

# The influence of preparation conditions on the formation and extent of interactions in chitosan/xanthan gum polyelectrolyte complexes as potential drug delivery carriers

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## Introduction

The formation and properties of polyelectrolyte complexes (PECs) based on chitosan (CH) and xanthan gum (XG) depend on various preparation parameters (pH value, ionic strength, mixing order of polyelectrolytes, etc.). The extent of polyelectrolytes interactions can significantly influence the achievement of the desired drug release kinetics from the PECs (Ćirić et al., 2022). The dissolution of CH is one of the essential requirements influencing the formation and properties of PECs. Previous research has shown that CH dissolves in dilute solutions of acids at a pH < 6.3 (Furuike et al., 2017). Therefore, this research aimed to determine the influence of pH and the type of pH-adjusting agent on the formation and extent of interactions in PECs based on CH and XG.

## Materials and methods

Six different PECs based on medium molecular weight CH (Sigma Aldrich, USA) and XG (Jungbunzlauer, Switzerland) were prepared by adding the XG solution (0.65%) into the corresponding CH solution (0.65%). Mixing was performed on a propeller mixer RZR 2020 (Heidolph, Germany). CH/XG mass ratio was 1:1. The pH of CH solutions was adjusted to 3.6, 4.6, or 5.6, using hydrochloric acid (H) or lactic acid (L) as the pH-adjusting agent. Therefore, formed PECs were labeled as H3.6, H4.6, H5.6, L3.6, L4.6, and L5.6.

The evaluation of PECs formation and the extent of interactions between the polyelectrolytes was performed by measuring the transmittance (%T) at 600 nm (Evolution 300, Thermo Scientific, USA), conductivity ( $\sigma$ ), (CDM

230, Radiometer, Denmark) and by rheological characterization (Rheolab MC 120, Paar Physica, Austria) by increasing the shear rate from 0 to 100 s<sup>-1</sup> and back to 0 s<sup>-1</sup> at 20 ± 0.2 °C, in triplicate.

## Results and discussion

%T of CH solutions were higher than 90% at all preparation conditions except pH 5.6, adjusted with H. The complete dissolution of CH was considered at %T > 90% (Kiechel and Schauer, 2013). It could be explained by the better solubility of CH at lower pH and using organic acid (i.e., lactic acid) as a pH-adjusting agent (Furuike et al., 2017). %T of the XG solution was 26.27 ± 2.09 %. During the formation of PECs, the %T of PECs continuously decreased. The measured %T values were 42.10 ± 0.13 % for H3.6, 54.48 ± 2.54 % for H4.6, 40.12 ± 1.12 % for H5.6, 10.41 ± 3.60 % for L3.6, 7.14 ± 0.80 % for L4.6, and 33.91 ± 4.59 % for L5.6 (Fig. 1).

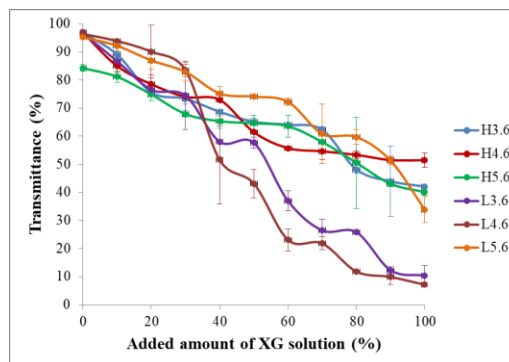


Fig. 1. Transmittance during the formation of PECs

A decrease of %T during the PECs preparation confirmed their formation. A lower %T can be associated with stronger intermolecular interactions in complexes (Ćirić et al., 2022). Lower %T was measured for samples prepared at pH 3.6 and 4.6 with L, indicating more extensive interactions between CH and XG in these PECs.

A continuous decrease in  $\sigma$  from the initial value measured for each CH solution was observed during the formation of PECs (Fig. 2). That confirmed the establishment of typical interactions between CH and XG. Significantly higher  $\sigma$  was measured when H was used as a pH-adjusting agent (the final  $\sigma$  for H3.6 was  $1927 \pm 54$   $\mu\text{S/cm}$ , for H4.6  $1320 \pm 13$   $\mu\text{S/cm}$ , for H5.6  $678 \pm 1$   $\mu\text{S/cm}$ , while for L3.6 was  $1122 \pm 3$   $\mu\text{S/cm}$ , for L4.6  $932 \pm 9$   $\mu\text{S/cm}$ , and for L5.6  $615 \pm 2$   $\mu\text{S/cm}$ ). These results could be explained by the higher degree of dissociation of H. Moreover, a higher decrease in  $\sigma$  can be observed and related with a greater extent of interactions in these PECs (Ćirić et al., 2022). Also, it was assumed that more extensive interactions between CH and XG were established at lower investigated pH values (3.6 and 4.6).

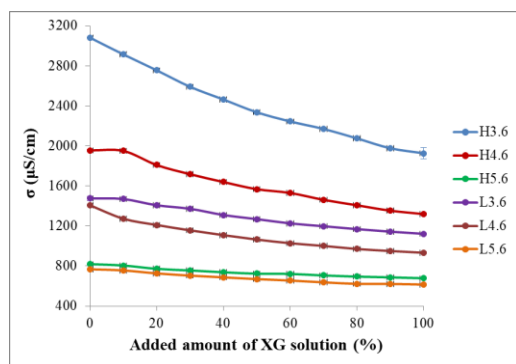


Fig. 2. Conductivity during the formation of PECs

To elucidate the interaction extent between CH and XG during and after the preparation of PECs, rheological characterization was performed for polymers' solutions and PECs. CH solutions had a Newtonian type of flow and dynamic viscosity varying from  $84 \pm 2$  mPa·s (pH 3.6 adjusted with L) to  $5 \pm 0$  mPa·s (pH 5.6 adjusted with H). XG solution was a pseudoplastic system with thixotropy (maximum apparent viscosity,  $\eta_{\max}$ ,  $214 \pm 8$  mPa·s, and minimum apparent viscosity,  $\eta_{\min}$ ,  $76 \pm 3$  mPa·s).

PECs were pseudoplastic systems with thixotropy. The  $\eta_{\max}$  and  $\eta_{\min}$  values of PECs are shown in Table 1. Measured apparent viscosities for PECs were higher than those of individual polymers' solutions used for their preparation, confirming the formation of PECs. The values of apparent viscosities of PECs may reflect the extent of interactions between the components of the complexes. By comparing them, it was confirmed that more extensive interactions were achieved at lower pH. Moreover, rheological characterization revealed that interaction

extent depended dominantly on pH and much less on the type of pH-adjusting agent.

Table 1.  $\eta_{\max}$  (at  $22.2 \text{ s}^{-1}$ ) and  $\eta_{\min}$  (at  $100 \text{ s}^{-1}$ ) of PECs

PEC	$\eta_{\max} \pm \text{SD}$ (mPa·s)	$\eta_{\min} \pm \text{SD}$ (mPa·s)
<b>H3.6</b>	$2080 \pm 16$	$660 \pm 7$
<b>H4.6</b>	$1685 \pm 7$	$477 \pm 6$
<b>H5.6</b>	$1090 \pm 9$	$291 \pm 4$
<b>L3.6</b>	$2380 \pm 14$	$660 \pm 40$
<b>L4.6</b>	$1635 \pm 23$	$396 \pm 1$
<b>L5.6</b>	$821 \pm 5$	$242 \pm 5$

## Conclusion

PECs based on CH and XG can be formed under different conditions including the pH adjustment agent and the pH value. %T values indicated that more extensive interactions between polyelectrolytes could be established when L was used as a pH adjusting agent due to better dissolution of CH in organic acids. However, the  $\sigma$  measurement and rheological characterization during the formation of PECs pointed out that the extent of interactions was more influenced by the pH value and less by the type of pH-adjusting agent. Also, it has been shown that the most extensive interactions were established at pH 3.6 and the less extensive at pH 5.6. The CH and XG based PECs formulated at different pH values can be further considered as prospectively versatile drug delivery carriers.

**Acknowledgments:** This research was funded by the Ministry of Science, Technological Development and Innovation, Republic of Serbia through Grant Agreement with University of Belgrade-Faculty of Pharmacy No: 451-03-47/2023-01/ 200161.

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