

# In situ gelling mucoadhesive eye drops: evaluation of physicochemical properties, in vitro dissolution and transcorneal permeability

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## Introduction

Local treatment of the eyes can be challenging, as corneal permeability is limited by the complex defense mechanisms of the eye (Ponnusamy et al., 2021). However, formulating in situ gels and providing good mucoadhesion could increase residence time. We may overcome some of the factors that limit ocular bioavailability of drugs with in situ gelling mucoadhesive eye drops (Szalai et al. 2022).

This study aimed to formulate in situ gelling eye drops that can be instilled into the eye in liquid state, then gelation occurs due to body heat. We added two mucoadhesive polymers to the formulations along with the thermosensitive polymer.

## Materials and methods

To solubilize 0.1 mg/mL dexamethasone (DXM; Pharmacia and Upjohn Company LLC), the lowest necessary amount of (2 - hydroxypropyl)- $\beta$ -cyclodextrin (DS~4.5; HPBCD; Cyclolab R&D Ltd.) was used. The thermosensitive property of the formulations was provided by Kolliphor® P 407 (P407; Sigma-Aldrich). It was combined with two mucoadhesive polymers, hydroxypropyl methylcellulose (HPMC; Colorcon) and zinc-hyaluronate (ZnHA; Gedeon Richter Plc.) to increase the mucoadhesion of the eye drops.

The effect of the concentration of the polymers and their interactions were determined according to a 3<sup>3</sup> full factorial design. The independent factors were the concentration of P407 (12%, 15%, 18%), HPMC (0%, 0.1%, 0.2%) and ZnHA (0.1%, 0.2%, 0.3%).

Rheological measurements were performed with a Physica MCR 302 Modular Compact Rheometer to determine the gelling time and the gelling temperature of the formulations.

Mucoadhesion of the eye drops was studied with a TA.XT plus Texture Analyzer applying a mucoadhesion test rig. A mucin covered surface was used to imitate the eye surface. Adhesive force of the formulations was determined based on the force-distance curves.

The dialysis bag method (Kiss et al. 2020) was applied to study the in vitro drug release of the samples. The dialysis membrane tubes were filled with the samples and placed in simulated tear fluid tempered at 35 °C for 6 h. The released amount of DXM was measured by HPLC.

The previously reported corneal parallel artificial membrane permeability assay (PAMPA) method (Kiss et al. 2020) was applied for the measurement of in vitro transcorneal permeability. The DXM concentration in the acceptor and donor phase was measured by HPLC.

## Results and discussion

Gelling temperature should be between 28–34 °C so the eye drops will turn into a gel at the temperature of the ocular surface but not at room temperature. Gelation of our formulations occurred at 23 to 37 °C, depending on the composition. The gelation process should be completed in less than 5 min. to reduce precorneal elimination. The gelling time of the samples ranged from 0 to 7 min. Both gelling temperature and gelling time were determined mainly by the P407 concentration (Fig. 1). Combining P407 with other polymers does not alter the gelation temperature but may slow the gelation process. HPMC and

ZnHA can increase the viscosity and may affect the orientation of the poloxamer chains during micelle formation and aggregation, thereby delaying gelation.

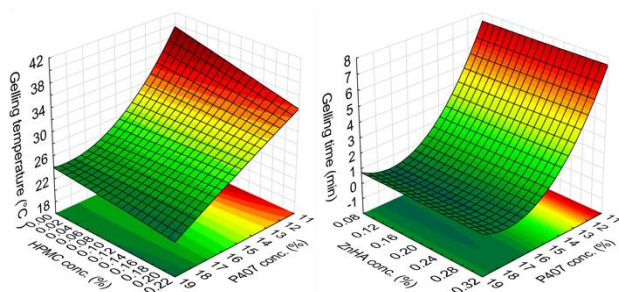


Fig. 1. Effect of the composition on the gelling temperature (HPMC and P407 concentration) and the gelling time (ZnHA and P407 concentration) (the 3rd factor is at level 0 in each case).

Most formulations showed adequate mucoadhesion, as the adhesive force values were between 800 and 2100 mN. In terms of the adhesive force, not only the P407 concentration but its interactions with HPMC and ZnHA were significant (Fig.2). In addition to P407, HPMC and ZnHA also play a significant role in the interpenetration of polymer chains, thus determining mucoadhesion.

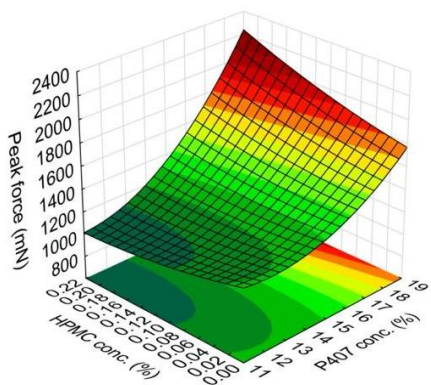


Fig. 2. Effect of the composition on the adhesive force (HPMC and P407 concentration; the 3rd factor is at level 0).

In 6 h, DXM was completely released from the DXM-HPBCD solution, while only about 51% of the DXM was released from the suspension. Regarding the in situ gels, the amount of DXM released was higher compared to the suspension; moreover, the dissolution was not complete in 6 h. The dissolution curves suggested that more DXM might have dissolved over a longer period. In view of these results and the increased mucoadhesion, sustained drug release can be predisposed.

In the corneal-PAMPA study, the permeability of the in situ gels was higher than that of the DXM suspension

and the solution containing DXM-HPBCD complex. P407 is known to facilitate permeation through complex mechanisms. The result of this study also suggests that the presence of P407 is responsible for increased permeability and not the inclusion complex.

## Conclusion

We managed to formulate in situ gelling mucoadhesive eye drops containing DXM-HPBCD inclusion complex. The complexation ensured the dissolution of the therapeutic concentration (0.1 mg/mL) of DXM in the formulations. Most of the eye drops had proper gelling properties: the gelling temperature was above room temperature and below the temperature of the eye surface. Furthermore, the sol-gel transition was rapid enough not to be washed away easily. Satisfying mucoadhesivity was achieved by adding mucoadhesive polymers to the formulations. The gels displayed better in vitro drug release properties than the DXM suspension while providing prolonged dissolution.

These results may be promising in formulating ocular in situ gels with prolonged residence time due to their mucoadhesive properties, thus increasing the bioavailability of the eye drops.

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