# Transdermal route of administration of diclofenac sodium

Agata Szeląg[1], Karolina Mołdoch[1], Beata Sarecka-Hujar[2]

[1] The fifth year Students of Pharmacy at the Faculty of Pharmaceutical Sciences, Medical University of Silesia in Katowice, Poland

[2] Department of Basic Biomedical Science, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia in Katowice, Poland

***European Journal of Medical Technologies***
*2020; 3(28): 19-26*

www. medical-technologies.eu
Published online 1.09.2020

**Corresponding address:**
Beata Sarecka-Hujar, PhD
Department of Basic Biomedical Science, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia in Katowice, Kasztanowa Str 3, 41-200 Sosnowiec, Poland
E-mail: bsarecka-hujar@sum.edu.pl; Phone +48 32 269 98 30

## Abstract

Drug formulations for topical administration have plenty of advantages, such as avoidance of drug-drug interactions, reduction of adverse effects as well as improvement of patient's compliance. Semisolid drug forms as preferable formulations for topical use of diclofenac sodium include among others gels, creams, paste and ointments or patches. Since non-steroidal anti-inflammatory drugs (NSAIDs) are most widely prescribed group of drugs worldwide, their transdermal use if of great importance due to decreased number of common gastrointestinal, renal and cardiovascular side effects. Development of topical forms containing diclofenac sodium enables to improve safety profile with simultaneous reduction of amount of administered drug and local treatment of pain. The aim of the present study was to review the available literature data regarding the transdermal transport of diclofenac sodium, a representative of non-steroidal anti-inflammatory drugs (NSAIDs).

## Key words:

diclofenac sodium, non-steroidal anti-inflammatory drugs, NSAIDs, semisolid forms, topical application, transdermal route of administration

## Introduction

Increased deposition of the active pharmaceutical ingredient (API) in the skin is essential in the case of pharmaceutical preparations which should exert a local effect. However, except for both the properties of the API and the skin barrier, also the composition of the semisolid formulation affects delivery of active substances through the skin.

Particularly semisolid base, which is the vehiculum of the active substance in topical preparations, has a significant influence on transdermal penetration of API [1, 2]. First of all, the components of the base interact with the skin, influencing its properties. Second of all vehiculum ingredients can also interact with the active substance, determining its diffusion rate both within the preparation and from the preparation onto the skin surface. Thus, the ointment

base determines the rate of penetration of the active substance into the *stratum corneum*. The selection of the physicochemical nature of the base (e.g. hydrophobic, hydrophilic or emulsion), which ensure increased skin retention, requires taking into account not only the physicochemical properties of the API but also the type of preparation to be obtained – ointment or water-removable ointment, cream or hydrogel. The nature of the base determines the value of the base/skin partition coefficient and the value of the API diffusion coefficient in the skin [3]. Depending on the ointment base nature, the same active substance used in the same concentration may show different pharmacological efficacy [4, 5]. The composition of the preparations for topical administration is reflected in their rheological properties, which are important determinants of the therapeutic effect of such a drug form.

The aim of the present study was to review the available literature data on the transdermal transport of diclofenac sodium, which is one of the most widely used representatives of non-steroidal anti-inflammatory drugs (NSAIDs).

## Semisolid formulations for topical usage

The skin is a tissue which protects the human body against adverse external factors. However, being external barrier is not the only role of the skin. Due to the huge surface area and in turn easy access to it, skin is often used in the treatment of many diseases, allowing active substances to penetrate into the body. Currently, the percutaneous route is used mainly to treat local ailments, but also to treat inflammations of deeper tissues and to cause a general effect on the body. The beneficial effect of such a treatment is avoidance of the first-pass effect, reduce the risk of gastrointestinal side effects, avoid drug interactions, and eliminate potential degradation of API in the gastrointestinal tract. However, the rate of absorption of a substance through the skin is related to the rate at which the substance is released from the base, which may consequently cause a delayed effect [6].

The semisolid drug forms are applied to the skin surface or mucous membranes for both to generate a local effect of the API and to protect or moisturize the skin. In some cases, e.g. nitroglycerin ointment, the systemic effect is caused.

Among the semisolid drug forms described in the monograph of the Polish Pharmacopoeia XI [7], the following types were distinguished: ointments, creams, gels, pastes, compresses and transdermal patches. Percutaneous absorption of APIs from semisolid preparations can be defined as the penetration of substances into deeper layers of the skin and subsequently, their penetration into the general circulation. The percutaneous absorption of the molecules is a complex process involving several stages, which are presented in Figure 1.

There are several routes of penetrating the active substances into the skin; the transcellular (i.e. transdermal route), intercellular (i.e transepidermal route) and through skin appendages (i.e. transfollicular route) [8].

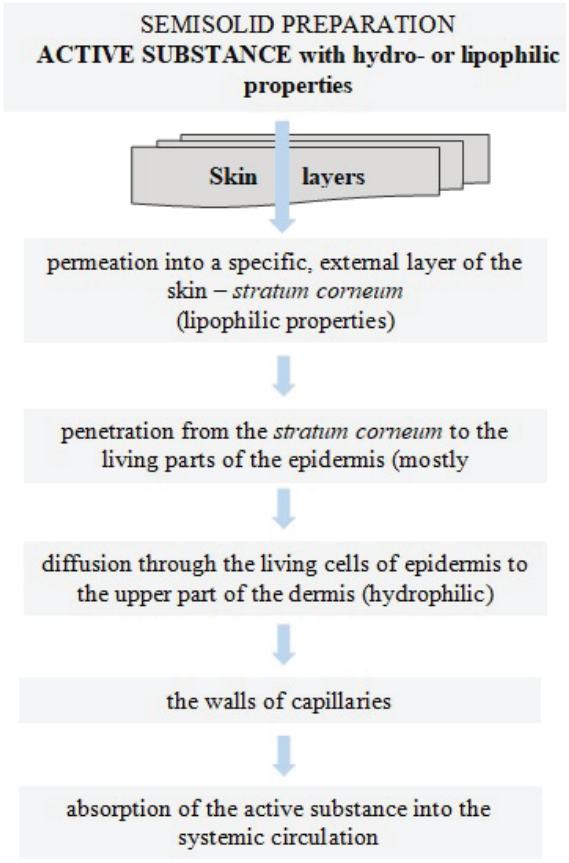


**Fig. 1.**
Scheme of the subsequent stages of percutaneous absorption of active substances

Many factors affect the rate of penetration of the API through the skin, including the condition of the skin, physicochemical properties of active substances as well as the use of absorption promoters [8, 9].

## Diclofenac sodium – a representative of non-steroidal anti-inflammatory drugs

Diclofenac sodium as a non-steroidal anti-inflammatory drug (NSAID) shows an analgesic, antipyretic and anti-inflammatory effect. NSAID are suggested to be the most frequently used drugs in the world [10-12]. NSAIDs are effective in reducing pain and inflammation. It is estimated that millions of people worldwide (even 100 millions) use NSAIDs every day [13]. A population study conducted on a large cohort – almost 700,000 primary care patients – demonstrated that 41% of them uses or used in the past drugs belonging to NSAID group [13].

Unfortunately, orally administered NSAIDs, whether taken for a long time or in high doses, may lead to gastrointestinal and renal side effects, or result in hepatotoxicity. The results of several meta-analyses, pooling data from many studies showed that the use of diclofenac sodium (especially when used in high doses) increased the risk of vascular events (myocardial infarction, ischemic stroke) and mortality, resulting from these disorders [10, 14].

The mechanism of action of NSAIDs is based on the inhibition of cyclooxygenase (COX). NSAIDs are competitive inhibitors of this enzyme, blocking it as a result of irreversible acetylation of the serine hydroxyl group, which is located at the N-terminal end of the COX molecule [11].

During cell damage, arachidonic acid is released from phospholipase A2 from phospholipids of cell membrane, which undergoes another series of enzymatic reactions in which the cyclooxygenase as well as lipoxygenase pathways can be distinguished. Inhibition of the COX pathway by the action of NSAID molecules blocks the synthesis of prostanoids, including prostaglandins, prostacyclins and thromboxanes. Blocking of prostaglandin synthesis by NSAIDs is responsible for most of their pharmacological effects, such as anti-inflammatory, analgesic, antipyretic, and inhibition of platelet aggregation. However, side effects, e.g. kidney failure and mucosal damage leading to gastric ulcer are also related to this action [11, 15, 16].

Diclofenac sodium blocks both isoforms of cyclooxygenase, i.e. the COX-1 and COX-2, but it has been shown that diclofenac had a higher affinity for COX-2 compared to traditional NSAIDs [16, 17]. After oral administration, absorption of diclofenac sodium is usually rapid and in direct proportion to the dose. About 60% of the drug reaches the systemic circulation through first pass metabolism. It is believed that the amount of diclofenac absorption may differ individually depending on the different pH of the gastrointestinal tract [16, 18]. The diclofenac sodium from oral solution reaches its maximum concentration in plasma after 10-14 minutes, whereas the enteral form of the drug after 1.5-2 hours. Taking the drug together with food does not significantly affect the area under the curve (AUC), although it delays the maximum concentration to 2.5-12 hours. Diclofenac, after getting into the synovial fluid, reaches its maximum concentration within 2-4 hours after the application [19].

4'-Hydroxy diclofenac, which is a metabolite of diclofenac, has weak analgesic and anti-inflammatory properties. Almost 65% of the diclofenac and its metabolites are excreted in urine while 35% in the bile. Due to the short biological half-life of about 2 hours, frequent dosing is usually required to reach therapeutic concentrations, which may exacerbate the side effects. [16, 18].

Diclofenac can be formulated as both the sodium or potassium salt. It has been shown that in the case of the sodium salt, diclofenac is more soluble in water and, consequently, more absorbed in the body. Such properties are crucial for achieving a rapid analgesic effect.

## Transdermal administration of diclofenac sodium

The results of the meta-analysis demonstrated that diclofenac not only causes gastroenterological

complications, such as gastric ulcers, but also increases the frequency of cardiovascular events by over 40% compared to the placebo group [11]. Considering that, alternative routes of NSAID administration are the subject of many studies. Topical administration of these molecules allows to reduce the incidence of side effects from the gastrointestinal tract, kidneys and cardiovascular system, and enables local treatment of pain and inflammation with reduced systemic absorption [9, 16]. Improved patient tolerance of the semisolid formulation most often contributes to more accurate adherence to medical recommendations and, consequently, to more effective pharmacotherapy.

In the study by Miyatake et al. [20] the concentrations of diclofenac sodium in the blood plasma after oral administration of the recommended doses were compared to the concentrations obtained after transdermal administration. The authors showed that transdermal route of diclofenac sodium was also an effective method of therapy in the case of plasma level of diclofenac. However, the diclofenac concentrations in the muscle as well as in the synovial membrane were significantly higher after topical application compared to oral route of administration [20].

Although some NSAIDs can reach the systemic circulation via the cutaneous microcirculation, systemic exposure to the drug is reduced. Plasma concentrations of diclofenac following transdermal administration have been shown to reach the peak within the range of 0.2% to 8.0% of the values achieved after oral administration. Values of AUC were also lower compared to those obtained after oral administration. In addition, a study comparing the efficacy of the epidermal and oral administration of diclofenac has shown that the maximum level is achieved later in the case of application to the skin than for orally administered diclofenac. After oral administration, the maximum concentration of diclofenac was usually achieved between 20 minutes to 6.5 hours, while after topical application it was from 1.25 to 30 hours [9]. The studies by Cordero et al. [21, 22] demonstrated a very good penetration of sodium diclofenac through cell membranes. On the other hand, the authors reported that after topical administration diclofenac reaches only 3-5% of the systemic concentration. In turn, the concentration in muscle tissue was much more satisfactory than after oral administration.

In order to demonstrate their therapeutic effect, the semisolid topical preparations must at first release the active substance from the base, which then has to penetrate the skin, a specific protective barrier of the human body. Its specificity is related to the tightness of the hydrophobic *stratum corneum*, which prevents particles larger than 500 Daltons to penetrate through the healthy epidermis. Several aspects influence the ability of diclofenac sodium to penetrate different layers of the skin, and consequently the effectiveness of its topical administration. The following ones are the most crucial: low molecular weight (296 g/mol) of diclofenac sodium, and both hydrophilic and lipophilic properties which allow to transfer diclofenac through the *stratum corneum* as well as cell membranes – such as in the case of the synovial membrane of the joints [9]. Diclofenac sodium is characterized by a very good bioavailability, which is important in the treatment of e.g. rheumatoid arthritis since it was detected in the synovial fluid [23].

Several factors influence the high deposition of diclofenac sodium at the site of inflammation. The high degree of binding of diclofenac to plasma proteins, especially albumin is one of these factors. Since the pH of the tissue within inflammation is low it reduces the efficiency of binding diclofenac to plasma proteins. In this case, the more acidic nature of the NSAID drug (characterized by low pKa values, e.g. pKa 3.9 for sodium diclofenac), the more effective the penetration through cell membranes [9]. Non-steroidal anti-inflammatory drugs are used as first line therapy in the treatment of pain and inflammation caused by sprains or during arthritis. Transdermal NSAIDs in treating osteoarthritis have been shown to be as effective as oral NSAIDs. In addition, transdermal administration is better tolerated by patients, which is particularly important since osteoarthritis most often affects the elder people, who are more prone to developing cardiovascular or gastrointestinal side effects. In the geriatric population, several diseases often coexist at the same time, which carries the risk of polypragmasia. Topical application allows to avoid drug interactions as well

as reduces the frequency of side effects, leading to better patient compliance [9, 16, 24].

The site of topical application has a significant impact on the efficiency of drug transport to the target tissue. Transdermal diclofenac formulations are indicated for the treatment of joints located within the fingers or the knee joint. These are however not recommended for use in the case of deeper joints, such as the hip joint [17].

## Pharmaceutical availability of diclofenac sodium from semisolid formulations

Previously, the analysis of the in vitro release of diclofenac sodium from different types of bases (i.e. emulsion, lipophilic, hydrogel) was carried out at two temperatures (32°C and 37°C) by Banyś et al. [25]. The authors analysed preparations based on white petrolatum, Eucerin, Lekobaza, Hascobaza and glycerol ointment as well as commercial preparations available on the Polish pharmaceutical market – Diclac Lipogel and Veral. From the formulation based on Lekobaza 3.36% and 3.06% of diclofenac sodium released after 3 hours of the study at 32°C and 37°C, respectively. On the other hand, for the preparation with diclofenac sodium based on Hascobaza, 3.48% and 3.81% were released at the same time and temperatures, respectively [25]. Thus, it was observed that at 32°C, Lekobaza released a greater percentage of the active substance than at 37°C, in opposite to Hascobaza formulation. The greatest release of diclofenac was demonstrated from the hydrogel, pharmacopoeial base – glycerol ointment, which can be explained by the lower viscosity of such a base. A lower and extended release of API may result from a high viscosity of semisolid preparation [25]. On the other hand, in the case of the lipophilic (white petrolatum) and absorption (eucerin) bases, 1.04% and 0.95% of diclofenac sodium was released at the temperature of 37°C after 3 hours, respectively. Thus, the lipophilic base was characterized by a slightly higher release of diclofenac sodium than the absorption base, but much lower than the other media used by the authors [25]. The first and most important skin barrier of which the active substances must pass through, i.e. the *stratum corneum*, is hydrophobic. Therefore, it would suggest that the use of lipophilic ointments would be the best solution for delivering API to deeper layers of the skin.

The study of the pharmaceutical availability of diclofenac sodium from semisolid foemulations was also the purpose of the study by Sann et al. [26]. The authors analysed a gel based on Carbopol, a cream with the addition of a surfactant – sodium lauryl sulfate and a cream with Carbopol. The formulation available on the pharmaceutical market containing diclofenac sodium, i.e. Voltaren Emulgel was used as reference. The authors demonstrated that the diffusion rate of the formulations differed depending on the type of membrane used (hydrophilic and hydrophobic), which indicates an interaction between the substrate and the membrane surface. However, the commercial product was characterised with the most effective diffusion in both cases. On the other hand, an in vivo study showed the effectiveness of the cream with sodium lauryl sulfate (inhibition of acute hyperalgesia in laboratory animals), while the other preparations did not show a similar relationship.

Increased effectiveness of the epidermal administration of diclofenac sodium can be achieved by the use of absorption promoters. In a study by Kamath et al. [27] the release of diclofenac sodium from various bases with the urea, dimethylsulfoxide (DMSO) and di (propylene glycol) methyl ether was compared. In the research, Voltaren 1% gel was also used as a reference preparation. Significant increase in the release of sodium diclofenac was observed from a 1% hypromellose gelled formulation containing 15% DMSO. In addition, the authors analysed the amount of the diclofenac sodium on its release process from the formulations at 0.5% and 1.5%. It was found that the higher concentration of API did not significantly increase the active ingredient release. This suggests that absorption promoters can effectively increase the release of diclofenac sodium even at reduced doses of the drug [27].

## Perspectives on transdermal route of administration of diclofenac sodium

In recent years, research has been carried out on new formulations which can be used to improve the permeability of various topically applied active substances, including diclofenac sodium. In the 1960s, studies on liposomes began, which were supposed to overcome the *stratum corneum* and deliver the active substance to the deeper layers of the skin and to the systemic circulation. These systems can be applied in many fields of science, e.g. in pharmacy, cosmetology, biotechnology, food industry and medicine. Liposomes are spheres at micro or nano scale having an aqueous core surrounded by one or two layers of lipid bilayer. They consist mainly of phospholipids. Liposomes have the ability to carry substances with both hydrophilic and hydrophobic nature. These vesicular structures arise spontaneously in the water environment and are characterized by sizes of 0.01-1 μm [28]. Preparations containing liposomes can be used in the parenteral, topical and ocular form. They are relatively safe for the patient and show low toxicity. All types of topical gels with liposomes are characterized by increased tissue availability, efficiency and sustained release compared to conventional forms. However, in the study by Banyś et al. [25], a commercially available preparation containing liposomes with diclofenac sodium was characterized by the release of the active substance at the level of 5.46% and 5.61% at 32°C and 37°C temperatures. The results indicated that the percentage of diclofenac sodium release was significantly lower than that of the pharmacopoeial glycerol ointment. The authors reported that the analysed commercial preparation contained decyl oleate as excipient [25]. As the studies showed, oleic acid is one of the most effective absorption promoters for diclofenac sodium, although it can also reduce its solubility. In contrary, Sacha et al. [29] demonstrated statistically higher transdermal permeability coefficient for the liposome 1% gel was than for the emulsion gel 1.16% and emulsion gel 2.32%. The authors observed such a significant difference between transdermal transport of diclofenac sodium from the liposome gel 1% and the emulsion gel 1.16% after 9 h [29].

The most recent study reported novel drug form called diclosomes (vesicular systems consisting exclusively of diclofenac sodium) [30]. The diclofenac sodium permeated with greater amount from diclosomal gels than from traditional niosomal gel, diclofenac sodium plain gel or commercial product. The authors suggested that such type of vesicles may increase the drug accumulation in the *stratum corneum* and promote its permeation across the skin [30].

On the other hand, the use of liposomes or other lipid vesicles may not completely fulfil its task. In the study by Fathi-Azarbayjani et al. [31], the percentage of diclofenac sodium from free unencapsulated drug in the cerosomal formulations significantly increased its permeation across the skin compared to other lipid vesicles with diclofenac sodium, among others conventional liposomes, ethosomes, transferosomes, proniosomes or niosomes. According to authors, low skin permeability of diclofenac sodium from the other than cerosomal lipid suspensions may result from the decreased solubility of the hydrophilic drug in the skin lipids as well as the partition coefficient of the drug from these vesicles into the *stratum corneum* [31].

## Conclusions

Topical application of a medicinal product has many advantages including the avoidance of drug interactions and the reduction of the frequency of side effects. Data show that transdermal treatment with diclofenac sodium may be as effective as oral administration. However, undoubtedly its main advantage over the oral route is avoiding gastroenterological complications of diclofenac sodium and its adverse effect on the kidneys and the cardiovascular system.

## References

1. Daniels R, Knie U. Galenics of dermal products- vehicles, properties and skin release. J Dtsch Dermatol Ges; 2007; 5: 367-383. doi: 10.1111/j.1610-0387.2007.06321.x

2. Jankowski A, Dyja R, Sarecka-Hujar B. Dermal and Transdermal Delivery of Active Substances from Semisolid Bases. Indian J Pharm Sci 2017; 79(4): 488-500.
3. Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification in vitro. Eur J Pharm Biopharm 2001; 52 (2):103-112.
4. Mekkawy IAA, Fathy M, El-Shanawany S. Study of fluconazole release from o/w cream and water soluble ointment bases. British J Pharm Res 2013; 3(4): 686-696.
5. Wiedersberg S, Leopold CS, Guy RH. Bioavailability and bioequivalence of topical glucocorticoids. Eur J Pharm Biopharm 2008; 68 (3): 453-466.
6. Cal K, Stefanowska J. Metody zwiększania przenikania substancji leczniczych przez skórę. Farm Pol 2010; 66 (7): 514-520.
7. Farmakopea Polska wydanie XI, Tom 1-3. Warszawa: Polskie Towarzystwo Farmaceutyczne; 2017.
8. Wolski T, Kędzia B. Farmakoterapia skóry. Cz. 2. Przenikanie substancji przez skórę. Post Fitoterapii 2019; 20 (2): 154-158.
9. Hagen M, Baker M. Skin penetration and tissue permeation after topical administration of diclofenac. Current Medical Research and Opinion 2017; 33 (9): 623-1634.
10. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta--analyses of individual participant data from randomised trials. Lancet. 2013; 382(9894): 769-779.
11. Samborski W, Niklas A, Filipiak KJ, Kaczmarczyk J, Dobrowolska- Zachwieja A, Tykarski A. Niesteroidowe leki przeciwzapalne a powikłania sercowo-naczyniowe i gastroenterologiczne – algorytm wyboru. Choroby Serca i Naczyń 2017; 14 (5): 238-247.
12. McGettigan P, Henry D. Use of non-steroidal anti--inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLoS Med. 2013;10(2):e1001388.
13. Reguła J, Wocial T, Kraszewska E, Butruk E. Stosowanie niesteroidowych leków przeciwzapalnych w Polsce — badanie ankietowe u 38 tysięcy chorych. Gastroenterologia Kliniczna 2011; 3 (2): 72-78.
14. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf. 2011; 20(12): 1225-1236.
15. Díaz-González F, Sánchez-Madrid F. NSAIDs: learning new tricks from old drugs. Eur J Immunol. 2015; 45(3): 679-686.
16. Altman R, Bosch B, Brune K, Patrignani P, Young C. Advances in NSAID development; evolution of diclofenac products using pharmaceutical technology. Drugs 2015; 75 (8): 859-877.
17. Derry S, Conaghan P, Da Silva JAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2016; 4: CD007400
18. Ulubay M, Yurt KK, Kaplan AA, Atilla MK. The use of diclofenac sodium in urological practice: a structural and neurochemical based review. Journal of Chemical Neuroanatomy 2017; 87: 32-36.
19. DrugBank. Diclofenac sodium. https://www.drugbank.ca/drugs/DB00586 [Access: 04.01.2020].
20. Miyatake S, Ichiyama H, Kondo E, Yasuda K. Randomized clinical comparisons of diclofenac concentration in the soft tissues and blood plasma between topical and oral applications. Br J Clin Pharmacol. 2009; 67(1): 125-129.
21. Cordero JA, Alarcon L, Escribano E, Obach R, Domenech J. A comparative study of the transdermal penetration of a series of nonsteroidal anti-inflammatory drugs. J Pharm Sci. 1997; 86 (4): 503-508.
22. Cordero JA, Camacho M, Obach R, Domenech J, Vila L. In vitro based index of topical antiinflammatory activity to compare a series of NSAIDs. Eur J Pharm Biopharm. 2001; 51 (2): 135-142.
23. Altman R, Bosch B, Brune K, Patrignani P, Young C. Advances in NSAID Development: Evolution of Diclofenac Products Using Pharmaceutical Technology. Drugs 2015; 75: 859-877.
24. Haltner-Ukomadu E, Sacha M, Richter A, Hussein K. Hydrogel increases diclofenac skin permeation and absorption. Biopharm Drug Dispos. 2019; 40 (7): 217- 224
25. Banyś A, Sarecka- Hujar B, Jankowski A, Zalewska M. Impact of base type on diclofenac sodium release from semisolid dosage forms. Annales Academiae Medicae Silesiens 2014; 68 (1): 1-8.
26. Sanna V, Peana AT, Moretti L. Effect of vehicle on diclofenac sodium permeation from new topical formulations: in vitro and in vivo studies. Current Drug Delivery 2009; 6 (1): 93–100.

27. Kamath S. Development and evaluation of dermatological formulations using lower level of diclofenac sodium with enhanced drug release. Long Island University, The Brooklyn Center, ProQuest Dissertations Publishing, 2020; 27923531.
28. Sarecka-Hujar B, Banyś A, Ostróżka-Cieślik A, Balwierz R, Dolińska B. Evaluation of the potential of nanoparticles containing active substances in selected chronic diseases. Adv Clin Exp Med. 2020; 29(3): 385-397.
29. Sacha M, Faucon L, Hamon E, Ly I, Haltner-Ukomadu E. Ex vivo transdermal absorption of a liposome formulation of diclofenac. Biomed Pharmacother. 2019;111:785-790.
30. Tavano L, Mazzotta E, Muzzalupo R. Innovative topical formulations from diclofenac sodium used as surfadrug: The birth of Diclosomes. Colloids Surf B Biointerfaces. 2018; 164: 177-184.
31. Fathi-Azarbayjani A, Xin Ng K, Weng Chan Y, Yung Chan S. Lipid Vesicles for the Skin Delivery of Diclofenac: Cerosomes vs. Other Lipid Suspensions. Adv Pharm Bull 2015; 5 (1): 25-33.