Viscosity of hydrogel pharmaceutical products and the rate of diffusion of ibuprofen hydrotropic binding through model phase boundary *in vitro*

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Summary

The aim of the carried out investigations was to establish relation between rheological parameters of market hydrogels containing ibuprofen and therapeutic agent diffusion coefficient dependent on their prescription. An attempt was made to estimate rheological parameters (structural viscosity, kinetics of volatile components loss) effect on pharmaceutical availability Q and the order of the process of mass exchange through artificial and natural phase boundary.

Designed for skin anti-inflammatory hydrogels containing ibuprofen in the form of hydrotropic adduct with lysine (*Ibufen*, *Dolofast*), in the form of sodium salt (*Nurofen*) and in the form of molecular fragmentation of acidic form (*Dolgit*) were tested.

The rate of volatile components loss was estimated with gravimetric method, viscosity measurements of therapeutic agents aqueous solutions were performed with Ubbelohde viscosimeter, while hydrogels rheological parameters – with cone-plate digital rheometer. The rate of ibuprofen penetration through phase boundary (Viscing dialysis membrane and pig perimastoid dermis) into dialysis fluid was determined *in vitro.* The kinetics of this process was monitored by measuring electric conduction $\Delta\lambda=f(t)$ of model dialysis fluid.

Viscometric measurements of aqueous solutions of ibuprofen lysine salt and ibuprofen sodium salt, by determining boundary viscosity gradient GLL(η) and calculation of hydrodynamic radius R_{obs}, enabled the applicative solution of Einstein-Smoluchowski equation ($D=kT/6\Pi r\eta$) and the estimation of structural value of therapeutic agent diffusion coefficient. Tracing the dependence between diffusion coefficient and shear rate enabled to

recognize the preferences of preparations to the process of mass exchange on the phase boundary.

An association was confirmed between the determined and calculated rheological parameters and the process of mass exchange on phase boundary through selected dialysis membranes. Mass exchange on phase boundary was found to be the derivative of the process of diffusion and its quantitative aspect depends on the kind of the applied membrane (it is the function of the quantity of statistically distributed pores on the unit of its surface (cm^2)).

Ibuprofen penetration through an artificial and natural phase boundary is complex. Its mechanism is between the kinetics of "O" and "II" order. The quantitative differentiation of the process of mass exchange between hydrotropic ibuprofen forms: ibuprofen lysine salt > ibuprofen sodium salt > ibuprofen in the form of acid molecule results from the carried out experimental study.

Key words: ibuprofen, anti-inflammatory hydrogels, volatile components, viscosity, dialysis membranes, pharmaceutical availability

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INTRODUCTION

Pharmacotherapeutic effectiveness of preparations applied on skin depends not only on the therapeutic agent penetration through *stratum corneum* and skin adnexa but also on partition coefficient (K_m), which becomes established in the course of the preparation exposure between the vehicle and epidermic corneal layer [1-4]. The highest adsorption of the therapeutic agent is observed when the concentration of non-ionized form on phase boundary: skin-preparation is the highest.

One of the methods facilitating the process of mass exchange of lipophil therapeutic agent (e.g. ibuprofen) on the phase boundary is its modification to a form of hydrotropic binding with lysine (pI=9,60) or with triethanolamine (pK_a=7,90) (formation of ion pairs – cation or anion carrier) [5]. This process is accompanied by the change of the level of acid-base equilibrium and also disturbances of the cycle of amino acids changes which delays keratosis and facilitates penetration of the therapeutic agent [6-8].

Basic mechanism and the effect of some rheological values (viscosity) on the process of therapeutic agent diffusion from ointments of solution, suspension or emulsion type were

presented in the studies of Higuchi [9, 10]. The use of viscosity values for the calculation of hydrodynamic parameters, such as among others the radius of the diffusing molecule (R_{obs}) enables the determination of practical numerical value of diffusion coefficient (D) by solving Einstein-Smoluchowski equation ($D=kT/6\Pi r\eta$). On this basis the amount of the diffusing therapeutic agent in isothermic conditions through a dialysis membrane to model dialysis fluid can be predicted [11].

This study concerns market anti-inflammatory preparations with ibuprofen designed for skin. Hydrogels containing ibuprofen in the form of hydrotropic adduct with lysine (Ibuf*en, Dolofast*) and also in the form of sodium salt (*Nurofen*) and in the form of molecular fragmentation of acidic form (*Dolgit*) were tested. The aim of the study was to determine basic viscosity values of the preparations and to investigate the rate of volatile components loss by their structure. On the basis of the obtained results an attempt was made to estimate theoretically the line of the trend of therapeutic agent pharmaceutical availability. The above was verified by the analysis of the course of the dependence between the quantity of the diffusing ibuprofen, determined experimentally *in vitro*, through an artificial and natural phase boundary in time function: $c_t = f(t, \sqrt{t})$.

MATERIAL AND METHODS

Reagents

Preparations being the subject of investigations:

Ibufen (100 mg/g of ibuprofen lysine salt, gel 10%), Medana Pharma Terpol Group S.A., Poland;

Dolofast (ibuprofen lysine salt, gel 10%), Bracco s.p.a. – Milano;

Dolgit (50 mg/g of ibuprofen, gel) Dolorgiet Pharmaceuticals, St. Augustin/Bonn;

Nurofen (50 mg/g of ibuprofen, gel) Farmasierra Manufacturing S.L. San Sebastian;

- ibuprofen, Mallinckrodt Chemical;
- ibuprofen sodium salt, Sigma;
- ibuprofen lysine salt, Sol. Chem. Italiana;
- ibuprofen lysine salt, Dipharma Francis;
- triethanolamine, Merck Sp. z o.o.

Apparatus

- cone-plate digital rheometer DV-III-Brookfield, version 3,0 with "Rheolac for Windows" software;
- bath thermostat PGW E1, Medingen;
- spectrophotometer Nicolet Evolution 300, version 1,0, Spectro-Lab;
- water-electric thermostat, Termometal, Thermal Engineering Co-operative, Andrzejów;
- laboratory balance, Precision Engineering Plant, Radwag.

Determination of the rate of volatile components loss from the tested hydrogels [11]

The determination of the rate of volatile components loss was performed from the surface of glass plates (Petri dish) of 55 mm diameter, which were covered with uniform layer of hydrogel. The plates were placed in thermostat at $37^0 \pm 0{,}1^0$C with gravitational air circulation and the sample mass was determined after every 15 or 30 min.

Determination of viscosity parameters of therapeutic agents aqueous solutions [12]

Boundary viscosity gradient (η) of aqueous solutions of ibuprofen hydrotropic adduct with lysine and triethanolamine and ibuprofen sodium salt was determined according to Polish standard with the use of Ubbelohde viscosimeter. Basic viscosity values M_η, R_o, R_{obs} and effective volume Ω of hydrotropic adduct were calculated on this basis.

Determination of rheological parameters of the tested hydrogels [13,14, 15]

Rheological determinations were performed at 37^0C with cone-plate digital rheometer, Brookfield DV-III, version 3,0 connected with Medingen bath thermostat PGW E1.

Determination of the kinetics of ibuprofen release from hydrogels through dialysis membrane to model dialysis fluid [16]

The rate of ibuprofen diffusion from hydrogel preparations through a standard Viscing membrane of wall thickness 0,1 mm and declared diameter d= 25 Aº (1 Aº=$1\cdot10^{-8}$cm) and pig

perimastoid dermis was investigated with the technique applied for transdermal therapeutic systems according to the requirements of European Pharmacopoeia, USP XXIV and British Pharmacopoeia [17].

The way of determination

The tested preparation was introduced into the dialysis container niche of the volume $V=\Pi r^2 \cdot h$ (d=2r=5,0 cm, h=0,51 cm) equal to 10,008 cm^3 and the area of exchange $P_w=\Pi r^2=19,625 cm^2$. The preparation surface was covered with dialysis membrane. The container cover was plugged by screwing. The dialysis container prepared in this way was placed into a dish with 1000 cm^3 of distilled water. The solution over the container was stirred mechanically at the rate not greater than 55 rpm. The rate of the process of mass exchange on phase boundary was estimated by determining the quantity of the diffusing ibuprofen. Approximation equation at p=0,05 and $r \geq 0,9988$: $A=0,0305 \cdot c+0,1247$, with which the dependence between absorbance (A) and therapeutic agent concentration (c) was described, transformed to the form: c=A-0,1247/0,0305 enabled to determine the quantity of ibuprofen diffusing in the time function: $c_t=f(t)$.

RESULTS AND DISCUSSION

The results of the determination of volatile components loss

Prescription composition of market hydrogels containing ibuprofen are presented in table 1.

Isopropyl alcohol is in the hydrogel vehicle of *Dolgit, Dolofast* and *Nurofen* and the prescription of *Dolgit* and *Dolofast* includes additionally ethereal oils (tab. I). The mentioned prescription components will form together with water azeotropic mixtures during therapeutic exposure. Thus, it can be anticipated that during therapeutic application the viscosity of these hydrogels will increase causing the decrease of the therapeutic agent diffusion coefficient ($D=kT/6\Pi r\eta$). It is difficult to estimate the effect of the system triethanolamine/water found in *Ibufen* hydrogel on the rate of volatile components loss and on the preparation rheological parameters during its application.

Figure 1 demonstrates the results of the determination of the rate of volatile components loss from the tested preparations as the course of a dependence of the change of the weighed sample mass expressed in per cent ($(m_0-m_t)/m_0 \cdot 100\%$) in time function (t, min.): (m_0-

$m_t)/m_0 \cdot 100\% = f$ (t, min.), where: m_0-weighed sample mass, m_t- weighed sample mass after time t.

The course of the above dependences described with the equation y=a+bx at the level of significance p=0,05 is the following:

for *Ibuprofen* at r=0,9992: $(m_0-m_t)/m_0 \cdot 100\% = 1{,}1751+0{,}2257 \cdot t$ (min.);

for *Dolofast* at r=0,9977: $(m_0-m_t)/m_0 \cdot 100\% = 1{,}5405+0{,}2286 \cdot t$ (min.);

for *Dolgit* at r=0,9861: $(m_0-m_t)/m_0 \cdot 100\% = 5{,}8508+0{,}1855 \cdot t$ (min.);

for *Nurofen* at r=0,9997: $(m_0-m_t)/m_0 \cdot 100\% = 0{,}3680+0{,}2401 \cdot t$ (min.).

Numerical values of the coefficient b (experimentally determined for the above mentioned conditions constant of the rate – k(b) of volatile components loss) indicate that Nurofen is the quickest to lose volatile components (b(k)=0,2401). *Ibufen* and *Dolofast* have comparable rate of volatile components loss (b(k)=0,2257 and 0,2286), while *Dolgit* is the slowest (b(k)=0,1855). As it results from table II, after 240 min of exposure *Nurofen* loses 57,867 % of volatile components from the weighed sample, *Ibufen* and *Dolofast* within the limits 54,130%-54,866%, while *Dolgit* only 48,845 %. The obtained results indicate that significant rheological changes will take place (increase of viscosity η) during application of the tested preparations on skin in consequence of which therapeutic agent diffusion coefficient D will decrease markedly ($D=kT/6\Pi r\eta$).

Comparative evalueation of hydrogel preparations rheological parameters before and after exposure in model dialysis fluid

In the tested pharmaceutical products, therapeutic agent is in the form of hydrotropic binding (salt) with lysine amino acid (*Ibufen, Dolofast*) or in the form of sodium salt (*Nurofen*) as well as in the form of real solution (*Dolgit*, acidic form of a therapeutic agent). Thus, to evaluate comparatively the effect of rheological parameters on the order of magnitude of diffusion coefficient D, boundary viscosity gradient GLL[η] was determined experimentally. Then, it was possible to calculate basic viscosity values including hydrodynamic radius –R_{obs} of ibuprofen hydrotropic adduct. Results of the calculations are presented in table II.

Radius r of ibuprofen molecule for the form of molecular fragmentation (Dolgit) was calculated acc. to Fedors from the dependence: $r=\sqrt[3]{3V/A\Pi}$, where V – volume of one ibuprofen molecule [18]. Basic structural values of ibuprofen molecule, including its volume

are presented in table III. Comparatively, parameters characterising other nonsteroidal anti-inflammatory agents are also demonstrated.

Numerical values of hydrodynamic radius R_{obs} of hydrotropic adduct (lysine, quaternary salt with triethanolamine, ibuprofen sodium salt) (tab. III) enabled to transform Einstein-Smoluchowski equation: $D=kT/6\Pi r\eta$ to the form:

$D=7,5897\cdot10^{-15}\cdot1/\eta$ for ibuprofen lysine;

$D=10,6743\cdot10^{-15}\cdot1/\eta$ for IV salt with triethanolamine;

$D=9,2739\cdot10^{-15}\cdot1/\eta$ for ibuprofen sodium salt;

$D=5,2694\cdot10^{-15}\cdot1/\eta$ for ibuprofen which was dissolved in lipophilic solvent.

The experimentally determined viscosity of the preparations before exposure (after squeezing out of a tube) and after exposure in model dialysis fluid (water) was the base for calculating ibuprofen diffusion coefficients D. Figure 2 presents the course of the dependence between ibuprofen diffusion coefficient D calculated on the basis of viscosity measurements before hydrogel exposure and the shear rate.

The course of the above dependence between diffusion coefficient (D) before hydrogel exposure and the shear rate was described at p = 0,05 with regression equations of the type y = a + bx.

They assume the following form:

-for I*bufen*: $D=0,2291\cdot10^{-19}+1,2747\cdot10^{-19}\cdot dv/dx$;

-for *Dolofast*: $D=1,3997\cdot10^{-19}+0,9045\cdot10^{-19}\cdot dv/dx$;

-for *Dolgit*: $D=0,1407\cdot10^{-19}+0,5272\cdot10^{-19}\cdot dv/dx$;

-for *Nurofen*: $D=3,0096\cdot10^{-19}+1,3952\cdot10^{-19}\cdot dv/dx$.

It results from the carried out viscosity measurements (Fig. 2) that the tested pharmaceutical preparations before exposure in model dialysis fluid (after squeezing out of a tube) are non-Newtonian systems. The course of the dependence D= f(dv/dx) (fig.2) indicates that they are liquids diluted with shear for which shear stress does not increase symmetrically in relation to mechanically increased shear rate. Taking into account the order of magnitude of changes of constant rate of diffusion coefficient, it may be anticipated that the process of mass exchange on phase boundary will be the most effective from *Nurofen* ($b(k)=1,3952\cdot10^{-19}$) and *Ibufen* ($b(k)=1,2747\cdot10^{-19}$), insignificantly less effective from *Dolofast* ($b(k)=0,9045\cdot10^{-19}$) and *Dolgit* ($b(k)=0,5272\cdot10^{-19}$). During estimation of the therapeutic agent pharmaceutical availability (diffusion through Viscing dialysis membrane to water within 240 min) it was found out that in the course of back diffusion preparations bind water in relation to weighed sample of the preparation in the amount: *Ibufen* - 65,97%, *Dolofast* - 81,19%, *Dolgit* -47,13%

and *Nurofen* - 40,97%. Water bond changes radically the rheological parameters of the preparations and affects the order of magnitude of the therapeutic agent diffusion coefficient (D_1). The course of the dependence between the diffusion coefficient (D_1) after hydrogels exposure and shear rate was described at p=0,05 of the regression equation. The highest correlation coefficients were obtained for:

- *Ibufen* for the equation y= a+b logx (r=0,9999): $D1=2,3891\cdot10^{-19}+3,3828\cdot10^{-19}\cdot\log dv/dx$;
- *Dolofast* for the equation y= a+b logx (r=0,9949): D1=-18,3850+ 0,5011 ·log dv/dx;
- *Dolgit* for the equation log y=a+b·1/x (r=0,9522): D1=-17,1947-0,1487·1/ dv/dx;
- *Nurofen* for the equation y=a+b·x (r=0,8400): $D1=9,2800\cdot10^{-20}+8,6958\cdot10^{-19}\cdot\log dv/dx$.

Taking into account the types of regression equations at the criterion of maximal value of the correlation equation r, with which the course of the above dependences was described, it should be stated that the process of mass exchange on the phase boundary (Viscing, perimastoid dermis) with back resorption of dialysis fluid (water), will be complex and individual for each preparation. In the conditions of practical pharmacotherapy, additionally the rate of volatile components loss on phase boundary (human skin) should be taken into consideration.

Diffusion of therapeutic agent (ibuprofen) from the tested hydrogels to model dialysis fluid

The quantity of the diffusing therapeutic agent (ibuprofen) to model dialysis fluid c_t was determined by spectrophotometric method. The mass exchange on phase boundary for each of the tested preparations was monitored through a symmetric measurement of electric conduction $\Delta\lambda_{pom}(\mu S)$. Mean values $\Delta\lambda_{pom} = \lambda_{pom} - \lambda_{H20}$ (x± ts, m=3-5) were the base for tracing the dependences : $\Delta\lambda_{pom}$= f(t, min.) which enabled to estimate the hydrotropic properties of diffusing adduct in a stream of ions. The course of the dependence $\Delta\lambda_{pom}$= f(t, min.) is presented in fig. 3.

The determined quantity of ibuprofen c_t during the container exposure in dialysis fluid in time t (240 min) was the base for calculating the coefficient Q (quantity of therapeutic agent diffusing through phase boundary (Viscing, perimastoid dermis) to model dialysis fluid in relation to its content in the container niche (hydrogel weighed sample): $Q = c_t/c_0\cdot100\%$. The course of the dependence between Q value characterising the ibuprofen rate of diffusion from the tested preparations to model dialysis fluid and time is presented in fig. 4.

Calculation of the value $(c_0-c_t)/c_0$ (the content of ibuprofen in dialysis niche) enabled to trace the course of regression in time function, which enabled to estimate the order of the process of mass exchange on phase boundary (fig. 5).

The course of the dependence presented in fig. 5 was described at p=0,05 with regression equations demonstrated in table IV.

Taking into account the numerical value of correlation coefficient r, it results from the presented equations that the process of diffusion of a stream of ions: $\Delta\lambda = f(t)$ and also associated with it process of ibuprofen release: $Q = f(t)$ takes place in accordance with logarithmic form of an exponential equation: $y= a +x^b$ ($\log y = a+ b \log x$). The process of mass exchange (diffusion) on phase boundary in time function: $c_0-c_t/c_0=f(t)$ is complex and its mechanism is within the kinetics of "O" and "II" order (insignificant difference in the numerical value of correlation coefficient r).

The presented in tab. IV regression equations of the type $y = a + bx$ at $p = 0,05$ were the base for calculating areas P under the curves demonstrated in fig. 3-5 and expressed in conventional units (c.u.). It results from numerical values of P (c.u.) (tab. IV), that the stream of ions diffuses most effectively from *Nurofen* hydrogel, in which therapeutic agent is in the form of sodium salt of the highest electrophoretic mobility. Preparations *Dolofast* and *Ibufen* are characterised by significantly smaller P (c.u.), in the prescription of which the therapeutic agent is in the form of hydrotropic bond with lysine and additionally in the prescription of *Ibufen* the manufacturers used triethanolamine for Carbopol cross-linking. The determined for *Dolgit* order of magnitude $\Delta\lambda_{pom}$ indicates that the therapeutic agent is not in the form of hydrotropic adduct (ibuprofen dissolved in appropriately selected mixture of lipophil solvents). The above finds confirmation in the value of the constant rate of diffusion of the stream of ions: K_d=0,3845 for *Nurofen*, K_d=0,2966 for *Dolofast*, K_d=0,1775 for *Ibufen* and K_d=0,0186 for *Dolgit*. It results from the course of the dependence Q = f(t, min.) (fig.3) that the biggest amount of therapeutic agent is in the stream of ions diffusing from *Ibufen* (P=3367,1 c.u.), significantly less in the stream of ions diffusing from *Dolofast* (P=2112,1 j.u.) and *Nurofen* (P=1595,3 c.u.). The least amount of therapeutic agent is released from *Dolgit*, in which ibuprofen is in the form of molecular fragmentation (lipophil medium decides on the definite applicative solubility of ibuprofen) (tab. IV).

To compare, investigations were carried out on the process of mass exchange through natural pig perimastoid dermis (material *in vivo*) from the tested preparations to model dialysis fluid – water (*in vitro*). The prepared and used for measurements pig perimastoid dermis had stable thickness (h, mm) and degree of hydration determined after the process of

diffusion (tab. V). The course of the dependence between electric conduction $\Delta\lambda_{pom}$ of model dialysis fluid increasing in time function t (min)(fig. 6) is described at the level of significance p = 0,05 with regression equations presented in table V. The determined quantity of the diffusing therapeutic agent c_t and calculated coefficient $(c_0-c_t)/c_0$ were the base for the determination of pharmaceutical availability: $Q=c_t/c_0 \cdot 100\%=f(t)$ and order of the process of mass exchange through a natural membrane (perimastoid dermis): $(c_0-c_t)/c_0=f(t)$ (fig.7 and 8).

The course of the above dependences is described with regression equations at p= 0,05 presented in tab. V. They were the base for calculating P (c.u.) and estimating applicative preferences of the tested preparations.

It results from the course of the dependence $\Delta\lambda_{pom}=f(t, min.)$ and calculated P (c.u.) that the stream of ions penetrates perimastoid dermis most effectively from Nurofen, where ibuprofen is in the form of sodium salt (P = 6017,5). Ibuprofen in the form of hydrotropic adduct with lysine demonstrates weaker intensity of penetration from *Ibufen* (P=3910,7 c.u.) and from *Dolofast* (P=2132,3 c.u.). The least effective is the stream of ions diffusing from *Dolgit* (ibuprofen in the form of molecular fragmentation of acidic form).

It results from the determined pharmaceutical availability Q in time function t (min) that ibuprofen diffuses through perimastoid dermis most effectively as regards quantity from *Ibufen* (P=982,9), and then from *Nurofen* (829,8), *Dolgit* (826,3) and *Dolofast* (155,44).

The order of the process of mass exchange through natural phase boundary – perimastoid dermis, described with regression equations, remains in full symmetry in relation to an artificial dialysis membrane of Viscing type, that is, the numerical value of correlation equation does not determine definitely whether the process of diffusion proceeds in accordance with kinetics of “O” and “II” order.

Quantitative differentiation of the process of mass exchange between ibuprofen hydrotropic forms: ibuprofen lysine salt > ibuprofen sodium salt > ibuprofen in the form of acid molecule results from the performed experimental studies.

CONCLUSIONS

1. The tested hydrogels lose volatile components during exposure at temp. 37^0C, which is associated with high content of water, triethanolamine or low-molecular adjuvant substances in their prescription composition. After application on skin, the process of volatile components loss from the surface layer of the preparation is

accompanied by the increase of structural viscosity, on the average by 50% (loss of hydrogel mass is within the limit 48,85-57,87%), which causes the decrease of pharmaceutical availability.

2. The calculated with the use of Einstein-Smoluchowskiego equation ($D=kT/6\Pi r\eta$) theoretical coefficients of diffusion (D) enabled to estimate the effect of structural viscosity of the preparations on the rate of mass exchange on phase boundary. The course of the dependence between the diffusion coefficient and shear rate is described with regression equations which enables to estimate the preferences of the tested preparations to effective diffusion of therapeutic agent *in vivo*. When applying the tested preparations, attention should be paid to the fact of back binding of water through hydrogel structure (a tendency to dehydration of deeper skin layers).
3. After exposure of the tested hydrogels in model dialysis fluid (t=240 min.) significant change of their rheological parameters and therapeutic agent diffusion coefficient (D_1) is observed, which markedly affects the process of mass exchange on phase boundary. Thus, penetration of ibuprofen in the form of hydrotropic adduct (Ibufen, Dolofast, Nurofen) or in the form of molecular fragmentation of acidic form (Dolgit) through standard membrane Viscing type and pig perimastoid dermis is complex and its mechanism is between the kinetics of “O” and “II” order.
4. The course of the dependence between $\Delta\lambda_{pom}(\mu S)=t(min.)$ through the calculated values P (c.u.) indicates that the order of magnitude of the stream of ions diffusing from hydrogel preparations is not symmetrical with the calculated pharmaceutical availability (coefficient $Q = c_t/c_0 \cdot 100\%$). It results from numerical values P (c.u.) calculated on the basis of the dependence: Q = f(t), that diffusion of ibuprofen is most effective from hydrogel preparations in the form of hydrotropic adduct with lysine (*Ibufen, Dolofast*). The release of ibuprofen in the form of sodium salt (*Nurofen*) and molecular fragmentation of acidic form (*Dolgit*) is significantly slower.