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The influence of selected excipients on the rheological behaviour of chitosan based ocular pharmaceutical systems

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Abstract. Aims: Chitosan, a modified natural carbohydrate polymer, has received great attention in diverse scientific fields including pharmaceutical and biomedical research areas. Besides its low toxicity, mucoadhesiveness and biodegradability its special favourable rheological feature makes it a unique gelling agent for the design of ocular systems. Chitosan based (2.0 w/v %) ocular systems containing selected excipients were formulated in order to investigate the rheological influence of applied auxiliary materials. Rotational and oscillatory rheological properties of propylene glycol (1.0-20.0 w/v %), glycerin (1.0-5.0 w/v %) and castor oil (1.0-5.0 w/v %) containing chitosan gels were evaluated. The rheological behaviour of formulated ocular gels were compared before and after steam sterilization.

Methods: Rotational and oscillatory rheological measurements were carried out with Kinexus Pro Rheometer. Comparison of flow curves and oscillatory frequency sweep measurements in the linear viscoelastic region made possible the evaluation of rheological effect of selected excipients.

Results: In the applied concentration range the effect of propylene glycol among the selected excipients presents the most significant impact on rheology of chitosan formulations. Steam sterilization results in reduced viscosity in most of chitosan gels. However, the presence of polyols appears to prevent the degradation of chitosan after steam sterilization.

1. Introduction
Chitosan is a widely used polysaccharide with outstanding rheological behaviour. The viscoelastic property of chitosan makes the polymer a unique gelling agent in many research areas including the pharmaceutical formulation development. Chitosan based pharmaceutical systems possess low toxicity, mucoadhesiveness and biodegradability. Furthermore, chitosan possesses viscoelastic behaviour, as human tear under physiologic conditions. This fact provides chitosan the ability to serve as an appropriate gelling agent in ocular dosage forms [1-2].

Glycerin, propylene glycol and castor oil are frequently used auxiliary materials in pharmaceutical technology. In ophtalmic formulations glycerin is mainly used as a solvent. Propylene glycol has become widely used as a solvent and preservative in a variety of pharmaceutical formulations. Application of castor oil in chitosan based ocular gels can be recommended in order to increase the solubility of lipophil active ingredients in the dosage forms. Required microbiological quality of the mentioned auxiliary materials can be achieved by steam sterilization [3].

Polyols such as glycerin and propylene glycol were used in this study because of the rheological protective effect attributed to polyols in chitosan formulations after steam sterilization [4-5].

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Our aim was to prepare chitosan based ocular systems and to investigate the effect of selected pharmaceutical excipients on the rheological behaviour of formulated gels before and after steam sterilization.

2. Materials and methods
Chitosan was purchased from Sigma-Aldrich Ltd. (Budapest, Hungary). All the other excipients such as acetic acid, glycerin, propylene glycol, castor oil were purchased from Hungaropharma Ltd., (Budapest, Hungary). Distilled water was produced by MilliQ-water device (Millipore Ltd., Budapest, Hungary).

Chitosan formulations 2.0 % (w/v) were prepared by dissolving chitosan powder in acetic acid solution 0.5 % (v/v) under stirring for 1 h. If the preparations contained other excipients such as glycerin or propylene glycol, were the excipients first dissolved in acetic acid solution then was chitosan added to the preparation followed by an 1-hour-long stirring procedure. Besides the reference chitosan formulations - 0.5 % (v/v) acetic acid containing 2.0 % (w/v) chitosan gel - three sequences (containing one of the selected excipient above the components of reference sample) were prepared. Glycerin (1.0-5.0 w/v %), propylene glycol (1.0-20.0 w/v %) and castor oil (1.0-5.0 w/v %) containing chitosan gels - named as glycerin, propylene glycol and castor oil sequences - were examined.

Rheological measurements were carried out with Kinexus Pro rheometer (Malvern Instruments Ltd, UK). Measured data were registered with rSpace for Kinexus Pro 1.3 software. Preparations were measured using a cone and plate geometry. The gap between the cone and plate of sample placement was 0.15 mm. The temperature of the samples was controlled with an accuracy of ± 0.1 °C, by Peltier system of the rheometer. In all measurements a cylindrical cover made of stainless steel was placed over the samples, in order to create a closed, saturated volume round the sample and to prevent evaporation of the sample. Rotational measurements of all chitosan formulations were determined at 25 °C. Oscillatory experiments were carried out at 33 °C. Our temperature choice during rotational and oscillatory measurements can be explained with the following facts: the temperature of ophthalmic dosage forms during storage and application is about 25 °C, while the temperature of human tears on the cornea surface is approximately 33 °C. In case of each sample at least two parallels were analysed; mean values are demonstrated in present article. Boxer 300_75LR steam sterilizer was used for sterilization (20 mins, 121 °C). The pH of the samples was measured by Mettler Toledo AG (Switzerland).

3. Results
The compositions and pH data for formulated chitosan gels are summarized in Table 1. The pH values of chitosan formulations were between 5.65 - 5.90 prior to sterilization. After sterilization the pH values vary between 5.71 - 5.95. Any significant changes can be observed in pH values after sterilization.
### Table 1. Compositions and pH of chitosan formulations

| Name of sequence          | Concentration of chitosan % (w/v) | Concentration of acetic acid % (w/v) | Concentration of excipient % (w/v) | pH before steam sterilization | pH after steam sterilization |
|---------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------|------------------------------|
| "glycerin sequence"      | 2.0                               | 0.5                                 | 1.0                                | 5.65                         | 5.74                         |
|                           | 2.0                               | 0.5                                 | 2.0                                | 5.66                         | 5.76                         |
|                           | 2.0                               | 0.5                                 | 3.0                                | 5.71                         | 5.72                         |
|                           | 2.0                               | 0.5                                 | 4.0                                | 5.76                         | 5.85                         |
|                           | 2.0                               | 0.5                                 | 5.0                                | 5.76                         | 5.78                         |
| "propylene glycol sequence" | 2.0                               | 0.5                                 | 1.0                                | 5.74                         | 5.89                         |
|                           | 2.0                               | 0.5                                 | 2.0                                | 5.73                         | 5.93                         |
|                           | 2.0                               | 0.5                                 | 10.0                               | 5.77                         | 5.94                         |
|                           | 2.0                               | 0.5                                 | 15.0                               | 5.80                         | 5.93                         |
|                           | 2.0                               | 0.5                                 | 20.0                               | 5.90                         | 5.95                         |
| "castor oil sequence"    | 2.0                               | 0.5                                 | 1.0                                | 5.69                         | 5.71                         |
|                           | 2.0                               | 0.5                                 | 2.0                                | 5.63                         | 5.71                         |
|                           | 2.0                               | 0.5                                 | 3.0                                | 5.70                         | 5.73                         |
|                           | 2.0                               | 0.5                                 | 4.0                                | 5.80                         | 5.79                         |
|                           | 2.0                               | 0.5                                 | 5.0                                | 5.86                         | 5.79                         |

3.1. Choice of excipients
The choice of glycerin can be explained by its frequent application in ophthalmic dosage forms. As it is known that glycerin decomposes on heating, with the evolution of toxic acrolein if the aqueous preparation contains more than 85 % glycerin. Thus glycerin containing samples can be sterilized by autoclaving if the preparation contains at least 20 % water and the conditions of steam sterilization follow the standard setting parameters (120 °C, 20 min). In ophthalmic preparations glycerin is commonly used in a concentration range of 0.5-3.0 %. In order to investigate the effect of glycerin on the rheological properties of chitosan gels, chitosan gels containing 1.0-5.0 % glycerin were prepared. The highest glycerin concentration was 5.0 %, regarding the applied concentrations in eye drops [3]. 

Propylene glycol is a frequently used excipient in pharmaceuticals. In parenteral formulations its concentration can reach 60 %, while in topical formulations 80 %. In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin. Propylene glycol can be sterilized by autoclaving. As in a concentration above 15 % propylene glycol possesses preservative effect, a further advantage of propylene glycol application in solutions and semisolid dosage forms is the preparation of pharmaceutical dosage forms without the traditionally used preservatives [3].
Based on the fact that chitosan containing gels 2.0 % (w/v) possess higher viscosity than aqueous solutions, castor oil in 1.0-5.0 % (w/v) can be dispersed homogeneously in chitosan gels. The highest concentration of castor oil used throughout our experiments was 5.0 % (w/v) in chitosan gels. Higher than 5.0 % (w/v) concentration of castor oil in gels would have required the application of emulsifiers which are regarded as irritant excipients in ocular systems.

3.2. Rotational measurements

Rotational and oscillatory measurements of reference samples and sequences were compared (Figure 1). The viscosity was measured as a function of shear rate in a range of 0.1-10.0 s⁻¹. The applied shear rate spectrum describes the shear conditions of several applications. The shear rate values of about 0.1 s⁻¹ characterize the leveling, 1.0 s⁻¹ the pumping and sample application and 10.0 s⁻¹ the brushing, mixing or stirring. The viscosity values of samples vary between 0.1 and 10.0 Pa·s.

![viscosity measurement graph](image)

**Figure 1.** Comparison of rotational measurements. Rotational measurement results for 2.0 % (w/v) chitosan gels with various excipients. Concentration of excipient is 5.0 % (w/v) in each case. ST denotes steam sterilized samples.

The highest viscosity values belong to the reference chitosan sample. The viscosity loss is most expressed in case of steam sterilized reference and sterilized castor oil 5 % (w/v) containing samples whose viscosity is below 1.0 Pa·s. Almost all the excipients reduce the viscosity of gels comparing to reference chitosan sample. Further viscosity loss can be observed after steam sterilization. However, the viscosity of polyol containing chitosan gels is not reduced in such an extent after steam sterilization than that of reference sample. The 5 % (w/v) polyol-content in chitosan gels results in a viscosity of approximately 1.0 Pa·s after steam sterilization.

In the propylene glycol sequence propylene glycol content reached 20 % (w/v). Regarding the rotational viscosity results the higher propylene glycol concentrations leads to higher viscosity values (Figure 2). The viscosity of 20 % (w/v) propylene glycol containing sample exceeds the viscosity of reference sample in the shear rate range of 0.1-1.0 s⁻¹. The viscosity loss of sterilized samples is not so expressed in case of higher propylene glycol content as for samples with relatively low propylene glycol concentrations. The presence of castor oil reduces the viscosity of gels compared to the viscosity of reference before steam sterilization. However, increased viscosity values can be measured as a result of addition of castor oil for samples after steam sterilization.
Figure 2. Rotational measurements of propylene glycol-chitosan gels. Rotational measurement results of propylene glycol-chitosan gels with various 5.0-20.0 % (w/v) propylene glycol concentrations. ST denotes steam sterilized samples.

3.3. Oscillatory measurements

In the present work the complex viscosity was used for the comparison of oscillatory measurement. The complex viscosity ($\eta^*$) published and introduced by Cox and Merz 1958 serves an empirical relationship for polymeric systems between rotational and oscillatory viscosity data as a function of shear rate ($\dot{G}$) and angular frequency ($\omega$) [6].

Complex viscosity can be represented by complex mathematics: $\eta^* = \eta' + i \eta''$. The terms $\eta'$ and $\eta''$ can be related to the $G'$ and $G''$ through the following relationships: $G' = \eta''\omega$, $G' = \eta'\omega$. The complex viscosity can be defined as $\eta^* = G^* / i \omega$, where $G^*$ means complex modulus and $i$ is the so-called imaginary unit considering the rules of complex mathematics [6].

The complex viscosity was measured in the angular frequency range of 1.0-100.0 (rad/s). The complex viscosity of samples varied between 0.1-3.5 Pa·s (Figure 3). Polyol (glycerin and propylene glycol) containing samples provide a protective effect against complex viscosity loss after steam sterilization.
Figure 3. Comparison of oscillatory measurements. Oscillatory measurement results for 2.0 % (w/v) chitosan gels with various excipients. Concentration of excipient is 5.0 % (w/v) in each case. ST denotes steam sterilized samples.

Propylene glycol – on a concentration dependent manner - increased the complex viscosity of chitosan gels comparing to reference sample (Figure 4). The most expressed viscosity increase was observed for the 20.0 % w/v propylene glycol containing sample. Comparing samples with same propylene glycol concentrations before and after steam sterilization, after steam sterilization lower viscosity values can be registered.

The presence of castor oil reduces the complex viscosity of formulations compared to the viscosity of reference before steam sterilization. However, increased viscosity values can be measured as a result of addition of castor oil for samples after steam sterilization.

Figure 4. Oscillatory measurements of propylene glycol-chitosan gels. Oscillatory measurement results of propylene glycol-chitosan gels with various 5.0-20.0 % (w/v) propylene glycol concentrations. ST denotes steam sterilized samples.
4. Discussion
Most of the pharmaceutical excipients used in the present study reduce the viscosity of chitosan formulations. Steam sterilization also results in viscosity loss in the investigated samples. Both rotational and oscillatory measurements demonstrate that the applied excipients help to avoid the viscosity loss of chitosan gels after steam sterilization. The protective effect of polyols (glycerin and propylene glycol) is more significant than that of castor oil. In the applied propylene glycol concentration range (1.0-20.0 % w/v) the 20.0 % (w/v) possesses the most effective protective influence on rheology of chitosan systems. Furthermore, the application of propylene glycol is advantageous in pharmaceutical dosage forms as it serves as a preservative beyond its protective rheological feature. The propylene glycol provides preservative effect if its concentration reaches 15.0 % (w/v). Considering that the formulated gels are intended to apply as ocular systems, further investigations are needed concerning the safety and irritative potential of propylene glycol containing gels.

5. Conclusions
The rheological effects of selected excipients – glycerin, propylene glycol and castor oil – in chitosan ocular formulations were described before and after steam sterilization. Rotational measurement results correspond to oscillatory measurements results. Steam sterilization reduces the viscosity of chitosan 2.0 % (w/v) formulations. Polyol excipients, such as glycerin and propylene glycol protect the chitosan gels against viscosity loss after steam sterilization. The most expressed protective effect was observed in case of chitosan formulation with the highest propylene glycol concentration (20.0 % w/v).

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