Chitosan as an Ocular Drug Delivery Vehicle for Vancomycin

Anutra Khangtragool,[1] Somsanguan Ausayakhun,[2] Phuriwat Leesawat,[3,4] Chutiporn Laokul,[5] Robert Molloy[5,6]

[1]*Division of Pharmacy, Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai 50200, Thailand*
[2]*Department of Ophthalmology, Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai 50200, Thailand*
[3]*Department of Pharmaceutical Science, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand*
[4]*Biomedical Engineering Center, Chiang Mai University, Chiang Mai 50200, Thailand*
[5]*Department of Chemistry, Biomedical Polymers Technology Unit, Faculty of Science, Chiang Mai University, Chiang Mai 50200, Thailand*
[6]*Materials Science Research Center, Faculty of Science, Chiang Mai University, Chiang Mai 50200, Thailand*

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ABSTRACT: The main objective of this research has been to study the efficiency of chitosan as an ocular drug delivery vehicle for topically applied vancomycin in rabbit eyes. Vancomycin 50 mg/mL was reconstituted in four preparations, namely: in Tears Naturale II™, in 0.9% w/v aqueous sodium chloride, and in 0.1% and 0.3% w/v chitosan solutions in 1% aqueous L(+)-lactic acid. Twenty-five microliters of vancomycin (50 mg/mL) were applied into the lower conjunctival eye sac in rabbit eyes. Tear samples were then collected after 0, 30, 60, 90, and 120 min to evaluate the pharmacokinetics of the topically applied vancomycin. Comparison of the results obtained showed that vancomycin 50 mg/mL eye drops in the 0.3% chitosan solution were similar to Tears Naturale II™ in terms of bioavailability. The main conclusion to be drawn from this study is that the 0.3% w/v chitosan solution appears to be a highly promising, cost effective candidate for biomedical use as a vehicle for vancomycin ocular drug delivery.
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Key words: chitosan; vancomycin; ocular drug delivery; pharmacokinetics; biomedical polymers

INTRODUCTION

Drug delivery in ocular therapy has a long research history. The main challenge in ocular drug delivery is to provide and maintain an adequate concentration of the drug in the precorneal area. Topical ocular medications are the most commonly used form of ocular drug treatment but a common shortcoming in their use is that they offer poor bioavailability of the drug. In eye drops, this is mainly due to precorneal loss factors which include high tear fluid turnover, insufficient time in the conjuctival sac and nonproductive absorption.[1,2]

Vancomycin, a glycopeptide antibiotic, was discovered in 1956 and is isolated from *Streptomyces orientals*.[3] Vancomycin is well known as an antibiotic with excellent antibacterial activity against gram positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and has been used for resistant enterococci.[4] Ocular infections with MRSA are mostly external ocular diseases which ophthalmologists need to treat with topically applied antibiotics. The most commonly isolated bacteria in cultures from bacterial keratitis are *Staphylococcus epidermidis* and *Staphylococcus aureus*.[5] Fleischer et al.[6] successfully treated two patients with severe *Staphylococcus epidermidis* blepharoconjuctivitis using a topical vancomycin solution (50 mg/mL) prepared with sterile water. However, at this time, there are no wholly satisfactory vancomycin topical eye drops available. Commercial topical eye drops have too low drug concentrations for adequate treatment, so higher drug concentrations need to be prepared extemporaneously.[7,8] The guidelines for the preparation of extemporaneous ophthalmic eye drops are described in a widely referenced book by Reynolds and Closson.[9] At the Maharaj Nakorn Chiang Mai Hospital in Chiang Mai, Thailand, vancomycin eye drops need to be prepared extemporaneously by a pharmacist. Vancomycin 50 mg/mL eye drops are not available commercially and must be prepared

Correspondence to: A. Khangtragool (akhangtr@mail.med.cmu.ac.th) R. Molloy (robert@chiangmai.ac.th).

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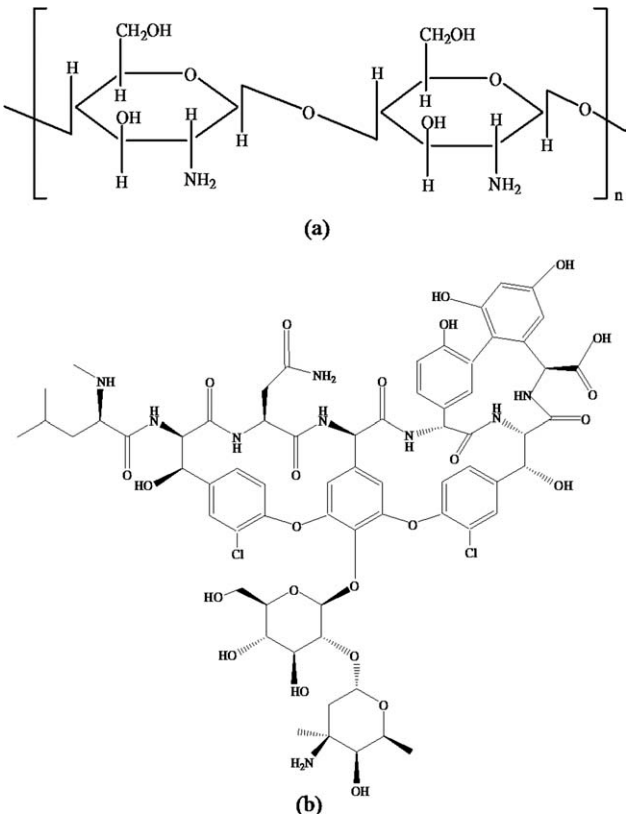

Figure 1 Chemical structures of (a) chitosan and (b) vancomycin.

from vancomycin powder for injection by an aseptic technique. According to the literature, vancomycin 50 mg/mL eye drops have so far been reported as having been prepared by reconstitution in artificial tears,[10] sterile water,[6,9] and 0.9% w/v aqueous sodium chloride (saline) solution.[11]

Chitosan, a well-known polycationic biopolymer, has been investigated and used as an excipient in the pharmaceutical industry.[12,13] Interest in chitosan stems from the fact that it shows excellent ocular compatibility, prolonged retention, and also the ability to interact with the negatively charged conjunctiva and cornea.[14] Felt et al.[15] showed by gamma scintigraphy that the presence of chitosan in an ophthalmic solution increased the precorneal residence time when compared with commercial control products. The use of chitosan as a vehicle slows down drug elimination by the lachrymal flow as a result of increased solution viscosity combined with its electrostatic interaction with the negative charges of the mucus.[15]

Thus, chitosan was chosen in this study for the ocular delivery of vancomycin. This paper compares the use of chitosan solution with other extemporaneous eye drop vehicles. Vancomycin 50 mg/mL eye drops were prepared in commercial Tears Naturale II™, 0.9% w/v aqueous sodium chloride solution and 0.1% and 0.3% w/v chitosan solutions in aqueous lactic acid. These formulations were designed to demonstrate the relative efficiencies of these four vehicles and the effect of the chitosan concentration by comparing their viscosities and pharmacokinetics in the tear films in rabbit eyes. Although chitosan and vancomycin have each been widely studied in drug delivery, their combination in an ocular drug delivery system and their comparison with other commercial systems has not yet been reported. The motivation for this study is that there is an urgent need in hospitals in Thailand for an efficient yet inexpensive ocular drug delivery system which can be locally prepared. This research is directed towards meeting this need.

MATERIALS AND METHODS

Materials

Chitosan prepared from squid chitin was purchased from Ta Ming Enterprises Co., Ltd., Thailand. Vancomycin for injection and Tears Naturale II™ were purchased from Lex Pharmaceutical and Alcon Laboratories respectively. The chemical structures of chitosan and vancomycin are shown in Figure 1. The chitosan was characterized by determining its viscosity-average molecular weight, $\overline{M}_v$, by dilute-solution viscometry using a Schott-Gerate AVS 300 Automatic Viscosity Measuring System. The solvent used was an aqueous solution containing 0.2*M* acetic acid, 0.1*M* sodium chloride, and 4*M* urea at 25°C. From the results, a value of $\overline{M}_v$ of 6.03×10^5 was obtained from the following Mark-Houwink equation.[16]

$$[\eta] = 8.93 \times 10^{-4} \overline{M}_v^{\,0.71} \text{ dL/g} \qquad (1)$$

where $[\eta]$ is the intrinsic viscosity of the chitosan in units of dL/g.

The degree of deacetylation, DD, of the chitosan was determined by chemical titration as 94.0%.[17] The moisture content of the chitosan as supplied was determined by heating at 60°C to constant weight in a vacuum oven and recording the weight loss. The calculated moisture content of 13.5% by weight reflected the hydrogel properties of chitosan. Consequently, the previous $\overline{M}_v$ and DD determinations and all chitosan solution preparations referred to in this paper were carried out using moisture-free chitosan which had been rigorously predried to constant weight.

Animals

Male albino New Zealand rabbits weighing 2.5 to 3.5 kg and free from any ocular damage were used throughout the study, as approved by the Ethics

Committee for Animal Experimentation (Faculty of Medicine, Chiang Mai University, Thailand). The animals were maintained under conventional, standardized conditions in a single cage with free access to pelleted food and drinking water.

Preparation of chitosan solutions

The chitosan solutions were prepared as described previously by Leesawat et al.[18] Chitosan 1% w/v was dissolved in 1% aqueous L(+)-lactic acid (Carlo Erba, 88%) at room temperature with magnetic stirring. This stock solution was then diluted to 0.1% and 0.3% w/v using Feldman's ophthalmic buffer to near pH 7.4 and sterilized by autoclaving at 121°C for 15 min at a pressure of 15 psi.

Preparation of vancomycin ophthalmic formulations

Ophthalmic solutions were prepared extemporaneously by dissolving 500 mg of vancomycin (as its hydrochloride salt) sterile powder in 10 mL of Tears Naturale II™ (i.e., to a concentration of 50 mg/mL) and placed into Tears Naturale II™ containers. Similarly, the vancomycin sterile powder was also dissolved in 0.9% w/v aqueous sodium chloride and the 0.1% and 0.3% w/v chitosan solutions to the same concentration of 50 mg/mL and the solutions placed into sterile eye drop containers.

Kinematic viscosity measurements

The kinematic viscosities of Tears Naturale II™, the 0.9% sodium chloride solution, the 0.1% and 0.3% w/v chitosan solutions, and their solutions containing vancomycin 50 mg/mL were determined with a Schott-Gerate AVS 300 Automatic Viscosity Measuring System according to German Standard Test Method DIN 51562 Part 1. For flow-time measurements, 15 mL of each solution were accurately pipetted into a calibrated Ubbelohde-type viscometer (Type and Capillary No. 532 10/I) clamped vertically in a constant temperature water bath at 25.0 ± 0.1°C. At least 15 min were allowed for temperature equilibration before making flow-time measurements. The kinematic viscosity, ν, in units of mm^2/s (= centistokes, cSt) was calculated using the equation (for Newtonian liquids):

$$\nu = kt \tag{2}$$

where k is the calibrated viscometer constant (in this case, 0.009679 mm^2/s^2) and t is the flow-time (s). Flow times were determined as the average of at least three readings, all of which agreed to within ±0.2% of their average value.

Topical administration and sampling

Vancomycin 50 mg/mL in Tears Naturale II™, the 0.9% sodium chloride solution, and the 0.1% and 0.3% w/v chitosan solutions were dropped into the eyes of the rabbits. After applying one drop containing 25 μL of vancomycin 50 mg/mL into the lower conjuctival eye sac, taking care to avoid spillage, tear samples were taken using 2.0 μL calibrated glass capillaries (Drummond Scientific Co.) as described by Felt et al.[19] Tear samples were collected after 0, 30, 60, 90, and 120 min. Each formulation was tested on six rabbit eyes.

Determination of vancomycin concentration in tears

The concentrations of vancomycin in the tear samples were determined by fluorescent polarization immunoassay (TDx-FLx System Abbott). Standard solutions with known concentrations of vancomycin, as provided by the manufacturer, were included in each run for calibration and quality control purposes.

Pharmacokinetic analysis

Pharmacokinetic calculations were performed on a personal computer using Microsoft Excel (Version 2003) with relevant add-ins (PK Functions for Microsoft Excel). Pharmacokinetic parameters were calculated using a noncompartment model.

RESULTS AND DISCUSSION

Preparation and characterization of chitosan solutions

The physicochemical properties of the chitosan used were characterized in terms of moisture content, degree of deacetylation (DD), and viscosity-average molecular weight ($\overline{M}_v$) and were found to be 13.5%, 94.0%, and 6.03×10^5, respectively.

The 0.1% and 0.3% chitosan solutions were prepared from the 1% chitosan stock solution diluted with Feldman's ophthalmic buffer. This was in an attempt to adjust their pH values to nearer that of the tear fluid pH of 7.4.[20] Khangtragool et al.[21] modified the chitosan solution preparation of Leesawat et al.[18] and found that Feldman's ophthalmic buffer solutions of pH 7.3 and 7.7 gave clear 0.1% and 0.3% w/v chitosan solutions, respectively. At pHs in excess of these values, the chitosan solutions started to become cloudy as the chitosan precipitated. The final pH values of the 0.1% and 0.3% w/v chitosan solutions were 5.95 and 4.56, respectively. After sterilization by autoclaving at 121°C for 15 min at a pressure of 15 psi, these pH values decreased to 5.17 and 3.91.

TABLE I
Comparison of the Kinematic Viscosities, ν, of the Various Vehicles Alone and Their Vancomycin 50 mg/mL Solutions at 25°C

Sample	Vehicle	Flow-time, t (s)	ν (mm^2/s)[a]
Solvent alone	Tears Naturale II™	568.3	5.50
	0.1% Chitosan solution	170.1	1.65
	0.3% Chitosan solution	450.3	4.36
	0.9% Sodium chloride solution	86.3	0.84
Vancomycin solution	Tears Naturale II™	619.7	6.00
	0.1% Chitosan solution	183.6	1.78
	0.3% Chitosan solution	462.2	4.47
	0.9% Sodium chloride solution	101.2	0.98

[a] Viscometer constant, $k = 0.009679\ mm^2/s^2$; kinematic viscosity, $\nu = kt = 0.009679\ t\ mm^2/s$ where $1\ mm^2/s = 1$ cSt (centistoke).

The preparation and stability of the 0.1% and 0.3% chitosan solutions were previously described by Khangtragool et al.[21] The 0.1% chitosan solution preparation was a modification of that described by Leesawat et al.[18] for an artificial tear formulation. The preparation of 0.3% chitosan solution was based on the same w/v concentration of hydroxypropyl methylcellulose used in Tears Naturale II™.

Preparation and characterization of vancomycin ophthalmic formulations

Vancomycin has a low pH and is stable over the pH range of 3 to 5.[22] Vancomycin in distilled water or 0.9% aqueous sodium chloride solution has a pH of about 3.9.[22] Khangtragool et al.[23] reported earlier that the pH values of vancomycin 50 mg/mL prepared extemporaneously using Tears Naturale II™, 0.9% sodium chloride solution, and 0.1% and 0.3% w/v chitosan solutions as vehicles were in the range of 3.1 to 4.0. Ideally, ophthalmic preparations should be formulated at a pH as near as possible to the tear fluid value of 7.4.[20,24] However, where the residence time is not too long, the eye does have quite a wide pH-tolerance range of 3.5 to 10.5. Thus, the ophthalmic formulations were prepared with the lower limit of this range in mind as well as the pH stability range of vancomycin. All of the formulations, after sterilization by autoclaving, had pH values which were within the required range.

Kinematic viscosity measurements

In this study, the kinematic viscosities, ν, of blank samples of Tears Naturale II™, the 0.9% sodium chloride solution and the 0.1% and 0.3% w/v chitosan solutions were determined as 5.50, 0.84, 1.65, and 4.36 mm^2/s respectively. When loaded with vancomycin 50 mg/mL, these kinematic viscosities increased to 6.00, 0.98, 1.78, and 4.47 mm^2/s respectively, (Table I). Thus, it can be seen that the kinematic viscosities of vancomycin 50 mg/mL in the 0.9% sodium chloride solution and in the 0.1% and 0.3% w/v chitosan solutions were significantly lower than in Tears Naturale II™.

Pharmacokinetics of topically applied vancomycin in rabbit eyes

In this work, the collection of tear samples after 0, 30, 60, 90, and 120 min was based on the minimum inhibition concentration (MIC) and the sensitivity of fluorescent polarization immunoassay (TDx-FLx System Abbott test kit) of vancomycin. Murphy et al.[25] reported that the MIC of vancomycin for gram-positive endophthalmitis causing pathogens is 4 mg/L and in the majority of cases is in the range of 0.5 to 1.0 mg/L.[26,27] The sensitivity of the fluorescent polarization immunoassay (TDx-FLx System Abbott) was 2 μg/mL. The method of determining the concentration of vancomycin assays by fluorescent polarization immunoassay was a modified version of those described by Huerva et al.[28] and Alster et al.[29] The limit of detection of the vancomycin concentration in the rabbit eyes tear fluid came from the small volume of sample taken in the glass capillaries (2 μL). Since the volume of sample determined by the TDx-FLx System Abbott test kit was 100 μL, each tear fluid sample was diluted by Abbott buffer to 100 μL before determination by fluorescent polarization immunoassay. The concentration of vancomycin at the last sampling time (120 min) was about 50 μg/mL, well above the MIC of vancomycin. The area under the concentration-time curve is taken as a measure of the bioavailability of the drug.

The concentrations of vancomycin in the tear film samples were determined after 0, 30, 60, 90, and 120 min following addition of the vancomycin eye drops. The relative efficiencies of the vehicles for the delivery of vancomycin over time were compared by studying their respective pharmacokinetics. The concentration-time profiles for vancomycin in the tear films are shown in Figures 2–5 and demonstrate clearly how the vancomycin was rapidly eliminated from the tear films in each case within 30 min.

The areas under the curves (AUC) are shown in Figure 6 and Tables II and III. It was found that there were statistically significant differences in the AUC values from 0 to 30 and 0 to 120 mins for vancomycin in Tears Naturale II™, the 0.9% sodium chloride solution and the 0.1% w/v chitosan solution (Tables II and III). In contrast, the AUC values from 0 to 30 and 0 to 120 min for vancomycin 50 mg/mL in the 0.3% w/v chitosan solution were not significantly different from those in Tears Naturale II™.

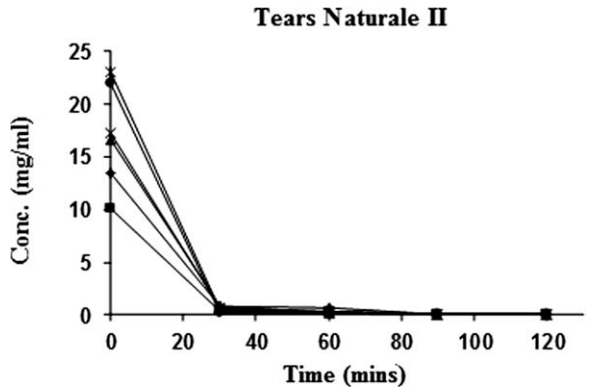

Figure 2 Tears Naturale II: concentration-time profiles of vancomycin in the tear films of six different rabbit eyes.

The AUC values from 0 to 30 and 0 to 120 min for 0.3% chitosan showed 1.15 and 1.22-fold improvements respectively, when compared with Tears Naturale II™.

Mechanism of controlled release

After applying the eye drops, the drug mixes with the lachrymal fluid. The contact time of the drug with the ocular tissue is very short, typically only about 1 to 2 min, because of the continuous production of lachrymal fluid.[1] Chitosan has been reported to enhance drug penetration through the mucosa, thereby increasing the transcorneal permeation of the drug.[14,30] In addition, other useful properties of chitosan in solution such as its ability to change into a hydrogel at ocular pH (pH 7.4), its viscous nature and its bioadhesiveness make it a promising candidate for ocular drug delivery.[15,30–33] These three properties are now discussed in more detail within the context of the results obtained in this study.

Sol-gel transition of chitosan solution

The phase change (sol to gel) of chitosan solution can be triggered by a change in pH and, usefully as far as this study is concerned, this sol-gel transition can occur at ocular pH.[30] After application of the eye drops, the transition from sol to gel of the vancomycin 50 mg/mL in 0.1% chitosan solution requires an increase of about 3 pH units to ocular pH. This is different from the study of Leesawat et al.[18] in which a 0.1% w/v chitosan solution was used as an artificial tear fluid and which had a pH of 5.97, close to the pK_a of chitosan (6.5). A chitosan solution of pH 5.97 can change more rapidly to a gel than a chitosan solution containing vancomycin 50 mg/mL. From Tables II and III, it is seen that the $AUC_{0\rightarrow30}$ and $AUC_{0\rightarrow120}$ values for vancomycin 50 mg/mL in Tears Naturale II™ is double that of vancomycin 50 mg/mL in 0.1% w/v chitosan solution. The discomfort caused by the low pH[34] of vancomycin 50 mg/mL prepared extemporaneously in a 0.1% chitosan solution may induce lachrymation leading to rapid drainage before the sol-gel transition can occur.

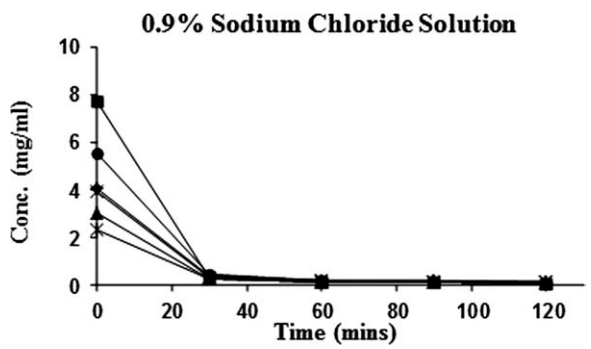

Figure 3 Sodium chloride solution (0.9%): concentration-time profiles of vancomycin in the tear films of six different rabbit eyes.

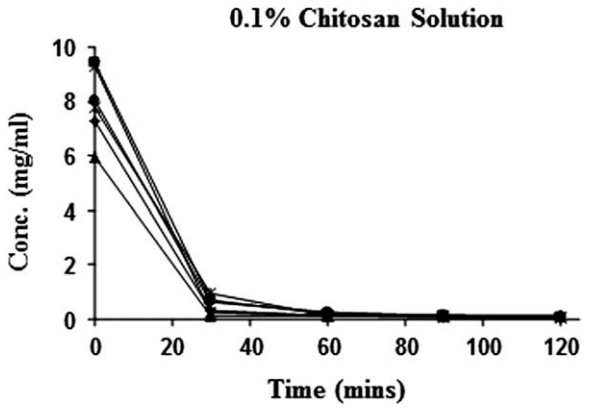

Figure 4 Chitosan solution (0.1%): concentration-time profiles of vancomycin in the tear films of six different rabbit eyes.

Viscous nature of chitosan solution

An increase in the bioavailability and hence in the duration of the therapeutic action of ocular drugs

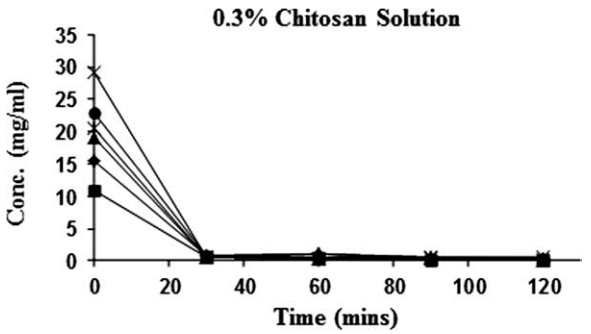

Figure 5 Chitosan solution (0.3%): concentration-time profiles of vancomycin in the tear films of six different rabbit eyes.

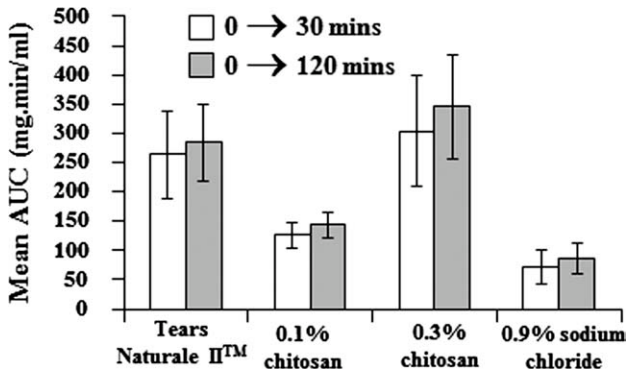

Figure 6 Mean areas under the curves (AUC) from the concentration–time profiles of vancomycin in the four different vehicles studied.

can be achieved in two ways.[35,36] The first is to use a sustained drug delivery system while the second involves maximizing corneal drug absorption and minimizing precorneal drug loss by, for example, increasing the viscosity of the delivery vehicle. In this study, the kinematic viscosities of vancomycin 50 mg/mL in Tears Naturale II™, the 0.9% sodium chloride solution and the 0.1% and 0.3% w/v chitosan solutions were determined by flow-time measurements and compared. Vancomycin 50 mg/mL in the 0.3% w/v chitosan solution had a higher kinematic viscosity and bioavailability than in the 0.1% w/v chitosan solution (Table I). Commercially available artificial tears are often acceptable vehicles for topical extemporaneous eye drops.[9] Artificial tears contain emollients and buffer systems for eye comfort as well as viscosity agents for prolonged contact time.[9]

Mucoadhesive properties of chitosan

The amino group (NH_2) in chitosan has a pK_a value of 6.5[13]; thus, chitosan is positively charged and soluble in weakly acidic solutions with a charge density dependent on pH and DD. As a result, chitosan is bioadhesive and readily binds to negatively charged surfaces such as mucosal membranes. The mucoadhesive character of chitosan is derived from the attraction between its positively charged protonated amino groups (NH_3^+) and the negatively charged residues of sialic acid in the mucus of the eye together with other forces such as hydrogen bonds.[2,14]

Although vancomycin 50 mg/mL in Tears Naturale II™ had a higher kinematic viscosity than in the 0.3% chitosan solution, the bioavailabilities of vancomycin from the AUC results were comparable. This is a clear reflection of how the mucoadhesive properties of chitosan can influence the bioavailability of vancomycin in eye drops.

Eye drops drain rapidly from the ocular surface, so that the time for drug absorption is of the order of only a few minutes and bioavailability is very low, typically less than 5%.[37] The AUC values from 0 to 30 and 0 to 120 min in 0.3% chitosan showed 1.15 and 1.22-fold improvements respectively, compared with Tears Naturale II™ which uses 0.3% hydroxypropyl methylcellulose as the vehicle. From these results, it appears that the combination of its polycationic nature and its suitable viscosity renders the 0.3% chitosan solution very similar in performance to commercial Tears Naturale II™.

Thus, these improvements may be explained in terms of the viscosity and mucoadhesive nature of chitosan prolonging the drug's residence time,[14] thereby increasing the bioavailabilty of topical eye drops.[15] Topical eye drops have a typically short contact time with the eye surface. With the aid of a mucoadhesive, the clearance of the drug is controlled by the mucus turnover rate which is much slower than the tear turnover rate.[14] Hence, a correspondingly prolonged drug residence time in tears can be expected based on the general hypothesis

TABLE II
Areas Under the Curves (AUC) of Vancomycin 0→30 min for the Four Vehicles Used

	Area under the curve $(AUC)_{0\rightarrow30}$ (mg.min/mL)			
No.	Vancomycin 50 mg/mL in Tears Naturale II™	Vancomycin 50 mg/mL in 0.1% chitosan solution	Vancomycin 50 mg/mL in 0.3% chitosan solution	Vancomycin 50 mg/mL in 0.9% sodium chloride
1	213.74	114.23	244.48	67.45
2	155.72	151.55	169.22	120.39
3	261.27	91.30	294.38	50.10
4	267.83	143.46	445.85	63.61
5	353.15	131.78	315.94	38.33
6	333.72	129.54	354.62	89.86
Mean	264.24	126.98*	304.08	71.62*
SD	73.59	21.64	94.47	29.54
AUC ratio[a]	1	0.48	1.15	0.27

[a] AUC ratio = mean AUC of vancomycin in vehicle/mean AUC of vancomycin in Tears Naturale II™.
* $P < 0.05$.

TABLE III
Areas Under the Curves (AUC) of Vancomycin 0→120 min for the Four Vehicles Used

No.	Area under the curve $(AUC)_{0\rightarrow120}$ (mg.min/mL)			
	Vancomycin 50 mg/mL in Tears Naturale II™	Vancomycin 50 mg/mL in 0.1% chitosan solution	Vancomycin 50 mg/mL in 0.3% chitosan solution	Vancomycin 50 mg/mL in 0.9% sodium chloride
1	245.98	129.92	306.02	86.60
2	171.32	171.16	192.72	133.92
3	281.01	101.28	354.49	62.27
4	284.89	155.60	488.36	79.68
5	373.40	153.29	346.45	52.50
6	348.20	150.95	389.02	106.90
Mean	284.13	143.70*	346.18	86.98*
SD	66.16	22.47	88.77	27.24
AUC ratio[a]	1	0.51	1.22	0.31

[a] AUC ratio = mean AUC of vancomycin in vehicle/mean AUC of vancomycin in Tears Naturale II™.
* $P < 0.05$.

that prolonging the precorneal residence time enables therapeutic drug levels to be maintained over longer periods of time.[19] Thus, the mucoadhesive nature of chitosan can control the clearance of vancomycin by slowing down the elimination of the drug by the lachrymal flow.

The results of this study indicate that the combined viscosity and mucoadhesive effects of chitosan are more important than the sol-gel transition, resulting in the 0.3% w/v chitosan solution exhibiting a bioavailability similar to Tears Naturale II™ for the delivery of vancomycin 50 mg/mL. Furthermore, the viscosity of the 0.3% chitosan solution is lower than that of Tears Naturale II™ which has the added advantage of providing greater ease of application for the patient.

Chitosan has also been proposed for use in artificial tear formulations since it exhibits good hydrating properties as well as an antibacterial effect that is desirable in cases of dry eye which are often complicated by secondary infections.[33] These findings are consistent with those of Singla and Chawla[38] and Ludwig[2] who also reported that chitosan has an antimicrobial effect. The antibacterial activity of chitosan is therefore an important advantage for treating bacterial keratitis when used for the delivery of eye drops. A previous report claimed that an artificial tear formulation containing chitosan caused no irritation in rabbits' eyes during testing.[18]

Finally, in economic terms, the cost of chitosan solution is much less than that of Tears Naturale II™ (about 200 times cheaper) due to the natural abundance in Thailand of chitin, the precursor for making chitosan. Also, only a small amount of chitosan is required for a 0.3% w/v solution. These are important considerations, especially for developing countries such as Thailand for which imported commercial products are prohibitively expensive.

CONCLUSIONS

This study has demonstrated quite clearly that a 0.3% w/v chitosan solution in 1% aqueous L-lactic acid offers several advantages as a vehicle for the ophthalmic delivery of vancomycin. These advantages include controlled drug delivery for the eye, biocompatibility, storage stability, and cost effectiveness. The results have shown that the 0.3% w/v chitosan solution enhances drug delivery due to a combination of viscosity and mucoadhesive effects. The sol-gel transition is not considered to exert a significant influence on the drug delivery. Additionally, the physical properties of the solution showed good compatibility when prepared extemporaneously as eye drops. Based on these findings, it is concluded that the 0.3% w/v chitosan solution shows considerable potential for the topical ocular administration of vancomycin. By enhancing the bioavailability of the drug, it holds the added attraction for health care teams of reducing the frequency of application of topical eye drops. Thus, it is both convenient to use and, due to its low cost, affordable by hospital administrations operating under strict budget limitations. In the wider context of this research, the conversion of chitosan, a relatively inexpensive derivative of a natural polymer (chitin) produced in Thailand, into a high value-added product for use in such a specialist application as this reflects the need for research to identify ways in which it can reduce the reliance on expensive imported products.

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