The effect of cross-linking base on the properties of hydrogels with Carbopol and on pharmaceutical availability of morphine sulphate

Grażyna Samczewska[1], Justyna Kołodziejska[1], Aleksandra Ciałkowska-Rysz[2], Magdalena Piechota-Urbańska[1]

[1]Department of Applied Pharmacy, Medical University of Lodz, Poland
[2]Chair of Oncology, Department of Palliative Care, Medical University of Lodz, Poland

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Corresponding author:
Aleksandra Ciałkowska-Rysz, MD, PhD
Chair of Oncology, Department of Palliative Care
Medical University of Lodz, Poland
Ciołkowskiego St. 2, 93-510 Lodz
Phone: +48 42 689 54 84
E-mail: olarysz@rmed.pl

Abstract

Introduction: The presence of opioid receptors in pathologically changed skin justifies undertaking trials of pain treatment with morphine preparations designed for topical application. The aim of the study was to investigate the effect of selected substances neutralizing carboxyl groups of polyacrylic acid (sodium and potassium hydroxide, trietanoloamine, borax) on physicochemical parameters of the produced hydrogels with Carbopol 980 and Carbopol Ultrez 10 and on pharmaceutical availability of morphine sulphate.
Material and methods: There were prepared variant hydrogels with morphine sulphate on the base of Carbopol 980 and Carbopol Ultrez 10. Extensometric method was used to test spreadability of the preparations, gravimetric method to determine the rate of volatile components loss, while viscosity parameters were determined with cone-plate digital rheometer. Potentiometric method was applied to measure pH of the produced hydrogels. The test for morphine sulphate pharmaceutical availability was performed with spectrophotometric method.
Results: No basic differences were observed in the spreadability, the kinetics of water loss or in the measured pH values of model hydrogels produced with different cross-linking bases. Higher pharmaceutical availability of morphine sulphate was demonstrated from hydrogels with Carbopol Ultrez 10 having lower viscosity. The lowest pharmaceutical availability was obtained independently of the applied Carbopol for hydrogels in the prescription of which trietanoloamine was used.
Conclusions: The most beneficial applicative properties (including rheological ones) were obtained for model hydrogels containing Carbopol Ultrez 10, but the kind of the cross-linking base practically did not affect the rate of morphine sulphate diffusion from the produced hydrogels.

Key words: morphine, hydrogels, Carbopol, spreadability, viscosity, pH, pharmaceutical availability.

Introduction

Considerable morphine hydrophilism and thus very low value of the logarithm of the coefficient of partition between octanol and water prove morphine's poor penetrability through healthy skin, precisely through undamaged corneal layer of epidermis [1-5]. Morphine absorption by pathologically changed skin or completely damaged stratum corneum, e.g. in skin painful neoplastic ulceration or in deep decubitis ulcers, is completely different. In such a situation it may be similar to that when the drug is

administered in another way than transdermally. Bioavailability of morphine applied to skin in diseases manifesting corneal layer damage is about 75% [6].

This new and, as clinical examinations indicate, effective way of morphine application to obtain local analgetic activity appeared after detecting opioid receptors, mainly type ĕ, in pathologically changed skin and mucus membranes [7-11]. The most important advantages resulting from topical application of morphine are the possibility to decrease the dose and to markedly limit side effects such as: reduction of respiratory function, increase of pressure in bile ducts and urinary tracts, constipation and others, so frequent in the case of oral administration, in injections or in the form of a suppository.

The therapeutic effectiveness of the drug form with morphine designed for skin (ointment, gel, cream) depends on the properties of the applied vehicle, which must fulfil certain criteria. The following requirements are mentioned: painless when spread, no skin and mucosa irritation, possibility of producing an aseptic product and providing optimal pharmaceutical availability of the therapeutic agent [12-15].

The assumption of the study was to work out a model prescription of a pharmaceutical agent in the form of hydrogel with morphine sulphate. The vehicle of the suggested form of the drug was produced on the base of polyacrylic acid (Carbomer, Carbopol) [16].

The aim of the study was to determine the effect of selected substances neutralizing carboxyl groups of polyacrylic acid (sodium and potassium hydroxide, trietanoloamine, borax) on physiochemical parameters of the produced hydrogels and on pharmaceutical availability of morphine sulphate.

Material and methods

The investigations were performed at the Department of Applied Pharmacy of the Medical University in Lodz. They included vehicles and hydrogel preparations freshly made from the following materials:

- morphine sulphate (*Morphini sulfas*), injection solution 20 mg/1 ml – Warsaw Pharmaceutical Plant Polfa, Poland;
- Carbopol 980 – Neveon Inc. Cleveland Ohio, USA;
- sodium hydroxide (*Sodium hydroxide*) – Polish Chemical Reagents Gliwice, Poland;
- potassium hydroxide (*Potassium hydroxide*) – Chemical Reagents Lublin Industrial and Trading Company, Poland;
- trietanoloamine (TEA) – Polish Chemical Reagents S.A., POCG Gliwice, Poland;
- sodium tetraborate (*Natrium tetraboricum*), Borax – PPF Hasco-Lek Wrocław, Poland.

The measurements of morphine sulphate pharmaceutical availability, rheological and morphological parameters of the produced vehicles and hydrogel preparations were performed with the following apparatus:

- spectrophotometer Nicolet Evolution 300, version 1.0, Spectro-Lab, England;
- digital rheometer DV-III Brookfield, version 3.0 with Reocalc for Windows software, USA;
- bath thermostat PGW E1, Medingen, Germany;
- microcomputer Multifunction Meter CX-551 with a complex electrode ESKP-301 WP – Eurosensor, Gliwice, Poland;
- CWE-2 – Termometal thermostat, Thermal Engineering Equipment Co-operative, Andrzejów, Poland;
- Tomofan of wall thickness d=0.0258, Paper Plant in Tomaszów, Poland;
- laboratory equipment: mutimer apparatus, picnometer, extensometer and others.

Preparation of model hydrogels

Hydrogels were prepared in accordance with the requirements of Polish Pharmacopoeia VI. Two kinds of polyacrylic acid – Carbopol Ultrez 10 (CU 10) and Carbopol 980 (C980) – were the base of model preparations (Table I). In both cases the following reagents were applied as substances serving for the polymer cross-linking by carboxyl groups neutralization:

- sodium hydroxide (NaOH),
- potassium hydroxide (KOH),
- trietanoloamine (TEA),
- sodium tetraborate (borax) (B).

The amounts of the above reagents were determined by acid-base titration, bringing the solution of gelating Carbopol to pH of about 7 with a solution of alkalizing substance of definite concentration (Table I).

Spreadability tests of model hydrogels

The spreadability was determined with an extensometer at 298 K. The measurement consists in determination of the degree of the increase of the tested preparation area with the increase of load [17].

Determination of model hydrogels' viscosity parameters

Viscosity parameters were determined at 310±0.1 K with digital cone-plate rheometer with a bath thermostat [18-20].

Tests of the rate of water loss from the model hydrogels

The determination of the rate of volatile component loss was performed from glass plates (Petri dishes) of 55 mm diameter, which were covered with a uniform layer of hydrogel. The plates were placed in a thermostat at 310±0.1 K with gravitational air circulation and the sample mass was determined after every 30 min.

Table I. Prescription composition of model hydrogels

Components	Name of hydrogel							
	CU 10 -NaOH	CU 10 -KOH	CU 10 -TEA	CU 10 -B	C 980 -NaOH	C 980 -KOH	C 980 -TEA	C 980 -B
Carbopol	Carbopol Ultrez 10				Carbopol 980			
	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Woda	78.525	78.273	77.613	77.75	78.525	78.265	77.71	77.75
NaOH	0.475	–	–	–	0.475	–	–	–
KOH	–	0.727	–	–	–	0.735	–	–
TEA	–	–	1.387	–	–	–	1.29	–
Boraks	–	–	–	1.25	–	–	–	1.25
Morphine sulphate	0.2*	0.2*	0.2*	0.2*	0.2*	0.2*	0.2*	0.2*
Razem	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0

** 10 amp. 20 mg/1ml*

Determination of pH

The determination of hydrogen ion activity (pH) was performed in accordance with the recommendations of Polish Pharmacopoeia VI.

Estimation of pharmaceutical availability of morphine sulphate from model hydrogels

The estimation of pharmaceutical availability was performed with a technique applied for transdermal therapeutic systems according to the requirements of European Pharmacopoeia [21].

The test was performed with the method of diffusion from the surface of the preparation through a dialysis membrane (Tomofan) to acceptor fluid (to water) with six modified Mutimer apparatuses. 2.0 g (±0.001 g) of the tested hydrogel was weighed into each apparatus and 10 cm^3 of distilled water was added. Then, in definite time intervals (after 5, 10, 30, 45, 60, 90, 120 min) the solutions from above the hydrogel were collected. The rate of the process of mass exchange was tested with spectrophotometric method determining the quantity of the diffusing morphine sulphate to the acceptor fluid. The approximation equation at p=0.05 and r=0.9999, A=87.9486.c – 0.0427, with which the dependence between absorbance (A) and the therapeutic agent concentration (c) was described, transformed to the form c=A+0.0427/87.9486, enabled the quantity of morphine salt diffusing through the phase boundary in the time function t (min) to be determined.

Results

The results of spreadability of model hydrogels produced with Carbopol Ultrez 10 and Carbopol 980 are presented in Figures 1 and 2.

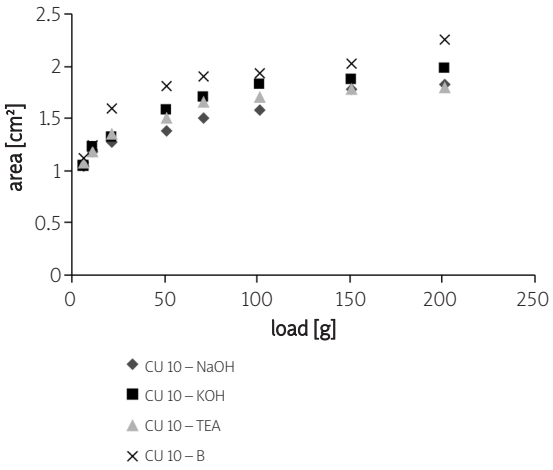

Figure 1. The course of dependences between the imposed load and the observed increase of the area of hydrogels with morphine sulphate and Carbopol Ultres 10

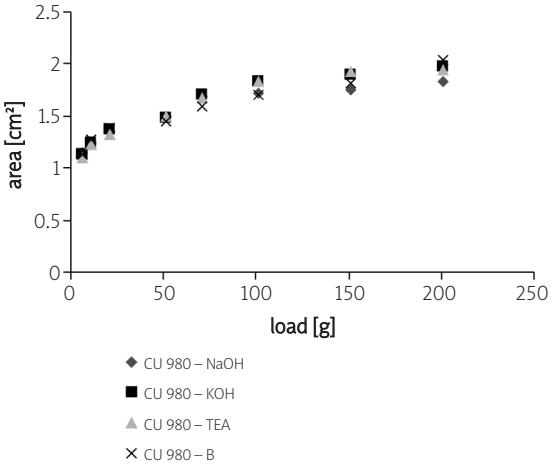

Figure 2. The course of dependences between the imposed load and the observed increase of the area of hydrogels with morphine sulphate and Carbopol 980

Table II. The parameters of correlation equation of the type y=ax+b describing spreadability of model hydrogels with morphine sulphate and Carbopol Ultrez 10 together with calculated areas under the spreadability curves

Name of hydrogel	Correlation equation coefficients a	b	Correlation coefficient r	Surface area [c.u.]
CU 10 – NaOH	4.6047 10-2	5.7485	0.9278	2052
CU 10 – KOH	4.7752 10-2	6.1209	0.9508	2160
CU 10 –TEA	4.8270 10-2	6.0386	0.9719	2154
CU 18 – B	7.1354 10-2	4.1065	0.9503	2244

Table III. The parameters of correlation equation of the type y=ax+b describing spreadability of model hydrogels with morphine sulphate and Carbopol 980 together with calculated areas under the spreadability curves

Name of hydrogel	Correlation equation coefficients a	b	Correlation coefficient r	Surface area [c.u.]
C 980 – NaOH	5.2297 10-2	5.5819	0.9635	2147
C 980 – KOH	4.9553 10-2	7.0238	0.9480	2129
C 980 – TEA	4.6415 10-2	5.8688	0.9041	2084
C 980 – B	4.9578 10-2	6.3641	0.9540	2244

The course of the dependence between the spread surface of model preparations with morphine sulphate and the value of the imposed load was described at the level of significance p=0.05 with a correlation equation of the type y = ax + b. Parameters a and b of this equation were used to calculate, with the integration method, areas P under the spreadability curves, expressed in conventional units [c.u.]. The results of the calculations are presented in Tables II and III.

Spreadability of all the tested preparations is within the narrow limit: 2052-2244 c.u. The viscosity of model hydrogels with morphine sulphate determined at freely selected shear rate 0.1 l/s is presented in Figure 3.

No dependences were observed between the determined viscosity and the kind of substance applied to neutralize carboxyl groups of polyacrylic acid in the composition of model gels. However, attention should be paid to the fact that all the hydrogels tested with Carbopol Ultrez 10 have lower viscosity (208740-292236 mPa.s) than model preparations with Carbopol 980 (306152-346906 mPa.s) (Figure 3).

The kinetics of the rate of water loss by hydrogels containing Carbopol Ultrez 10 is presented in Figure 4, those by hydrogels with Carbopol 980 in Figure 5.

The course of the above dependences was described by a correlation equation which allowed the integration method to be used to calculate areas expressed in conventional units [c.u.] under the curves of the rate of water loss by the tested hydrogels. The results of the calculations are presented in Tables IV and V.

It results from the above statement that independently of the applied prescription components (Carbopol and cross-linking base), the

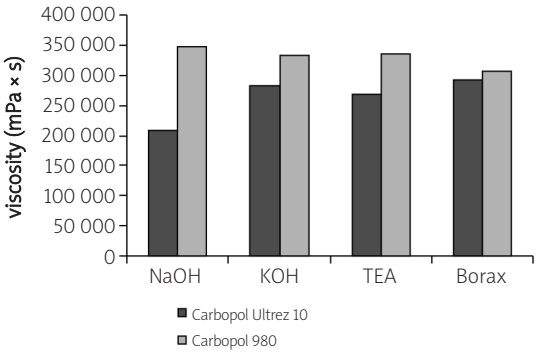

Figure 3. Viscosity of model hydrogels with morphine sulphate

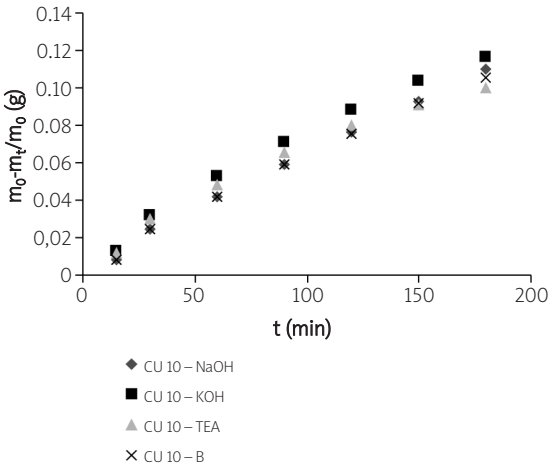

Figure 4. The rate of water loss by model hydrogels with morphine sulphate and Carbopol Ultrez 10

tested model hydrogels have comparable kinetics of water loss (P[c.u.]= 10.1228-11.5500).

The results of pH measurements of model hydrogels with morphine sulphate are presented in Table VI.

The activity of hydrogen ions (pH) of the tested hydrogels is within the limits 6.2-6.85. Independently of the kind of applied Carbopol the highest pH value was obtained for hydrogel in which trietanoloamine was used, while the lowest was obtained for the hydrogel with borax in its prescription.

The results of the performed in vitro studies on the rate of therapeutic agent release from the tested hydrogels to the acceptor fluid are presented in Figures 6 and 7 as the dependence between the quantity of the released morphine sulphate and time, and in Figures 8 and 9 as the dependence between the quantity of the released morphine sulphate and the square root of the time of release $t^{1/2}$ ($min^{1/2}$).

The analysis of functional dependence presented in Figures 8 and 9 demonstrated a lack of rectilinear dependence between the quantity of morphine sulphate released from model hydrogels and the square root of the time of release ($t^{1/2}$) (22, 23).

The course of the dependence between the quantity of the released morphine sulphate and the time was described with equations of the type y=ax+b, which allowed the integration method to be used to calculate the areas under the release curves, expressed in conventional units (c.u.). The results of the calculations are demonstrated in Tables VII and VIII.

Constant rates of the reaction of morphine sulphate release from model hydrogels produced on the base of Carbopol Ultrez 10 to the acceptor fluid

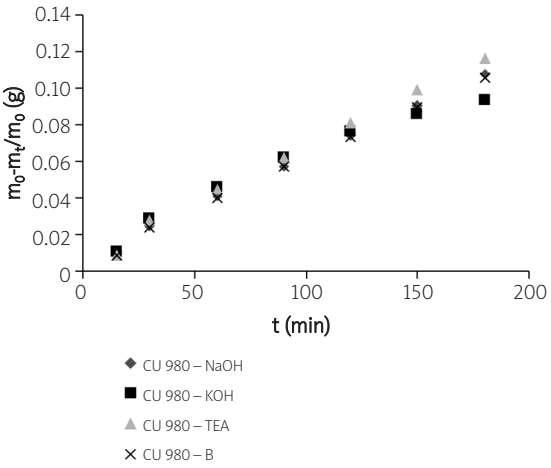

Figure 5. The rate of water loss by model hydrogels with morphine sulphate and Carbopol 980

Table IV. Parameters of correlation equation of the type y=ax+b describing the kinetics of water loss from model hydrogels with morphine sulphate and Carbopol Ultrez 10 together with calculated areas under the curves of water loss

Name of hydrogel	Correlation equation coefficients a	b	Correlation coefficient r	Surface area [c.u.]
CU 10 – NaOH	0.0006	0.0038	0.9976	10.4040
CU 10 – KOH	0.0006	0.0115	0.9911	11.5500
CU 10 – TEA	0.0005	0.0128	0.9840	10.2615
CU 18 – B	0.0006	0.0050	0.9963	10.4775

Table V. Parameters of correlation equation of the type y=ax+b describing the kinetics of water loss from model hydrogels with morphine sulphate and Carbopol 980 together with calculated areas under the curves of water loss

Name of hydrogel	Correlation equation coefficients a	b	Correlation coefficient r	Surface area [c.u.]
C 980 – NaOH	0.0006	0.0047	0.9980	10.4280
C 980 – KOH	0.0005	0.0126	0.9636	10.1228
C 980 – TEA	0.0006	0.0051	0.9971	10.4940
C 980 – B	0.0006	0.0043	0.9979	10.3620

Table VI. Activity of hydrogen ions (pH) of model hydrogels with morphine sulphate produced on the base of Carbopols

Hydrogels with Carbopol Ultrez 10	pH	Hydrogels with Carbopol 980	pH
CU 10 – NaOH	6.59	C 980 – NaOH	6.53
CU 10 – KOH	6.59	C 980 – KOH	6.56
CU 10 –TEA	6.75	C 980 – TEA	6.85
CU 18 – B	6.2	C 980 – B	6.3

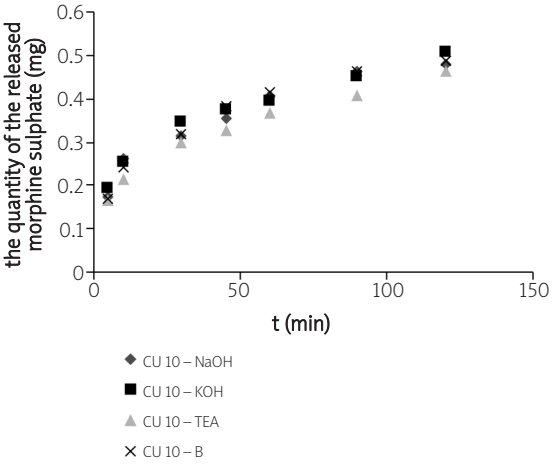

Figure 6. The kinetics of morphine sulphate release from hydrogels produced on the base of Carbopol Ultrez 10

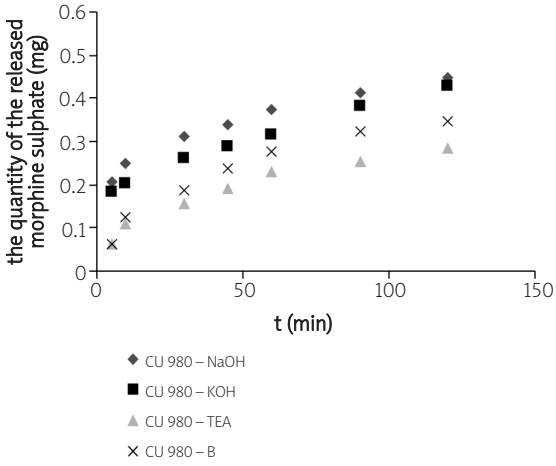

Figure 7. The kinetics of morphine sulphate release from hydrogels produced on the base of Carbopol 980

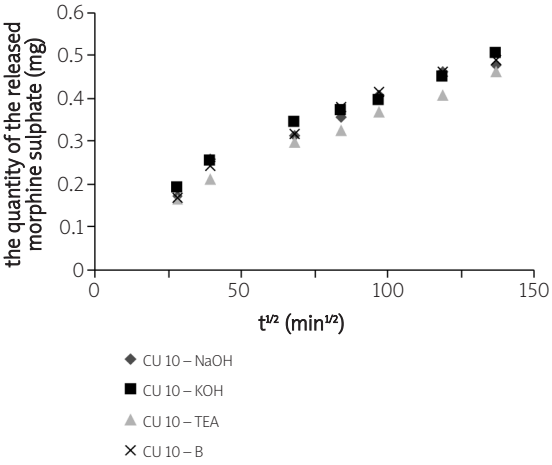

Figure 8. The kinetics of morphine sulphate release from hydrogels produced on the base of Carbopol Ultrez 10

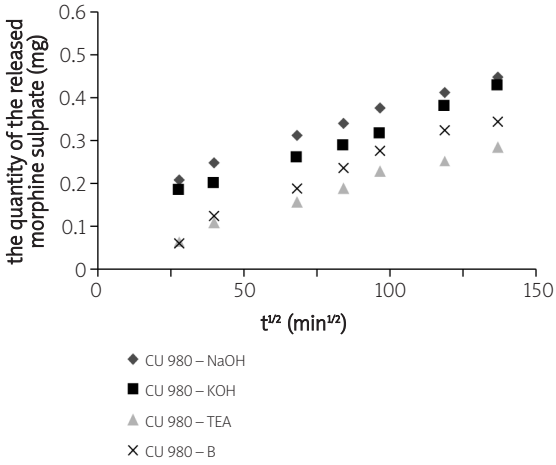

Figure 9. The kinetics of morphine sulphate release from hydrogels produced on the base of Carbopol 980

Table VII. The parameters of correlation equation of the type y=ax+b describing the kinetics of morphine sulphate release from model hydrogels with Carbopol Ultrez 10 together with calculated areas under the release curves

Name of hydrogel	Correlation equation coefficients a	b	Correlation coefficient r	Surface area [c.u.]
CU 10 – NaOH	0.0025	0.2238	0.9424	61.67
CU 10 – KOH	0.0025	0.2332	0.9576	62.76
CU 10 – TEA	0.0024	0.1954	0.9649	56.97
CU 18 – B	0.0026	0.2196	0.9382	62.63

Table VIII. The parameters of correlation equation of the type y=ax+b describing the kinetics of morphine sulphate release from model hydrogels with Carbopol 980 together with calculated areas under the release curves

Name of hydrogel	Correlation equation coefficients a	b	Correlation coefficient r	Surface area [c.u.]
C 980 – NaOH	0.0020	0.2339	0.9630	55.65
C 980 – KOH	0.0021	0.1863	0.9940	47.89
C 980 – TEA	0.0018	0.0901	0.9558	36.24
C 980 – B	0.0024	0.1009	0.9491	46.09

are within the limits $0.24.10^{-2}$ to $0.26.10^{-2}$ mol1dm-3min^{-1}. Lower values were obtained for model hydrogels with Carbopol 980, from $0.18.10^{-2}$ to $0.24.10^{-2}$ mol1dm-3min^{-1}. The calculated values of the areas under morphine sulphate release curves confirm the obtained results. Higher values of the areas were obtained for preparations containing Carbopol Ultrez 10 (56.97-62.76 c.u.) than for preparations with Carbopol 980 (36.24-55-65 c.u.).

It is worth noticing that independently of the kind of applied Carbopol, the lowest pharmaceutical availability was observed for preparations in which trietanoloamine was used as a substance neutralizing polyacrylic acid carboxyl groups (Tables VII and VIII).

Discussion

No significant differences were found in the spreadability of model hydrogels dependently on the gelating component and the selected cross-linking base applied in their prescription.

After application to the skin, the process of water loss from the surface layer of all produced preparations will be accompanied by comparable increase of structural viscosity of hydrogels ($D=kT/6\pi r\eta$). Thus, the decrease of the rate of morphine sulphate diffusion into the external compartment, resulting from changes of viscosity during exposure, will be similar in the case of all the produced model preparations.

The reaction of hydrogel vehicles before introduction of morphine sulphate was neutral (pH=7). The increase of hydrogel preparations acidity (manifested by a decrease of pH value) is a consequence of morphine sulphate cationic hydrolysis and its value depends on the strength of the cross-linking base. Among the applied bases sodium borate is the weakest base, which is why the decrease of pH was the highest in preparations with sodium tetraborate (Table VI).

The kind of cross-linking base in practice did not affect the rate of morphine sulphate diffusion from hydrogels with Carbopol Ultrez 10 (Figure 8, Table VII). This may be a consequence of uniform cross-linking and balanced strength of the interaction between morphine salt particles and gelified polymer. More differentiated course of the process of morphine sulphate diffusion from hydrogels with Carbopol 980 (Figure 9, Table VIII) is associated with the chemical nature of the applied base, which affects the way of polymer cross-linking and the strength of effects between morphine and the environment.

Conclusions

1. The spreadability of model hydrogels with morphine sulphate does not depend on the kind of base cross-linking polyacrylic acid or on the kind of cross-linked Carbopol.
2. The kinetics of water loss points to the comparable increase of structural viscosity of all the tested preparations and to similar changes of morphine sulphate pharmaceutical availability during application of the hydrogels.
3. Higher pharmaceutical availability of morphine sulphate was observed from hydrogels with Carbopol Ultrez 10, which may be related to their lower viscosity. The least beneficial results of the release test were obtained independently of the applied Carbopol for hydrogels cross-linked by trietanoloamine.
4. No essential differences were observed in pH values of the tested hydrogels. Hydrogen ion activity of model preparations is within the limits 6.2-6.85.

References

1. Kostowski W, Herman ZS (red.). Farmakologia. Podstawy farmakoterapii [Polish]. Wyd. III. Wydawnictwo Lekarskie PZWL, Warszawa 2003.
2. Hatanaka T, Manabe E, Sugibayashi K, Morimoto Y. An application of the hydrodynamic pore theory to percutaneous absorption of drugs. Pharm Res 1994; 11: 654-8.
3. Yamashita F, Bando H, Koyama Y, Kitagawa S, Takakura Y, Hashida M. In vivo and in vitro analysis of skin penetration enhancement based on a two-layer diffusion model with polar and nonpolar routes in the stratum corneum. Pharm Res 1994; 2: 185-91.
4. Sznitowska M, Janicki S, Williams AC. Intracellular or intercellular localization of the polar pathway of penetration across stratum corneum. J Pharm Sci 1998; 87: 1109-14.
5. Cornwell PA, Barry BW. Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. J Pharm Pharmacol 1994; 46: 261-9.
6. Westerling D, Hoglund P, Lundin S, Svedman P. Transdermal administration of morphine to healthy subjects. Br J Clin Pharmacol 1994; 37: 571-6.
7. Wiśniewski M, Szpinda M, Krakowiak-Sarnowska E. Zastosowanie żelu z morfiną w leczeniu bolesnego owrzodzenia nowotworowego. Opis przypadku [Polish]. Pol Med Paliat 2002; 1: 89-92.
8. Cerchietti LC, Navigante AH, Korte MW, et al. Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. Pain 2003; 105: 265-73.
9. Krajnik M, Zylicz Z, Finlay I, Luczak J, van Sorge AA. Potential uses of topical opioids in palliative care-report of 6 cases. Pain 1999; 80: 121-5.
10. Bigliardi PL, Bigliardi-Qi M., Buechner S, Rufli T. Expression of mu-opiate receptor in human epidermis and keratinocytes. J Invest Dermatol 1998; 111: 297-301.
11. Stein C. The control of pain in peripheral tissue by opioids. N Engl J Med 1995; 332: 1685-90.
12. Rysz J, Potargowicz E, Banach M, et al. Increased whole blood chemiluminescence in patients with chronic renal failure independent of hemodialysis treatment. Arch Immunol Ther Exp 2006; 54: 347-55.
13. Samczewska G, Zgoda MM., Ciałkowska-Rysz A, Kaźmierczak SF. Wpływ parametrów reologicznych vehiculum (hydrożele, podłoża absorpcyjne typu w/o) na szybkość dyfuzji w warunkach in vitro do kompartmentu zewnętrznego siarczanu morfiny [Polish]. Pol Med Paliat 2003; 2: 147-56.

14. Samczewska G, Zgoda MM. Wpływ parametrów reologicznych modelowych preparatów stosowanych w opiece paliatywnej na szybkość dyfuzji chlorowodorku morfiny w warunkach in vitro do kompartmentu zewnętrznego [Polish]. Farm Pol 2004; 10: 450-5.
15. Samczewska G, Zgoda MM., Bodek KH. Badania porównawcze dostępności farmaceutycznej chlorowodorku i siarczanu morfiny z hydrożeli przeznaczonych do stosowania zewnętrznego w opiece paliatywnej [Polish]. Farm Pol 2005; 10: 481-7.
16. Rybacki E, Stożek T. Substancje pomocnicze w technologii postaci leku [Polish]. Wydawnictwo Lekarskie PZWL, Warszawa 1980.
17. Zgoda MM. Wpływ siarczanu gentamycyny na dostępność farmaceutyczną trokserutyny (Venorutonu) z kosmetycznych podłoży absorpcyjnych i hydrożelowych [Polish]. Pol J Cosmetol 2000; 3: 267-79.
18. Kołodziejska J, Zgoda MM. Detal gel viscosity parameters and pharmaceutical availability of non-steroidal anti-inflammatory drugs. Acta Polon Pharm-Drug Research 2004; 61: 419-24.
19. Kołodziejska J. Possibilities of application of non-ionic surfactants belonging to Rofam, Rokopol and Rokanol class in the prescription of dental anti-inflammatory gels. Polim Med 2005; 3: 49-66.
20. Kołodziejska J. Parametry reologiczne past do zębów a dostępność farmaceutyczna jonu fluorkowego [Polish]. Bromat Chem Toksykol 2004; 1: 77-83.
21. European Pharmacopoeia. Third Edition. Pharmaceutical technical procedures, Council of Europe – Strasburg Codex, 1997.
22. Bodek KH. Badania porównawcze kinetyki uwalniania diklofenaku z hydrożelu mikrokrystalicznego chitozanu i hydrofilowej maści farmakopealnej [Polish]. Farm Pol 2000; 15: 753-62.
23. Czarnecki W, Wiktorowicz M. Wpływ właściwości reologicznych maści na uwalnianie chloramfenikolu [Polish]. Farm Pol 1994; 10: 409-15.