PRACA ORYGINALNA

Impact of base type on diclofenac sodium release from semi-solid dosage forms

Wpływ rodzaju podłoża na uwalnianie diklofenaku sodu z półstałych postaci leku

Anna Banyś, Beata Sarecka-Hujar, Andrzej Jankowski, Monika Zalewska

ABSTRACT

BACKGROUND

Semi-solid preparations for the skin are very popular. Bases affecting the release of active substances are the main component of this group of preparations. Among dermal formulations, a large percentage are those that contain non-steroidal anti-inflammatory drugs, including diclophenac sodium. Unfortunately, the permeation of diclofenac sodium through the skin is negligible, hence, numerous studies are conducted on its pharmaceutical availability.

AIM OF THE STUDY

The aim of the study was to assess the impact of the base on the release of diclophenac sodium from semi-solid dermal preparations. The following types of bases have been analyzed: gel-type, lipophilic, absorption and emulsion.

MATERIAL AND METHODS

The study compared two commercial preparations: Veral and Diclac Lipogel, and five formulations prepared with a prescription blender. The pharmaceutical availability of diclophenac sodium was examined using Kerckhoffs and Huizing apparatus. The release of diclophenac sodium was carried out at 37°C and 32°C. The absorbance of the samples was measured spectrophotometrically.

RESULTS

The ointment formulation based on glycerol possessed optimum pharmaceutical availability, which showed a high percentage of released diclofenac sodium, a high velocity release constant (k) and a low half-time release (t1/2). The least suitable bases for diclophenac sodium were the lipophilic vehicle – Vaseline and the absorption medium – eucerine. The pharmacokinetic parameters obtained from the glycerol ointment proved to be more advantageous than those from the gels based on carbopol. The kinetics of the other drugs turned out to be less favorable than for the commercial gels. Faster and greater release of diclophenac sodium occurred at 37°C.

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CONCLUSIONS
The study showed that the best release of diclofenac sodium was observed in the case of the prescription formulation (glycerol ointment), even compared to the commercially available preparations. The temperature influenced the amount and rate of diclofenac sodium released from the two analyzed gels.

KEY WORDS
semi-solid dosage forms, diclophenac sodium, release, pharmaceutical availability, Diclac Lipogel, Veral, bases

STRESZCZENIE

WSTĘP
Półstałe preparaty na skórę cieszą się dużym zainteresowaniem. Podstawowym ich komponentem są podłoża mające wpływ na uwalnianie substancji czynnych. Wśród preparatów podawanych na skórę duży procent stanowią te, które zawierają niesteroidowe leki przeciwzapalne, w tym diklofenak sodu. Niestety, przenikanie diklofenaku sodu przez skórę jest niewielkie, stąd prowadzone są liczne badania nad jego dostępnością farmaceutyczną.

CEL PRACY
Celem pracy była ocena wpływu zastosowanego podłoża na uwalnianie diklofenaku sodu z półstałych preparatów podawanych na skórę. Analizie poddano podłoża typu żelowego, podłoże lipofilowe, absorpcyjne oraz podłoża emulsyjne.

MATERIAŁ I METODY
W pracy porównywano preparaty gotowe Veral i Diclac Lipogel oraz pięć preparatów wykonanych przy użyciu miksera recepturowego. Dostępność farmaceutyczną diklofenaku sodu zbadano aparatem Kerckhoffsa i Huizinga. Uwalnianie diklofenaku sodu przeprowadzono w temperaturze 37°C oraz 32°C. Absorbancję pobranych próbek mierzono spektrofotometrycznie.

WYNIKI
Optymalną dostępność farmaceutyczną miał preparat na bazie maści glicerolowej, który wykazywał wysoki procent uwolnionego diklofenaku sodu, wysoką stałą szybkości uwalniania k i niski czas połowicznego uwalniania $t_{1/2}$. Podłożami najmniej odpowiednimi dla diklofenaku sodu okazały się podłoże lipofilowe – wazelina, oraz absorpcyjne – euceryna. Parametry farmakokinetyczne uzyskane z udziałem maści glicerolowej okazały się korzystniejsze niż parametry uzyskane z gotowych żeli na bazie carbopolu. Kinetyka pozostałych preparatów okazała się mniej korzystna niż gotowych żeli. Większe i szybsze uwalnianie diklofenaku sodu następowało w temperaturze 37°C.

WNIOSKI
Przeprowadzone badania wykazały, że diklofenak sodu najlepiej uwalniał się z preparatu recepturowego (maść glicerolowa), nawet w porównaniu z komercyjnie dostępnymi preparatami. Podłożami najmniej odpowiednimi okazały się wazelina i euceryna. Temperatura badania wpływała na ilość i szybkość uwolnionego diklofenaku sodu z dwóch badanych żeli.

SŁOWA KLUCZOWE
półstałe postacie leku, diklofenak sodu, uwalnianie, dostępność farmaceutyczna, Diclac Lipogel, Veral, podłoże

INTRODUCTION

Semi-solid dosage forms intended for external dermal usage are an important group of preparations that are an alternative for other dosage forms. They possess many advantages for example non-invasive dosage, no first pass effect, target action and easy application. The preparations can contain substances which have local effects (antibiotics, anti-inflammatory drugs), surface effects (disinfectants) and systemic effects (hormones, painkillers). They are used for protection or softening of the skin. The main component of semi-solid dosage forms is a base where one or more active substances is dissolved or dissipated [1]. A base can be basic or complex, it can contain natural or synthetic substances and it can be single or multiphase. Choosing adequate components for the base affects the depth of skin penetration. The lipophilic nature of *stratum corneum* is the reason why similar substances are easily excreted into it. Such substances will easily dissolve in a lipophilic base but will diffuse with difficulty because of their substantial interaction with the base and their decreased partition coefficient. This results in using a hydrophilic base for lipophilic substances and a lipophilic base for hydrophilic substances.

Aim of the study

The aim of the study was to assess the influence of the applied base on the release of diclophenac sodium from semi-solid dermal preparations. The following types of bases have been analyzed: gel-type (glycerol ointment, commercial preparations based on carbomer), lipophilic (Vaseline), absorption (eucerine) and emulsion (Hascobaza, Lekobaza).

MATERIALS AND METHODS

Two commercial preparations – Veral (gel 10 mg/g, 55 g, produced by Zentiva) and Diclac Lipogel (gel 10 mg/g, 50 g, produced by Sandoz) as well as five semi-solid preparations prepared with a prescription blender were used in the study. Each of the prepared preparations contained the same amount of diclophenac sodium (Sigma) as the commercial preparations.

The study of the release of diclophenac sodium from semi-solid preparations was conducted using Kerckhoffs and Huizing apparatus. The apparatus consists of two identical glass cylindrical vessels which enable studying two samples simultaneously. The study was carried out in the Department of Applied Pharmacy of the Silesian Medical University in Katowice. Each vessel consists of two chambers: an external one which constitutes a heating mantle and an internal one where the studied samples were located. The external chamber is linked with a thermostat and the internal chamber is linked with a peristaltic pump guaranteeing a constant flow of acceptor fluid. The release of diclophenac sodium from all of the preparations was carried out at 37°C. The assessment of pharmaceutical availability at 32°C, the temperature recommended by FP IX, was carried out for the prescription preparations based on Hascobaza, Lekobaza, glycerol ointment and two commercial preparations – Veral and Diclac Lipogel. The preparation was separated from the acceptor fluid with a prepared dialysis membrane with an MWCO of 1000 Daltons (Da). 250 ml of purified water was put into each of the chambers as the acceptor fluid. 2 ml samples were collected after 10, 20, 30, 60, 90, 120, 150 and 180 minutes of the experiment. The loss of acceptor fluid was replenished at the same time. The absorbance of the samples was measured with a UV/VIS Cecil CE 3021 spectrophotometer (produced by Cecil Instruments) using a 275.5 nm wave length.

The concentration of the solutions stated in μg/ml, was determined using a model curve regression equation. Next, the concentration was converted into mg standing for the amount of released diclophenac sodium and then into percentages.

Statistical analysis was conducted using the STATISTICA 10.1 program (STATSOFT; Statistica, Tulsa, OK, USA). Comparison of the average amount of released diclophenac sodium P [%] and the release velocity constant k [h-1] among the studied preparations was carried out by means of two tests: Student's t-test on normal distributions and the non-parametric Mann-Whitney U test on non-normal distributions. Values at the $p < 0.05$ level were statistically significant.

RESULTS

It was observed that the glycerol ointment base releases the highest amount of diclophenac sodium at 37°C (18.92%). The ointment released nearly twice as much diclophenac sodium as the Veral preparation (11.63%) which released twice as much diclophenac sodium as Diclac Lipogel (5.61%). The preparations based on Hascobaza and Lekobaza released comparable amounts of diclophenac sodium (3.81% and 3.06% respectively) but significantly smaller amounts than the gel preparations. A similar amount of the active substance was released from the lipophilic base – – Vaseline and from eucerine (1.04% and 0.95% respectively) (Fig. 1).

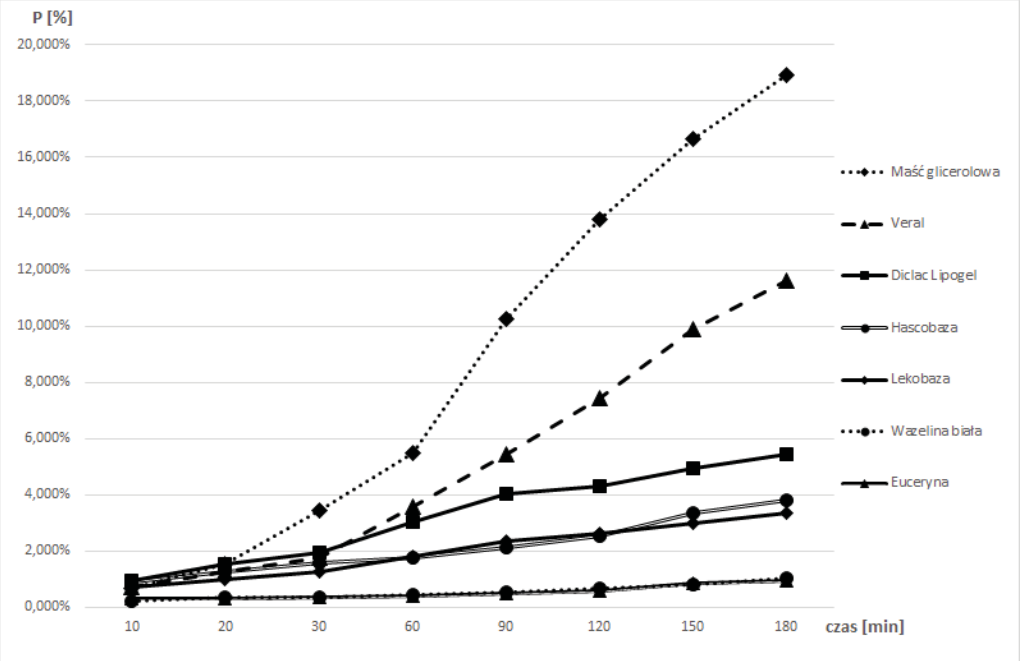

Fig. 1. Diclofenac sodium release kinetics at 37°C.
Ryc. 1. Kinetyka uwalniania diklofenaku sodu w temperaturze 37°C.

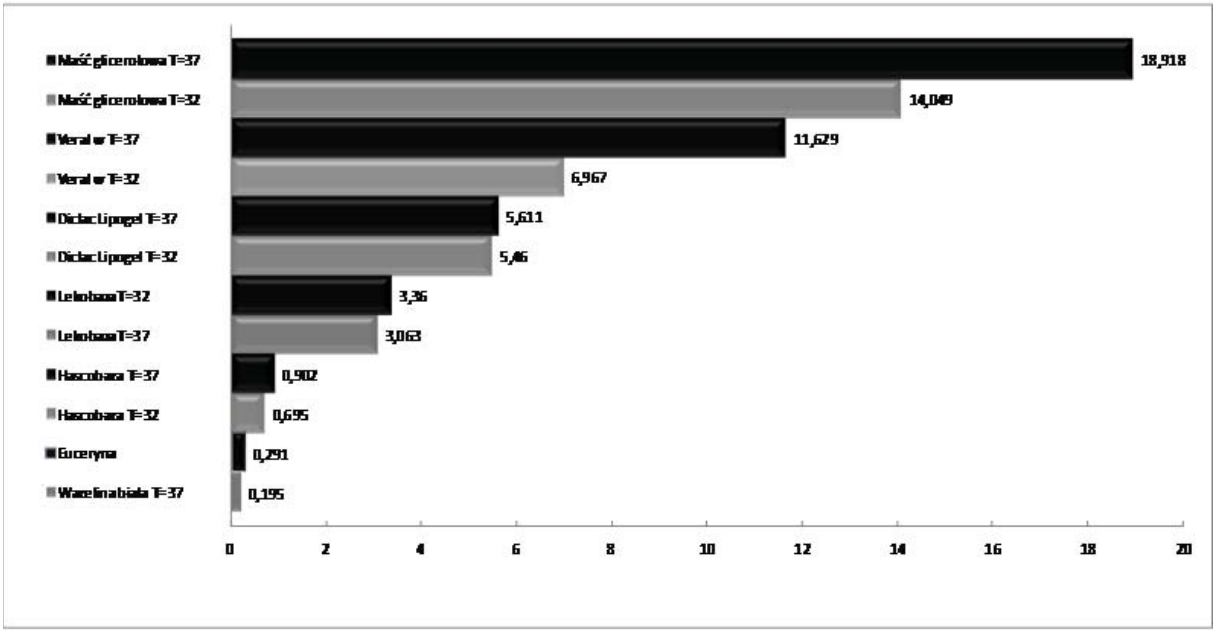

Fig. 2. Comparison of diclofenac sodium amounts released from all analyzed preparations at 32°C and 37°C within 3 hours.
Ryc. 2. Porównanie ilości uwolnionego diklofenaku sodu z wszystkich analizowanych preparatów w temperaturze 32°C i 37°C w czasie 3 godzin.

Taking the released diclophenac sodium into account, a similar order of preparations was obtained at 32°C. The highest amount of active substance was released by the glycerol ointment – 14.05%. Veral and Diclac Lipogel released 6.97% and 5.46% of the active substance respectively. Similar results were obtained for the preparations based on Lekobaza and Hascobaza (3.36% and 3.48% respectively). The glycerol ointment released more diclophenac sodium at 32°C than the rest of the preparations at 37°C.

The temperature significantly affected the release of diclophenac sodium from Veral and the glycerol ointment. The differences in the release of diclophenac sodium for the rest of the preparations at different temperatures were lower than 10%. The preparations with Vaseline and eucerine were studied only

at 37°C because even at that temperature the amount of released diclophenac sodium was small (1.04% and 0.95% respectively) (Fig. 2).

The release of diclophenac sodium from all of the studied preparations proceeded in accordance with first-order kinetics. The release velocity constant k for the preparation based on the glycerol ointment was higher than the velocity constant of the rest of the preparations at both temperatures (Table I).

Table I. Velocity release constant values k and release half-time $t_{1/2}$ according to primary kinetics
Tabela I. Wartości stałych szybkości uwalniania k oraz czasu połowicznego uwalniania $t_{1/2}$, dla badanych preparatów według kinetyki I rzędu

Preparations	k [h^{-1}]		$t_{1/2}$ [h]	
	32°C	37°C	32°C	37°C
Veral	2.37×10^{-2}	3.99×10^{-2}	29.24	17.39
Diclac Lipogel	1.90×10^{-2}	1.94×10^{-2}	36.57	35.74
Gel-type preparation (glycerol ointment)	4.90×10^{-2}	7.00×10^{-2}	14.14	9.91
Lipophilic preparation (Vaseline)	–	7.29×10^{-4}	–	951.09
Absorption preparation (Eucerine)	–	4.68×10^{-4}	–	1481.86
Emulsion preparation (Lekobaza)	2.36×10^{-3}	2.53×10^{-3}	293.22	273.47
Emulsion preparation (Hascobaza)	2.55×10^{-3}	2.69×10^{-3}	272.06	258.10

The obtained pharmacokinetic parameters show that temperature affects the release of diclophenac sodium from the glycerol ointment – the process proceeds faster at 37°C (Fig. 2). High values of the release velocity constant were noticed in Veral. The greatest influence of temperature on the release velocity was also noted in Veral. The release velocity constant was almost twice as low at 32°C than at 37°C and the period of half-life release was almost twice as great. The kinetics of Diclac Lipogel at both temperatures was similar to the kinetics of Veral at 32°C. The preparations based on Lekobaza and Hascobaza had similar pharmacokinetic parameters at both temperatures. Lekobaza, which released insignificantly more active substance at 32°C, released the active substance faster at 37°C according to the pharmacokinetic parameters. Differences in the release velocity constant and half-life release can be noticed when comparing the parameters of the ointments based on Vaseline and eucerine. However, after comparing these parameters with the rest of the preparations, it can be assumed that the release velocity from the Vaseline and eucerine bases is similar. After the analysis of all the studied preparations, it turned out that the lipophilic and absorption bases were the slowest in releasing diclophenac sodium.

In the case of the statistical analysis of the average amount of released diclophenac sodium P [%] at 37°C, the most considerable differences were noted when studying the following pairs of preparations: Diclac Lipogel vs. the Vaseline based preparation, Diclac Lipogel vs. the eucerine based preparation, the Vaseline based preparation vs. Hascobaza and the eucerine based preparation vs. Hascobaza. Statistically significant differences for those combinations were obtained, at the $p \leq 0.001$ level. A lack of statistical significance was noted for: the Vaseline and eucerine preparations, Hascobaza and Lekobaza preparations, Veral and Diclac Lipogel preparations, Veral and glycerol ointment preparations and for Diclac Lipogel and Hascobaza preparations.

The compared values for the released diclophenac sodium at 32°C were statistically significant for the following combinations: Lekobaza preparation vs. the glycerol ointment and Hascobaza preparation vs. the glycerol ointment ($p < 0.05$). After the analysis of release velocity constant k, it was noted that the glycerol ointment preparation and Veral preparation demonstrated the highest velocity constants which, after comparing them to the rest of the preparations at both temperatures, were statistically significant ($p \leq 0.001$). Smaller differences were noted for the combinations of gel preparations: Veral vs. the glycerol ointment preparation and Veral vs. Diclac Lipogel. The eucerine and Vaseline based preparations had the lowest velocity constants. The kinetic parameters of those preparations differed significantly from the parameters of the rest of the preparations. The differences in the release kinetics of diclophenac sodium for the Vaseline and eucerine preparations and Hascobaza and Lekobaza preparations were not statistically significant. The temperature significantly affected the Veral velocity constants only ($p \leq 0.001$).

DISCUSSION

The study revealed that the glycerol ointment is the base which released the highest amount of diclophenac sodium. This result is supported by the amount of active substance which was released into the acceptor fluid (14.05% and 18.92%) and the pharmacokinetic parameters ($k = 4.90 \times 10^{-2}$ and 7.00×10^{-2} [h-1] and t1/2 = 14.14 and 9.91 [h]). It can be explained by the lowered viscosity of the glycerol ointment as compared to the rest of the studied bases. In the Thanh-Blicharz et al. study [4], the viscosity of the glycerol ointment components is many times lower than the viscosity of carbopol gels used in commercial preparations. The Einstein-Smoluchowski equation results in an inversely proportional dependence of the base

release velocity of a healing substance on the viscosity of the base [5].

In the study, diclophenac sodium release from two commercial preparations – Veral and Diclac Lipogel – – was also studied. It was observed that their release was lower than from the glycerol ointment based preparation and significantly higher than from the other studied preparations. The commercial preparations consist of carbomer which is a polymer characterized by high viscosity [6]. The high viscosity can lower the amount of released active substance and slow down the release from those preparations when compared to glycerol ointment based preparations.

When comparing the release of diclophenac sodium from both of the commercial preparations, it was noted that Veral had a quicker release. It can be caused by the ethyl alcohol which mediates in the release process. The alcohol increases the solubility of diclophenac sodium [7]. Taking Diclac Lipogel into account, the liposomal form of diclophenac sodium can be the reason for the slowing down of its release *in vitro*. However, the healing effect obtained by using liposomes can be strengthened by promoting the transdermal absorption of liposomes [8]. Moreover, the gel also contains decyl oleate (an ester consisting of oleic acid and decanol). Studies show that oleic acid is one of the most effective absorption agents for diclophenac sodium and a factor that reduces the solubility of this substance [9,10]. Decanol, on the other hand, as an alcohol with a shorter hydrocarbon chain than oleic acid and not characterized by a double bond, may slightly enhance penetration and slightly diminish solubility [10]. That is why decyl oleate can cause lower solubility of diclophenac sodium in Diclac Lipogel comparing to Veral, and enhance actual skin penetration at the same time [10].

Prabha et al. analysed the pharmaceutical availability of gels with diclophenac sodium from four commercial gel preparations which released much more diclophenac sodium after 50 minutes (53–86%) than in the present research. Ethanol was used as the acceptor fluid in that experiment because diclophenac sodium dissolves better in ethanol than in water [11]. The type of acceptor fluid used in pharmaceutical availability research is one of the main factors affecting release kinetics.

The Lekobaza and Hascobaza based preparations were characterized by lower release. Both preparations demonstrated similar release thanks to their almost identical composition. The release from these bases was lower and slower than from the gel bases but greater and faster than that from Vaseline and eucerine. Similar results were achieved in two other studies [12,13]. In the Stożkowska experiment [12], the surface of the release was larger in comparison to the surface applied in the present research thus influencing the amount of released diclophenac sodium. Additionally, the author analyzed the viscosity of the bases and its influence on pharmaceutical availability. The lipophilic ointment had the highest viscosity and the lowest release [12].

The release of diclophenac sodium from Lekobaza and Hascobaza was two times higher than from the Vaseline and eucerine based ointments. It can be explained by the lower viscosity of emulsion bases such as Lekobaza and Hascobaza in comparison to lipophilic or absorption bases [12]. On the other hand, Lekobaza and Hascobaza contain many substances which increase the solubility of diclophenac sodium such as propylene glycol, glycerol monostearate and cetostearyl alcohol. It is also possible that some of the ingredients of those bases can enhance the penetration of the active substance as absorption agents [9,10].

The Vaseline and eucerine bases were characterized by the slowest diclophenac sodium release. In other studies, similar results were achieved for Vaseline based lipophilic ointments with an addition of excipients [12,13]. The release of diclophenac sodium from Vaseline and from eucerine was not compared. Such a slow Vaseline base release can be caused by the low solubility of diclophenac sodium in that base, problematic diffusion of the healing substance and high base viscosity. Hydrocarbon bases demonstrate a "lag time" effect – during the first several dozen minutes, release does not take place or is very low [14]. In the present research, the Vaseline and eucerin based preparations demonstrated slightly slower release during the first 60 minutes. In the research, the influence of temperature on the release of diclophenac sodium from semi-solid dosage forms was also analyzed. All of the preparations demonstrated faster release at 37°C. However, in most of the cases such differences were statistically insignificant. Veral and the glycerol ointment based preparation were characterized by the greatest influence of temperature on the release velocity whereas Diclac Lipogel was characterized by the smallest influence. The influence of temperature on the pharmaceutical availability of diclophenac sodium in Diclac Lipogel as well, was analyzed by Pluta et al. [15]. The amount of released diclophenac sodium and the release velocity were higher in the presented study. This was influenced by the different surface of the release. The Pluta et al. study noted greater influence of the temperature on the release from the Diclac Lipogel preparation when compared to our study which can be connected to the decrease in the viscosity during the temperature increase.

In the cited studies, diclophenac sodium was not 100% released during 24 h from any of the studied bases. In the present research, the release was studied for three hours. As the Stożkowska study [12] shows, the amount of active substance released from the different preparations can reach the same level after 24

hours. In such a situation, analyzing the amount of released diclophenac sodium after less time or analyzing the pharmacokinetics of the process is more useful than analyzing it after 24 hours since none of the preparations applied onto skin will release a substance for 24 hours because it is not likely that such a preparation will remain on the skin for such a long time.

In all of the cited research results, the pharmacokinetic parameters were determined according to first-order kinetics. Additionally, other mathematical models were used in some of the experiments: the Higuchi model, diffusion models (based on Fick's law) or zero-order kinetics [15,16].

The study on pharmaceutical availability with the use of mouse skin can show the actual penetration of diclophenac sodium through human skin and confirm that we do not always encounter the simple correlation *in vitro – in vivo* at the same time [14]. The results of this study show that solubility is not the only factor determining substance release from the base. The substance partition coefficient between the base and the acceptor fluid is also extremely important. The lowest partition coefficient and almost the smallest penetration through the mouse skin was obtained for the base where diclophenac sodium dissolved in the best way (the smallest penetration was obtained for the diclophenac sodium and white Vaseline preparation). On the other hand, the bases where the solubility of the active substance was lower, they demonstrated a lower partition coefficient and their skin penetration was higher. Moreover, it was confirmed that the absorption agents increase the skin transition of the substance [14].

To sum up, this study confirms that the best diclophenac sodium releasing bases are gel bases which explains the fact that all of the semi-solid skin preparations registered in Poland are gels. Experimenting with Lekobaza, Hascobaza or lipophilic bases is not beneficial because of the large differences in the amount of released diclophenac sodium and in the kinetic parameters between gel preparations and ointments. Even occlusion, which can be caused by Vaseline, does not seem to crucially affect the release [17,18]. Conducting research using gel preparations by altering their viscosity and adding different skin penetration enhancing substances is more beneficial. Moreover, patients prefer gel preparations because of application and esthetic reasons, and positive feelings of patients can lead to higher effectiveness of the preparations. It should be noted that researching pharmaceutical availability using an ordinary synthetic membrane does not necessarily emulate the conditions of the preparations after being applied to skin. It is only a certain indicator that shows the preferred path for future research and suggests which bases should be analyzed in an *in vivo* like way.

CONCLUSIONS

1. Gel bases proved to be the most suitable bases for diclophenac sodium.
2. Among all the studied preparations, commercial preparations included (carbomer based), the glycerol ointment based preparation demonstrated the highest pharmaceutical availability and optimal pharmacokinetic parameters. Vaseline and eucerine proved to be the least suitable bases for diclophenac sodium.
3. The temperature during the research significantly influences the amount and velocity of the released diclophenac sodium from two of the studied gels (glycerol ointment and Veral preparation). Greater and faster release of diclophenac sodium took place at 37°C.

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