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Tamarind seed polysaccharides and their nanocomposites for drug delivery: An economical, eco-friendly and novel approach

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Review Article

Tamarind seed polysaccharides and their nanocomposites for drug delivery: An economical, eco-friendly and novel approach

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Abstract

The biomedical engineering field has shown to foster innovation in nanotechnology. Facilitated by engineering and biotechnology, biomedical engineering has the potential to significantly influence the pharmaceutical industry. Advancements in nanotechnology can resolve current issues with drug delivery techniques by increasing efficacy or improving patient safety and patient compliance. Natural polysaccharide-based biomaterials are proving to be important in creating innovative drug delivery devices. Biodegradability and biological activity that can be controlled are important properties of polysaccharides. The tamarind industry has various by-products, including the tamarind seed. Tamarind kernel powder (TKP), also known as the decorticated flour of tamarind has been explored for its use in drug delivery. The hemicellulose component, xyloglucan (XG) is a non-expensive agro-based material that is non-toxic and biocompatible, making it suitable for controlled drug delivery systems. Nanocomposites such as tamarind seed polysaccharide (TSP) are being expansively studied. Mixing cloisite 30B solution with polyvinyl alcohol (PVA) and TSP in various ratios displayed a sustained drug delivery. We can predict that bioadhesive carriers, especially mucoadhesive nanopolymers, have significant potential to be an effective solution in achieving bioavailability of various drugs administered systemically or topically.

Keywords: Drug delivery, tamarind seed polysaccharide, xyloglucan

1 Introduction

Tamarind Seed Polysaccharide (TSP)

Researchers are continuously exploring the use of agro-based biopolymers for various biomedical applications.[1] The agro-based TSP is derived from the tamarind seed. The *Tamarindus indica L*, also known as the tamarind tree or 'Indian date' is found in a range of subtropical areas. This tree species is significant and valuable in South East Asia, thus is widely cultivated throughout India, except certain dry areas.[2] Tamarind is grown both for commercial and non-commercial reasons. Tamarind is cheap and has various uses in the food industry. However, national programs have recognised tamarind as an underutilised crop with wider potential.[3] Animal-based products and biodegradable-based plants have been investigated in recent times for their potential use (Figure 1).[4-7] It is worthwhile to note that every part of the tamarind tree has a use, be it in the food industry, textile industry, chemical industry or pharmaceutical industry.[8]

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Tamarind Kernel Powder (TKP)

Tamarind kernel powder (TKP) is manufactured by removing the outer cover of the seed and grinding creamy white kernels (Figure 1). To obtain a yield

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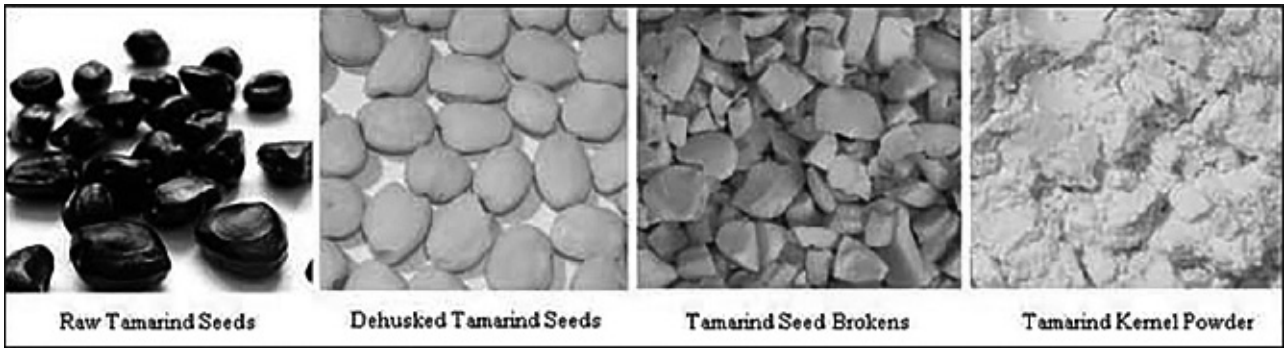

Figure 1: Preparation of Tamarind Kernel Powder

of 55-60%, machines grind the decorticated seed to the needed size. The powder is conventionally stored in a dry place due to increased risk of deterioration in humid environments. Prevention of enzymatic deterioration is achieved by mixing 0.5% sodium bisulphite with the TKP pre-packing. Inadequate storage of TKP causes a rancid odour and colour change to brown, the colour change can be reversed by the process of defatting.[9]

Tamarind Xyloglucan

The main structural polysaccharide in the cell wall of vascular plants is xyloglucan (XG). Cell growth is controlled by fastening the cellulose microfibrils shaped as a thin net. Cross-linking of the cellulose microfibrils by XG provides the flexibility needed during cell growth. XG is mainly found in tamarind seeds.[10] Tamarind seed xyloglucan (TXG) has various applications in the food industry in countries like Japan, such as acting as a food thickener, emulsion stabilizer, food additive, etc. TXG solutions possess behaviours similar to Newtonian fluids, whilst being steady against shear forces, pH changes and high temperatures.

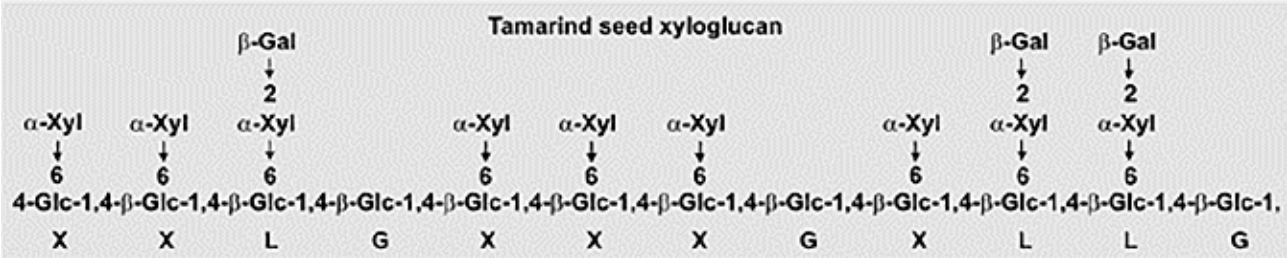

Figure 2a

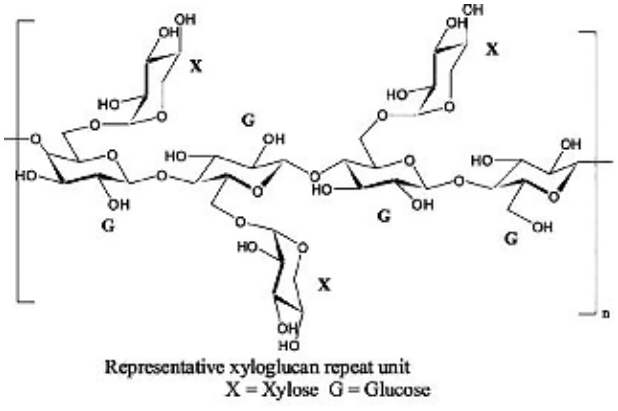

Figure 2b

Figure 2a and 2b: Biochemical structure of Xyloglucan

Figure 2a and 2b shows the purified, refined TXG, which is permitted in countries like Japan as a thickening, stabilizing and gelling agent. TXG has a (1→4)-β-D-glucan backbone that is partially substituted at the O-6 position of its glucopyranosyl residues with α-D-xylopyranose.[11] β-D-galactosylated at O-2[18] is among the few xylose residues. While TXG does not form a gel naturally, under appropriate conditions gel can be acquired.

Xyloglucan Composites and Nanocomposites:

The term 'composite' refers usually to materials, where the distinct phases are separated on a scale

larger than the atomic scale, whilst changing the properties significantly in comparison to the homogenous material (Figure 3). Composite materials are solids containing two or more distinct constituent materials or phases. It is known that the nanocomposites are multiphase solid materials. One of these phases can have 1, 2 or 3 dimensions that are less than 100 nanometers. This further applies to porous media, colloid, gel, and copolymers. Figure 3 shows the electron microscopic picture of XG composites, where solid combinations of the nano-dimensional phase(s) and bulk matrix differ in properties due to differences in structure as well as chemical composition.

Pongsawatmanit et al.[13] investigated the influence of TXG on thermal stability and rheological properties of tapioca starch (TS).[13] It was found that a 5% (w/w) TS/XG blend changed the solution from being gel-like to being a concentrated solution and thus, displayed increased loss tangent (G00/G0) as XG concentration was increased. Analysing the viscosity of 5% TS/XG blends with altering ratios showed that as XG content increased, the viscosity also increased. It was also observed that at 25°C, steady shear measurements showed the viscosity of the gelatinized TS/XG blend being higher than the TS paste alone. The flow curves in TS paste and TS/XG blends exhibited shear thinning behaviour.

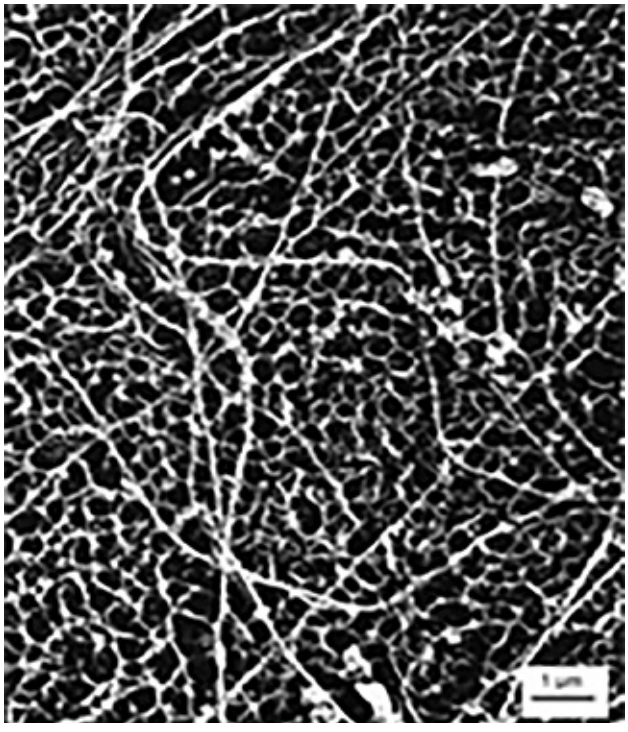

Figure 3: Electron microscopic picture of Xyloglucan Composite

Mucoadhesive Properties of TSP

The definition of 'mucoadhesion' is adhesion between two or more materials, with one or more material being a mucosal surface. Over the years, there has been significant research interest pertaining to mucosal drug delivery systems. Innovative designs have attempted to prolong maintenance at the site of drug administration, allowing for increased control of drug release, ultimately aiming to enhance the therapeutic effect (Figure 4). TSP fulfils this criterion, as it is established to be a neutral non-ionic, branching polysaccharide constituting a cellulose-like backbone consisting of galactoxylase and xylose components.[14] TSP has a molecular structure which is 'mucin-like,' ultimately facilitating for ideal mucoadhesive properties.[15]

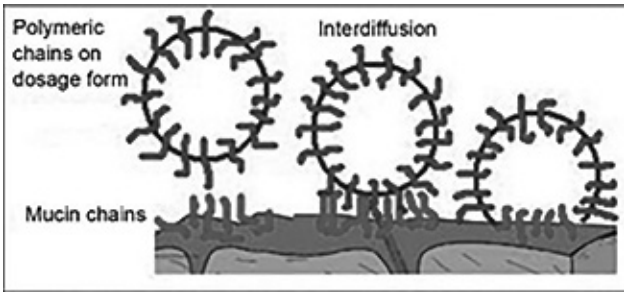

Figure 4: Mucoadhesion mechanism

Mannuci et al.[16] determined that TSP can crystallise into a fern-like shape, making it alike to natural tears.[16] The likeness between endogenous mucin and TSP makes the solution a viable candidate to provide symptomatic relief to dry eyes, as the solution is able to adhere to the ocular surface for lengthy periods of time.[17] Current studies have suggested that TSP has the additional benefit of providing a longer ocular retention time in comparison to hyaluronic acid, which may make TSP more ideal in treating dry eye symptoms. It has been postulated that XG may possibly enhance the viscosity of solutions due to its mucoadhesive properties.[18]

TSP is an ideal medium for ophthalmic medicaments for various reasons; TSP is not ocular-toxic and has been found to improve the corneal wound healing rate. TSP is established as an adequate replacement for tear fluids in keratoconjunctivs sicca, reducing the likelihood of complications. Moreover, TSP has been found to influence pharmacokinetics, for

example, fluoroquinolones, timolol, and methiolate all have a reduced toxicity effect on human conjunctival cells when administered with TSP. Pertaining to pharmacokinetics, TSP has also been found to improve the topical administration of ofloxacin and gentamicin in rabbits, by improving intraocular penetration and increasing corneal accumulation.[19]

TSP for Drug Delivery System

The use of TSP as a means to improve controlled drug release is well established, including water-soluble drugs and water-insoluble drugs. Drugs like indomethacin, which have limited solubility can achieve zero order release kinetics with TSP. Microcrystalline cellulose and lactose are appropriate diluents in controlling the release of such drugs. Cross-linking the matrix partially can aid in regulating the quantity of water-soluble drugs released. Changing the extent of cross-linking can influence the quantity of drug release.[20]

Use as an Emulsifying Agent for Oral Preparations

TSP has demonstrated its ability in facilitating ingestion of an oral preparation. When acting as a stable suspending agent, TSP was able to reduce the rate of settlement and help re-dispersion of settled matter in a Nimesulide suspension.[21] Further studies have highlighted the superiority of TSP in comparison to gum acacia when emulsifying with castor oil.[22]

Use as Binders for Tablets

Multiple studies have proven TSP to be an efficacious binder for tablet formulations[23]. Phani et al.,[24] investigated the development of tramadol hydrochloride sustained-release tablets by direct compression. Other rate controlling polymers such as hydroxypropyl methylcellulose (HPMC) K4M, sodium carboxymethyl cellulose (Na CMC) and guar gum were also used in the same ratio to that of TSP as the binder. The results showed that TSP reduced the release rate, with the reduction being directly proportional to increases in the TSP percentage. A formulation containing 30% of TSP was found to maintain the zero-order release for 24 hours by swelling, diffusion and erosion. This outcome was better than the established commercially branded product, Urgendol SR.[24] Kulkarni et al. [25] explored the binding characteristics of TSP with ibuprofen tablets. It was found that the ibuprofen tablets exhibited slow dissolution profiles, which was thought to be directly linked to the properties of the polysaccharide. Overall, this highlights the satisfactory physicochemical properties of TSP, making them comparable to that of corn starch.[25]

Use as Novel Controlled Release Modifiers

The term 'controlled release' refers to modifying the administration of compounds with the influence of stimuli or time. Controlled release methods have been applied in the fields of agriculture, cosmetics, pharmaceuticals and the food industry. In the pharmaceutical industry, controlled release usually refers to time-dependent release in oral dose formulations. The hydrogel properties of TSP have proven to be beneficial as a release modifier in various formulations.

Kulkarni et al.[26] explored the impact of variables on making the spheroids, which attain optimal shape, size, density and flow properties. It involved preparing diclofenac sodium spheroids with TSP using an extrusion spheronisation technique. Results showed TSP to be promising for use as a release modifier. This was justified by the spheroids showing a strong correlation between in vitro dissolution profile, viscosity, the swelling index and the surface roughness properties of the polysaccharide. These spheroids also demonstrated efficient drug release over eight hours.[26]

TSP combined with alginate was also used to develop pH-sensitive composite beads of diclofenac sodium by an ionotropic gelation method. This study revealed the efficacy of TSP in aiding controlled delivery for a prolonged period. It was concluded from the study that the TSP to sodium alginate ratio and cross-linker ($CaCl_2$) concentration influenced the efficacy of drug encapsulation and drug release. The study highlighted that the pH values of the test medium had an effect on the swelling and degradation of the developed beads.[27]

Sahoo et al., investigated the influence of TSP on Paclitaxel, a chemotherapy agent. Sahoo et al., found that controlled release devices that utilised

biodegradable polymers yielded better results than delivery systems that needed surgical removal of the device. Of note, TSP allowed for a more controlled release of Paclitaxel. Since TSP is a non-expensive agro-based material that is non-toxic and biocompatible, there is a role for its use in controlled release material.

Use as Matrix Oral Drug Release Modifiers

Matrix systems are utilised in creating controlled or sustained release formulations. Depending on the need, the release modifiers utilised are release retardants. Hence, the use of TSP as a matrix material becomes a promising excipient for oral matrix tablets, as it acts as a release retardant. In ketoprofen, a non-steroidal anti-inflammatory drug (NSAID), the XG isolated from the TKP has been used as an effective matrix material acting as a release retardant, through a process of non-aqueous wet granulation. The tablet with suitable hardness and friability showed a continuous release of the drug, over a 12-hour period.[28] It has been observed that by increasing the concentration of polymer proportionately, the drug release could decrease, thus allowing for a sustained release. This probably was due to the creation of a gel-layer of polymer encapsulating the drug. At high polymer concentrations, release kinetics for the formulation seemed to match the matrix model.[29] Both the swelling study and in vitro release study proved that TSP is a promising tool for oral sustained release tablets.[30]

Lamivudine, an anti-viral drug used to manage HIV was investigated, with TSP being used as an efficient excipient in a hydrophilic matrix drug delivery system[31]. A direct compression method was used to combine TSP and ethyl cellulose, allowing for the development of matrix tablets which would continuously release the Lamivudine in the management of HIV. The addition of ethyl cellulose with an increase in TSP concentration lead to a decrease in drug release. In vivo, studies on rabbits were also carried out for the sustained release pharmacokinetic profile of the matrix tablets formulated using TSP and ethyl cellulose.

Use as Buccal Drug Release Modifiers

TSP has been used in the development of buccal metronidazole patches, via cross-linking with epichlorohydrin. The drug release depends on the efficiency of the cross-linking, where lower levels of cross-linking show higher drug permeation. The mucoadhesive strength and buccal residence time were better studied in an in-vitro permeation study. In this study, TSP did not show any incompatibility with the drug, confirmed through a FTIR study.[32-33] Buccal tablets which are mucoadhesive and contain nitrendipine were prepared using natural polymers (Ziziphus mauritiana and TSP) and synthetic polymers (Na CMC and HPMC K15M). The formulations comprising natural polymers were superior to the synthetic polymers in relation to physiochemical parameters, including swelling index and mucoadhesive strength. It was found that 100% drug release was achieved in tablets containing TSP. Mucoadhesive buccal nifedipine tablets, which avoided first-pass metabolism and thus prolonged the duration of action could be created by combining Na CMC, HPMC K4M and Carbopol with TSP.[46]

Use as Ocular Drug Release Modifiers

Studies have established for TSP to have a role in the management of dry eye. Further studies have attempted to investigate the effectivity of TSP in ocular preparations. Due to aforementioned properties of TSP, including the mucoadhesive strength and high viscosity, TSP is suitable in the formation of topical ocular preparations, as it increases pre-corneal residence time.

D'amico et al., investigated the timolol and TSP blended ocular preparation effect on intraocular pressure (IOP) of rabbits. The blended preparation lasted for 12 hours, making it effective in managing raised IOP in rabbits.[36] Mehra et al., investigated timolol with tamarind gum as a bioadhesive. It was recognised that the mixture of chitosan, alginate and tamarind gum achieved a continuous administration of 80% of the drug over 12 hours. Further studies in rabbits, highlighted how utilising tamarind gum constructed formulations did not cause irritation and caused a lasting decrease in pupil diameter.[37]

Ghelardi et al., employed TSP as a mucopolysaccharide blended in with ocular preparations of ofloxacin and gentamicin.[38] Administering the mixture into rabbits caused the concentration of the drug in the cornea and aqueous humour to accumulate, making the concentration significantly higher in comparison to the preparation itself. Utilising TSP was also found to extend the time needed to absorb and eliminate the drug. This was seen in the management of keratoconjunctivitis, as the concentration of active drug in the cornea surpassed the minimum inhibitory concentration (MIC). The unpleasant odour produced by TSP and the fact that it degrades rapidly can be addressed by utilising carboxymethyl, acetyl, and hydroxyalkyl. Kaur et al., explored ocular drug delivery systems, in particular, the use of nanoparticles such as carboxymethyl tamarind kernel polysaccharide (CMTKP).[39] Carboxymethylating the TSP made it anionic. This lead to the viscosity and shelf life of TSP to increase, whilst augmenting the solubility in cold water and decreasing the biodegradability. An ionotropic gelation method was utilised to create a formulation of tropicamide in CMTKP nanoparticles. The formulation was non-irritant and when comparing the permeation of the formulation to the aqueous solution of the drug, no significant difference was found.

With the hopes of producing an ideal excipient for ocular drug delivery, both TSP and hyaluronic acid (HA) were investigated in vivo, using rabbits.[40] Ascertaining the interaction between HA and TSP was achieved by nuclear magnetic resonance (NMR), which will help in identifying the optimal HA and TSP ratio in a formulation. Uccello-Barretta et al., found that a 3:2 ratio of TSP:HA in formulations manifested more effective mucoadhesivity in comparison to both individual components and other formulations.

Use of its Nanoparticles

Nanotechnology is strongly predicted to become more widely utilised in drug delivery, with many ongoing studies. Nano sized particles can be formed by the calcination of metal salts and TSP with the appropriate time and temperature. Controlled drug delivery systems (DDS) have numerous benefits over traditional drug delivery methods, as the drugs are transported to the site of action and undesirable side effects are reduced. Singha et al., investigated the mixture of tamarind seed kernel polysaccharide-silica (TKP-Si) nanohybrids, produced by a base catalysis sol-gel reaction of TSP and tetraethyl orthosilicate (TEOS).[42] Endeavouring to achieve the optimal mixture, various ratios of reactants such as EtOH, water, TEOs, and polysaccharide were further investigated. In order to enhance binding performance, the mixtures were calcined at 200°C (in air). It was found that even in lower concentrations, the nanoparticle formulation maintained the cytotoxic effects of PST001.[43] The XG was extracted[44] from *Hymenaea courbaril* (jatobá) seeds, which were one of the Brazilian species. The XG was utilised to protect the layered hydroxide (LDH) and permit the drug to pass through the gastrointestinal tract.

Role as a Wound Dressing Materials and in Wound Healing Activity

As part of the wound-healing pathway, various cell types including fibroblasts migrate towards the wound site after sensing damage signals. Molecules such as fibronectin leak from damaged blood vessels to indicate tissue damage. Patil et al., utilised TSP to cross-link epichlorohydrin in the preparation of novel wound dressing films. This was achieved by loading with povidone-iodine solution, using a soaking method. The elasticity and tensile strength exhibited by TSP was dependant on the thickness and the extent of cross-linking. The in vivo efficacy of wound healing and antibacterial property was explored using the albino rat model. The groups treated with TSP film demonstrated faster epithelialisation and increased wound contraction, with significantly increased collagen content and tensile strength in the regenerated tissue.[45] The use of TSP for corneal epithelium wound healing was investigated by Burgalassi et al.[46] As TSP facilitates adhesion of cells to laminin, it is an ideal adjunct in encouraging ocular wound healing. TSP was also found to help in wound healing in rabbits, however, this was contingent on the varying concentration of TSP. Nie et al.[47] explored the role of TSP xyloglucan in promoting skin regeneration. Copper complex precipitations (TSc) and cold water (TSw)

was used to extract two xyloglucans from the *T. indica* seed. The two xyloglucans were examined in vitro for composition and influence on cell viability, proliferation, cell cycle progression, migration, MAPK phosphorylation, and the gene expression of human skin keratinocytes (NHEK and HaCaT) and fibroblasts (NHDF) in vitro. Nie et al., highlighted that TXG can directly affect cell proliferation and migration, assisting skin regeneration. It was concluded that there were no signs of carcinogenicity or other adverse effects on both the sexes.[48]

Conclusion

In conclusion, numerous studies have shown that TSP has a strong adhesion to cellulose. Moreover, the properties of TXG and plant cell wall XG are alike. The advantageous mechanical properties of tamarind XG are due to the high molar mass. There exists a wide scope of potential use of biodegradable glycosaminoglycan and a galactoxyloglucan polysaccharide in the pharmaceutical industry for controlled drug delivery. Due to the mucomimetic and mucoadhesive properties of XG, it has been described as a viscosity enhancer. TSP is ideal in its role in ocular drug delivery due to aforementioned properties, leading to a longer duration of action and according to the food and drug administration (FDA), being an adequate tear substitute. Attempts have been promising in attempting to identify further roles for TSP and its nanocomposite for topical delivery of other ocular drugs such as Gentamicin, Timolol, and Fluoroquinolones. These attempts have extended to using TSP as a drug vehicle including anticancer drug therapy and colon targeted drug therapy.

Finally, numerous studies have proven that the nanocomposite protectively coated with XG is efficient in obtaining a slow release of various systemically applied drugs. Being a natural polymer the biodegradable, mucoadhesive and non-toxic properties should favour XG as an ideal choice for future research on sustained drug delivery systems.

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