NATURAL POLYMER OF TAMARIND SEED: A PROSPECTIVE CARRIER FOR OCULAR DRUG DELIVERY

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Abstract

Natural polysaccharide-based biomaterials are currently being explored as novel drug delivery devices. Important properties of the polysaccharides include controlled biological activity and biodegradability. The tamarind seed is a by-product of the tamarind industry. The decorticated flour, known as tamarind kernel powder has been tried for various biomedical applications such as drug delivery carriers. The xyloglucan component of it, a hemicellulose, was found to be a biocompatible, non-toxic and cheap agro-based material that could be used safely for controlled drug delivery systems. Studies with tamarind-seed polysaccharide nanocomposites have been conducted, where tamarind and polyvinyl alcohol were blended with Cloisite 30B solution in different ratios showing a sustained delivery of drugs. We certainly foresee the prospect of bio-adhesive carriers, such as muco-adhesive polymers of tamarind-seed polysaccharides an effective solution of achieving bioavailability of various ocular drugs when used as topical preparations.

Keywords: Tamarind seed polysaccharide, xyloglucan, drug delivery, ocular

Introduction

The recent use of biopolymers derived from agricultural feed stocks has attracted the attention of many researchers for various biomedical applications (Kalia S 2011). One such cheap and agro-based biomaterial is tamarind seed polysaccharide (TSP) obtained from tamarind seed. Tamarindus indica L, is a multipurpose tropical fruit tree primarily used for its fruits which are eaten fresh or processed to be used as a seasoning or spice. The fruits and seeds can also be processed for non-food uses. Recently various biodegradable based plants and animal based products have been explored for the use as drug carriers (Sahoo R 2010, Sahoo S 2010, Sahoo S

2011).Tamarindus indica L., commonly known as tamarind tree is one of the most important multipurpose tree species in the Indian sub-continent. It is a large evergreen tree with an exceptionally beautiful spreading crown, and is cultivated throughout almost the whole country, except in the Himalayas and western dry regions (ICFRE 1993, Rao Y S 1999). The major industrial use of the seeds is in the manufacture of TKP. It is prepared by decorticating the seed and pulverising the creamy white kernels (Khoja AK 2001).

However the medical use; especially the prospective use in drug delivery of TSP has not been reviewed extensively in literature. Therefore we wanted to have a review covering the various experimental studies those have explored the possibility of using TSP polysaccharides either through in-vitro or in vivo studies. We searched the articles published & featured in Science direct through electronic search. All the studies covering the ocular drug delivery aspects were included in review. The studies mentioning drug delivery to other parts of body were excluded from this review.

Tamarind Xyloglucan

Xyloglucan is a major structural polysaccharide in the primary cell wall of higher plants. Cell growth and enlargement are controlled by the looseness of a thin net of microfibrils made of cellulose. Xyloglucan cross-links these cellulose microfibrils and provides the flexibility necessary for them to slide. (Glicksman M 1986).

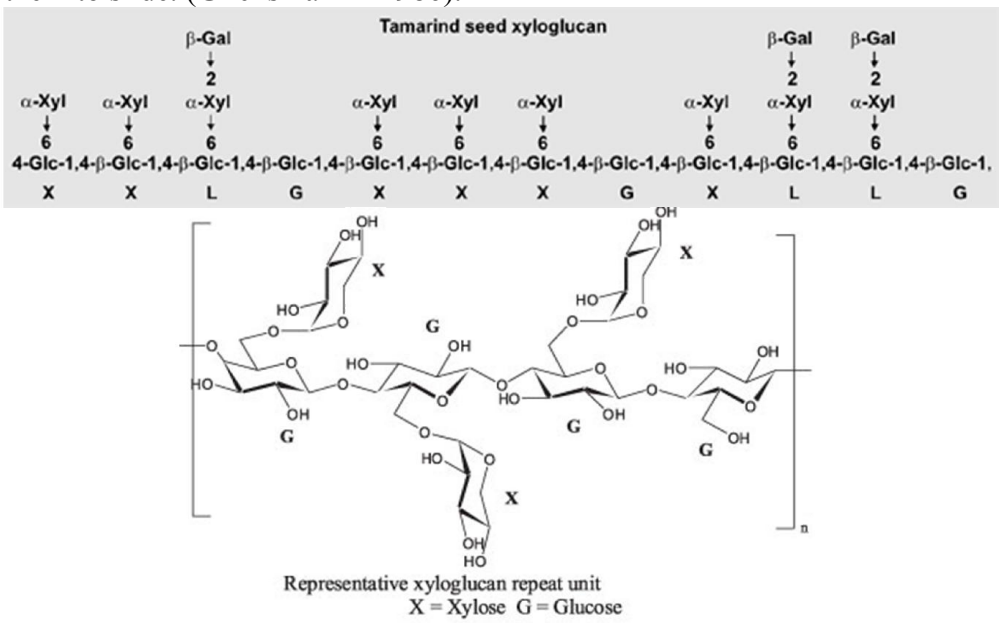

Figure.1 Biochemical Structure of Xyloglucan

Purified, refined tamarind XG is produced in Japan and is permitted as a thickening, stabilizing, and gelling agent.spaceTamarind XG has a (1→4)-β-D-glucan backbone (Figure.1) that is partially substituted at the O-6 position of its glucopyranosyl residues with α-D-xylopyranose (Gidley MJ 1991). In DSC measurements, the gelation was detected as a peak that appeared at higher temperatures than a peak arising from helix-coil transition of gellan alone . It was also detected as a change in circular dichroism which was not observed in tamarind XG alone and gellan alone .Judging from the results it was concluded that tamarind XG and gellan may associate to form a gel network (Nitta Y 2003).

Kochumalayil et al (Kochumalayil JJ 2013) oriented bionanocomposite coatings with strong in-plane orientation of clay platelets for the first time prepared by continuous water-based processing. Montmorillonite (MTM) and a "new" unmodified biological polymer XG were combined. The resulting nanocomposites were characterized by field emission SEM, transmission electron microscopy (TEM), and x-ray defraction (XRD). XG adsorption on MTM was measured by quartz crystal microbalance analysis. Mechanical and gas barrier properties were measured, also at high relative humidity. The reinforcement effects were then modeled and XG dimensions in composites estimated using atomistic simulations. The nanostructure showed highly oriented and intercalated clay platelets .

Mucoadhesive Properties of Tamarind seed polysaccharide (TSP)

Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Over the past few decades, mucosal drug delivery has received a great deal of attention. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome.TSP is a new formulation derived from the tamarind seed having mucoadhesive characterestics. The main component of tamarind seed has been identified as a non-ionic, neutral, branched polysaccharide consisting of a cellulose-like backbone that carries xylose and galactoxylose substituents (Saettone M 1997). The configuration of TSP gives the product a 'mucin-like' molecular structure, thus conferring optimal mucoadhesive properties (Mannucci LL 2000) .

Research has also shown that at the concentrations present in the ophthalmic formulations studied, TSP has an important characteristic that makes it similar to natural tears, whereby it is able to crystallise into a fern-like shape (Mannucci LL 2004). It has been suggested that the similarity of the structure of TSP to endogenous mucin may allow a formulation containing this polymer to adhere readily to the ocular surface for prolonged periods and provide sustained relief from the symptoms of dry eye

(Burgalassi S 1999). Indeed studies undertaken to date suggest that TSP may have some benefits over hyalurnic acid in relation to ocular retention time, wound healing properties and relief of dry eye symptoms (Mannucci LL 2000, Rolando M 2007). Overall, TSP has several physicochemical properties that make it suitable for the management of dry eye syndrome and which potentially have distinct advantages over currently available preparations.

Sahoo et al studied that the mucoadhesive polymer XG extracted from tamarind seeds could serve as a viscosity enhancer showing mucomimetic, mucoadhesive properties. The researchers described that several features make TSP an attractive candidate as a vehicle for ophthalmic medicaments for instance: (i) it is completely devoid of ocular toxicity; (ii) it has recently been put on the market as a tear fluid substitute because of its effectiveness in preventing alterations of the corneal surface for keratoconjunctivitis sicca; (iii) it increases the cornealwound healing rate; (vi) it reduces the in vitro toxicity exerted by timolol, methiolate, and fluoroquinolones on human conjunctival cells; and (v) it significantly increases the corneal accumulation and intraocular penetration of gentamicin and ofloxacin when administered topically to healthy rabbits (Sahoo S 2010).

TSP for Drug Delivery System:

Amongst all of the hydrophilic polymers, polysaccharides have become most recognised due to their widespread uses. TSP in particular, is conventionally known to bind, stabilise, thicken, suspend and emulsify agents as well as enhance viscosity. Its role in wound healing and as a carrier in novel drug delivery systems via ocular, oral, buccal, and colonic routes has also become increasingly acknowledged. In addition, TSP also has non-medical uses in nanofabrication, cosmetics and the food industry. Increasing discovery of the multiple roles of TSP has been possible due to its non-toxic nature and general acceptability by regulating authorities.

Other than the well-known uses of TSP, it has been identified to potentiate controlled release of both water soluble and water insoluble drugs. For instance, zero order release can be achieved by taking a sparingly soluble drug like indomethacin from TSP. The rate of release for these drugs can be controlled by using suitable diluents such as lactose and microcrystalline cellulose. Specific to water-soluble drugs, the release amount can also be controlled by partially cross-linking the matrix, here the degree of cross-linking can be altered thus modifying the extent of drug release (Sumathi S 2002).

Sahoo et al studied the nanocomposite of TSP in the controlled release of an anti-cancer drug, Paclitaxel (Sahoo R 2010). It was noticed that controlled delivery devices with biodegradable polymers had greater positive

significance over delivery systems that required surgical removal of the device. TSP as a biocompatible, non-toxic and cheap agro-based material was used safely for this controlled drug delivery system. A prolonged release of Paclitaxel was proven by use of TSP as the controlled release material. Swelling studies of the nanocomposites have also reported to be effective in releasing in a controlled manner.

Use as Ocular Drug Release Modifiers

Much research is currently in progress studying the efficacy of TSP for ocular preparations. Few studies have reported that TSP could be useful as artificial tears for the treatment of dry eye syndrome due to its mucoadhesive properties and pseudoplastic rheological behaviour (Khounvilay K 2011, Rolando M 2007). Alongside this, the high viscosity and unique mucoadhesive strength of TSP make it an ideal candidate for increasing the pre-corneal residence time for many topical ocular preparations.

The effect of an ophthalmic preparation containing 0.5% timolol (β-adrenergic blocker solution) plus 1 or 2% TSP on intraocular pressure (IOP) was evaluated in rabbits. It was concluded that timolol with TSP could be a good formulation for treating high IOP as the duration action of the formulation lasted for 12hours (D′amico M 1999). Similarly, another ocular drug pilocarpine, known to lower IOP has also been studied using tamarind gum as a novel bioadhesive material forming in situ gelling systems. The combination of alginate, tamarind gum and chitosan was identified as the most successful for sustained delivery of 80% of the drug for 12 hours. In vivo mitotic studies and ocular irritation studies have showed a significant long-lasting decrease in pupil diameter of rabbits with a well-tolerated non-irritating effect with a tamarind gum based formulation (Mehra GR 2010).

Ghelardi et al (Ghelardi E 2010) employed ocular administration of hydrophilic and hydrophobic antibiotics such as gentamicin and ofloxacin using TSP as a mucopolysaccharide. When TSP viscosified solutions of the drug were instilled into rabbits, the aqueous humour and corneal concentration of the dose was remarkably higher than the drug itself. It was also noted that the absorption and drug elimination was prolonged by use of TSP, for example, the concentration of drug in the cornea exceeded the minimum inhibitory concentration (MIC) found in cases of keratoconjunctivitis.

Other studies have postulated the effectiveness of ocular delivery of antibiotics, rufloxacin and ofloxacin with mucoadhesive polymer extracted from tamarind seed, for the treatment of bacterial keratitis experimentally induced by Pseudomonas aeruginosa and Staphylococcus aureus in rabbits. They found that the formulation significantly increased the intra-aqueous

penetration of the drugs in both infected and uninfected eyes. The effect of TSP on delivery of rufloxacin for a significant reduction of bacteria in the cornea was better than using rufloxacin alone. This was most probable due to the prolongation of the pre-corneal residence time subsequently increasing drug availability (Khounvilay K 2011).

In order to mask the unpleasant odour and to prevent the fast degradation of the TSP, it has been subjected to chemical modification by treatment with various groups such as acetyl, hydroxyalkyl and carboxymethyl . In a study by Kaur et al (Kaur H 2012), nanoparticles of carboxymethyl tamarind kernel polysaccharide (CMTKP) were used for ophthalmic drug delivery. TSP was carboxymethylated in order to impart an anionic nature to the polymer; this helped to increase its viscosity with an increase in shelf life and decreased biodegradability. The solubility of TSP in cold water was also enhanced. In the study nanoparticles of CMTKP loaded with tropicamide were formed by an ionotropic gelation technique. The in vitro study result of tropicamide-loaded CMTKP nanoparticles showed no significant difference in the permeation of the nanoparticles compared to that of the aqueous solution of the drug. The formulation was found to be non-irritant.

Uccello-Barretta et al (Uccello-Barretta G 2010) studied the interaction between TSP and hyaluronic acid (HA) with the aim of developing a promising excipient for ocular delivery. Nuclear Magnetic Resonance (NMR) spectroscopy was performed to determine the interaction between TSP and HA, this also helped to determine the optimum ratio of the TSP and HA in the mixture. A TSP:HA of 3:2in the mixture showed significant mucoadhesivity. An in vivo study on rabbits was also performed by the researchers, this was done by calculating the mean and maximum residence time of various TSP and HA mixtures in pre-corneal area. The results of these in vivo studies showed that the TSP:HA mixture in a 3:2 ratio showed strong mucoadhesivity compared to individual components and other mixtures. They concluded in saying that the enhanced ocular drug availability by the TSP and HA mixture was attributed to the strong mucoadhesivity. The same authors also used ketotifen fumarate (KT) for the ophthalmic dosage forms which showed more favourable affinity towards TSP rather than towards hydroxyethylcellulose (HEC) or HA. The higher affinity of TSP compared to HEC and HA was demonstrated with the use of NMR spectroscopy and this result was confirmed by a dynamic dialysis technique, which showed that the fraction of KT bound to TSP was significantly higher than that bound to HEC or HA .This proves that KT with TSP helps in stabilising the tear film, and thus prolonging the residence time of KT tear fluid. The strong mucoadhesive nature of TSP is responsible for its enhanced ocular drug availability.

Burgalassi et al (Burgalassi S 2000) carried out a study on corneal epithelium wound healing using TSP. TSP being a natural polymer helps in the adhesion of cells to laminin, thus promoting ocular wound healing. The work of these researchers on rabbits showed that TSP could help in would healing, although this was dependant on its varying concentrations.

Conclusion

This review found that multiple previous studies have shown TSP used to have strong adsorption to cellulose. In addition, the basic characteristics of tamarind seed XG have been proven to be similar to those of plant cell wall XG. Furthermore, tamarind XG has a very high molar mass making it mechanically advantageous. This biodegradable glycosaminoglycan and a galactoxyloglucan polysaccharide have been found to have a wide application in the pharmaceutical industry for controlled drug delivery. The xyloglucan component has been described as a viscosity enhancer as it is mucomimetic and mucoadhesive. For ocular drug delivery, several features make TSP an attractive candidate as a drug delivery system. As mentioned earlier it's non-toxic & mucoadhesive nature helps retaining topically applied drug for longer duration of action. One study shown the enhancement of penetration of drug to aqueous humour of eye when delivered through TSP. These dual properties like longer stay in cornea & permeability enhancer makes TSP as an ideal carrier for ocular drug delivery. Apart from its FDA approved commercial use as one of the tear substitutes , researchers have experimentally tried TSP & it's nanocomposite for topical delivery of ocular drugs like Timolol, Fluoroquinolones, Gentamycin etc.

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