Rheology and Dissolution study for *In Situ* Gel Forming Ophthalmic Drug Delivery Systems

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Introduction

Ophthalmic drug delivery is one of the most challenging routes of administration because of the distinctive anatomy and physiology of the eye. The static and the dynamic protective mechanisms of the eye causes dilution and drainage of administered ophthalmic solutions, resulting in poor bioavailability. To overcome this, *in situ* gel forming ophthalmic drug delivery systems have been developed that are formulated as liquid and administered as eye drops but undergoes transition into a gel phase *in situ*. Gellan gum is one material that forms i*n situ* gels on the surface of the eye due to ionotropic gelation caused by metal ions that are abundant in lachrymal fluid (K^+, Na^+ and Ca^{2+}) and has been successfully utilized in commercially available ophthalmic formulations of the glaucoma drug timolol maleate. Interactions between the drug and the polymer are poorly understood and measuring rapid gelling events that in such systems is particularly difficult using a conventional rheometer preventing optimisation of *in situ* drug delivery systems during development. Here we have investigated the interaction between timolol maleate and gellan gum and the impact on drug release.

Method

Preparation of the Formulation–The gel forming eye drop solution was prepared at pH 4 based on a currently marketed formulation Timoptol LA (0.5%) which contains 0.4% low acyl gellan gum as the gel former and 6.8 mg/ml timolol maleate as the drug.

Oscillatory Rheological Analysis– Rheological analysis was performed for the control (gellan gum) and for the formulation without any cations. The cooling rate was 2°C/min from 90°C to 20°C for the cooling scan. The frequency was 1.592 Hz and the strain was 0.5%. Measurements of elastic modulus (G') and the viscous modulus (G") were taken as a function of strain, frequency, and temperature using a Bohlin Gemini HR Nano Rheometer.

Gellan gum-Timolol Maleate Interaction–To evaluate the interaction between gellan gum and timolol maleate the pH of the solutions were varied below (pH 4) and above (pH 10) the pKa of timolol (pKa 9.21).

Drug Release Study–The formulation (2 ml) was placed in 100 ml of simulated tear fluid ($NaHCO_3$ 0.2% w/w, $CaCl_2$ 0.008% w/w and NaCl 0.67% w/w) at 35°C and samples of the tear fluid were taken for up to 3h and analysed using HPLC. Drug release study was performed at both pH 4 and pH 10.

FTIR–Fourier transform infrared spectra (FTIR) analysis were performed on the gel collected at 0 hours and the end of 3 hours for the formulation at both pH (pH 4 and 10).

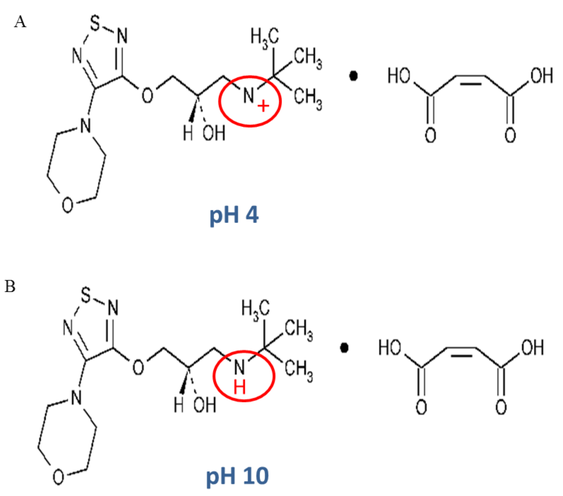

Fig.1 Structure of timolol maleate showing pH dependent ionization at (A) pH4 and (B) at pH 10

Results and Discussion

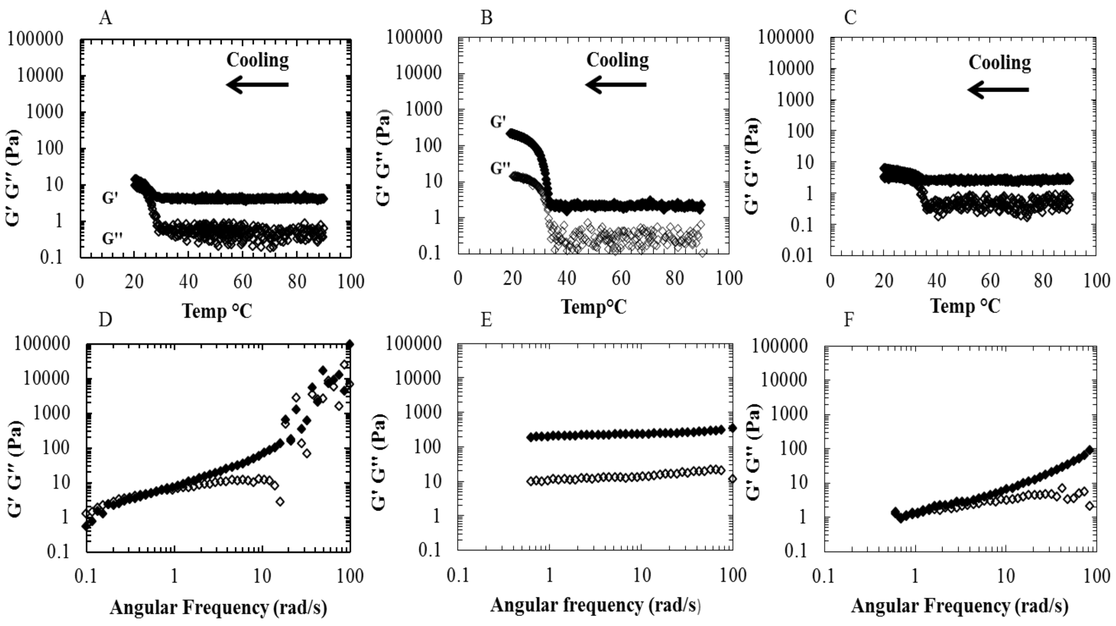

Fig.2 Cooling scan of (A) gellan at pH 4 (B) gellan and timolol maleate at pH 4 (C) gellan and timolol maleate at pH 10; Mechanical spectra of (D) gellan at pH 4 (E) gellan and timolol maleate at pH 4 (F) gellan and timolol maleate at pH 10

Oscillatory Rheological Analysis– Cooling scan and mechanical spectra of control (fig2A and fig 2D) shows the formation of a weak gel at pH 4 The formulation at pH 4 however, (fig 2B and 2E) indicates the formation of a strong gel. Whereas at pH 10 shows a weak gel (fig 2C, 2D) which was similar to the rheological analysis of control. This indicates an electrostatic interaction between the gellan and the positively charged timolol. High H^+ concentration causes the amino group to be positively charged at pH 4 at pH 10 however, the amino group is unionized therefore, interactions with the gellan helices are lost which results the formation of a weak gel (fig 2B, 2E).

Drug Release Study– At pH 4 the release of timolol maleate after 3 hours was 45.97% (fig 3A). At pH 10, drug release was increased to 55% (fig 3B). The electrostatic interactions between the protonated amino groups of the timolol maleate cations at pH 4 and the anionic charges of gellan gum is thought to be responsible for the incomplete release of timolol maleate.

FTIR–The presence of amino groups in the gel at 3 hours, even at pH 10, confirms the presence of timolol. The peak at 833 cm^{-1} however, is assigned to NH wagging which increases in intensity at pH 10 when the amino group is protonated (fig 4). The presence of timolol in the unionized form and the incomplete release shown in fig 3b, indicates that interactions other than electrostatic may be occurring between the gellan and the drug.

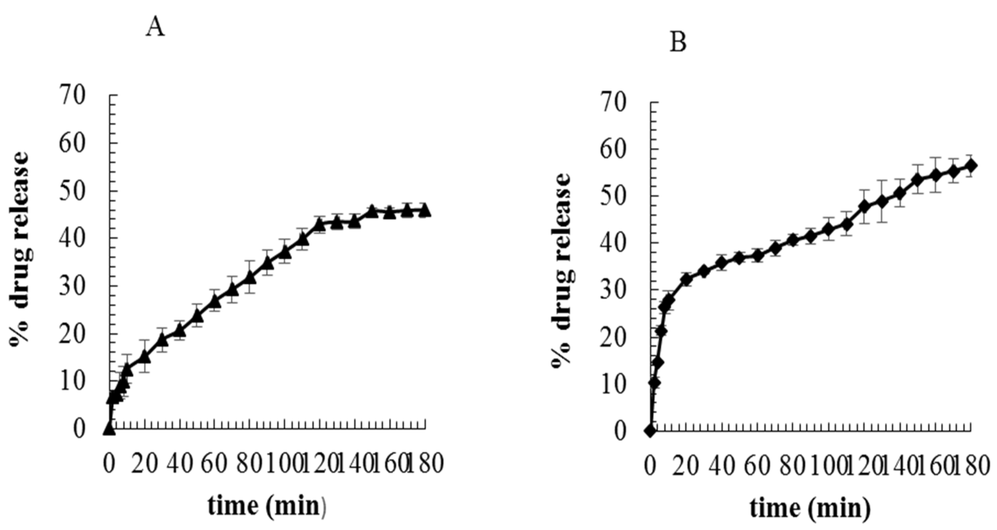

Fig.3 Release profile of timolol at (A) pH 4 (B) pH 10

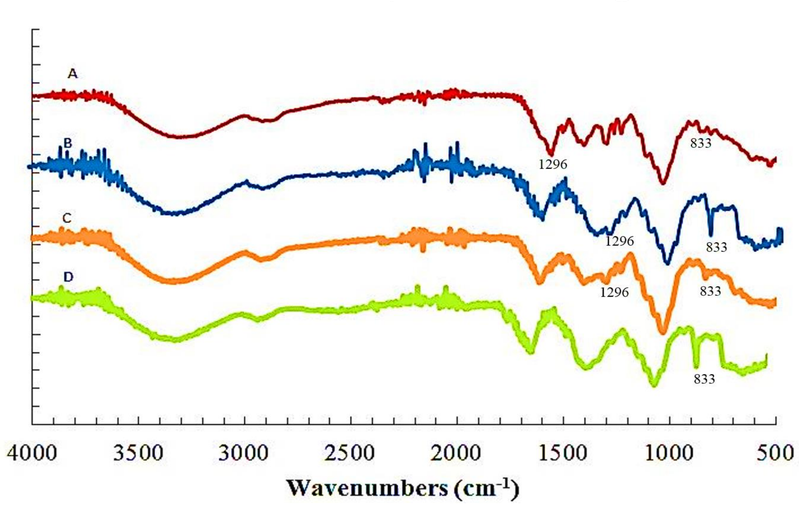

Fig.4 – FTIR spectra (A) 0 hr at pH 4 (B) 0 hr at pH 10 (C) 3 hr at pH 4 (D) 3hr at pH 10

Conclusions

This study has demonstrated the interaction between the gel former and the drug which has a significant impact on rheological behavior of the *in situ* gel forming formulation. This study also highlights that drug-vehicle interactions can limit the release from *in situ* gelling systems and should be an important consideration when designing such formulations.

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