Department of Pharmaceutical Technology, Wrocław Medical University, Wrocław, Poland

Influence of selected tensides on the hydrocortisone concentration equilibrium balance in micelles and the dispersing center

M. Szcześniak, A. A. Kubis

Received February 25, 2005, accepted May 16, 2005

Prof. Dr. Aleksander Alfons Kubis, Department of Pharmaceutical Technology, Wrocław Medical University, ul. Szewska 38, 50-139 Wrocław, Poland

Pharmazie 61: 316–317 (2006)

The degree of hydrocortisone binding, was investigated by means of equilibrium dialysis in the presence of 1% or 3% micellar solutions of polysorbate 20 and 80. Stabilization of the concentration equilibrium was found in all the cases investigated. The degree of hydrocortisone binding in micelles depends on the concentration and type of tenside used.

1. Introduction

The use of surface-active compounds has a significant effect on the pharmaceutical availability of numerous active substances (Shukła et al. 2002; Wu et al. 2001; Kokot et al. 2001).

Studies of hydrocortisone release from hydrophilic gels in the presence of polysorbants demonstrate a slowing of the process depending on the type and concentration of the compounds due to binding of the active substance in micelles (Kubis et al. 2000). The process of hydrocortisone release from the systems may be interpreted according to a two-compartment model in which the hydrogel forms the external compartment while the internal compartment is formed by the active substance which is bound in the micelles (Kubis et al. 2002). In the first phases release is from the hydrogel, while in the second phase it depends on the rate of hydrocortisone diffusion from the micelles to the gel. This is conditioned by the concentration equilibrium between the active substance dissolved in the gel and that bound in the micelles.

The aim of this work was to investigate the rate of hydrocortisone binding in micelles on the basis of equilibrium diffusion in the presence of polysorbate 20 or polysorbate 80 micellar solution.

2. Investigations, results and discussion

The effect of tensides on the equilibrium diffusion of hydrocortisone was investigated in the presence of 1% or 3% polysorbate 20 and 80. Results of the measurement of diffusion rate in relation to time are presented in the Fig.

The measurements confirmed that there was stabilization of the concentration equilibrium between the donor and acceptor chambers. The concentrations of hydrocortisone in the presence of 1% polysorbate 80 in the two chambers were 71.9% and 27.3% respectively, giving a the total of 99.1%. Similar results were obtained for the remaining preparations and they are presented in Table 1. In all cases the concentration of hydrocortisone under conditions of balanced equilibrium was lower in the acceptor chamber than in the donor chamber, in which the active substance was bound in tenside micelles. Thus where tensides are used, only that hydrocortisone concentration which is in balance with the micelle-bound hydrocortisone is able to contact the skin. In the preparations investigated, 27% to 33% of the hydrocortisone contained in the external compartment of the preparation will have direct contact with the skin. As the amount of hydrocortisone in this compartment decreases as a result of absorption, the loss is compensated by diffusion from the internal compartment formed by the tenside micelles.

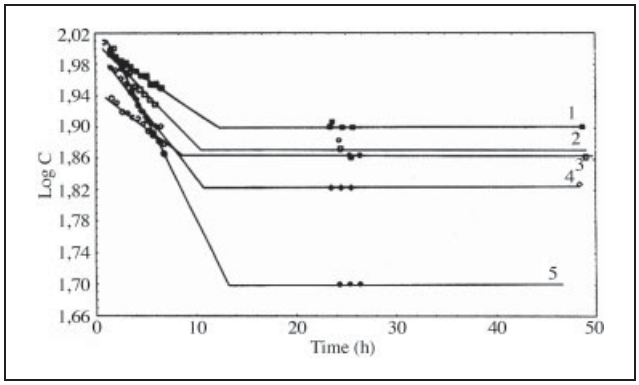

Fig.: Influence of polysorbates on hydrocortisone equilibrium rate

Table 1: Influence of polysorbates on concentration equilibrium and hydrocortisone diffusion rate

No	P 80	P 20	H	H_2O ad	Concentrations of: Hydrocortisone (%) Donor chamber	Acceptor chamber	Total	Time to achieve equilibrium concentration T(h)
1	1		0.01	100	71.85	27.29	99.14	9.53
2	3		0.01	100	71.62	28.13	99.75	7.39
3		1	0.01	100	66.11	33.87	99,98	10.04
4		3	0.01	100	77.60	27.41	99.01	11.25
5			0.01	100	49.20	49.55	99.75	12.24

P 80-polysorbate 80; P20 polysorbate 20; H-hydrocortisone

Table 2: Statistical evaluation of the measurement of hydrocortisone diffusion from tenside micelles to the dispersing centre

No	r(X,Y)	r_c	t	p	N
1	−0.98995	0.979994	−20.9965	5.91E-09	11
2	−0.9924	0.984849	−24.1871	1.69E-09	11
3	−0.98953	0.979168	−20.5678	7.09E-09	11
4	−0,99412	0.988275	−27.543	5.32E-10	11
5	−0.99802	0.996044	−47.6044	3.99E-12	11

No – Number of the trial; r(X,Y) – correlation coefficient; r_c – determination coefficient; t – t statistic; p – confidence level; N – number of valid measurements

Contact of the skin with hydrocortisone at a lower concentration than the level contained in the dermatological preparation prevents concentration-related undesirable effects of the substance.

As can be seen from the Fig., the rate of hydrocortisone diffusion is consistent with first order kinetics. The times to achieve equilibrium T (Table 1) were determined, as with hydrocortisone solution, by extrapolation from the slopes of the line determining the diffusion rate and the line showing the concentrations after 24 and 48 h. For hydrocortisone solution the time is 12.2 h, while if tensides are used, it ranges from 7.4 to 11.25 h. Moreover, comparison of the slopes of the lines representing the diffusion rate in the preparations investigated containing polysorbants with the slope of the line representing the diffusion rate of hydrocortisone in aqueous solution, indicates that the use of tensides may lead to prolonged activity, illustrated quantitatively by the rate constant K given in Table 1. Table 2 presents a statistical evaluation of the hydrocortisone diffusion processes investigated. The high correlation coefficients and low computed confidence levels prove that the findings are reproducible.

3. Experimental

3.1. Materials

Hydrocortisone (Jelfa, Poland), Polysorbate 20 and 80, (Koch-Light Lab. Ltd., England), semi-permeable dialysis membrane as used in artificial kidneys (Germany), purified water to the Polish Pharmacopoeia 6th Ed.

3.2. Diffusion of surfactants through a semi-permeable membrane

In view of the aim of the study, it was essential to check whether the surfactants used for the study diffuse through the semi-permeable membrane used.

Thus 1% or 3% polysorbate 20 or 80 solution was placed in the donor chamber, and the acceptor chamber was filled with distilled water with a surface tension 71.1 dyn/cm^2. This value was corresponds to the Polish Pharmacopoeia 6th Ed. The system was shaken and the surface tension was measured every half hour by the stalagmometric method. The measurements did not indicate any change in the surface tension of the water in the acceptor chamber. The surface tension in the donor chamber both before and after the study was 49.85 dyn/cm^2 for polysorbate 20 and 61.85 dyn/cm^2 for polysorbate 80. The results obtained prove that the surfactants used in the study do not diffuse through the semi-permeable membrane.

3.3. Hydrocortisone equilibrium diffusion

The equilibrium diffusion was studied by a method based on active substance diffusion through a semi-permeable membrane (Poet et al. 2002; El-Kattan et al. 2000). Thus two chambers, donor and acceptor, isolated from each other by a semi-permeable membrane were filled with the study solution and distilled water, respectively. Next the system was shaken. Samples were taken for analysis every half hour and the hydrocortisone contents were quantitatively determined.

The donor chamber was filled with 0.01% hydrocortisone solution, while the acceptor chamber was filled with water. The system was shaken as above and samples were taken every half hour for 6 h and then after 24 h. The hydrocortisone content was assessed spectrophotometrically in the donor and the acceptor chambers.

Measurements taken three times at one-hourly intervals after 24 h point to concentration equilibrium in the study system. The slope of the straight line indicating the hydrocortisone diffusion rate and concentration rate under equilibrium conditions in the acceptor chamber was used to calculate by extrapolation the time of achieving equilibrium of the concentrations. The time for hydrocortisone was 12.2 h. Equilibrium concentrations in the donor and the acceptor chambers were 49.2% and 49.5% respectively.

The results obtained confirm that hydrocortisone is able to diffuse freely through the semi-permeable membrane and reaches stability at equal concentrations in both chambers.

3.4. Determination of hydrocortisone

Hydrocortisone was determined with a spectrophotometric method according to Polish Pharmacopoeia 6th ed. at a wavelength of 248 nm. Hydrocortisone determination was carried out with a Cecil Instruments CE 5510 spectrophotometer.

References

El Kattan A, Asbil CS, Haidar S (2000) Transdermal testing: practical aspects and methods. Pharm Sci Technol Today 3: 426–430.

Kokot Z, Żmidzińska H (2001) Solubility and dissolution rate of ibuprofen in ionic and non-ionic micellar systems. Acta Pol Pharm Drug Res 58: 117–123.

Kubis AA, Musiał W, Szcześniak M (2002) Influence of some polysorbates on hydrocortisone release from hydrophilic gels considered as two compartment models. Pharmazie 57: 479- 481.

Kubis AA, Szcześniak M, Musiał W (2000) 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. Ars Pharm 41: 397–403.

Poet TS, McDougal JN (2002) Skin absorption and human risk assessment. Chem Biol Interact 140: 19–34.

Shuka A, Krause A, Neubert RHH (2003) Microemulsions as colloidal vehicle systems for dermal dry delivery. J Pharm Pharmacol 55: 741–748.

Wu H, Ramachandran C, Weiner ND, Roessler BJ (2001) Topical transport of hydrophilic compounds using water- in- oil nanoemulsions. Int J Pharm 220: 63–75.