Revista de Ciências Farmacêuticas Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

ISSN 2179-443X

LETTER TO THE EDITOR

Tamarind seed polysaccharide (TSP) uses in ophthalmic drug delivery

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Abstract

At present, ophthalmic drug delivery remains a major challenge, given the eye's protective structure and susceptibility to irritation, resulting in poor patient adherence. In order to overcome these constraints, new formulations are continually being developed. The inclusion of Galactoxyloglucan (Tamarind seed polysaccharide (TSP) in such formulations, a natural substance extracted from the seeds of *Tamarindus indica*, has shown great potential due to its physico-chemical properties, high biocompatibility and safety profile. Such properties, have led to its use in formulations for the treatment of dry eye disease, glaucoma, and bacterial keratitis, as well as in dilating eye drops used in eye examinations. In this article, we highlight the most recent TSP-based ophthalmologic formulations, which indicate that this polymer is a strong candidate to reduce adverse effects, improve patient tolerability and drug bioavailability.

Keywords: TSP. Galactoxyloglucan. Tamarind. Drug Delivery. Ophthalmology.

How to cite

Castro MA, Prata WM, Silva-Cunha A. Tamarind seed polysaccharide (TSP) uses in ophthalmic drug delivery. Rev Ciênc Farm Básica Apl. 2022;43:e757. https://doi.org/10.4322/2179-443X.0757

INTRODUCTION

Tamarind (*Tamarindus indica*) is a medium-sized evergreen tree native to Africa with a history of use in traditional medicine across tropical Asia. It is cultivated as a commercial crop on a large scale throughout a number of different countries in tropical regions including India, Thailand, Brazil, Mexico and the United States (Figure 1), with annual fruit production reaching up to 275 tonnes in sub-tropical countries alone[1]. According to research, each part of the tree contains different components that are used in a number of applications[2] including the food, clothing, and pharmaceutical industries, and also aid in environmental matters[3].

Financial support: MAC - received masters scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES. WMP - None. ASC - None.
Conflicts of interest: All the authors declare that there was no conflict of interest during research.
The study was carried out at Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.
Received on September 15, 2021. Accepted on November 08, 2021.

Figure 1. *Tamarindus indica* global distribution. The blue arrows indicate the countries in which Tamarind is cultivated.

Pharmacological interest in tamarind seed and its components (TSP) first arose with the discovery of their use in traditional medicine for the treatment of diarrhea, dysentery and bleeding, and intensified following the identification of many active constituents[2,4]. TSP, also known as galactoxyloglucan, is composed of the monomers glucose, galactose and xylose in a 3:1:2 ratio, with a molecular weight of roughly 52 kDa (Figure 2). According to literature, TSP is hydrophilic, stable over a wide pH range, has no ionic charge, and is neither toxic nor carcinogenic, making it an excellent candidate for use in pharmaceutical preparations[5]. In this article we will demonstrate TSP's potential for use in ophthalmic formulations, especially for those diseases/conditions in which TSP's properties prove especially useful such as: dry eye disease (DED), glaucoma, bacterial keratitis, in addition to improving the performance of mydriasis stimulants used in clinical examinations.

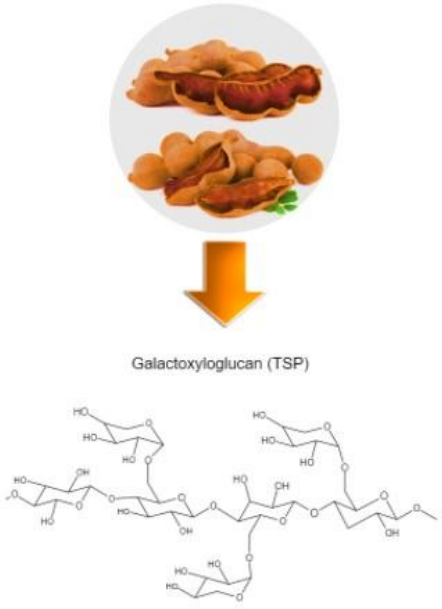

Figure 2. TSP (Galactoxyloglucan) Chemical structure.

OPHTHALMIC POTENTIAL OF TSP

Several findings have verified TSP's beneficial properties. Historically, TSP has been used throughout Asia in healing skin wounds, and in intestinal and ocular drug delivery[6-8]. TSP has ideal properties for ocular administration, such as a tendency to swell, favouring ocular bioadhesion, non-Newtonian rheological behaviour and a ferning pattern similar to natural tear film[9]. Furthermore, TSP is a "mucin-like" compound, conferring properties similar to the MUC1 glycoprotein, which also provides mucoadhesive properties[10]. Studies evaluating TSP's interaction with hyaluronic acid, an excipient commonly used in ophthalmic formulations, have shown a positive synergistic relationship between the two[11,12]. A summary of the ophthalmic formulations to which this study refers is provided in Tables 1 and 2 below.

Table 1. TSP based formulations used in the studies evaluated and their purpose.

TSP-based formulation	Formulation Composition	Purpose
1,0% TSP/0,5%TSP	-	Dry eye disease
Visine Intensiv 1%®	1% TSP	Dry eye disease
Xiloial®	0,2% TSP and 0,2% HA	Dry eye disease
0.4% HA and 0.2% TSP	HA: Hyaluronic Acid	Dry eye disease
TSP 0.5% ®	TSP 0,5%	Dry eye disease
2% TSP/Timolol	-	Glaucoma
TSP/Timolol	-	Glaucoma
TSP-Alginate Pilocarpine	-	Glaucoma
Oftagen®	0,5% TSP	Glaucoma
TSP/Prostaglandin	-	Glaucoma
BDNF/TSP	-	Glaucoma
TSP 1%	-	Glaucoma
0,3% TSP-Rufloxacin	-	Bacterial Keratitis
1% TSP/Rufloxacin zwitterion 1%TSP/CD/Rufloxacin 1% TSP/Rufloxacin hydrochloride	CD: Cyclodextrin	Bacterial Keratitis
TSP/RBO Ciprofloxacin	Rice Bran Oil	Bacterial Keratitis
2% TSP/Ciprofloxacin	-	Bacterial Keratitis
1% TSP	-	Bacterial Keratitis
Tropicamide-TSP (0,1%) nanoparticles	-	Mydriasis
Tropicamide-TSP nanoaggregates	-	Mydriasis

Table 2. Non-TSP based formulations used in the studies evaluated and their purpose.

Non-TSP formulations	Formulation Composition	Purpose
Hyalistil®	Hyaluronic Acid (0.2%)	Dry eye disease
Lacrisifi®	HPMC	Dry eye disease
Viscotears gel®	Polyacrylic acid	Dry eye disease
Systane UD ®	HP Guar	Dry eye disease
Optive ®	CMC	Dry eye disease
0.15% HA crocin and liposomes	-	Dry eye disease
Etacortilen®	Sodium Phosphate Dexamethasone	Glaucoma
Droptimol®	Timolol Maleate	Glaucoma

Table 2. Continued...

Non-TSP formulations	Formulation Composition	Purpose
Timoptic®	Timolol Maleate	Glaucoma
Glaucomol®	Timolol Maleate	Glaucoma
BDNF/CMC	-	Glaucoma
0,3% Ofloxacin solution 0,3% Rufloxacin solution Rufloxacin zwitterion	-	Bacterial Keratitis
CD/Rufloxacin Rufloxacin hydrochloride	CD: Cyclodextrin	Bacterial Keratitis
Tropicamide solution	-	Bacterial Keratitis
Tropicacyl®	Tropicamide	Bacterial Keratitis

TSP in Formulations for Dry Eye Disease (DED)

As part of a study, an animal model for DED was developed and commercially available eye drops (Lacrisif®, Hyalistil® and Viscotears®) containing commonly used polysaccharides were compared to 1.0% TSP in relation to their power to reduce the signs and symptoms of DED[13]. The study found that Hyalistil® and the eye drops developed with TSP produced type I fern structures, which are directly linked to the formulation's muco-mimetic properties. The capabilities of commercially available eye drops containing TSP (Xiloial® and 0.5%TSP®) were measured in an *in-vitro* model for dry eye disease, significantly improving inflammatory indicators, increasing the lipid layer, and enhancing mucin production within 24 hours[14].

A study was undertaken comparing the effectiveness of 0.5% and 1.0% TSP eye drops to a hyaluronate-based eye lubricant (Hyalistil™)[15,16]. In this study, in which 30 patients were monitored for 90 days, improvements in tear breakup time (TBUT) were detected in comparison to the commercial formulation, as well as reduced clinical symptoms. In addition, 1.0% TSP achieved even better results when taking into consideration patient-score levels and the absence of any side effects, suggesting that the formulations of both concentrations of TSP are interesting candidates for further development. A further randomized clinical study involving 28 TFOS DEWS severity level 2 patients compared VISINE INTENSIV® 1% (commercially available eye drops containing 1.0% TSP), and SYSTANE UD® (composed of HPC-guar)[17]. The use of VISINE INSENTIV® 1% resulted in substantial Ocular Surface Disease Index (OSDI) improvement (from 50.0 to 34.1). Schrimer's test results also improved in comparison to the baseline for both eye drops (15.3 SYSTANE UD -11.9 baseline; 15.1 VISINE - 10.75 baseline).

In a comparison of Xiloial Monodose® (0.2% TSP and 0.2% hyaluronic acid (Farmigea, Italy)) and Optive® (Allergan, USA), comprising 49 patients with moderate DED, OSDI values demonstrated that the response to the former was twice that observed in the Optive® group (-14,8 and -7,9 respectively)[18]. More recently, the synergistic relationship between hyaluronic acid and TSP was further evaluated in a study involving 25 patients. The study compared two formulations: one containing 0.4% uncross-linked hyaluronic acid and 0.2% TSP (Tear A), the other containing 15% cross-linked hyaluronic acid, crocin, and liposomes (Tear B)[19]. The study found that the results of all evaluated parameters (TBUT, OSDI) showed significant statistical improvement for both formulations ($p < 0.0001$).

In a further study aimed at assessing discomfort related to disposable soft contact lenses, participants were submitted to treatment with Xiloial® for 60 days[20]. Significant reduction in subjective symptoms was observed after one month of treatment, according to OSDI, with 80% of patients reaching normal scoring (8.5 ± 3 versus 20.2 ± 1.6). Schirmer's test results showed a significant increase at the endpoint evident after two months of treatment (14.6 ± 1.1 versus 12 ± 2.1). Overall, TSP use in formulations demonstrates several benefits for DED (Table 3).

TSP in Formulations for Glaucoma

TSP has been used in the development of new formulations containing timolol and pilocarpine, two drugs widely used to treat glaucoma. The first of these consisted of an experimental formulation containing 5 mg/ml timolol which was developed and tested on rabbits, comparing it to the commercially available formulations Droptimol® and Timoptic® (based on in-situ gelling system). The TSP-based formulation saw higher concentrations of timolol in tears, aqueous humour and cornea, alongside lower concentrations in plasma, indicating lower systemic absorption and greater local absorption. The formulation containing TSP reduced intraocular pressure to 3.1 mm Hg, lasting 19 hours and returning to basal values after 24 hours, suggesting a long-lasting hypotensive effect[21]. A novel ocular film timolol-based formulation containing TSP has also been subject to comparative testing against a regular commercial eye drop formulation (Glaucomol)[22]. According to Draize testing, this formulation was found to be non-irritant. In addition, the reduction in the animals' IOP was found to be rapid upon the eye drop formulation reaching maximum reduction (AUC 88 mmHg) four hours after instillation, whereas the hydrogel reduction peaked (AUC 148.425 mmHg) after six hours and was maintained for a total of 12 hours.

Pilocarpine was investigated through the development of an in-situ gelling system[23]. It released approximately 25% of the drug in the first hour and 80% during the next 12 hours, and was considered the most sustained release. In comparison to a standard eye drop solution, the longer drug activity and higher pharmacodynamic activity strongly suggest that pilocarpine bioavailability had improved.

Benzalkonium chloride (BAK) is an antibacterial substance widely used in eye drop-formulations in varying concentrations. However, despite its usefulness as an excipient, it causes conjunctival and corneal damage, representing a problem for long-term therapies in patients with glaucoma associated with cellular damage and inflammation[24]. TSP has shown potential as an antioxidant in the food industry (decreasing visual changes in naturally sensitive products), though not as a preservative[25,26]. TSP's efficacy in reducing toxicity has also been subject to evaluation in a formulation containing 0.5% TSP (Oftagen®) as part of a prospective clinical study involving 20 patients[27]. Corneal epithelial defects assessed by fluorescein staining completely disappeared after three months. Improvements in the results of clinical parameters, such as TBUT and Schirmer's test, were also detected. In addition, a further study involving 42 patients from different ophthalmic centers evaluated the benefits of using 0.5% TSP-containing eye drops in patients undergoing treatment with BAK-containing prostaglandins (PGAs)[28]. After three months of daily instillation, a decline in the incidence of conjunctival hyperaemia was observed, as well as a reduction in subjective symptoms such as discomfort, swelling, and itching resulting in ocular irritation. However, an increase in Schirmer's and TBUT test results was also observed.

Recently it has been reported that the use of nerve growth factor (BDNF) can assist in retinal recovery in an animal model for glaucoma[29]. Evaluations of how different excipients for ocular formulations increased BDNF bioavailability in animals with light-induced retinal damage (LE) have also been conducted[30]. A pre-LE BDNF/TSP topical treatment maintained fERG responses while avoiding dramatic a and b-wave shifts. Compared to vehicle-treated retinas, LE eyes treated with a single drop of BDNF/TSP revealed a substantially higher number of rows of photoreceptor nuclei. Pharmacokinetic analysis of BDNF/TSP topical eye application revealed that, six hours after application, retinal BDNF levels were higher than in the control eye and remained elevated for 12 hours. Protection against damage induced by UV radiation in corneal-derived cells (SIRC) was obtained when using a formulation containing TSP. This formulation led to a decrease in the number of reactive species, significantly reducing DNA damage to corneal cells[31]. In conclusion, TSP would appear to offer several benefits when used in glaucoma formulations (Table 3).

Table 3. Main studies outcomes for TSP-based products.

TSP-based formulations	Non-TSP formulations	Main outcomes for TSP formulations	Reference
1.0% TSP	Hyalistil® Lacrisifi® Viscotears gel®	Improved results in Schirmer's/ferning testing and protection in rabbits with DED.	-13
0.5% TSP 1.0% TSP	Hyalistil™	Improved OSDI profile in DED patients, and similar in another parameters.	-15
VISINE INTENSIV 1%®	SYSTANE UD®	Both formulations improve tear film stability in DED patients.	-17
Xiloial®	Optive®	Improved OSDI profile in DED patients. Improvement in all parameters compared to baseline.	-18
0.4% HA and 0.2% TSP	0.15% HA crocin, and liposomes	Equally improved results in DED patients (OSDI, TBUR and Schirmer's test)	-19
Xiloial®	Control group	Improved OSDI, TBUT, Schirmer's test, ferning test and corneal damage in DED patients.	-20
Xiloial®/TSP 0.5®	Etacortilen® Hyalistil® Optive®	Improved inflammatory indicators and increased lipid layer (*in-vitro*).	-14
2% TSP/Timolol	Droptimol® Timoptic®	Enhanced drug concentration in site of action and prolonged IOP reduction for glaucoma	-21
TSP/Timolol	Glaucomol®	IOP reduction and enhanced drug concentration in site of action for glaucoma	-22
TSP-Alginate Pilocarpine	Control group	Prolonged drug delivery in glaucomatous rabbits.	-23
0.5% TSP (Oftagen®)	Control group	Improved Schirmer's test and TBUT results. Increased sub-basal nerve fibers in glaucoma patients.	-27
TSP/Prostaglandin	Control group	Improved Schirmer's test and TBUT results, reduced ocular hyperemia and increased conjunctival goblet cells in glaucoma patients.	-28
BDNF/TSP	BDNF/CMC	Preserved photoreceptor and fERG pattern. Increased retinal BDNF levels in mice.	-30
TSP 1%	Control group	Protection for UV-B DNA damage	-31
0.3% TSP-Rufloxacin	0,3% Ofloxacin 0,3% Rufloxacin	Substantial reduction in corneal *P. aeruginosa* and S. *aureus* in rabbits.	-32
1% TSP/RUF zwitterion 1% TSP/CD/RUF 1% TSP/RUF-HCl	RUF zwitterion CD/RUF RUF-HCl	Improved drug solubilization and concentration in site of action. Decreased *Enterobacteriaceae* and *Pseudomonas aeruginosa* ocular levels in rabbits.	-33
TSP/RBO Ciprofloxacin	Control group	Improved drug permeation dependent on RBO concentration. Improved activity against *E. coli* and *B. subtilis*.	-34
2% TSP/Ciprofloxacin	Control group	Improved antibacterial activity and drug concentration in site of action. *S. aureus* inhibition in eyes of rabbits.	-35
Tropicamide-TSP (0.10%) nanoparticles	Tropicamide solution	Similar results in corneal permeation testing and improved safety (HET-CAM)	-36
Tropicamide-TSP nanoaggregates	Tropicacyl®	Improved corneal permeation test results and similar safety (HET-CAM)	-37

TSP in Formulations for Bacterial Keratitis

In order to investigate TSP's ability to increase the concentration of antibiotics in the cornea, formulations of rufloxacin either containing or not containing TSP were compared in an animal model for keratitis, in addition to a traditional formulation of oflocaxin[32]. TSP-

rufloxacin administration resulted in slightly higher intraocular drug levels than rufloxacin alone, as shown by the values observed in uninfected (4.62 g/ml; P 0.01), *P. aeruginosa*-infected (5.63 g/ml; P 0.01), and S. aureus-infected (6.91 g/ml; P 0.001) eyes. In the cornea, TSP-rufloxacin was slightly more effective than rufloxacin alone in regulating *P. aeruginosa* bacterial proliferation. With regard to *S. aureus,* TSP-rufloxacin administration resulted in a significant drop in corneal bacteria relative to both rufloxacin-treated and ofloxacin-treated eyes (P 0.05). A further study was conducted evaluating different formulations of rufloxacin (RUF) with TSP, namely two pH 7.2 suspensions of non-salified rufloxacin base, one of which was thickened with TSP; two pH 7.2 solutions of RUF obtained using hydroxypropyl- β-cyclodextrin (CD), one with TSP; and two pH 5.0 solutions of rufloxacin hydrochloride (RUF-HCl), one containing TSP[33]. In this study, the suspension containing TSP showed twice the concentration in aqueous humor compared to S-RUF (187.88 vs 67.63 min µg/mL), given the viscosity potential of the polysaccharide. Additionally, pH levels were also shown to influence drug concentration, since the concentration was higher at pH 7.2 when compared to the same formulation at pH 5.0. Rufloxacin solubilization in HP-β-CD (pH 7.2) irrespective of whether or not it contained TSP, showed, poor performance in the final concentration. This could be explained by the fact that the drug interacted strongly with the cyclodextrins and that combination with the viscous agent proved a greater hinderance to drug delivery. Accordingly, the viscosity of the final formulation required further evaluation.

Recently, an emulgel formulation containing different concentrations of rice bran oil (RBO) and TSP has been developed for controlled release of ciprofloxacin[34]. To evaluate the formulation's effectiveness in inhibiting the growth of microorganisms, an *ex-vivo* corneal permeation test was performed in goats. This revealed that the drug's ability to penetrate tissue increased relative to RBO concentration. The formulation was tested against *B. subtilis* and *E. coli*, inhibiting microorganism development based on an increase in RBO concentration and the stabilization of TSP levels, indicating an increase in permeability and drug release into the medium.

An additional study using ciprofloxacin was conducted with the objective of developing a TSP (2%) based ocular film formulation[35]. When tested for the efficacy of drug release against *S. aureus*, the formulation succeeded in inhibiting microbiological growth throughout the test period (48 hours) with no signs of irritation found (Draize test).

Results suggest that TSP provides for a more effective antibacterial reaction, potentially raising the antibiotic's precorneal residence period and increasing drug concentration in the cornea (Table 3).

TSP in Formulations for Mydriasis

Tropicamide - TSP (0.1%) suspension was developed as a safe and effective alternative method of drug delivery. In comparison to the commercial formulation, the suspension scored much lower (between 0 and 1 point) in *ex-vivo* biocompatibility testing (HET-CAM) (between 3 and 4 points). In bioadhesion testing, the formulation adhered to 88% of the mucin[36], indicating mucoadhesive characteristics. Mydriasis improvement was addressed with a TSP/poloxamer-based nanoaggregates formulation[37]. The tropicamide nanoaggregates permeated the cornea more intensely in an *ex-vivo* study (0.661%) than the commercial solution Tropicacyl (0.573%), explained by its capacity to stimulate organism endocytic system and the absence of preservative in the developed formulation. However, the premise of increasing corneal permeation in future *in-vivo* studies remains. In bioadhesion testing, the formulation succeeded in binding to 87.35% of the mucin, a finding that is closely associated with the formulation's TSP. In addition, there was no significant score in the HET-CAM test for the developed formulation and Tropicacyl®, nor any relevant cytotoxic activity (Table 3).

CONCLUSION

After careful analysis of recent articles regarding ophthalmic formulations, TSP undoubtedly shows potential to increase drug corneal permeation by prolonging precorneal retention time in eye drop formulations, therefore safely increasing patient adherence by improving ocular comfort. Further research of TSP-based ophthalmic formulations should therefore be encouraged. This paper paves the way for new research involving this natural polymer.

ACKNOWLEDGMENTS

The authors would like to thank CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) for their financial support.

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Authors' contributions

MC - Data acquisition, interpretation and writing; WMP – Data acquisition and support; ASCJr – Project conceptualization, funding and draft revision.