Viscosity of pharmacopeial multimolecular ointment vehicles and pharmaceutical availability of a model therapeutic agent

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Summary

Viscosity was tested of basic ointment vehicles such as: white petrolatum, yellow petrolatum, anhydrous lanolin and eucerin produced by different manufacturers.

Ointment vehicles of definite type differ significantly in rheological parameters. In the same group of products, the experimentally determined viscosity value of some vehicles is two-fold (petrolatum, anhydrous lanolin) or even three-fold (eucerin) higher than that of others.

On the basis of rheological tests, using Einstein-Smoluchowski equation ($D = kT/6\pi r\eta$), theoretical coefficient was calculated of a model therapeutic agent – salicylic acid diffusion ($-\log x_2^i=1,22$) from the tested vehicles to the external compartment. The obtained results were related to the performed in vitro measurements of the rate of salicylic acid release from the above mentioned ointment vehicles to model acceptor fluid.

High correlation was observed between theoretical values of diffusion coefficients calculated on the basis of viscosity measurements and tested experimentally pharmaceutical availability of salicylic acid. It was confirmed by describing this dependence with regression equations of high correlation coefficients ($r\geq0,9667$).

Marked disproportions between rheological parameters of the vehicles of definite type produced by individual manufacturers are the cause of differences in pharmaceutical availability of therapeutic agents contained in these vehicles.

Key words: ointment vehicles, salicylic acid, viscosity, pharmaceutical availability

INTRODUCTION

Ointments are not only a well-tried form of a non-prescription drug but they are also a dominating group of prescription drugs. It is known that the quality of manufactured preparations depends on numerous factors such as: chemical properties of the used components, order of their addition and even the applied technique of production [1, 2]. It has been found out that first of all the kind of the used ointment vehicle, in which therapeutic agent forms real solutions at the moment of liquefaction on phase boundary, affects the rate of therapeutic substance supply to skin surface [3, 4]. Thus, the vehicle components which predominate in the preparation applied on skin may change its physicochemical properties and affect the process of mass exchange on phase boundary [5, 6].

In the available literature, a dependence has been demonstrated between physicochemical properties of ointment vehicles and kinetics of therapeutic agent release to the external compartment. The above points to the possibility of obtaining an effective form of a drug applied on skin through a quantitative change of auxiliary substances [3, 7-9].

From among fundamental properties of ointment vehicles, which must be taken into account in the evaluation of applicative properties of the preparations, attention should be paid first of all to rheological parameters. Characteristic internal network structure of a vehicle formed by solid and liquid phase connection decides most frequently on its viscosity and thus, on the value of therapeutic agent diffusion coefficient.

The aim of the carried out studies was to estimate rheological properties of standard pharmacopeial bases which are vehiculum for prescription and market pharmaceutical products applied on skin. The effect of basic viscosity parameters on the process of mass exchange on phase boundary was assessed (*in vitro*) by formulating a model preparation on the base of lipophil and adsorptive ointment vehicles with 2% salicylic acid.

MATERIAL AND METHODS

Reagents

Ointment vehicles:

- white petrolatum produced by different manufacturers:
  - WB-1 (Lefarm, Galen Laboratory);
  - WB-2 (PPF Hasco-Lek S. A.);
  - WB-3 (Eucerine Works, Pharmaceutical Laboratory S. J.);

- yellow petrolatum produced by different manufacturers:
  - WŻ-1 (PPF Hasco-Lek S. A.);
  - WŻ-2 (Eucerine Works, Pharmaceutical Laboratory S. J.);
  - WŻ-3 (Galen Laboratory Olsztyn);
- anhydrous lanolin produced by different manufacturers:
  - LB-1 (Lefarm, Galen Laboratory);
  - LB-2 (PPF Hasco-Lek S. A.);
  - LB- (PPF Gemi);
  - LB-4 (Eucerine Works, Pharmaceutical Laboratory S.J.);
- eucerine produced by different manufacturers:
  - E-1 (Ziaja Ltd);
  - E-2 (Eucerine Works, Pharmaceutical Laboratory S.J.).

Model therapeutic agent: salicylic acid – P.O.Ch. S.A. Gliwice, batch 01330203.

Micronized salicylic acid was a non-homogeneous system. Micronization caused degradation of primary crystallographic structure with the tendency of particles adherence with contact surfaces. Mean value of micronized particles was $1{,}25 \cdot 10^{-3}$ (l) x $0{,}625 \cdot 10^{-3}$ (h) cm^2.

Apparatus

- digital cone-plate rheometer DV-III-Brookfield, 3,0 with "Rheocalc for Windows" software;
- bath thermostat PGW E1, Medingen;
- Nicolet Evolution 300 spectrophotometer, version 1,0, Spectro-Lab;
- general laboratory balance, Precision Engineering Plant „Radwag";
- analytical balance, Precision Engineering Plant „Radwag";
- mechanical stirrer R50D, CAT M. Zipperer GmbH.

Way of model preparations formulation with the content of 2% salicylic acid

2% ointments with micronized salicylic acid were prepared. White petrolatum, yellow petrolatum, anhydrous lanolin and eucerine were used as vehicles. Small amount of sterile liquid paraffin was used for salicylic acid grinding [1].

Determination of viscosity parameters [10-12].

Viscosity of ointment vehicles was determined at 37^0C with Brookfield cone-plate digital rheometer (DV-III, version 3.0) connected with Medingen bath thermostat (PGW E-1).

Predictable real solubility – log x_2 of selected nonsteroidal therapeutic agents in some auxiliary substances included into the ointment vehicles composition.

Using general principles of Hildebrand-Scatchard-Fedors theory of solubility, from dependences presented in publications [13] there were calculated thermodynamic parameters of saturated hydrocarbons and saturated and unsaturated fatty acids, which in the conditions of liquefaction on skin surface can form real solutions with nonsteroidal therapeutic agents. Basic parameters characterizing the above mentioned components of ointment vehicles are demonstrated in tables I, II and III.

The calculated parameters were the base for counting out salicylic acid real solubility as well as that of aceclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and tenoxicam. Topological structure of nonsteroidal therapeutic agents was characterized by indices IC and SIC, which is demonstrated in table IV and V.

Testing the kinetics of therapeutic agent penetration from the model ointments containing 2% salicylic acid into the external compartment

Testing pharmaceutical availability of salicylic acid from model preparations was performed by membrane method with a plastic container (modified Mutimer et al. apparatus) at 37^0C. The niche of the apparatus was filled with 7g of model preparation containing micronized salicylic acid and the preparation was fixed with earlier prepared cellophane dialysis membrane (24 h exposure in double distilled water). The container cover was connected to the niche with set screws. The Mutimer et al. apparatus was placed in a round-bottom beaker, in which a mechanical stirrer of regulated rate of rotations was installed. The rate of the process of mass exchange was investigated by determining the amount of salicylic acid diffusing into acceptor fluid (double distilled water) at defined time intervals by spectrophotometric method. Approximation equation at $p=0,05$ i $r \geq 0,9996$: $A=0,0629\ c + 0,0003$, with which the dependence between absorbance (A) and the therapeutic agent concentration (c) was described, transformed to the form: $c=A-0,0003 / 0,0629$ enabled to

determine the amount of therapeutic agent diffusion through the phase boundary in the time function t(min).

RESULTS AND DISCUSSION

The results of viscosity measurements obtained at 37^0C at two freely selected shear rates are presented in tables VI-X. The measured viscosity values enabled to calculate the theoretical value of diffusion coefficient of a model therapeutic agent (salicylic acid) to the external compartment. Einstein-Smoluchowski equation was used for this purpose [14, 15]:

$$D = \frac{kT}{6\pi r \eta},$$

where:

D – diffusion coefficient, k – Boltzman constant, T –temperature in Kelvin scale, r – observed radius of salicylic acid particle [16], η – viscosity.

The observed salicylic acid radius r, being beside viscosity of the tested vehicle the base for the above calculation was estimated theoretically on the basis of known volume V of salicylic acid particle [13]. Independently of the compound particle symmetry axis, with the assumed equivalence of axially or equitorially arranged substituents in its rotational model of Mark, Kuchn, Houwink, the following equation can be used:

$r = \sqrt[3]{\frac{3V}{4\pi}}$, introduced after transformation from the dependence: $V = \frac{4}{3}\pi r^3$ (Table VI).

White petrolatum WB-1 is characterized by the lowest viscosity values determined at freely selected shear rates and the highest values of salicylic acid diffusion coefficient. At shear rate 0,6 l/s, the salicylic acid diffusion coefficient calculated on the basis of this petrolatum viscosity is as high as $64{,}7199 \cdot 10^{-19}$ (m^2/s) and nearly two-fold exceeds parallel values obtained for the other ointment vehicles in this group (Table VII).

Ointment vehicle WŻ-3 should be distinguished from among the tested yellow petrolatums. It demonstrated markedly lower viscosity than the other yellow petrolatums. At shear rate 0,6 l/s it was 11 597 mPa·s, whereas for other yellow petrolatums the obtained values were 21 868 and 24 187 mPa·s. Also, the diffusion coefficient obtained at this shear rate for the product WŻ-3 was two-fold higher than in the case of other yellow petrolatums (Table VIII).

Among the tested anhydrous lanolins, LB-3 had the lowest viscosity (17561 and 12922 mPa·s). The diffusion coefficient of the therapeutic agent from this lanolin, calculated in these conditions of the experiment, exceeded several times the values obtained for the other products in this group of vehicles (Table IX).

Eucerine E-2 has lower viscosity (8615 mPa·s at shear rate 0,6 l/s) than eucerine E-2 (27 832 mPa·s). That is a cause of analogous differences in the values of the calculated coefficients of therapeutic agent diffusion: respectively $79{,}6547 \cdot 10^{-19}$ and $24{,}6560 \cdot 10^{-19}$ at the same shear rate.

A model course of the dependence between the amount of released salicylic acid (in μg) on surface unit (in cm^2) from an ointment vehicle in a time function is presented in figure 1.

The course of the above dependences for all the tested ointment vehicles was described with correlation equations and the areas under the curves of salicylic acid release to the external compartment expressed in conventional units were calculated with an integral method. The results of the calculations are presented in tables X-XIII.

Saturated hydrocarbons with the percentage advantage of n-eicosane are in the composition of white petrolatum and thus, the temperature of liquefaction of this class of lipophil vehicles is close to the temperature of a human body ($35{,}7^0$C). With the disproportion of n-eicosane in the composition of white petrolatum and with comparable numerical value of the solubility parameter $\sigma_{1/2}$, its share will decide on the quantitative course of mass exchange on phase boundary. The above is proved by the calculated values of the areas under salicylic acid release curves.

Among the tested white petrolatums the vehicle WB-1 (P(c.) is 120.630) has the largest area under the curve of salicylic acid release. Insignificantly lower value was obtained for white petrolatum WB-3 (103.734 c..) (Table XI).

In the group of yellow petrolatums no significant differences were observed in the values of the areas under the curves of salicylic acid release to the dialysis fluid. The highest value was obtained for the vehicle WŻ-3 (77.957 c. u.) (Table XII).

In the case of anhydrous lanolins, long chain fatty acid esters (lanolin is structurally a mixture of sterol alcohol esters and long chain fatty acids) decide on effective mass exchange on phase boundary. Their quantitative share decides on the numerical value of the so called hydrous number. As lanolin does not liquefy at human body temperature and during application binds water on phase boundary, it will favour solubility of salicylic acid and its molecular diffusion into a model dialysis fluid. The calculated values of the areas under

salicylic acid release curves prove significant difference in the hydrous number of the tested lanolins (Fig. 2-4).

The largest area under the curve of therapeutic agent release from anhydrous lanolin was obtained for LB-3 vehicle (148.731 c.u.) and then for LB-4 product (130.734 c.u.). Insignificantly lower values of the areas are the measure of salicylic acid release from LB-1 and LB-2 vehicles (119.950 and 111.280 c.u., respectively) (XIII).

Among eucerins E-2 vehicle is distinguished. The area under the curve of salicylic acid release from an ointment manufactured on the base of E-2 to dialysis fluid is nearly two-fold larger than the area under the curve of release from E-1 vehicle (195.474 vs 100.520 c.u.).

CONCLUSIONS

1. Ointment vehicles of definite type produced by various manufacturers differ significantly in rheological parameters. Within the same group of products, the experimentally determined viscosity value of some vehicles is two-fold (petrolatum and anhydrous lanolin) or even three-fold (eucerin) higher than that of others.

2. Prediction of therapeutic agent pharmaceutical availability on the basis of ointment vehicles viscosity parameters is possible with the use of Einstein-Smoluchowski equation. Theoretical values of diffusion coefficients calculated on its basis have been confirmed in the studies *in vitro* of the kinetics of therapeutic agent release to the acceptor fluid. The dependence of the areas under the curves of salicylic acid release on the calculated on the basis of viscosity parameters, diffusion coefficients of therapeutic agent from ointment vehicles are presented in figures 2, 3, 4.

3. Close correlation was observed between theoretical values of diffusion coefficient and tested experimentally pharmaceutical availability of salicylic acid. It was confirmed by describing this dependence with linear equations of high correlation coefficients ($r \geq 0{,}9667$) (fig. 2-4).

4. As it results from the calculations presented in table IV, the value $-\log x_2^i$ for the applied model therapeutic substance (salicylic acid) is 1,22. It should be expected that for nonsteroidal therapeutic agent whose value is $-\log x_2^i < 1{,}22$ or $> 1{,}22$, there will respectively come to the decrease or increase of the amount of substance diffusing through phase boundary.

The obtained results of the study lead to the conclusion that marked disproportions in the measured values of vehicles viscosity, which according to the Polish Pharmacopoeia VI

are identical, will translate into differentiation of the therapeutic agent pharmaceutical availability.