Influencia de los tensides en la liberación de las sustancias medicinales de los geles hidrófilos: influencia del polisorbato 20 y polisorbato 80 en la liberación del hidrocortisona de los geles hidrófilos

Influence of tensides on liberation of medical agents from hydrophilic gels: effects of polysorbate 20 and polysorbate 80 on liberation of hydrocrotisone from hydrophilic gels

KUBIS, A.; SZCZESNIAK, M. AND MUSIAL, W. S.

Department of Pharmaceutical Technology, Faculty of Pharmacy, "Silesian Piasts" memorial Wroclaw Medical University, 50-139 Wroclaw, Szewska 38/39, Poland. E-mail: witold@bf.uni.wroc.pl

RESUMEN

El proceso de liberación de hidrocortisona de los hidrogeles con la adición del 1% y del 3% del polisorbato 20 o polisorbato 80, en la presencia de propilenglicol - 1,2 o PEG 200, tiene dos fases. Durante la primera fase las velocidades de liberación son más altas, comparando con la segunda fase. La segunda fase de liberación corresponde a la cinética de primer orden. Los periodos de semiliberación en el transcurso de esta fase oscilan entre 15,67 y 23,50.

PALABRAS CLAVE: Hidrogeles, Propilenglicol - 1,2, PEG 200, Polisorbato 20, Polisorbato 80, Hidrocortisona.

ABSTRACT

The process of hydrocortisone release from the hydrogels with the addition of 1% and 3% polysorbate 20 or polysorbate 80, in the presence of 1,2-propylene glycol or PEG 200 has two phases. In the first phase the liberation rates are higher in comparison with the second phase. The second release phase conforms to the first order kinetics. Semiliberation rates in this phase are in the range from 15,67 to 23,50.

KEY WORDS: Hydrogels; 1,2-Propylene glycol, PEG 200; Polysorbate 20; Polysorbate 80; Hydrocortisone.

INTRODUCTION

Hydrophilic ointment bases are recommended by many authors because of their beneficial effect on skin. They are easily rubbed into skin even when wet. Exudate is well absorbed so they are applied in the treatment of diseases in which oozing and maceration occur (Banaszkiewicz, 1970), (Zesch and Schaefer, 1975). Hydrophilic ointment bases are also recommended in the treatment of allergic diseases and photodermatosis and in the case of sensitive skin to the reaction of fatty ointment base (Krasowska, 1987), (Hanifin, 1983). In her study on the reaction of fatty ointment base Krasowska (1994) quotes that administering corticosteroids in a fatty ointment

base, when badly tolerated in the acute phase of a disease, may suppress the anti-inflammatory activity of the due or even aggravate the acute disease phase.

Hydrophilic ointment bases do not cause irritation and sensitisation (Toole et al., 1999), (Krueger et al., 1998), (Lukaszczyk, 1995), (Krasowska, 1994), (Bialik, 1992), (Lukaszczyk, 1992). Due to their exsiccating and cooling activity they are indicated for oily skin (Krasowska, 1994).

Releasing of some of the medicinal agents from hydrophilic base is more intensive than from lipophilic base, (Malecka and Kubis, 1998), (Kubis and Szczesniak, 1992), (Szczesniak et al., 1992) (Kus et al., 1988), (Srcic et al., 1983), (Voigt et al., 1978).

It was found out that indomethacin release from a hydrophilic base is faster than from a lipophilic base (Beetge et al., 2000), (Liu et al., 1995), (Miyazaki et al., 1995). The same dependence was observed in the case of chloramphenicol (Farouk et al., 1989). Other authors obtained similar results in the research on the release of medicinal agents such as mefenamic acid and acetylsalicylic acid (Grabowska and Kubis, 1986), retinal acid (Krueger et al., 1998), (Jensen et al., 1991), neomycin sulphate (Dumitriu et al., 1993), (Paluch et al., 1991) from hydrophilic ointment bases. Therapeutic preparations containing hydrogel base are also widely used in dentistry (Bawden, 1998), (Malecka and Kubis, 1998), (Taware et al., 1997), (Chang et al., 1996), and the surgery of burn wounds treatment, trauma wounds and ulcers (Misterka, 1991), (Paluch et al., 1991), (Kus et al., 1988). Chang and Banga (1998) and also Barry and Bennett (1987) observed that propylene glycol in hydrophilic base increases the solubility of hydrocortisone as well as skin penetration.

This is why in a hydrophilic base the concentration of hydrocortisone in contact with skin is higher than in ointments and suspensions. It was interesting to find out if part of the dissolved hydrocortisone is bonded in micellas created by tensides. This phenomenon may lead to the minimisation of hydrocortisone concentration remaining in contact with skin (Muller et al., 1999), (Haapasaari et al., 1995), (Wohlraub et al., 1990).

MATERIALS AND METHODS

Materials

Ethyl alcohol 96% (POCH Gliwice, Poland), N,N-dimethyl acetamide (Reachim, USSR), 1,2-propylene glycol (VEB Laborchemie Apolda, Germany), polyoxyethylene glycol 200 (LOBA CHEMIE, Germany) of analytical grade, semipermeable membrane as used for dialyze in artificial kidney (Germany), hydrocortisone (Jelfa, Poland) methylcellulose (LOBA CHEMIE, Germany), polysorbate 20 (Koch-Light Lab. Ltd., England), polysorbate 80 (Koch-Light Lab. Ltd., England) were used. The water used was de-ionized and purified by destillation.

Preparation of hydro-gels

The 4% methylcellulose gels were prepared ex tempore by mixing of solid and liquid components in a closed container (Szczesniak et al., 1992). Their composition is shown in Table 1. The solid component was obtained by mixing hydrocortisone and methylcellulose, whereas the liquid component – by mixing of hydrophilizing agent (1,2-propylene glycol or PEG 200) with dimethyl acetamide, tenside and distilled water. Gels were prepared by dissipation of the powdered solid mixture on surface of the liquid in a closed container and stirring for 2 min., to provide a homogenous consistence.

Dynamic viscosity measurements

Rheological measurements were carried out by means of Rheotest-2, using the cone-plate K2 and the gap 8.64 mm in the 1 a range. The consecutive α angle readings were taken every 10 seconds. During measurements shearing rates were increased then decreased in 12 steps. Basing on the α angle the τ value, shearing strength and dynamical viscosity, were calculated for particular shearing rates.

Determination of pharmaceutical availability of hydrocortisone

The process of liberation of hydrocortisone from gel substrates was examined by measurement of drug diffusion rate through a semi-permeable membrane, acc. to Olszewski and Kubis (1969). Exactly weighed samples of 1,00 g gel were placed with a syringe on semi-permeable membrane at 37ºC. Every 15 minutes 5 m^2 of solution were sampled into calibrated tubes.

Quantitative determination of hydrocortisone

Concentration of hydrocortisone was determined with the CECIL INSTRUMENTS spectrophotometer of the CE 5501 type at wavelength of 248 nm, acc. to Polish Farmacopoeia 5th Ed. Amount of hydrocortisone released was determined by reading from the standardization curve.

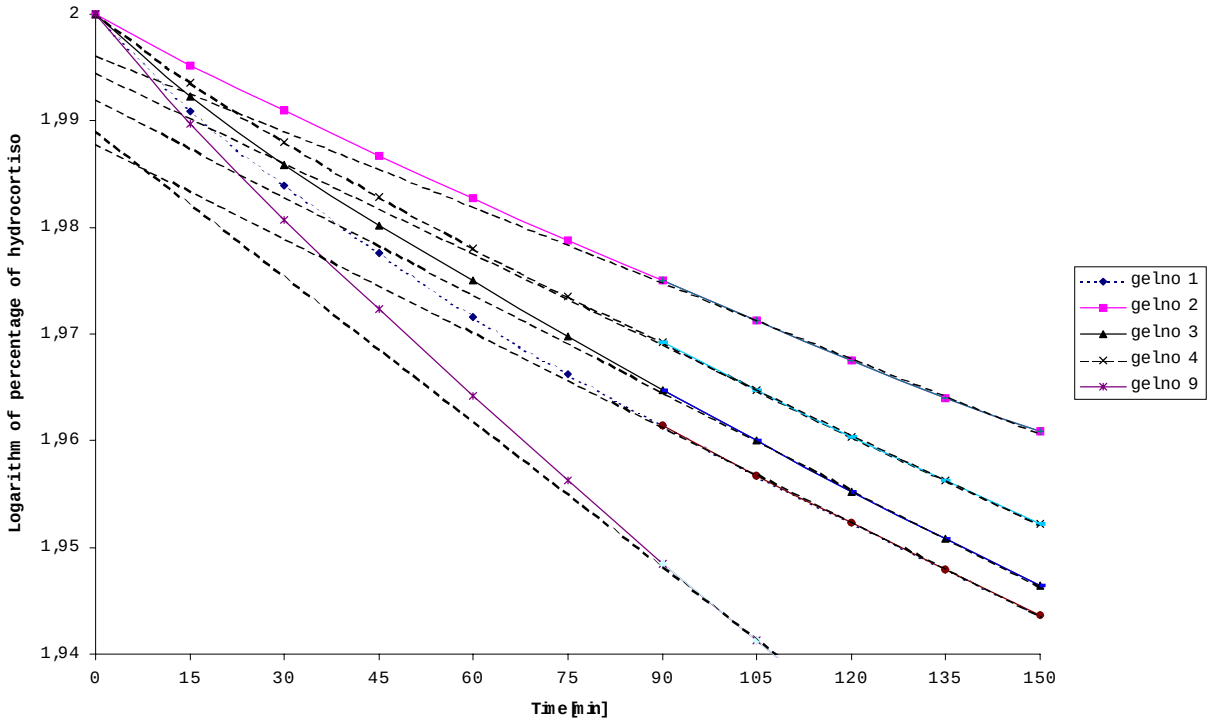
RESULTS AND DISCUSSION

The influence of polysorbate 20 and 80 on the pharmaceutical availability of hydrocortisone from metylcellulose gel in the presence of 1,2-propylene glycol and PEG 200

The process of hydrocortisone released from the examined gel with the addition of 1% and 3% polysorbate 20, or by polysorbate 80, was analysed in accordance with the accepted procedure for first order kinetics process as a function of the medicinal agent residue concentration logarithm to t time. At the initial release period curves were obtained.

The analysis of the obtained semi-logarithmic graphs shows that in a hydrocortisone release process there are two phases. In the first phase the release rate is a function of changes in its concentration in micellas and the rate of its diffusion from micellas to gel. This is pictured by the curve section on a semi-logarithmic graph (Fig. 1 and 2).

FIG. 1.- Influence of 1% and 3% of polysorbate 20 or 80 additive on of liberation of hydrocortisone from methylcellulose substrate comprising polyoxyethylene glycol-1,2.



In the second phase the release is only limited by hydrocortisone diffusion rate. It is represented by a straight line. A rate constant for the second phase of the release process was determined in the interpretation of hydrocortisone release from the examined gels. Semiliberation rates for hydrocortisone were determined (Table). The enclosed Table shows that hydrocortisone semiliberation rate from gel containing 10% 1,2-polypropylene glycol without the addition of tensides, which constitute a reference gel, makes 10.44 hours. If we compare hydrocortisone release process from gels in the presence of 1 and 3% polysorbate 20 and polysorbate 80 it will turn out that the release process was longer in comparison with the reference gel.

FIG. 2.- Influence of 1% and 3% of polysorbate 20 or 80 additive on of liberation of hydrocortisone from methylcellulose substrate comprising PEG 200.

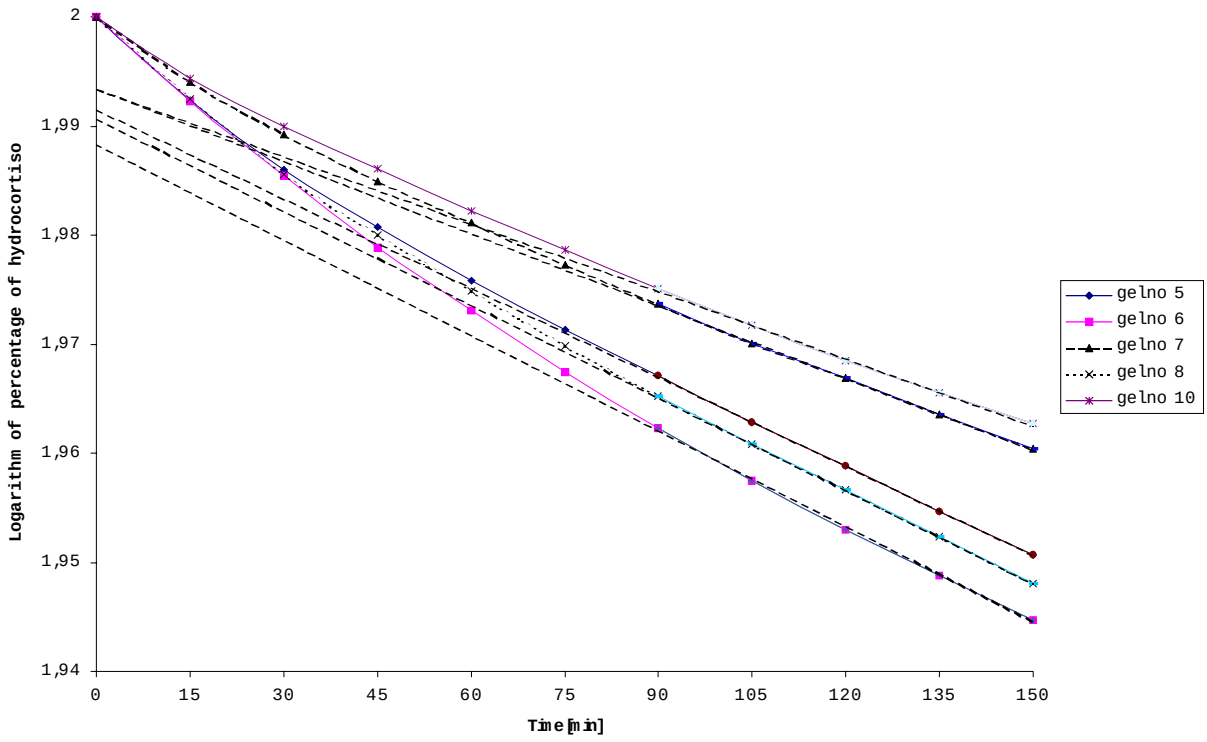


TABLE. Rate constants (K) and semiliberation rates ($T_{0,5}$) of hydrocortisone liberation process for methylcellulose gels with tenside additives.

Gel No	Concentrations of:							K	$T_{0,5}$	R^2
	H	MC	DMA	1,2-PG	PEG 200	P20	P80	[h^{-1}]	[h]	Pearson's Coefficient
1	1%	4%	10%	10%	-	1%	-	$4.24 \cdot 10^{-2}$	16.35	0.9990
2	1%	4%	10%	10%	-	3%	-	$3.50 \cdot 10^{-2}$	19.79	0.9893
3	1%	4%	10%	10%	-	-	1%	$4.42 \cdot 10^{-2}$	15.67	0.9955
4	1%	4%	10%	10%	-	-	3%	$4.05 \cdot 10^{-2}$	17.09	0.9962
5	1%	4%	10%	-	10%	1%	-	$3.98 \cdot 10^{-2}$	18.80	0.9953
6	1%	4%	10%	-	10%	3%	-	$4.15 \cdot 10^{-2}$	16.71	0.9973
7	1%	4%	10%	-	10%	-	1%	$2.95 \cdot 10^{-2}$	23.50	0.9954
8	1%	4%	10%	-	10%	-	3%	$3.87 \cdot 10^{-2}$	17.91	0.9987
9	1%	4%	10%	10%	-	-	-	$6.63 \cdot 10^{-2}$	10.44	0.9977
10	1%	4%	10%	-	10%	-	-	$2.67 \cdot 10^{-2}$	25.94	0.9934

Where: H: hydrocortisone, MC: methylcellulose, DMA: dimethylacetamid, 1,2-PG: 1,2-propylene glycol, PEG 200: polyoxyethylene glycol 200, P20: polysorbate 20, P80: polysorbate 80.

Semiliberation rate for gel containing 1 and 3% polysorbate 20 varies from 16.35 to 19.79 hours and for polysorbate 80, 15.67 to 17.09 respectively.

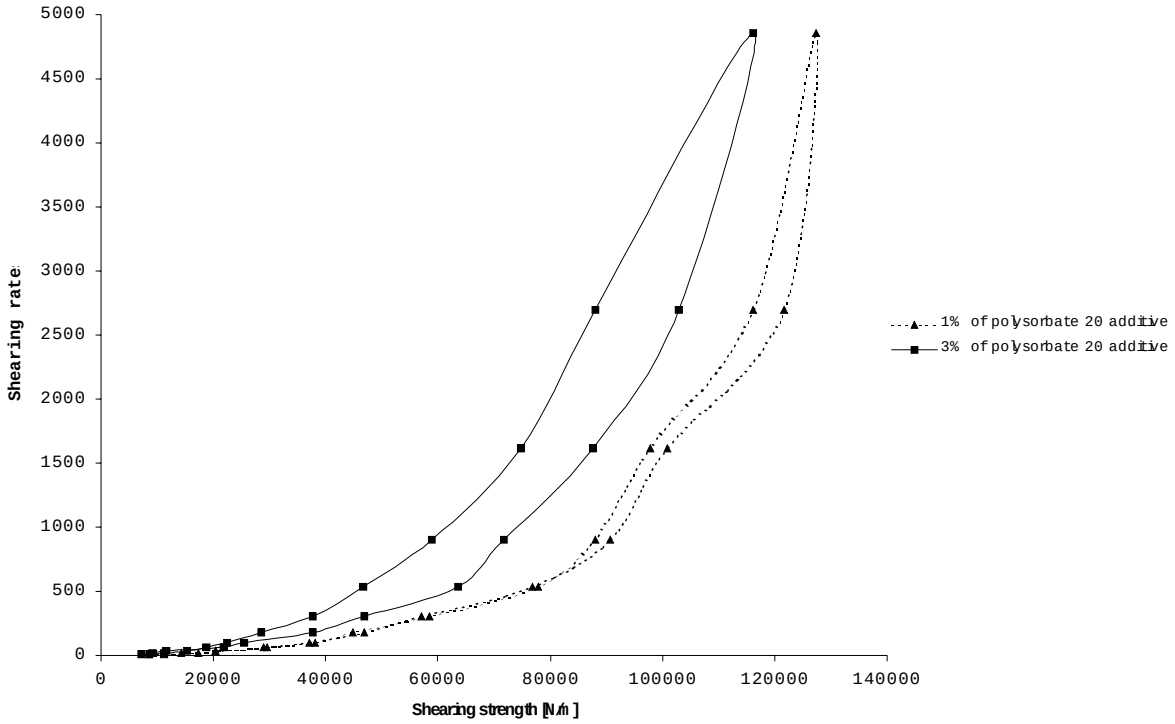
Semiliberation rate for gel containing 10% of PEG 200 is of 25.94 hours. The addition of examined tensides to the above gel accelerates hydrocortisone release from gel containing 3% polysorbate 80 with 17.91 hours as semiliberation rate except from gel containing 1% polysorbate 80 where semiliberation rate is 23.50 hours.

For gels containing 1 and 3% of polysorbate 20, semiliberation rate is in the range of 16.71 to 18.81 hours.

Rheological measurements

Rheographs of some of the gels are shown in Fig. 3.

FIGURE 3.- Rheographs of the 4% methylcellulose gels comprising 10% of 1,2-propylene glycol, 10% of dimethylacetamide and 1% or 3% of polysorbate 20 additive.



It should be noted that gels are thixotropic. Flow limits of the gels are within the range from zero up to 19,339 N/m^2. The maximum shearing strength of these gels, measured at shearing rate of 4860 s, is within the range from 116097.60 N/m^2 to 245434.40 N/m^2. Increase in tenside concentration was accompanied by slight decrease of the maximum shearing strength values. The remaining gels, both with 2,2-propylene glycol and with PEG-200, showed similar properties.

CONCLUSION

The research shows that the addition of tensides with HLB value within the range of 15.0 to 16.7 modifies the release process by slowing it down in accordance with first order kinetics dependent on the initial concentration of free hydrocortisone in gel. In the presence of examined tensides the concentration of free hydrocortisone is lower than in the reference preparation due to the fact that part of it was bonded in micellas. The skin is in touch with a lower concentration of this hormone when the hormone contents in gels is the same in comparison with a reference preparation. The present research results show that they remain in accordance with the assumptions made before the work was started. In the following phase tensides with lower HLB value will be examined.

REFERENCES

Banaszkiewicz H. (1970). Clinical studies on the use of corticosteroid ointments with polyethylene bases in some skin diseases. *Przeg. Derm.,* **57**:88-91

Bawden J.W. (1998). Fluoride varnish: a useful new tool for public health dentistry. *Journal of Public Health Dentistry,* **58**: 266-9.

Beetge E., du Plessis J., Muller D.G., Goosen C., van Rensburg F.J. (2000). The influence of the physicochemical characteristics and pharmacokinetic properties of selected NSAID's on their transdermal absorption. *Int. J. Pharm.,* **193**: 261-4.

Barry B. W., Bennett S. L. (1987). Effect of penetration enhancers on the permeation of mannitol**,** hydrocortisone and progesterone through human skin**.** *J. Pharm. Pharmacol.,* **39**:535-46.

Bialik Z. (1992). Research on some properties of hydrogel ointments containing amphotensides. *Acta Pol. Pharm.,* **49:** 101-4.

Chang L.C., Auyeung L., Lin Y.T. (1996). In vivo study of potassium oxalate gel in tooth hypersensitivity. *Chang-Keng i Hsueh Tsa Chih.,* **19**: 343-7.

Chang S.L., Banga A.K. (1998). Transdermal iontophoretic delivery of hydrocortisone from cyclodextrin solutions**.** *J. Pharm. Pharmacol.,* **50**:635-40.

Dumitriu S., Popa M.I., Dumitriu M., Dumitriu D., Tara A. (1993). Bioactive polymers 68-controlled release of neomycin-furazolidone bicomponent system from xanthan hydrogel. *J. Biomat. Appl.,* **7**: 265-76.

Farouk A., Bela S., Geza R., Mohamed S., Abdei Hadi I. (1989). Bioactivity of some chemotherapeutic agents in selected polyethylene glycol ointment bases. *Acta Pharm. Hung.,* **59**: 87-94.

Grabowska-Bochenek J., Kubis A. (1986). Investigation of dressings developed for the treatment of alveolitis sicca dolorosa. Part 2: Influence of glycerol and PEG 200 on the properties of tablets and dressings comprising mefenamic acid and Nipagin P. *Pharmazie,* **41**: 648-50.

Haapasaari K.M., Risteli J., Koivukangas V., Oikarinen A. (1995). Comparison of the effect of hydrocortisone, hydrocortisone-17-butyrate and betamethasone on collagen synthesis in human skin in vivo. *Acta Derm. Venereol.,* **75**: 269-71.

Hanifin J.M. (1983). Atopic dermatitis. Special clinical complications. *Postgraduate Medicine,* **74**: 188-93.

Jensen B.K., McGann L.A., Kachevsky V., Franz TJ. (1991). The negligible systemic availability of retinoids with multiple and excessive topical application of isotretinoin 0.05% gel (Isotrex) in patients with acne vulgaris. *J. Am. Acad. Derm.,* **24**: 425-8.

Krasowska H., Krówczynski L. (1994). Onitments according to Polish Pharmacopoeia - 5th Edition. *Farm. Pol.,* **50:** 937-42.

Krueger G.G., Drake L.A., Elias P.M.., Lowe N.J., Guzzo C., Weinstein G.D., Lew-Kaya D.A., Lue J.C., Sefton J., Chandraratna R.A. (1998). The safety and efficacy of tazarotene gel, a topical acetylenic retinoid, in the treatment of psoriasis. *Arch. Dermatol.,* **134**: 57-60.

Kubis A.A., Szczesniak M. (1992). The influence of hydrophilizing agents on gel formulation rate of cellulose derivatives. Part 1: Influence of 1,2-propylene glycol on homogenity of methyl cellulose gel. *Pharmazie,* **47:** 362-5.

Kus H., Misterka S., Pielka S., Juszkiewicz M. (1988). Local treatment of burn injuries and traumatic wounds with a hydrogel - Geliperm dressing. *Polymers in Medicine,* **18**: 211-9.

Liu C.H., Ho H.O., Hsieh M.C., Sokoloski T.D., Sheu MT. (1995). Studies on the in-vitro percutaneous penetration of indomethacin from gel systems in hairless mice. *J. Pharm. Pharmacol.,* **47**: 365-72.

Lukaszczyk J. (1995). Investigations on preparation and properties of modified polyacrylamide hydrogels for application as wound dressing materials. *Polymers in Medicine,* **25**: 15-23.

Lukaszczyk J., Schacht E. (1992). Some novel applications of synthetic polymers in drug delivery. *Polymers in Medicine,* **22**: 3-29.

Malecka K., Kubis A.A. (1998). Studies on dressings for mucosa of the oral cavity. Part 4: Influence of technology used in the preparation of dental xerogel dressings in the presence of acetone on their properties.

Misterka S. (1991). Clinical evaluation of hydrogel-type dressing materials after their 8-year use. ***Polymers in Medicine,*** **21** :23-30.

Miyazaki S., Tobiyama T., Takada M., Attwood D. (1995). Percutaneous absorption of indomethacin from pluronic F127 gels in rats. *J. Pharm. Pharmacol.,* **47**: 455-7.

Muller-Goymann C.C., Alberg U. (1999). Modified water containing hydrophilic ointment with suspended hydrocortisone-21-acetate - the influence of the microstructure of the cream on the in vitro drug release and in vitro percutaneous penetration. *Eur. J. Pharm. Biopharm.,* **47**: 139-43.

Olszewski Z., Kubis A. (1969). Method of study of the course of release of active substances from ointment bases by means of an apparatus of personal construction. *Acta Pol. Pharm*., **26**: 447-51.

Paluch D., Staniszewska-Kus J., Szymonowicz M., Solski L. (1991). Experimental studies of new Polish hydrogel dressing materials HDR. *Polymers in Medicine,* **21**: 9-21.

Srcic S., Eros I., Smid-Korbar J. (1985). Rheologic study of Eudispert-ammonium hydrogels. ***Pharmazie,* 40:** 128-9.

Szczesniak M., Kubis A.A., Grimling B. (1992). The influence of hydrophilizing agents on gel formulation rate of cellulose derivatives. Part 1: Influence of additional polymers on homogeneity of viscosity in methylcellulose gels ex tempore prepared in presence of hydrophilising agents. *Pharmazie,* **47:** 150-1

Szyszymar B., Wachowska L. (1975). Some contemporary ointment bases and their therapeutic use. ***Przegl. Derm.,* 62**:809-15.

Taware C.P., Mazumdar S., Pendharkar M., Adani M.H., Devarajan PV. (1997). A bioadhesive delivery system as an alternative to infiltration anesthesia. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, & Endodontics.* **84**: 609-15.

Toole J.W., Lockhart L., Potrebka J., Bowman J.P., Novack G.D. (1999). Comparative irritancy study among retinoid creams and gels. *J. Cutan. Med. Surg.,* **3**: 298-301.

Voigt R., Gulde C.H., Fechner H. (1978). Interactions between macromolecular excipients and drugs. 14. Results of equilibrium dialysis detected in drug excipient compounds on the liberation behavior in hydrogels. *Pharmazie,* **33:** 732-8.

Wohlrab W., Taube K.M., Kuchenbecker I. (1990). Penetration and effectiveness of hydrocortisone in reduced concentration in vehicles. *Zeitschrift fur Hautkrankheiten,* **65**: 534-7.

Zesch A., Schaefer H. (1975). Penetration of radioactive hydrocortisone in human skin from various ointment bases. II. In vivo-experiments. *Arch. Derm. Forsch.,* **252**: 245-56.