoxylated apple pectin yields the highest value of drug dissolution/diffusion number as compared to the highly charged citrus pectin. Malviya *et al.* [25] prepared matrix tablets of Diclofenac sodium using pectin polymer in different concentrations and studied its release profile. It was found from the whole study that 1:1.5 drug: polymer ratio proved to be the best formulated oral sustained release tablet.

Tamarind Seed Polysaccharide (TSP). Tamarind Seed Polysaccharide (TSP) is a galactoxyloglucan (a monomer of mainly three sugars- galactose,

xylose and glucose- in a molar ratio of 1:2:3) isolated from seed kernel of *Tamarindus indica*. TSP is a non toxic, biocompatible and cheap agro-based material which could be safely used for controlled drug delivery systems. Sahoo *et al.* [26–28] formulated tablets using 10%, 20%, 30%, and 40% Tamarind Seed Polysaccharide (TSP) as a natural binding agent and observed that highest binder concentration showed maximum hardness and minimum friability. Thus, tablets with 20% TSP showed maximum drug release while tablets with 40% TSP showed minimum drug release after 24 hrs. It was concluded that increasing the amount of TSP decreases the release rate. As TSP showed controlled release of both water-soluble and water insoluble types of drugs, thus when evaluated for tablets it showed slow drug release over 24 h. Kumar *et al.* [29] again observed the sustained release kinetics of both water-soluble and water insoluble drugs using TSP. Water insoluble drugs like indomethacin showed zero order release from TSP. The extent and amount of release of water-soluble drugs such as acetaminophen, caffeine, theophylline and salicylic acid can be controlled by partially cross linking the matrix at various degrees of cross-linking. Rajesh *et al.* [30] observed the cumulative release of Paclitaxel at various pH from TSP matrix and found that at increased pH accelerated drug release occurs due to weakened facilitated swelling. This follows that drug release from matrices occurs after water penetration in the matrix, followed by hydration. It then swells and the dissolved drug (polymer hydro fusion) either diffuses out of the matrix, and/or erodes out of the gelatinous layer. Malviya *et al.* [31] prepared the matrix tablets of Diclofenac sodium using tamarind gum as release modifier in different drug: polymer concentration (1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5). It was found from the study that 1:2.5 ratio of drug and polymer served to be the optimized oral sustained release tablet of Diclofenac sodium.

Mimosa pudica seed mucilage. Tapia *et al.* [32] studied the sustained release effect of *Mimosa pudica* seed mucilage on Diclofenac sodium which depends upon the mucilage to drug ratio. Increased concentration of mucilage retarded the drug release due to the increased gel strength with longer path of drug diffusion through gel layer that resulted in reduction in diffusion coefficient of the drug. Lower mucilage concentration released the drug by diffusion and erosion mechanism, while higher mucilage concentration released the drug by diffusion through the swollen matrix. Thus, Mimosa mucilage acts as a matrix forming agent for sustained drug delivery of formulations.

Leucaena leucocephala seed polysaccharide. Leucaena leucocephala seed polysaccharide (LLSP) is a galactoxyloglucan hydrophilic gum isolated from seed kernel of *Leucaena leucocephala*. LLSP can be used for controlled delivery of both water-soluble as well as water-insoluble drugs [33, 34]. It possesses good swelling capacity. Verma *et al.* [35] found that on contact with water the pressure is generated which initiates disintegration well before the gelling occurs.

Guar gum. Guar gum is a nonionic naturally occurring, hydrophilic polysaccharide obtained from the seeds of *Cyamopsis tetragonolobus*. It is used in solid dosage forms (binder and disintegrant), possess release retarding property and susceptibility to microbial degradation. It swells in cold water and forms viscous colloidal dispersions or sols. It is this gelling property that retards release of the drug from the dosage form. It was observed that guar gum alone acts as the release retarding polymer which follows a first-order release kinetic [11, 36]. Guar gum showed release pattern that best fits higuchi models in various studies [37].

Deshmukh *et al.* [38, 39] observed that the increased concentration of guar gum decreases the drug release. Increased gum concentration raises the swelling index value, thereby resulting in slow erosion of gelled layer which favoured slow release of zidovudine from this viscous layer. Hence, there occurs diffusion through gel matrix coupled with erosion of matrix backbone mechanism for the drug release from Guar gum based formulations.

Sodium alginate. Sodium alginate is a natural polysaccharide obtained from marine brown algae, seaweeds as well as produced by some bacteria such as *Pseudomonas aeruginosa* or *Azobacter vinelandi*. It is a hydrophilic salt of alginic acid consisting of two uronic acids, β-D-mannuronic acid (M) and α-L-glucouronic acid (G). It is composed of homopolymeric blocks MM or GG. Soni *et al.* [40] prepared spherical microspheres of theophylline using sodium alginate to prolong the release rate of drug. It was concluded from the results that increased alginate concentration decreased the percent drug release. Thus, alginate microspheres showed extended in vitro drug release thereby offering sustained release profile along with improved drug delivery.

Kesavan *et al.* [41] studied the release kinetics of Gatifloxacin using sodium alginate as a polymer. It was observed that the release of the drug was fast and the system got completely depleted of drug within 2 h. 0.4 % to 2 % w/v concentration of sodium alginate modulated drug release significantly. Higher alginate concentration improves the gelling proper-

ties and lower concentrations of sodium alginate sustain the drug release for an extended period.

***Terminalia catappa* gum (TC).** It is a gum exudates obtained from *Terminalia catappa* Linn. It is a natural release retarding polymer. Patel *et al.* [42] and Kumar *et al.* [43] studied the release retarding behavior of TC gum in oral controlled drug delivery system of dextromethorphan hydrobromide (DH) as a model drug. It was found that the drug release was sustained in formulations containing TC gum as compared to the pure drug. This was attributed due to the excellent swelling properties of TC gum in water. They prepared three formulations of drug by aqueous wet granulation, non aqueous wet granulation and solid dispersion technique. When drug release was studied, it was observed that in case of non aqueous and solid dispersion, the release was sustained upto 8 h. while in case of aqueous the release was sustained for more than 8 hr. The higher sustaining effect in case of aqueous wet granulation was attributed due to the hydration and swelling of TC gum. This resulted in particles lodging in the spaces of the swollen gum that yielded stronger binding of gum and drug molecules and took more time for diffusion of drug out of the matrix tablet. While no swelling process occurred in case of non aqueous and solid dispersion which released the drug at faster rate.

Grewia gum. It is a natural, hydrophilic polysaccharide obtained from the inner bark of the tree, *Grewia mollis*. It has the property to be used in oral controlled drug delivery system. Grewia gum hydrates on contact with water and swells to form a highly viscous dispersion. Odeniyi *et al.* [44] studied the *in vitro* release behavior of cimetidine tablets containing Grewia gum and found that the release can be controlled for 12 h following Higuchi kinetic models. It acts as an excipient when used alone and modify the release of soluble drugs when used in combination with other polymers. It was observed that when grewia gum is used alone, only 16% drug release occurs after 2 h. It shows almost similar drug release characteristics to gum arabic. Grewia gum swell on contact with water to form gel layer. This gelled layer gradually dissolves or erodes to release the drug.

Gellan gum. Gellan gum is a hydrophilic, high molecular weight, anionic deacetylated exocellular polysaccharide gum isolated as a fermentation product from a pure culture of *Pseudomonas elodea*. It consists of a tetrasaccharide repeating unit of one β-D-glucuronic acid, one α-L-rhamnose, and two β-D-glucose residues [45, 46]. Nep *et al.* [47] prepared and studied the drug release behavior of different concentration of gellan gum based hydrogel microbeads loaded with ketoprofen. It was found that increased concentration of polymers decreased drug release which followed non-Fickian mechanism. Thus, gellan gum based microbeads served as useful carriers for controlled release of ketoprofen. Dabhi et al. [48] prepared periodontal gel using different concentration of gellan gum (0.1–0.8% w/v) and obtained the drug release data from all formulations that was best fitted to Korsemeyer-Peppas model. It was found that the drug release decreased with increased polymer concentration. Similarly, Agnihotri *et al.* [49] studied drug release kinetic using gellan gum beads of cephalexin drug and counterions. Release studies performed at 0.1 N HCl or pH 7.4 phosphate buffer showed the controlled release behavior.

Mucuna gum. Mucuna gum is a biodegradable, amorphous polymer composed of mainly D-galactose along with D-mannose and D-glucose and isolated from the cotyledons of plant *Mucuna flagillepes*. It swells in water to form a viscous mass. Mucuna gum acts as a good suspending agent/ stabilizer in dosage formulations such as suspensions and emulsions, a good binder in tablets and a good candidate for bioadhesive drug delivery. It was found from studies that 5% (*m*/*V*) mucuna gum with crosslinking time of 5 h possessed the prolonged drug release profile while 10% (*m*/*V*) mucuna gum with crosslinking time of 1 h delayed the release of drug. However, the formulations without crosslinking showed the fastest drug release [50].

Gum copal (GC): It is a naturally occurring hydrophobic resin isolated from the plant *Bursera bipinnata*. Attama *et al.* [51] observed the effect of gum concentration on the release rate of glibenclamide and found that when the concentration of gum copal and gum damar (GD) was increased, the drug release rate was decreased due to the formation of a dense matrix around drug molecules that prevent them to escape and dissolve. When drug release was studied using gum copal alone, it was found to follow zero order kinetics, hence used to prepare sustained release formulations.

Gum dammar. It is a naturally occurring hydrophobic gum obtained from plant *Shorea Wiesneri*. GD in the concentration range of 10–20% forms insoluble plastic matrix and releases the drug by mechanism of diffusion. When release data was applied to different models, it was found that formulation with 10-20% w/w gum concentration best fitted to Higuchi square root kinetic but when examined with 30% w/w gum concentration, it obeys zero order release kinetics. Hence, GD could be used in sustained drug delivery formulation [51].

Karaya gum. It is a hydrophilic naturally occurring gum obtained from *Sterculia urens* and composed of galactose, rhamnose and glucuronic acid. It swells in water and thus used as release rate controlling polymers in different formulations. It possessed very low hydration capacity and higher erosion. When release studies were investigated, karaya gum was found to produce zero order drug release along with erosion of matrices [52, 53]. Gangadharappa *et al.* [54] used Karaya gum to develop gastric floating drug delivery system of verapamil hydrochloride and studied its effect on drug release. It was observed that it swells on contact with aqueous medium and at a specific concentration of 23.3% produced sustained drug release for 8 h. Similarly, Moin *et al.* [55] prepared sustained release tablets of diltiazem hydrochloride using locust bean gum (LB) and karaya gum along with hydroxypropyl methylcellulose (HPMC) in different ratios. It was found from the investigation that LB gum alone could not control the drug release while Karaya gum possessed the better drug retarding capability.

CONCLUSION

In the present review different natural polymers and gums were studied in terms of their release kinetics when used in various formulations. The release behavior of both hydrophilic and hydrophobic natural polymers exhibits distinct mechanism when used in different ratios. Hence, it is this behavior based on which a drug formulation could be prepared to give sustained, controlled, immediate or any other type of effect.

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