

Polyoxyethylene fatty acid esters as potential promoters of transdermal absorption for morphine hydrochloride and sulphate

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Summary

The presence of opioid receptors μ in pathologically changed skin and mucosa justifies application of preparations with morphine salts to obtain topical analgesic activity. Numerous factors associated with the vehicle and therapeutic agent physiochemical properties affect the capability and rate of penetration of a therapeutic substance in the form of a drug into dermis. Promoters of transcutaneous absorption, which weaken the integrity of epidermal corneal layer and thus, increase therapeutic substance penetration play more and more important role. In this study non-ionic macromolecular surface active compounds from Rokacets group were suggested as potential promoters of transdermal absorption for morphine sulphate and hydrochloride.

The aim of the study was to work out prescription composition of ointment with morphine salts of optimal rheological and morphological parameters and high pharmaceutical availability of the therapeutic agent (morphine sulphate, hydrochloride).

Three model emulsive ointment vehicles were prepared and selected promoters of transdermal absorption were introduced into them. On the basis of the formed vehicles ointments were made with morphine sulphate and hydrochloride. The obtained vehicles and ointment preparations were subjected to rheological tests. Spreadness was determined by extensometric method and viscosity with digital cone-plate rheometer. Morphological parameters of the vehicles and ointments, such as: pH and pharmacopeal density were estimated. Carrying out direct diffusion from the surface of the preparation to acceptor fluid (to water), the amount of the released therapeutic substance in time function was determined by spectrophotometric method.

The performed tests demonstrated that the investigated vehicles and ointments are non-Newtonian systems, viscoelastic and highly thixotropic. The kind of morphine salt affects the

spreadness and viscosity of model ointments. Preparations with morphine hydrochloride have higher spreadness than viscosity and more alkaline pH.

From among the investigated non-ionic surface active compounds Rokacet R-40 appeared to be the most beneficial promotor of transdermal absorption for both pharmacopeal morphine salts. Pharmaceutical availability of morphine sulphate and hydrochloride is the highest from ointments with its content in the vehicle prescription.

Key words: morphine, Rokacets, ointments rheology pharmaceutical availability

INTRODUCTION

Detection of opioid receptors in skin and mucosa made possible to battle against neurogenic pain by topical application of morphine in the form of an ointment, gel, cream and the like [1, 2]. Analgesic activity of morphine topically applied on pathologically changed skin appears after its penetration to dermis, because in this part nerve endings are found and opioid receptors μ become active by which pain stimuli conduction to cerebral cortex is blocked.

Many factors affect the capability and rate of therapeutic substance (including morphine) penetration into dermis [3]. One of the most important is distribution coefficient *octanol - water* (P) strictly correlating with distribution coefficient *epidermal corneal layer – vehicle* (K_m). It enables to determine the therapeutic substance affinity to skin [4]. Very low morphine coefficient P ($P=1,48$ [5]) proves hydrophilic character of the molecule and faint absorption by normal skin. However, after application of morphine preparation on pathological skin with pathologically changed or damaged epidermis, the absorption may be highly effective. It depends to a large degree on the vehicle prescription composition and on the applied promoters of transdermal absorption [6].

In this experiment, model ointments with morphine salts were produced on absorptive vehicles the base of which was eucerine. Owing to non-ionic emulsifiers of the type w/o being in the composition of eucerine (cetyl alcohol, cholesterol), there comes to the seal of morphine salt aqueous solution in the internal phase of emulsion during ointment production. This phenomenon should contribute to regular and prolonged process of therapeutic agent diffusion from the surface of the preparation to dermis. According to Polish Pharmacopoeia VI

requirements, wound ointments must be aseptic, that is why a significant argument confirming the rightness of selection of this type of a vehicle is the possibility of thermal sterilization of all its components. Non-ionic macromolecular surface active compounds from Rokacets group were suggested as potential promoters of transdermal absorption for the selected therapeutic agents (morphine sulphate and hydrochloride). Rokacets (polyoxyethylene esters) are formed as the result of oxyethylation of fatty acids, essential fatty-acid glycerides or some pharmacopeal waxes [7]. They belong to biodegradable compounds, practically non-toxic, devoid of own pharmacological activity, not irritating skin and mucosa, not inducing allergic reactions [8, 9, 10, 11, 12, 13].

The aim of the study was to determine the effect of selected promoters of transdermal absorption on rheological (spreadness, viscosity) and morphological (pH, pharmacopeal density) parameters of model vehicles and ointment preparations and on pharmaceutical availability of pharmacopeal morphine salts (hydrochloride and sulphate) from the suggested forms of a drug.

MATERIAL AND METHODS

Reagents

- Eucerine – Eucerine Works, Pharmaceutical Laboratory S.C. Kraków;
- Glycerol 86% FP VI – Pharmaceutical-Cosmetic Laboratory PAMPA, Piaseczno;
- Morphine hydrochloride (Morphini Hydrochloridum), POLFA Kutno S.A., Kutno;
- Morphine Sulphate (Morphini Sulfas), injection solution 20 mg/ 1 ml – Warsaw Pharmaceutical Plant POLFA, Warszawa;
- Rokacet R-70 – Chemical Plant Rokita S.A., Brzeg Dolny;
- Rokacet R-40 – Chemical Plant Rokita S.A., Brzeg Dolny;
- Rokacet R-26 – Chemical Plant Rokita S.A., Brzeg Dolny.

Apparatus

- Nicolet Evolution 300 Spectrophotometer, version 1,0, Spectro-Lab;
- Digital rheometer DV-III Brookfield 3,0 with computer program “Reocalc for Windows”;
- Bath thermostat PGW E1, Medingen;
- Microcomputer Multifunction Meter CX-551 with a complex electrode ESKP-301 WP-EURO-SENSOR, Gliwice;

- laboratory equipment: Multimer apparatus, pyknometer, extensometer and others.

Prescription composition of model vehicles and ointments

The composition of 3 model emulsive ointment vehicles was worked out (table I). Eucerine with glycerol were the vehicle base. Selected promoters of transdermal absorption from Rokacets group were added.

Basing on the above vehicles 3 ointments were produced, containing 0,225% of morphine hydrochloride (MCl), and 3 ointments containing 0,2% of morphine sulphate (MS). Despite different percentage share of morphine salts, the content of free alkaloid in the produced preparations was the same. Model vehicles and ointments were made in accordance with the Polish Pharmacopoeia VI requirements. Prescription compositions of model ointments are presented in table II.

Spreadness tests of model vehicles and ointments

The spreadness was determined with an extensometer at 298 K. The measurement consists in the determination of the degree of the increase of the tested preparation area together with the increase of load [14].

Determination of model vehicles and ointments viscosity parameters.

Viscosity parameters were determined at $310 \pm 0,1$ K with digital cone-plate rheometer with a bath thermostat [12, 13, 15].

Determination of model vehicles and ointments pH and pharmacopeal density (d).

Determination of hydrogen ions activity (pH) and density of the tested preparations was performed in accordance with Polish Pharmacopoeia VI recommendations [16].

Estimation of pharmaceutical availability of morphine hydrochloride and sulphate from the produced model ointments.

The estimation of pharmaceutical availability was performed with a technique applied for transdermal therapeutic systems according to the recommendations of European Pharmacopoeia [17].

Testing of the rate of diffusion of morphine salts from the produced model preparations was performed with the method of free diffusion from the surface of the preparation to water with six modified Multimer apparatus. 2,0 g (± 001 g) of the tested ointment was weighed

into each apparatus, then it was slightly liquefied at 310 K to assure uniform filling of the containers and 10 cm³ of distilled water were added. Then, in the given time intervals (after 15, 30, 45, 60, 90, 120 min) the solutions from above the ointment were collected and *ex tempore* the values of maximal absorbance were measured spectrophotometrically (A) at $\lambda=285$ nm. Basing on the equation of calibration curves described at the level of significance $p=0,05$, the concentrations (C_s) of morphine hydrochloride and morphine sulphate were calculated.

The equations have the form:

- for the ointment with MCL: $A=20,8745 \cdot 10^{-5} + 84,45439 \cdot C_s$, ($r=0,9999$);
- for the ointment with MS: $A= -42,7089 \cdot 10^{-3} + 87,94855 \cdot C_s$, ($r=0,9999$).

RESULTS AND DISCUSSION

Model ointments with morphine hydrochloride

The results of spreadness tests were presented in figure 1. The course of dependence between the spread surface of the vehicle and the model preparations with morphine hydrochloride and the value of the imposed load was described at the level of significance $p=0,05$ with correlation equations of the type $y = ax + b$. Parameters a and b of the equation were used to calculate, with integration method, areas P under the spreadness curves expressed in conventional units [c.u.]. To make the comparative analysis easier, basing on the calculated areas, the values of indices i (P) were determined – being a quotient of the area under the spreadness curve of the preparation and the vehicle on the base of which it was produced. The results of the calculations are presented in table III.

Introduction of aqueous solutions of morphine hydrochloride into adequate vehicles produced on the base of Rokacets increases their spreadness. It is proved by the ointment i(P) indices values >1 in relation to a unit index of an adequate vehicle, e.g. i(P) of model ointment with morphine hydrochloride produced on vehicle with Rokacet R-26 (M1Cl) is 1, 2 (tab. III).

The kind of the applied Rokacet affects spreadness of the ointment with morphine hydrochloride. The highest spreadness was observed after application of Rokacet R-70 in the prescription of model ointments (33692 c.u.) (Tab. III).

Viscosity measurements enabled to determine flow curves (the dependence of shear stress on shear rate) in the form of hysteresis loop. They were obtained by increasing shear

rate to a certain maximal value and then its rapid decrease to zero. Figure 2 presents an exemplary hysteresis loop for ointment with morphine hydrochloride made on the vehicle with Rokacet R-26 [12].

Viscosity measurements demonstrated that the tested ointment vehicles and preparations with morphine hydrochloride produced on their base are non-Newtonian systems and viscoelastic because their flow curves are not straight lines and they do not cross the start of co-ordinate system. They belong to rheologically unstable thixotropic systems, because in isothermic conditions ($T = 310\text{ K}$) the values of shear stress of their ascending flow curve are significantly higher than the values of shear stress of the descending curve (fig. 2) [13].

Viscosity parameters are the base for predicting pharmaceutical availability of the therapeutic agent from the tested forms of an ointment. High pharmaceutical availability of the therapeutic agent is explained to a certain degree by low viscosity of systems at 310 K with preservation of hysteresis loop of small area [18].

Ascending and descending curves of hysteresis loop were described with correlation equations and areas under these curves and the area drawn by hysteresis loop were calculated by integration method. The obtained results expressed in conventional units are presented in table IV.

The smallest hysteresis loop was obtained for model ointment with morphine hydrochloride and Rokacet R-70 (3542 c.u.). The value of $i(P)$ index of this ointment is <1 in relation to a unit index of a vehicle with Rokacet R-70, which before the introduction of a therapeutic agent has high thixotropy (5601 c.u.). Viscosity of model ointments with morphine hydrochloride determined at 310 K at three freely selected shear rates is presented in fig. 3.

Model ointment with Rokacet R-70 demonstrated the lowest viscosity at all shear rates and the smallest area of hysteresis loop. The value of viscosity noted for this preparation at shear rate 260 l/s was $110,1\text{ mPa}\cdot\text{s}$ on descending curve. In the same conditions of the experiment the viscosity of an ointment with Rokacet R-40 and Rokacet R-26 was: $118,5$ and $141,5\text{ mPa}\cdot\text{s}$, respectively.

The results of pH measurements and the density of vehicles and model ointments with morphine hydrochloride is presented in table V.

Activity of hydrogen ions (pH) of the tested vehicles and ointments is >7 , but in each case pH of vehicles is higher than pH of corresponding ointments with morphine hydrochloride. For model ointments the obtained values of pH were within the limit: $7,91$ - $8,25$.

Comparative analysis of pharmacopeal densities (d) of vehicles and ointments with morphine hydrochloride measured according to the recommendations of Polish Pharmacopoeia VI indicates that they are lower than 1 g/cm^3 and very similar.

The diffusion kinetics of morphine hydrochloride from model ointments to acceptor fluid (to water) was described by correlation equations of the type $y = a + bx$. The parameters of this equation are presented in table VI.

Constant rates of morphine hydrochloride diffusion from model ointments to acceptor fluid are within the limits: $0,01\text{-}6\text{-}0,0114 \text{ mol}^1\text{dm}^{-3}\text{min}^{-1}$. The highest value of the constant was noted for the process of release from the ointment with Rokacet R-70 characterized by low viscosity and small area of hysteresis loop (Fig. 2, 3, tab. IV).

Model ointments with morphine sulphate

The results of the spreadness test are presented in figure 4. Correlation equations of the type $y = ax + b$ describing spreadness of model vehicles and ointments with morphine sulphate at $T = 298 \text{ K}$ together with calculated areas under spreadness curves are presented in table VII.

The differences in spreadness of ointments with morphine sulphate produced on different vehicles are less distinct than in the case of model preparations with morphine hydrochloride (fig. 4). Nevertheless, similar dependences were observed here as after introduction of morphine hydrochloride into the vehicle prescription. The highest spreadness was observed in an ointment with morphine sulphate produced on the vehicle with Rokacet R-70 (27693 c.u.).

Rheological instability (thixotropic features) of model ointments with morphine sulphate is documented by presented in fig. 5 exemplary hysteresis loop obtained for the preparation in the composition of which Rokacet R-40 was applied [12].

The areas of hysteresis loops obtained for model ointments with morphine sulphate are presented in table VIII.

The smallest area of hysteresis loop was obtained, similarly as in the tests of systems with morphine hydrochloride, for an ointment with Rokacet R-70 (2355 c.u.).

The value of viscosity of model ointments with morphine sulphate determined at 310 K at three freely selected shear rates is presented in fig. 6.

Similarly as after introduction of morphine hydrochloride, the lowest viscosity at all shear rates was noted for the ointment with morphine sulphates and Rokacet R-70. At shear

rate 260 l/s in the descending curve, viscosity of this preparation was 97,9 mPa's and viscosity of an ointment with Rokacet R-40 and R-26: 130,7 and 148,3 mPa's, respectively.

The results of the measurements of pH and density of model ointments with morphine sulphate are presented in table IX.

Activity of hydrogen ions of ointments with morphine sulphate is within the limit 7,64-7,80, it is lower than pH of corresponding vehicles and than pH of model ointments with morphine hydrochloride (7,91-8,25).

The density of model ointments with morphine sulphate does not differ basically (0,881-0,899 g/cm³) and is similar to the density of ointments with morphine hydrochloride (0,844-0,908 g/cm³) (tab. V).

The kinetics of diffusion of morphine sulphate from model ointments to acceptor fluid (to water) was described with correlation equations of the type $y = a + bx$. Parameters of these equations are presented in table X.

Constants of the rate of diffusion of morphine sulphate from model ointments to acceptor fluid are within the limit: 0,0186-0,0241 mol¹dm⁻³min⁻¹ and are higher than the constants describing the process of diffusion of morphine hydrochloride from the same ointment vehicles (0,0106-0,0114 mol¹dm⁻³min⁻¹) (tab. VI). The highest value of the constant of morphine sulphate diffusion was observed for the process occurring from the ointment with Rokacet R-70 which has low viscosity and small area of hysteresis loop (fig. 5, 6, tab. VIII).

CONCLUSIONS

1. The tested vehicles and ointments with the content of Rokacets in the prescription are non-Newtonian, viscoelastic and highly thixotropic systems.
2. The kind of the applied Rokacet affects the spreadness and viscosity of model ointments with morphine salts. Preparations with Rokacet R-70 have the highest spreadness and the lowest viscosity which allow to assume that the process of their application on pathologically changed skin will be the easiest and the least painful.
3. Low viscosity of the system with preservation of small hysteresis loop at 310 K indicates that from among non-ionic surface active compounds used for testing, Rokacet R-70 is the most beneficial promotor of transdermal absorption for both pharmacopeal morphine salts.

4. The carried out *in vitro* studies on the kinetics of therapeutic agent penetration to the acceptor fluid point to higher pharmaceutical availability of morphine sulphate.
5. All model ointments with morphine salts have similar density. The pH values of ointments with morphine hydrochloride are higher than those of ointments with morphine sulphate.