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Influence of some polysorbates on hydrocortisone release from hydrophilic gels considered as two-compartment models

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Hydrocortisone release from hydrogels containing of 1% and 3% polysorbate 20 or polysorbate 80, in the presence of 1,2-propylene glycol or PEG 200 has two stages. In the first one the release rates are higher than those of the second stage. Half-release times in the first stage are in the range 0.31 h to 0.48 h and in the second stage 16.65 h to 23.22 h. Hydrocortisone release from the gels containing of 1% to 3% of polysorbate 21 or 81, in the presence of 1,2-propylene glycol or PEG 200 conform to second order kinetics. Release rates in this stage are in the range from $3.80 \times 10^{-4}\% \cdot h^{-1}$ to $5.97 \times 10^{-4}\% \cdot h^{-1}$.

1. Introduction

Hydrophilic gels are recommended by many authors due to their favorable effects on the skin [1–5]. It was shown that some medical agents are more intensively released by hydrophilic than by lipophilic ointments. Moreover, 1,2-propylene glycol stimulates hydrocortisone release from methylcellulose gels more intensively than PEG 200 [6–11]. Bendas et al. [12] found that 1,2-propylene glycol in hydrogel stimulates both solubility of hydrocortisone and its penetration rate through epidermis. More intensive release may result in undesirable rise of concentration of hydrocortisone at the skin and affect biosynthesis of skin collagen [13]. Water, present in the substrate, loosens the cornified skin layer, stimulates resorption and penetration of medicinal agents [14].

The aim of this study was the reduction of detrimental effects developed by excessive concentration of hydrocortisone on the skin. Application of polysorbates, such as polysorbate 20 and 80, in hydrogel composition and binding of hydrocortisone in micelles, formed by tensides, may diminish hydrocortisone concentration in gel beds. There should be a concentration equilibrium between hydrocortisone bound inside micelles and dissolved in hydrophilic gel. This should provide long and uniform action on the skin. Deficiency of the liberated medicinal agent occurring in the hydrophilic gel phase will be supplemented by diffusion of hydrocortisone from micelles, according to the established concentration equilibrium. Such a process should stabilize the concentration of free hydrocortisone in a hydrophilic gel phase, preventing detrimental effects of excessive cumulation of the drug on skin surface.

In contrast to polysorbates 20 and 80 having HLB values below 13.0, polysorbates 21 and 81 do not form clear solutions [15]. Studies on the release of non-steroidal anti-inflammatory drugs from hydrophilic gels [16] proved reduction of the drug release rate in presence of tensides characterized by relatively hydrophilic properties. Increased rates were observed in the case of relatively lipophilic tensides. The possibility for application of polysorbates with two fatty acid groups in a molecule, like polysorbates 21 and 81, in studies on hydrocortisone release rate from methylcellulose gels seemed also interesting.

2. Investigations, results and discussion

2.1. Effects of polysorbate 20 and polysorbate 80

Some attempts were made to determine release rates of hydrocortisone from methylcellulose gels, doped with 1% and 3% polysorbate 20 or 80 additives, considered as the kinetic reaction rates, measured as slope of the curves: logarithm of the rest concentration of medical agent versus time. However, none of the curves: of zero order, first order, second order and even concentration vs. $t^{0.5}$, was straight. Bearing in mind the concentration equilibrium maintained between hydrocortisone bound in micelles and dissolved in gel, it was assumed that the system should be considered as a two-compartment system, where micelles are the internal compartment (dispersed phase) and gel is the external compartment (continuous phase). After release of hydrocortisone from the external compartment, the concentration equilibrium becomes first upset then restored, due to diffusion of hydrocortisone from micelles. The curves proved that the hydrocortisone release process may be divided into two stages. In the first stage, the release rate is dependent both upon the concentration in the external compartment and on the diffusion rate from the internal compartment into gel (Fig. 1A, B). It may be illustrated by the semi-logarithmic curve (Fig. 2).

In the second stage, the release rate depends upon the diffusion rate only (Fig. 2). It is illustrated by the straight part of the curve.

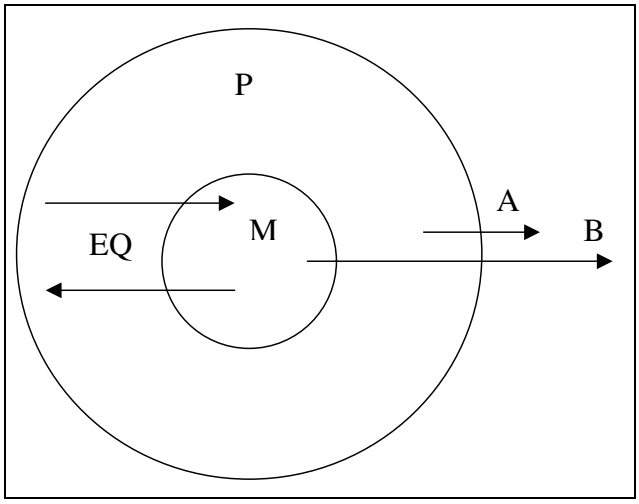

Fig. 1: Scheme of release ofhydrocortisone from hydrophilic polymer gel
A – release from hydrophilic polymer bed; B – release from micelles of polysorbates; EQ – concentrations equilibrium between hydrocortisone in polymer bed and in micelles; M – dispersed, micelles phase – internal compartment; P – continuous, polymer bed phase – external compartment

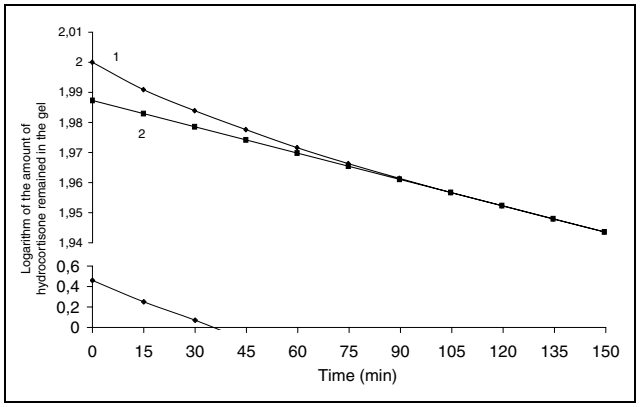

Fig. 2: Effects of polysorbate 20 additive on release of hydrocortisone from 4% methylcellulose gel containing 10% of 1,2-propylene glycol and 10% dimethylacetamide, 1 – experimental curve, 2 – extrapolated values for concentration of hydrocortisone, the first order process assumed (β) $y = -0.0003x + 1.9873$, 3-values for concentration of hydrocortisone as calculated for the initial step of the liberation process (α) $y = -0.013x + 0.4549$.

Assuming the two-compartment model of the system, the hydrocortisone release rates, α and β, were determined separately for the first stage, and for the second stage of the process, respectively (Table 1).

Table 1 shows the effects of polysorbate 20 and polysorbate 80 additives on the α and β release rates. The determination coefficients, calculated for the α and β curves are close to 1. For the α stage, the half-release time amounts to 0.31–0.45 h. According to the assumed model, it determines release of hydrocortisone in the α stage, when the concentration equilibrium between the both compartments is maintained.

The half-release times for the β stage amount from 16.65 to 23.22 h. It should be assumed that in the β stage proceeds diffusion of the medicinal agent from micelles into gel. As it can be seen, release rates α exceed the release rates β.

2.2. Effects of polysorbates 21 and 81

Analysis of hydrocortisone release kinetics from the gels containing 1% and 3% polysorbate 21 or polysorbate 81 proved that it is not a first order process, because of the curve drawn for logarithm of the residual concentration of the drug vs. time was not a straight line. Moreover, none of the curves: of zero order, second order and even concentration vs. $t^{0.5}$, was the straight. Nevertheless, a half of the gels examined (numbers 10, 11, 15 and 16, Table 2) followed the second order kinetics in the initial stage of the drug release process. For these gels the release rates were determined, of the initial stages of release, only. See Fig. 3, section A, for the gel number 16, as the example. The second order kinetics in the first stage of the process is confirmed by high determination coefficients (Table 2). The further steps of the hydrocortisone release process do not follow the pattern – the mechanism seems to be more complex.

2.3. Viscosity of examined gels

It should be noted that the gels are thixotropic. The flow limits of the gels are within the range from zero up to 19 N/m^2. The maximum shearing strengths of these gels, measured at shearing rate of 4860 s, are within the range from 116 000 N/m^2 to 245 000 N/m^2. Increase in tenside concentration was accompanied by a slight decrease of the

Table 1: Composition, release rates and half-release times for the first and for the second phase of the hydrocortisone release process (α and β) for methylcellulose gels with polysorbate 20 and 80

Gel No	Concentrations							α (h^{-1})	β (h^{-1})	$t_{0.5\alpha}$ (h)	$t_{0.5\beta}$ (h)	Determination coefficient r^2
	H	MC	DMA	1,2-PG	PEG 200	P20	P80					
1	1%	4%	10%	10%	–	1%	–	$5.12 \cdot 10^{-4}$	$1.12 \cdot 10^{-5}$	0.38	17.22	0.9990
2	1%	4%	10%	10%	–	3%	–	$4.27 \cdot 10^{-4}$	$8.90 \cdot 10^{-6}$	0.45	21.62	0.9893
3	1%	4%	10%	10%	–	–	1%	$4.80 \cdot 10^{-4}$	$1.16 \cdot 10^{-5}$	0.4	16.65	0.9955
4	1%	4%	10%	10%	–	–	3%	$5.47 \cdot 10^{-4}$	$1.07 \cdot 10^{-5}$	0.35	17.96	0.9962
5	1%	4%	10%	–	10%	1%	–	$6.23 \cdot 10^{-4}$	$1.03 \cdot 10^{-5}$	0.31	18.62	0.9953
6	1%	4%	10%	–	10%	3%	–	$4.64 \cdot 10^{-4}$	$1.09 \cdot 10^{-5}$	0.41	17.66	0.9973
7	1%	4%	10%	–	10%	–	1%	$5.20 \cdot 10^{-4}$	$8.29 \cdot 10^{-6}$	0.37	23.22	0.9954
8	1%	4%	10%	–	10%	–	3%	$5.34 \cdot 10^{-4}$	$1.08 \cdot 10^{-5}$	0.36	17.79	0.9987

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

Table 2: Composition of hydrogels and release rates for the first stage of the hydrocortisone release process for methylcellulose gels with polysorbate 21 and 81

Gel No	Concentrations							Release rate (1/% · h)	Determination coefficient r^2
	H	MC	DMA	1,2-PG	PEG 200	P21	P81		
9	1%	4%	10%	10%	–	1%	–	None	None
10	1%	4%	10%	10%	–	3%	–	$5.97 \cdot 10^{-4}$	0.9998
11	1%	4%	10%	10%	–	–	1%	$3.87 \cdot 10^{-4}$	0.9996
12	1%	4%	10%	10%	–	–	3%	None	None
13	1%	4%	10%	–	10%	1%	–	None	None
14	1%	4%	10%	–	10%	3%	–	None	None
15	1%	4%	10%	–	10%	–	1%	$3.80 \cdot 10^{-4}$	0.9999
16	1%	4%	10%	–	10%	–	3%	$4.79 \cdot 10^{-4}$	0.9998

Note: H = hydrocortisone, MC = methylcellulose, DMA = dimethylacetamide, 1,2-PG = 1,2-propylene glycol, PEG 200 = polyoxyethylene glycol 200, P21 = polysorbate 21, P81 = polysorbate 81

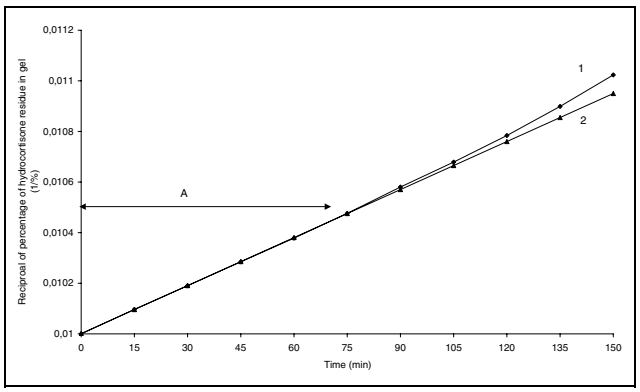

Fig. 3: Effects of 1% of polysorbate 81 on kinetics of release of hydrocortisone release from methylcellulose gel containing PEG 200. A – initial stage of release, 1 – hydrocortisone release curve, 2 – straight line curve drawn by extrapolation of the experimental data obtained in the initial stage of the process, following the equation $y = 6.2933 \cdot 10^{-6} + 0.01$; $r^2 = 0.9999$

maximum shearing strength values. The remaining gels, both with 1,2-propylene glycol and with PEG-200, showed similar properties.

3. Experimental

3.1. Materials

Ethyl alcohol 96%, analytical grade (POCH Gliwice, Poland), water bidestilled and deionised, semi-permeable membrane as used for dialyze in artificial kidney (Germany), *N,N*-dimethyl acetamide, analytical grade (Reachim, USSR), 1,2-propylene glycol, analytical grade (Laborchemie Apolda, Germany), polyoxyethylene glycol 200 (LOBA CHEMIE, Germany), methylcellulose (LOBA CHEMIE, Germany), hydrocortisone (Jelfa, Poland), Tween 20, Tween 21, Tween 80 and Tween 81 (Koch-Light Lab. Ltd., England) were used.

3.2. Preparation of hydrogels

The 4% methylcellulose gels were prepared *ex tempore* by mixing of solid and liquid components in a closed container [6, 7]. Their compositions are shown in Tables 1 and 2. The solid component was obtained by mixing hydrocortisone and methylcellulose, the liquid component by mixing 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 the surface of the liquid in a closed container and stirring for 2 h, to provide a homogenous consistence. Due to mixing in the closed container, evaporation of the liquid solvent was avoided and precise sampling was enabled.

3.3. Dynamic viscosity measurements

Rheological measurements were carried out by means of a 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 s. In course of 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.

3.4. Determination of hydrocortisone release

The release of hydrocortisone from gels was examined by measurement of the drug diffusion rate through a semi-permeable membrane [17]. Exactly weighed samples of gel were placed with a syringe on semi-permeable membrane at 37 °C. Then the samples of gel were equally spread all over the surface of the membrane by continuos circular movements of a spatula. Weight of the samples was determined by weighing of the syringe before and after application of gel. Every 15 min 5 cm^3 of gel was sampled into calibrated tubes.

3.5. Quantitative determination of hydrocortisone

Concentration of hydrocortisone was determined with the CECIL INSTRUMENTS spectrophotometer of the CE 5501 type at wavelength of 241.5 nm [18]. The amount of hydrocortisone released was determined by reading from the standarisation curve.

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