

## Rheological and diffusion evaluation of topical gels with naproxen

Elena-Emilia Tudoroiu<sup>1</sup>, Mihaela Violeta Ghica<sup>1</sup>, Cristina-Elena Dinu-Pîrvu<sup>1</sup>, Lăcrămioara Popa<sup>1</sup>, Adriana-Elena Tăerel<sup>2\*</sup>, Răzvan Mihai Prisada<sup>1</sup>, Mădălina Georgiana Albu Kaya<sup>3</sup>, Bruno Ștefan Velescu<sup>4</sup>, Valentina Anuța<sup>1</sup>

<sup>1</sup>Department of Physical and Colloidal Chemistry, Faculty of Pharmacy, Carol Davila University of Medicine and Pharmacy, 6 Traian Vuia Str., 020956, Bucharest, Romania

<sup>2</sup>Department of Pharmaceutical Management and Marketing, Faculty of Pharmacy, Carol Davila University of Medicine and Pharmacy, 6 Traian Vuia Str., 020956, Bucharest, Romania

<sup>3</sup>Department of Collagen, Division Leather and Footwear Research Institute, National Research and Development Institute for Textile and Leather, 93 Ion Minulescu Str., 031215 Bucharest, Romania

<sup>4</sup>Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Carol Davila University of Medicine and Pharmacy, 6 Traian Vuia Str., 020956, Bucharest, Romania

### Introduction

Drug penetration throughout the skin represents a sophisticated process frequently rate-restricted by the stratum corneum (Herkenne et al., 2007).

Topical administration of drugs presents several advantages compared to the oral one because it can generate suitable local pharmacological action, avoiding the systemic side effects and the drawbacks of the first pass effect (Leppert et al., 2018). The bioavailability of the active pharmaceutical ingredient increases which allows maintaining adequate and effective drug concentrations at the damaged cutaneous tissue. Comparing to injectable administration, topical pharmaceutical formulations can be easily applied on the skin surface, without causing any trauma or discomfort, which promotes the patient's adherence to the treatment (Singh Malik et al., 2016).

Topical products are conditioned in various forms, the most usually used being the semisolid systems, which are extensively studied to be applied in diverse cutaneous disorders due to their higher adherence on the skin surface than the liquid forms (Chang et al., 2013). One of the most used semisolid dosage forms are gels due to their high biocompatibility, biodegradability, and physicochemical properties.

The variety of gels products consists in the possibility to incorporate many active substances, such as antibiotics, antimycotics, corticosteroids, or non-steroidal anti-inflammatory drugs (NSAIDs). In commercially available topical formulations, among the most numerous substances encountered are NSAIDs that exhibit anti-inflammatory, analgesic, and antipyretic effects. Naproxen is a hydrophobic NSAIDs used to alleviate pain and to reduce the inflammation that accompanies a lesion to restore the integrity of the stratum corneum. Topical administration of naproxen avoids the systemic side effects (gastrointestinal and renal) that occur at oral ingestion (Wang et al., 2019).

Consequently, the main objective of this present work is to accomplish a comparative study of some commercially available carbopol-based gels with naproxen, regarding the rheological characteristics, and diffusion properties using two different kinetic devices.

### Materials and methods

Four different commercially available carbopol-based gels with naproxen in a concentration of 10% were studied. For these semi-solid systems, rheological and kinetic properties were analyzed. Rheological determinations of gels were conducted with a rotational viscometer, using a standard spindle TR10. The measure was conducted at

33°C which represents the skin temperature, and it was kept constant because the rheological properties are strongly affected by this parameter. The evaluation of *in vitro* release kinetics of naproxen from carbopol-based gels was performed using an immersion cell device adapted to a dissolution equipment (USP 2) and a Franz diffusion cell, in dynamic conditions.

## Results and discussion

The results of the rheological experiments were illustrated through forward and backward rheograms, plotted as viscosity versus shear rate. These graphs indicate that the increase of shear rate led to a decrease of gels viscosity, pointing out that the semi-solid systems have a non-Newtonian pseudoplastic with a shear-thinning behaviour. This characteristic has an important role regarding the formulations flow and, consequently, their administration. The decrease of shear stress as a result of the viscosity decrease is due to the agitation produced in the system by shear. The Power law model was applied to evaluate the gels pseudoplastic behaviour.

The capacity of a semi-solid system to recover its rheological properties after a period of rest is called thixotropy. Thus, to evaluate the thixotropic behaviour of gels, the rheological profiles corresponding to forward and backward curves – shear stress as a function of shear rate – carried out at 33°C were recorded. All tested gels show thixotropic behaviour at 33°C because the backward curve is placed under the forward curve, which means that at the same shear rate, the shear stress for the backward curve is lower. For all tested gels, the value of the thixotropy index is higher than 5% at 33°C.

Consequently, analyzing the pseudoplastic and thixotropic behaviour of the four gels, the influence of formulation factors on rheological parameters is strongly noticed. For three gels, the viscosity and the thixotropy area have close values due to their identical qualitative composition compared to the other one that registered the maximal value of viscosity and thixotropic descriptors. These differences are due to the different content in cosolvents.

*In vitro* release profiles are intensely meaningful to investigate the diffusion rate of the active pharmaceutical ingredient throughout the polymeric gel network. The kinetic patterns plotted as cumulative amount of drug released per unit area versus time were presented. The release experimental data were fitted with the Higuchi mathematical model, and the diffusion coefficient was evaluated. Similar to the results recorded for the rheological characterization, the diffusion coefficients obtained with both kinetic apparatus for the three gels with identical composition have close values, being higher than those of the other gel, suggesting the various content of

cosolvents. The comparative analysis of diffusion profiles of naproxen illustrates higher values of diffusion coefficients for immersion cell adapted to USP 2 apparatus, this perspective being explained by the manner that the gel is placed into the immersion cell, compared to Franz cell, where the diffusion of gel through the membrane is slower.

## Conclusion

All tested gels exhibited a non-Newtonian pseudoplastic flow with shear thinning and thixotropic behaviour, these characteristics representing desired requirements for topical semi-solid systems because this property promotes their conditioning and spreadability on the skin surface, generating a continuous thin film at the application site. Regarding the kinetic analysis, a Fickian drug release mechanism was noticed, the diffusion coefficient being strongly influenced by the testing conditions. In conclusion, bringing together all the results, the *in vitro* kinetic patterns of naproxen and rheological parameters are firmly influenced by the qualitative composition of the commercially available gels.

**Acknowledgments:** This work was financially supported by the University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania, through Contract No. CNFIS-FDI-2023-F-0708.

## References

- Chang, R.-K., Raw, A., Lionberger, R., Yu, L., 2013. Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products. *AAPS J.* 15, 41-52. doi: 10.1208/s12248-012-9411-0.
- Herkenne, C., Naik, A., Kalia, Y. N., Hadgraft, J., Guy, R. H., 2007. Ibuprofen Transport into and through Skin from Topical Formulations: In Vitro–In Vivo Comparison. *J. Invest. Dermatol.* 127, 135-142. doi: 10.1038/sj.jid.5700491.
- Leppert, W., Malec-Milewska, M., Zajackowska, R., Wordliczek, J., 2018. Transdermal and Topical Drug Administration in the Treatment of Pain. *Molecules.* 23. doi: 10.3390/molecules23030681.
- Singh Malik, D., Mital, N., Kaur, G., 2016. Topical drug delivery systems: a patent review. *Expert Opin. Ther. Pat.* 26, 213-228. doi: 10.1517/13543776.2016.1131267.
- Wang, Y., Pang, X.L., Luo, J., Wen, Q., Wu, Z.X., Ding, Q.X., Zhao, L., Yang, L.L., Wang, B.Q., Fu, S. Z., 2019. Naproxen Nanoparticle-Loaded Thermosensitive Chitosan Hydrogel for Prevention of Postoperative Adhesions. *ACS Biomater. Sci. Eng.* 5, 1580-1588. doi: 10.1021/acsbiomaterials.8b01562.