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Application of Innovative Strategy in the Characterization of Ketoprofen Gels Authorized in the Republic of Serbia

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SUMMARY

Introduction: Topical ketoprofen formulations provide localized analgesic and anti-inflammatory effects while reducing systemic adverse events associated with oral administration. Franz diffusion cells, are widely used to evaluate the permeation and dissolution rate of active pharmaceutical ingredient in topical formulations.

Aim: The aim of this study was to perform macroscopic and microscopic analysis of ketoprofen gel formulations available in the Republic of Serbia, to examine the *in vitro* release rate using 3D printed Franz cells, as well as to analyze the influence of the type of receptor medium on the release rate of ketoprofen.

Material and Method: Two ketoprofen gel formulations were examined. Macroscopic and microscopic analysis were performed under normal and polarized light. Ketoprofen content was determined by UV/VIS spectrophotometry. *In vitro* release studies were carried out using 3D-printed Franz diffusion cells with synthetic membranes as diffusion barriers. Phosphate buffer pH 7.4 and 70% (v/v) ethanol were used as receptor media.

Results: Both ketoprofen gels were transparent, and exhibited similar gloss. Formulation A demonstrated lower structural integrity and stickiness than Formulation B. The ketoprofen in both formulations was within ± 5% of the declared value. *In vitro* release test showed that Formulation A exhibited a faster release of ketoprofen compared to Formulation B in both phosphate buffer and ethanol. Formulation B had lower spreadability comparing to Formulation A.

Conclusion: These results highlight the potential of 3D printed Franz diffusion cells in future for *in vitro* evaluation of authorized topical formulations in the Republic of Serbia, where different receptor media can be used, which further allows better comparison of formulations under different experimental conditions.

Keywords: Ketoprofen, Topical Gel, *In vitro* Dissolution, Franz Cells, 3D Printing

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INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. Its mechanism of action is the inhibition of the enzyme cyclooxygenase (COX), whereby it inhibits the isoenzymes COX 1, which is responsible for the synthesis of prostaglandins with physiological functions, and COX 2, whose role is the synthesis of pro-inflammatory prostaglandins at the site of inflammation [1]. With the advancement of personalized medicine, it becomes necessary to develop different pharmaceutical forms of the same active substance, allowing flexibility in the route of administration and dosing [2]. Topical NSAID formulations were developed as an alternative to oral formulations with the aim of achieving analgesic efficacy comparable to that of oral NSAID formulations, while minimizing the risk of adverse events associated with systemic exposure [3]. The frequent or prolonged use of oral NSAIDs in chronic conditions raises safety concerns, especially in more vulnerable populations, such as the elderly and patients with predisposing comorbidities (high cardiovascular risk, type 2 diabetes mellitus, and renal insufficiency) [4].

Franz diffusion cells are a widely used for the *in vitro* evaluation of topical drug permeation, with advantages such as minimal tissue handling, no need for continuous sampling, and a small amount of drug required for analysis [2]. According to the United States Pharmacopeia (USP) chapter on topical and transdermal drug products, the Franz diffusion cell consists of two compartments: the donor and the receptor, separated by a membrane which can be synthetic (artificial) or skin (animal or human) [5, 6]. By default, Franz diffusion cells are made of glass, with different dimensions and shapes, and depending on the needs of the experimental process, they can be modified [7]. However, their glass construction makes them fragile and prone to damage, necessitating careful handling [7,8]. Consequently, alternative diffusion cells made of different materials that do not adsorb or interact with the tested samples are increasingly being used [8].

Additive manufacturing (AM) or 3D printing, can be very useful in producing a wide range of laboratory equipment [8]. AM allows the fabrication of components from various materials, enabling cost-effective production. Among the different 3D printing techniques, fused deposition modeling (FDM) is widely used due to its simplicity, accessibility, and ability to produce precise objects [9]. In this research, 3D-printed Franz diffusion cells were employed.

AIM

The aims of this study were to perform detailed characterization of authorized ketoprofen gel formulations, commercially available in the Republic of Serbia, and to investigate their *in vitro* release profiles using aforementioned 3D-printed Franz cells across different receptor media.

MATERIAL AND METHODS

This study was conducted as part of an academic experimental research project.

Ketoprofen was obtained from Farmalabor (Italy). Topical ketoprofen gel formulations (Fastum Gel, A.Menarini Manufacturing Logistics and Services s.r.l., Italy; Ketonal Gel Salutsa Pharma GmbH, Germany) registered on the market of the Republic of Serbia were purchased at a local pharmacy.

A phosphate buffer solution with a pH value of 7.4 (50 mM) was prepared according to the requirements of the United States Pharmacopoeia (USP) using sodium hydroxide (Centrohem, Serbia), potassium dihydrogen phosphate (Centrohem, Serbia), and purified water [10].

A 70% (v/v) solution ethanol was prepared according to the guidelines of the Magistral Formulas 2008 [11], from 96% (v/v) ethanol (Zorka, Serbia) and purified water. The purified water used for the purposes of the experiment was obtained by distillation (AC – L8, Optic Ivymen System, J.P. Selecta, Spain) at the Department of Pharmacy, Faculty of Medicine in Novi Sad.

Macroscopic appearance assessment

Assessment of the appearance, which includes color, gloss, integrity and stickiness of the pharmaceutical preparation, is one of the quality control tests according to the guidelines of 11th European Pharmacopoeia (Eur. Ph 11), monographs Pharmaceutical formulations (lat. *Pharmaceutica*) [12]. Gloss is defined as

the extent of light reflection from the surface of the product. Structural integrity is defined as the degree to which the preparation retains its shape at rest, and stickiness as the difficulty of separating the index finger from the thumb when the preparation is placed between them. Each parameter was scored on a scale from 1 to 10, where a score of 1 indicates the lowest expression of the observed characteristic and a score of 10 indicates the highest degree of expression [13].

Microscopic analysis of samples

Microscopic analysis was performed in compliance with the guidelines of Eur. Ph. 11, monograph on Optical Spectroscopy [12]. A ZEISS STEMI 508 stereo microscope equipped with an AXIOMCAM ERc 5s camera (ZEISS, Germany) was used for microscopic analysis of the samples. All samples were observed under bright-field and polarized light under 10 times magnification. In order to identify ketoprofen crystals in topical formulations, pure ketoprofen was used as control. A sample of pure ketoprofen was prepared for microscopic analysis by dispersing a small amount of ketoprofen in water, transferring it onto a glass slide, and covering it with a cover glass. Samples of topical formulations for microscopic analysis were individually applied in a thin layer onto clean glass slides, and carefully covered with a cover glass.

Determination of ketoprofen content

The content of ketoprofen in topical formulations was determined in 96% (v/v) ethanol, using the validated UV/VIS spectrophotometric method at a wavelength of 255 nm [12]. The test was performed in triplicate. Samples of topical formulations (10 mg) were measured in a 10ml standard vessels. Each standard vessel was filled to the appropriate volume with ethanol. Then, the samples were placed in an ultrasonic bath for a period of 15 minutes to ensure complete dissolution of ketoprofen. Absorbance was measured on a spectrophotometer (Agilent 8453, USA). The calibration curve made from a solution of ketoprofen with a concentration of 100 µg/ml was linear in the range from 5.2 µg/ml to 52 µg/ml (R^2=0.9972). Results are presented in % (w/w) as mean ± standard deviation.

In vitro dissolution rate of ketoprofen using 3D printed Franz diffusion cells

In vitro release test (*IVRT*) was performed in line with the recommendations of the European Medicines Agency (EMA) [14], the United States Pharmacopeia (USP) [5] and the Food and Drug Administration (FDA) [15]. FDM 3D-printed Franz diffusion cells made of polylactic acid (PLA) were used for testing purposes [16]. The receptor chamber had an outer diameter of 17 mm, a height of 68 mm, and a volume 12 of mL with an effective diffusion surface of 1.5386 cm^2. Membrane filters (pore size of 0.45 µm), made of mixed cellulose esters (Porafil, Macherey-Nagel, Germany), were used as synthetic membranes. Prior to testing, the synthetic membranes were conditioned for 2 hours in the appropriate receptor medium, which consisted of either phosphate buffer (pH=7.4, 50mM) or 70% (v/v) ethanol. The test was performed in six replicates using a sample mass of 200 mg. Franz cells were kept in a thermostatic water bath (Witeg, Germany), and the stirring speed during the test was constant (50 revolutions per minute). The receptor medium temperature was maintained at 32 ± 1 °C, and the test lasted 6 hours. Aliquots of 300 µl were withdrawn at predetermined time points after 0.5, 0.75, 1, 2, 3, 4, 5 and 6 h. In order to protect against evaporation and light, the samples were covered with elastic laboratory film and aluminum foil before the test.

Ketoprofen quantification in IVRT samples was performed using a UV–Vis spectrophotometric method. The measurement was performed on a spectrophotometer (Agilent 8453, USA) at the appropriate wavelength depending on the receptor medium (261nm for buffer pH 7.4 (50mM); and 255nm for 70% (v/v) ethanol). Calibration curves were made from a ketoprofen solution with a concentration of 100 µg/ml for both media. The calibration curve for phosphate buffer was linear over the concentration range of 0.75–40 µg/mL (R^2 = 0.9999), while for ethanol, linearity was observed over the range of 0.78125–25 µg/mL (R^2 = 0.9998).

Compatibility of ketoprofen with 3D printed Franz diffusion cell

To confirm that ketoprofen has no adsorbing or retention affinity to the PLA 3D printed Franz diffusion cell, a compatibility test was

performed. A ketoprofen solution of known concentration was prepared in phosphate buffer pH 7.4. This solution is exposed to the same conditions as in *IVRT*, where the change in the concentration of ketoprofen is monitored over time in the receptor chamber of the Franz cell. The chamber was protected from evaporation and light with laboratory film and aluminum foil. As a control, in closed glass tubes protected from light, the concentration of ketoprofen was measured and monitored.

Spreadability

The spreadability of the topical formulations at room temperature was assessed. Two glass plates were used in order to construct the extensometer [17]. The lower glass plate is used to apply the measured sample, while weights of precisely determined mass are placed on the upper plate. Weights of 50, 100, 200, 300 and 500 g were used for the purpose of the test. The mass of each individual sample was 0.5 g. The diameter of the preparation was measured after one minute, and each measurement was performed in triplicate. The area occupied by the formulation after exposure to the applied weights was calculated according to Equation 1:

$$P=(D/2)^2 \pi \qquad (1)$$

where: P – the surface of the formulation after spreading (cm^2); D – diameter of the formulation after spreading (cm).

RESULTS

By macroscopic assessment of appearance, both tested gels were identified as completely transparent, while the gloss, integrity and stickiness ratings are shown in Figure 1. Both formulations have the same gloss, while Formulation A has lower shape integrity and stickiness than Formulation B.

Formulation	Content (% of declared value) ± SD
Formulation A	102,12 ± 2,72
Formulation B	102,36 ± 2,46

Table 1. Determination of ketoprofen content in authorized gel formulations

SD - standard deviation

Figure 2 represents microscopic analysis of ketoprofen powder and ketoprofen gel formulations under bright-field and polarized light. Figures 2A and 2B represent the microscopic analysis of pure ketoprofen powder. Under the microscope, rectangular to needle-shaped crystals of different sizes are observed. By passing polarized light through the preparation (Figure 2B), different refraction of light is observed in the form of blue and orange colors. Microscopic analysis of both authorized gels confirmed the presence of ketoprofen crystals. Figures 2C and 2D depict ketoprofen crystals in Formulation A, where the crystals are rectangular and various sizes. In contrast, Figures 2E and 2F illustrate ketoprofen crystals in the registered Formulation B, where smaller, needle-like crystalline structures are evident under microscopic examination. Additionally, observation of crystals from both gels under polarized light showed refraction in blue and orange tones.

The test for determining the content of ketoprofen in gel formulations using the UV/VIS method is presented in Table 1. The results indicate that ketoprofen in both formulations was within the range of ± 5% of the declared value, while a slightly higher value of variation was observed in Formulation A.

The results of the *in vitro* dissolution test of ketoprofen through a synthetic membrane are shown in Figure 3 and Figure 4, in phosphate buffer pH 7.4 and 70% (v/v)

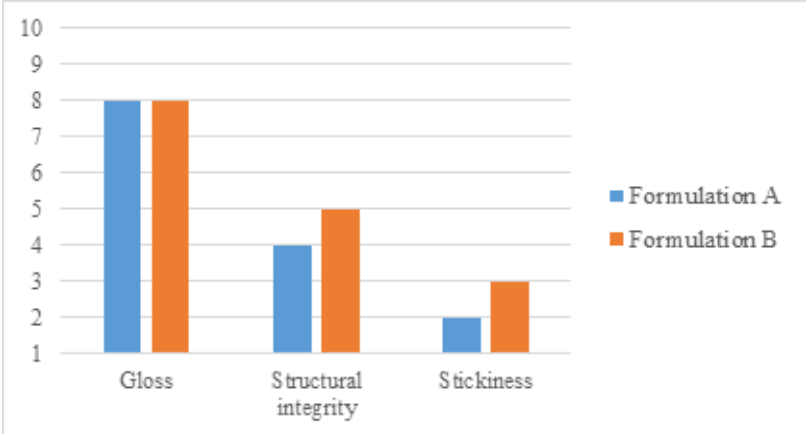

Figure 1. Gel visual appearance: comparative scores

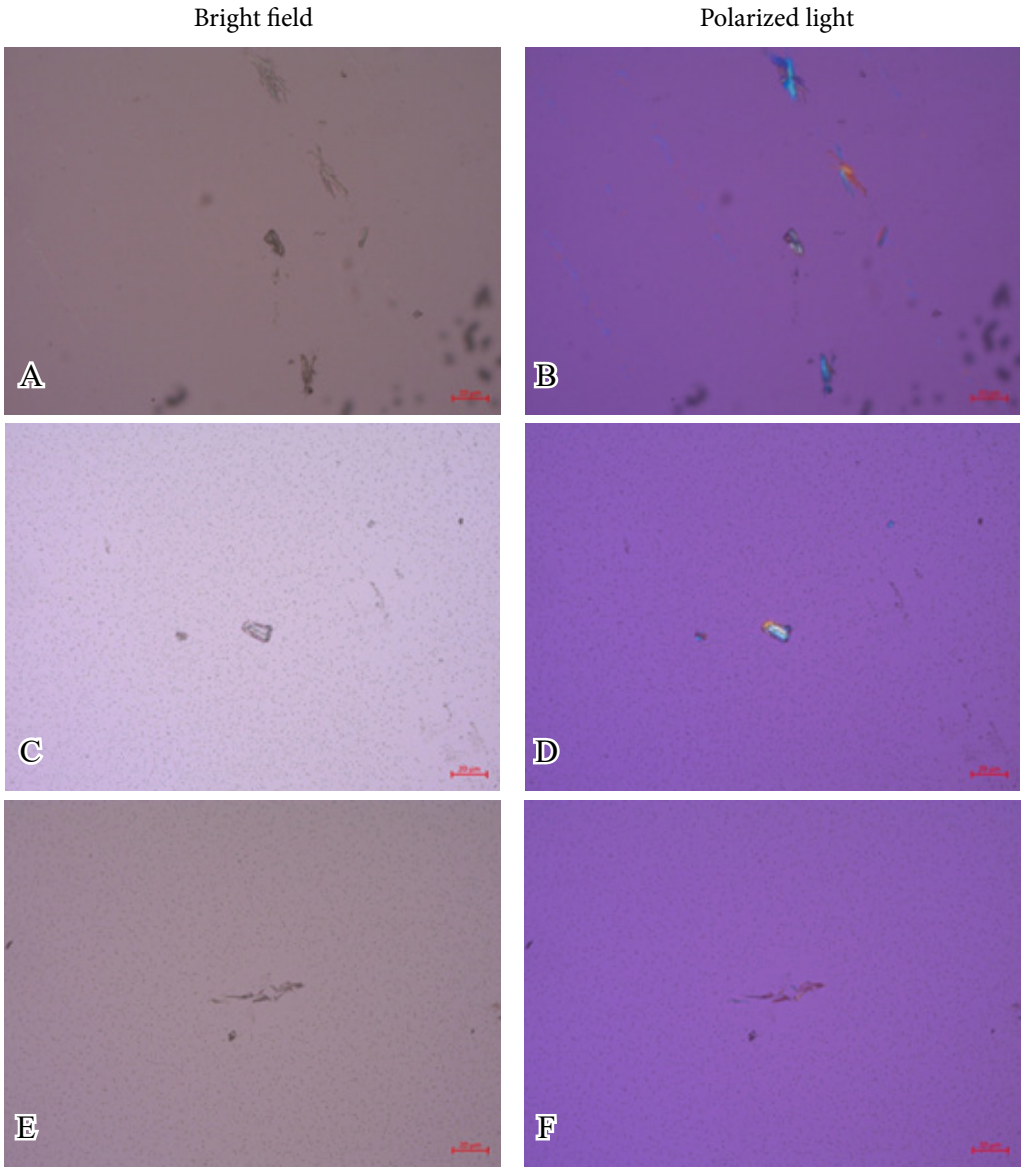

Figure 2. Microscopic analysis of ketoprofen samples. (A, B) Pure ketoprofen powder; (C, D) Formulation A; (E, F) Formulation B. Images were obtained under bright field (A, C, E) and polarized light (B, D, F) (Magnification 10×; the scale bar represents a range of 20 µm).

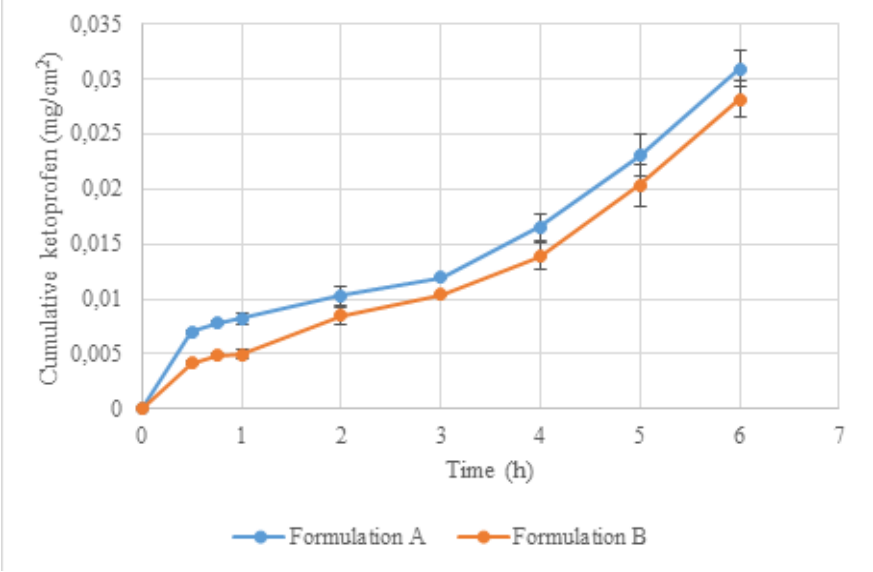

Figure 3. *In vitro* release rate of ketoprofen in the phosphate buffer

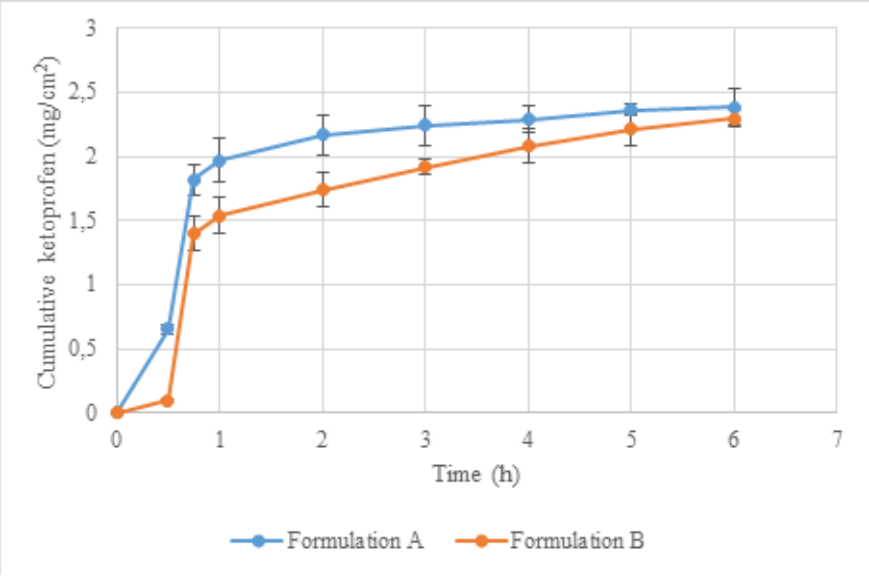

Figure 4. *In vitro* release rate of ketoprofen in ethanol

ethanol, respectively. By observing the *in vitro* dissolution rate of ketoprofen in buffer through a synthetic membrane, a faster release of the active substance from the Formulation A preparation is observed (Figure 3). At the initial points of the test, the release of ketoprofen from both formulations starts gradually. After the first hour, the release rate increases sharply, but still reaches low values. At the end point of the measurement (6 h), Formulation gel reaches a higher concentration of released ketoprofen compared to Formulation B.

When ethanol is used as the receptor medium, Formulation B formulation released ketoprofen more slowly than the Formulation A (Figure 4). Both formulations exhibited a rapid initial release within the first 30 minutes, continuing up to the 1h measurement point. After a period of one hour, both gels show a slower and more gradual release compared to the beginning of the test. At the end of the test, the amount of cumulative ketoprofen reaches very similar values for both formulations, although Formulation A demonstrated an overall faster release of the active pharmaceutical ingredient.

The compatibility study confirmed that ketoprofen does not adsorb to or interact with the 3D-printed Franz diffusion cells. The concentration of ketoprofen remained stable over time in both the 3D-printed cells and the glass tube controls.

Spreadability testing indicated that, for both ketoprofen formulations, increasing the applied weight resulted in greater spreading of the gels (Figure 5). Notably, differences were observed between the two formulations, with Formulation A exhibiting higher spread-

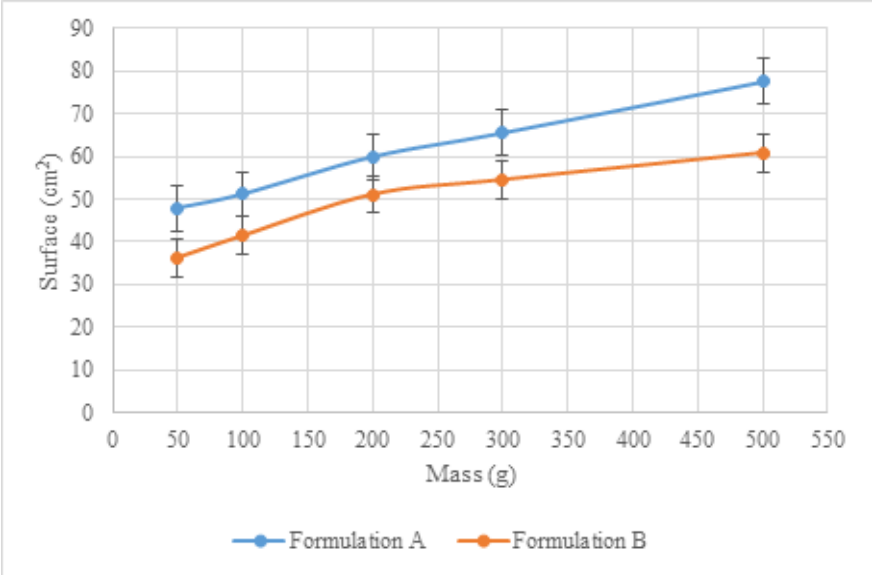

Figure 5. Spreadability of registered topical formulations of ketoprofen

ability than Formulation B under all applied weights.

DISCUSSIONS

Analysis of samples of both authorized gel formulations under a microscope confirmed the presence of ketoprofen crystals. Under bright-field and polarized light, rectangular to needle-shaped crystals of various dimensions can be observed. The appearance of crystals of different colors due to the passage of polarized light through the observed samples of ketoprofen (birefringence) is a consequence of the pronounced anisotropy of ketoprofen crystals, which originates from its triclinic crystal structure [18,19]. The presence of crystals indicates that ketoprofen in the tested gels is present in a suspended form rather than being dissolved in the gel base.

Several previous studies have investigated the applicability of 3D-printed Franz diffusion cells, reporting results comparable to traditional glass systems, while also highlighting certain material-related limitations. For example, Sil et al. 3D-printed cells were produced using a transparent resin (GPCL04), and although the devices were robust and leak-proof, interactions between the resin and active substances sometimes led to reduced drug recovery [20]. Subsequent studies of the same group demonstrated that when tested with hydrophilic molecules such as caffeine, these SLA-printed cells exhibited comparable permeation and preserved structural stability, confirming their practical utility in experimental studies [7]. Additionally, surface modifications using inert coatings have been shown to minimize interactions with drug molecules, improving reliability in permeation testing [21]. In contrast, our study employed PLA-based Franz cells fabricated via FDM 3D-printing, which represent an alternative material and printing approach that helps mitigate issues such as drug adsorption to the printed surfaces. Our recent study employing FDM 3D-printed Franz cells for in vitro evaluation of topical simvastatin confirmed both the reproducibility and versatility of this approach [16]. Consistently, this research on ketoprofen gel formulations, using FDM-fabricated Franz diffusion cells for testing *in vitro* dissolution rate in two different media, provided a more comprehensive understanding of the formulation's dissolution behavior.

The dissolution rate of ketoprofen varied depending on the type of receptor medium used. Ketoprofen, according to the Biopharmaceutics Classification System (BCS), belongs to class II, which is characterized by low solubility and high permeability. This feature may explain the differences in ketoprofen release kinetics observed in different receptor media during this study [22]. In phosphate buffer pH 7.4, the release of ketoprofen from both formulations occurs gradually at first, then after 1h it increases rapidly, but still reaches low values. In contrast, in ethanol, a faster increase in ketoprofen concentration was observed in the initial phase of the experiment, after which the release became slower and more gradual during the rest of the experiment. The choice of the receptor medium is an important factor in the design of *in vitro* release studies, because the receptor phase directly collects the drug that diffuses through the membrane and must ensure sufficient solubility of the test substance [23]. Therefore, different receptor media can lead to different conclusions about drug release. Phosphate buffer is one of the most commonly used receptor media in *in vitro* release rate studies, as it provides stable pH conditions and simulates the physiological environment [23]. Ketoprofen is a weak acid, the solubility of which increases with the increase in the pH value of the medium due to the ionization of the molecule. In phosphate buffer pH 7.4, which is significantly higher than the pKa of ketoprofen (~4.5), the active substance is ionized to a greater extent, which increases its solubility in the aqueous phase [22]. However, by examining the dissolution rate in phosphate buffer, during this experiment, low concentrations of ketoprofen were obtained. This could be explained by the fact that ketoprofen is trapped in the matrix of the gel system, which protects it from pH-dependent ionization and subsequent faster dissolution [2]. In contrast, ethanol, an organic solvent, facilitated higher ketoprofen solubility due to the drug's lipophilic nature, resulting in higher concentrations in the receptor medium [24].

Considering that Formulation A has less shape integrity, greater spreadability and shows a faster release of ketoprofen, one of the possible explanations could be the difference in the concentration of carbomer in the formulation. An increase in the concentration of carbomer in hydrogels leads to an increase in viscosity and the formation of a denser poly-

mer network, which can further slow down the diffusion of the active substance through the gel. It has been shown in the literature that a higher concentration of carbomer leads to a reduced percentage of drug release, which is explained by the formation of a more compact gel-structure that hinders the diffusion of molecules through the polymer network [25]. This mechanism could potentially explain the observed differences in shape integrity, gel spreadability, and release rate, although the exact concentration of carbomer in the tested formulations is not known. In addition to the concentration of carbomer, the structure and viscosity of the gel can also be affected by the degree of neutralization of the polymer. Carbomers are acidic polymers and must be neutralized with a base (e.g. trometanol, triethanolamine) to form a gel. Neutralizing agents lead to the ionization of the carboxyl groups of the carbomer and the expansion of the polymer network, thereby increasing the viscosity of the gel, which can indirectly affect the diffusion and release of the active substance from the formulation, as described in the literature [26]. In this context, greater spreadability and faster release of ketoprofen in Formulation A may indicate a less dense gel-structure, which enables easier diffusion of the active substance, although due to the lack of data on the exact composition of the formulations, this mechanism cannot be confirmed with certainty.

Limitations of this study include the use of commercial formulations with undisclosed excipient concentrations, which precludes definitive attribution of observed differences to specific components. Additionally, the study was conducted using a synthetic membrane, which does not fully replicate the physicochemical and biological properties of human skin. Therefore, for a more comprehensive and physiologically relevant evaluation, future studies should consider performing experiments on natural skin models, such as excised human or animal skin, to obtain results that more accurately reflect *in vivo* conditions.

CONCLUSION

This study provided a detailed characterization of ketoprofen gels authorized in the Republic of Serbia. The present study demonstrated that both Formulation A and Formulation B exhibit similar visual characteristics, while microscopic analysis confirmed the suspended form of ketoprofen in both formulations. *In vitro* release testing using FDM 3D-printed Franz cells revealed differences in release profiles, with Formulation A showing faster dissolution, particularly in ethanol as a receptor medium. These findings highlight the potential of applying 3D printed Franz cells in future for *in vitro* assesment of authorized topical formulations in the Republic of Serbia, where different receptor media can be used, which further allows better comparison of formulations under different experimental conditions.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Primena inovativnih strategija za karakterizaciju ketoprofen gelova dostupnih u Republici Srbiji

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KRATAK SADRŽAJ

Uvod: Formulacije za lokalnu primenu ketoprofena omogućavaju analgetski i antiinflamatorni efekat na lokalnom nivou, istovremeno smanjujući sistemske neželjene efekte povezane sa oralnom primenom. Francove difuzione ćelije široko su korišćene za procenu permeacije i brzine rastvaranja aktivnog farmaceutskog sastojka iz preparata za lokalnu primenu.
Cilj: Cilj ovog rada bio je da se izvrši makroskopska i mikroskopska analiza gel preparata ketoprofena dostunih u Republici Srbiji, da se ispita *in vitro* brzina oslobađanja primenom 3D štampanih Francovih ćelija, kao i da se analizira uticaj tipa receptorskog medijuma na brzinu oslobađanja ketoprofena.
Materijal i metode: Ispitana su dva preparata ketoprofen gela (Formulacija A i Formulacija B). Makroskopska i mikroskopska analiza su sprovedene pod običnom i polarizovanom svetlošću. Sadržaj ketoprofena je određen UV/VIS spektrofotometrijom. *In vitro* studije rastvaranja su sprovedene korišćenjem 3D štampanih Francovih difuzionih ćelija sa sintetičkim membranama kao difuzionim barijerama. Fosfatni pufer pH 7,4 i 70% (v/v) etanol su korišćeni kao receptorski medijum.
Rezultati: Oba ketoprofen gela su bila transparentna, istog sjaja. Formulacija A je imala manji integritet oblika i lepljivost od Formulacije B. Ketoprofen u obe formulacije je bio u opsegu od ± 5% deklarisane vrednosti. *In vitro* test rastvaranja je pokazao da Formulacija A ima brže oslobađanje ketoprofena u poređenju sa Formulacijom B i u fosfatnom puferu i u etanolu. Formulacija B gel je imala manju razmazivost u poređenju sa Formulacijom A.
Zaključak: Ovi rezultati ističu potencijal trodimenzionalnih štampanih Francovih difuzionih ćelija u budućnosti za *in vitro* evaluaciju odobrenih topikalnih formulacija u Republici Srbiji, gde se mogu koristiti različiti receptorski medijumi, što dodatno omogućava bolje poređenje formulacija pod različitim eksperimentalnim uslovima.

Ključne reči: ketoprofen, topikalni gel, *in vitro* oslobađanje, Francove ćelije, 3D štampa

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