

Influencia de los tensidos en la liberación de las sustancias medicinales de los geles hidrófilos: influencia del polisorbato 20 y polisorbato 80 en la liberación del hidroclotisona 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 hydrocortisone from hydrophilic gels

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RESUMEN

El proceso de liberación de hidroclotisona 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, Hidroclotisona.

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 oint-

ment bases are also recommended in the treatment of allergic diseases and photodermatitis 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 drug or even aggravate the acute disease phase.

Hydrophilic ointment bases do not cause irritation and sensitisation (Toole et al., 1999), (Krueger et al., 1998), (Lukaszczuk, 1995), (Krasowska, 1994), (Bialik, 1992), (Lukaszczuk, 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 micelles 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), (Wohlrab 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, semi-permeable membrane as used for dialysis 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 distillation.

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 37°C. Every 15 minutes 5 m² 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

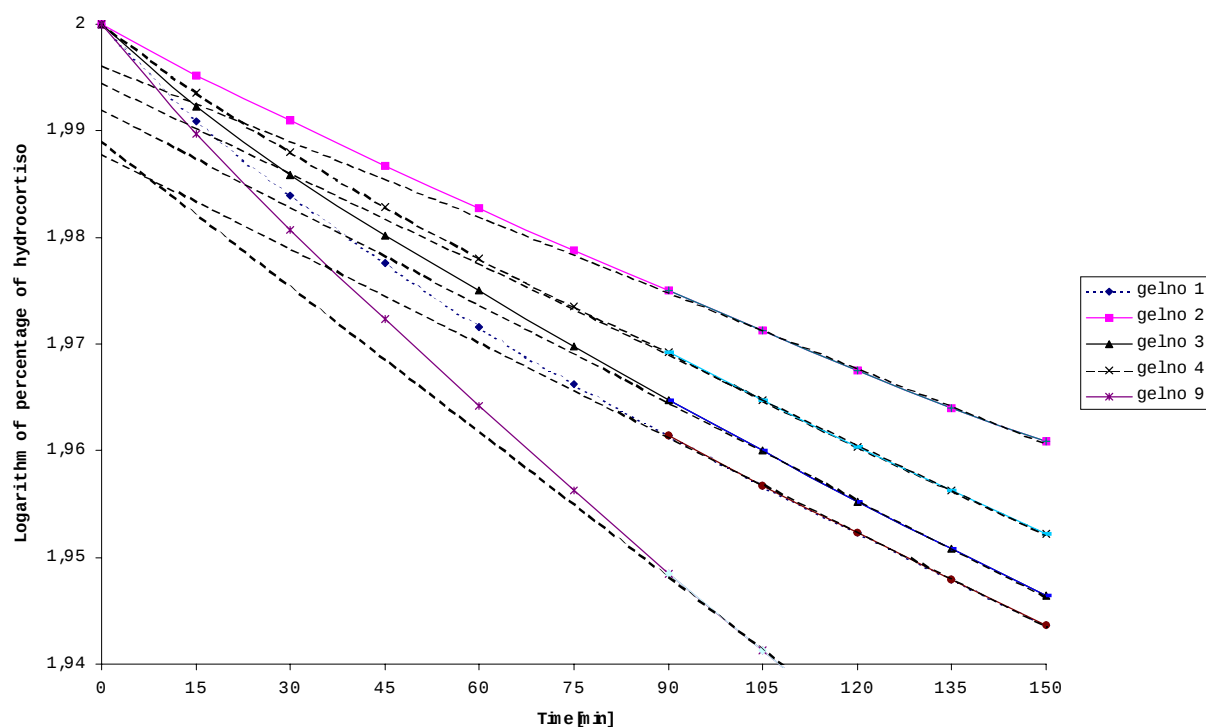
The influence of polysorbate 20 and 80 on the pharmaceutical availability of hydrocortisone from metylcellulose gel in the presence of 1,2-propylene glycol and PEG 200

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 lo-

garithm 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 hydrocorti-

sone 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.

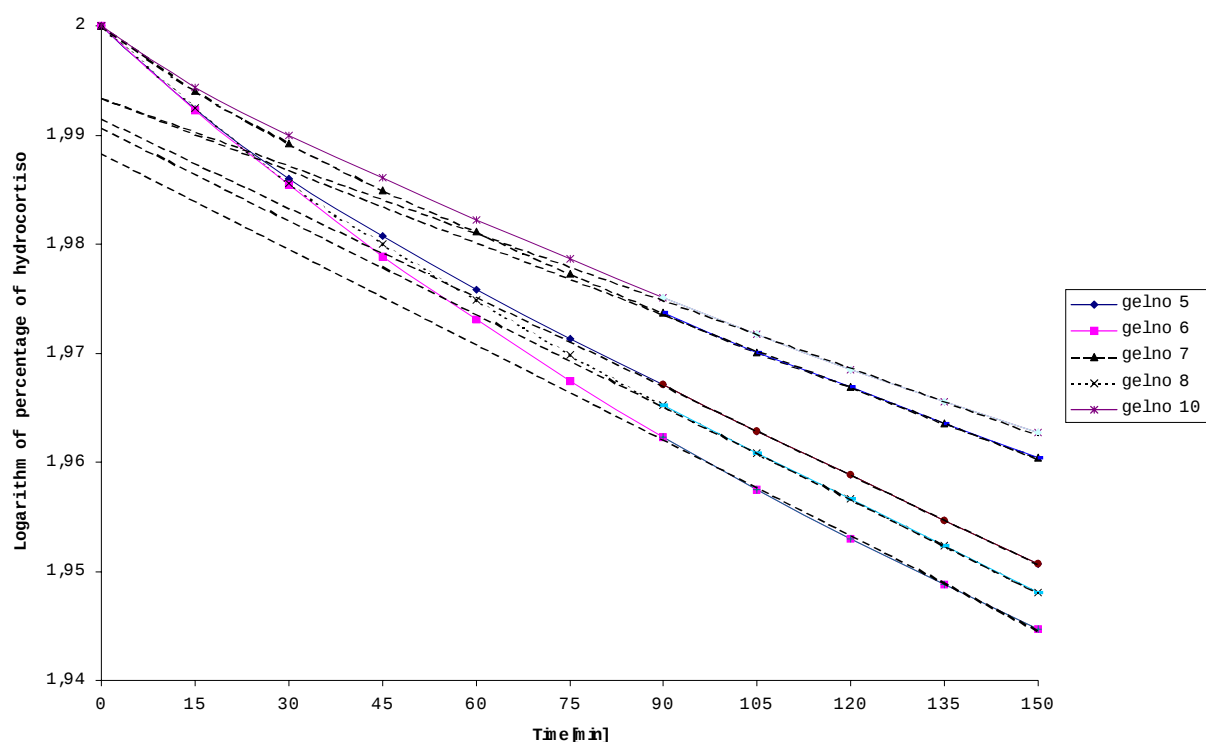


TABLE. Rate constants (K) and semiliberation rates ($T_{0.5}$) of hydrocortisone liberation process for methylcellulose gels with tenside additives.

Gel No	Concentrations of:							K [h ⁻¹]	T _{0.5} [h]	R ² Pearson's Coefficient
	H	MC	DMA	1,2-PG	PEG 200	P20	P80			
1	1%	4%	10%	10%	-	1%	-	4.24·10 ⁻²	16.35	0.9990
2	1%	4%	10%	10%	-	3%	-	3.50·10 ⁻²	19.79	0.9893
3	1%	4%	10%	10%	-	-	1%	4.42·10 ⁻²	15.67	0.9955
4	1%	4%	10%	10%	-	-	3%	4.05·10 ⁻²	17.09	0.9962
5	1%	4%	10%	-	10%	1%	-	3.98·10 ⁻²	18.80	0.9953
6	1%	4%	10%	-	10%	3%	-	4.15·10 ⁻²	16.71	0.9973
7	1%	4%	10%	-	10%	-	1%	2.95·10 ⁻²	23.50	0.9954
8	1%	4%	10%	-	10%	-	3%	3.87·10 ⁻²	17.91	0.9987
9	1%	4%	10%	10%	-	-	-	6.63·10 ⁻²	10.44	0.9977
10	1%	4%	10%	-	10%	-	-	2.67·10 ⁻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% poly-

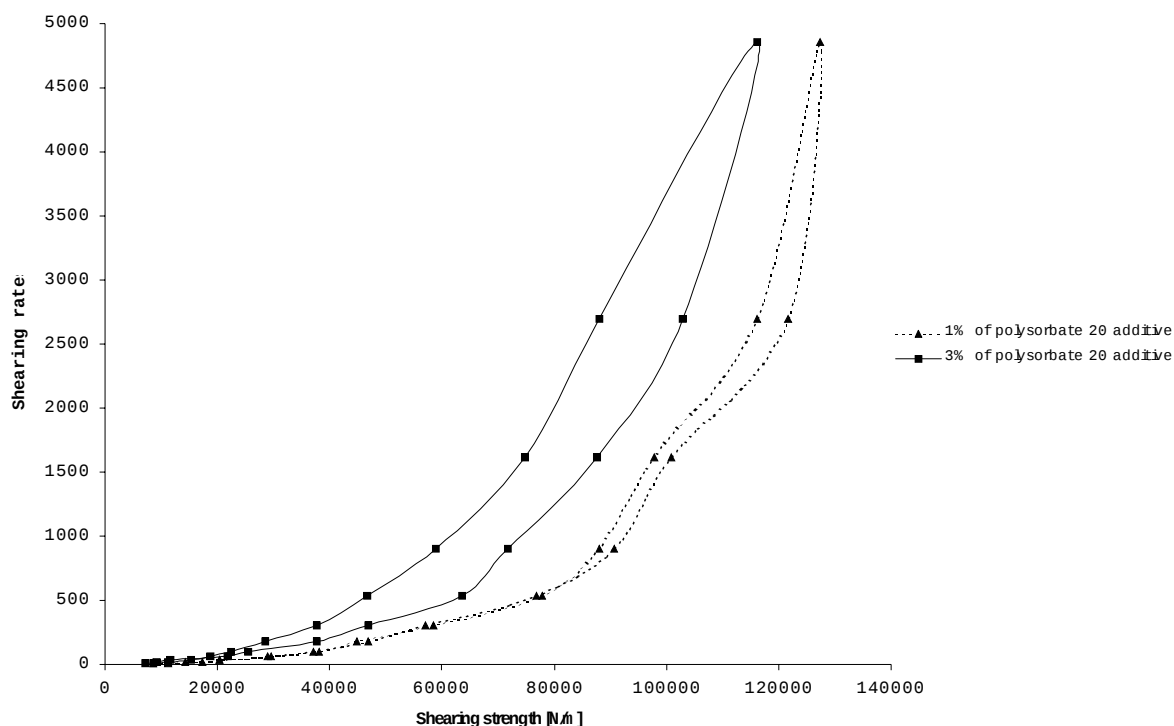
sorbate 80 where semiliberation rate is 23.50 hours.

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/m². The maximum shearing strength of these gels, measured at shearing rate of 4860 s, is within the range from 116097.60 N/

m² to 245434.40 N/m². 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.

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