

# Development and evaluation of stable hydrogel formulations with enhanced diclofenac sodium concentration for effective topical drug delivery

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## Introduction

The delivery of active pharmaceutical ingredients through the skin is challenging for pharmaceutical technology due to the barrier function of the skin and inadequate penetration properties. As the aging population increases, there is a growing need for effective, painless topical musculoskeletal therapy (De Luca et al., 2022). Aside from oral non-steroidal anti-inflammatory drugs (NSAIDs), there is a growing interest in developing dermally administered products. Various semi-solid preparations containing diclofenac sodium are available to alleviate the symptoms of these ailments. These products are popular among the general public due to their non-prescription availability and ease of use, but more research and development are necessary to improve their efficacy.

The aim of the research was to develop and evaluate a novel diclofenac sodium formulation with a higher drug content to improve drug release and permeation; thus, providing more reliable and effective therapy. The results of tests on our formulations were compared to *reference* products available on the market.

## Materials and methods

### Materials

Diclofenac sodium was supplied by Sigma-Aldrich (Budapest, Hungary). Isopropanol and Polyethylene glycol 300 were from Avantor (Radnor, Pennsylvania, USA). Methocel E4M (Hydroxypropyl methylcellulose - HPMC) was obtained from Colorcon (Budapest, Hungary). Polyethylene glycol 200 was purchased from Merck KGaA

(Darmstadt, Germany). Polyethylene glycol 400 was provided by Molar Chemicals Ltd. (Budapest, Hungary). Vertsatil PC was handed by Biesterfeld GmbH (Hamburg, Germany). Purified and deionized water was used (Milli-Q system, Millipore, Milford, MA, USA). The cellulose acetate filter (Porafil membrane filter, pore diameter: 0.45 µm) was acquired from Macherey-Nagel GmbH & Co. KG (Düren, Germany).

### Methods

#### *Solubility of diclofenac sodium*

Preformulation studies were conducted to enhance the solubility of diclofenac sodium. Various water-based binary and ternary mixtures were examined for their ability to dissolve the drug. The solvent mixtures were prepared with the aim of keeping the organic solvents below 30% to avoid potential skin-related issues with prolonged use. The solubility test utilized Ultra High Performance Liquid Chromatography (UHPLC) to measure the amount of soluble drug in different systems. Based on the obtained solubility results, the two solvents that demonstrated the highest increase in the solubility of diclofenac sodium were selected.

#### *Preparation of hydrogels*

The formulations (GEL 1a, GEL 5a, and GEL 7a) were prepared with three different concentrations (1, 5, and 7%) of the active ingredient. The viscosity of the formulations was maintained by the presence of HPMC, while the hydrogel was preserved by phenoxyethanol. The

concentrations of the excipients remained the same across all compositions.

*In vitro* drug release test (IVRT) with Franz Diffusion Cell System

A vertical Franz diffusion cell was used to model the drug release and diffusion through a synthetic membrane. The drug diffusion test lasted 6 hours, with sampling at 0.5, 1, 2, 3, 4, 5, and 6 hours, and the quantity of diclofenac sodium released was detected using UHPLC. Commercially available preparations containing 1 and 5% of diclofenac sodium (REF1 and REF5), were employed as reference formulations.

### *Investigation of drug permeation with Raman Spectroscopy*

Diclofenac sodium-containing hydrogels were applied to human abdominal skin sections, which were then placed on filter papers soaked in saline solution. After a 3-hour exposure, the residue was removed, and the treated skin was frozen, sectioned, and analyzed using a Raman spectrometer. Raman mapping was conducted with a 780 nm laser, capturing images of a 200 x 500  $\mu\text{m}$  skin area with a step size of 50  $\mu\text{m}$ . Data acquisition and analysis were performed using the OMNIC™ 8.2 software.

## Results and discussion

### *Solubility of diclofenac sodium*

A study was conducted to investigate binary mixtures of six organic solvents with water, based on existing literature and initial observations. Based on the results, two solvents, Isopropanol and Macrogol 200 were selected for their significant increase in solubility of the active substance. By systematically varying the amounts of these solvents, the solubility of diclofenac sodium was examined in three-component ternary mixtures. Using a contour plot, a solvent composition was determined to potentially offer higher drug content in the formulation compared to the 1% and 5% reference formulations available on the market. The stability of the formulation formulated with ternary systems was observed when the quantity of Isopropanol exceeded that of Macrogol 200.

### *In vitro drug release test (IVRT)*

The 1% formulation exhibited slightly higher drug release compared to the commercially available 1% diclofenac sodium formulation. In the case of the 7% concentration, as there is no commercially available formulation, a comparison was made with the 5% diclofenac formulation, revealing significantly higher drug release for both the 5% and 7% formulations compared to the reference formulations. Figure 1 illustrates the *in vitro*

drug release over a 6-hour period. On this basis, it can be concluded that the formulated preparation showed better diffusion properties than the marketed products.

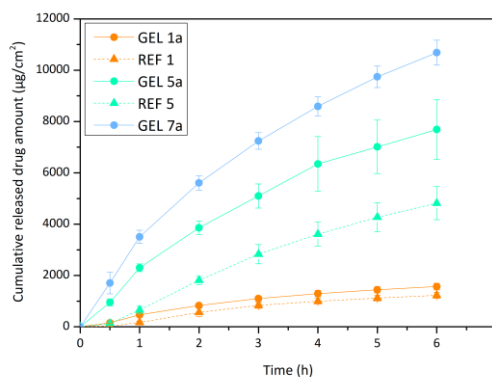


Fig. 1. Comparative figure of the results of drug release tests of formulated and reference products.

### *Investigation of drug permeation with Raman Spectroscopy*

The results indicated that compared to REF 5, which had a higher concentration of the API in the upper layer of the epidermis, the GEL 5a and GEL 7a formulations successfully delivered the API to deeper skin layers. The highest concentration of the API, similar to REF 5, was found in the upper layers of the epidermis.

## Conclusion

As a result, a stable hydrogel with an increased diclofenac sodium content of 7% was formulated, which also provided an increased drug release compared to marketed references. In conclusion, in order to achieve better skin permeation, it is crucial to choose the appropriate excipients.

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## References

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