Institut für Pharmazeutische Technologie der TU Braunschweig, Germany

Larvated incompatibilities of hydrocortisone cream preparations upon dilution with different cream bases

H. REFAI und C. C. MÜLLER-GOYMANN

Dedicated to Prof. Dr. G. Zessin, Halle (Saale) on the occasion of his 65th birthday

Water-containing hydrophilic ointment (WHS) with 1% hydrocortisone was diluted with various hydrophilic and lipophilic cream bases. Liberation experiments were carried out to examine the liberation of hydrocortisone from the undiluted hydrophilic and lipophilic bases containing 1% hydrocortisone as well as from the different diluted formulations. Moreover, the solubility of hydrocortisone in the different systems was determined. The o/w systems showed very high liberation profiles in comparison to the anhydrous hydrophilic and also to the lipophilic systems (with or without water content). The dilution of WHS with other o/w systems resulted in significantly high liberation rates whereas dilution with anhydrous hydrophilic or lipophilic bases decreased the liberation of hydrocortisone drastically. The release of hydrocortisone from the various cream bases agrees well with its solubility in these bases.

1. Introduction

Dilutions of cream preparations with other cream bases are often prescribed by dermatologists in order to reduce the drug concentrations in these creams. It is very important to choose a suitable base for the dilution, otherwise it could lead to apparent or larvated incompatibilities. Larvated incompatibilities are more serious as they are not easily discovered [1]. A previous investigation [2] showed a larvated incompatibility upon diluting Topisolon® ointment with Unguentum Cordes®. Macroscopically the formulation appeared homogeneous, however, microscopical examination revealed large water drops indicating coalescence of the emulsion. Undesired variations in the pH values and reduced preservative concentrations could also be regarded as larvated incompatibilities. One of the most serious larvated incompatibility that may occur upon diluting a cream preparation with an unsuitable base is the unexpected change in drug liberation. The aim of this study was to investigate the influence of diluting a cream base with other bases on drug liberation. For this purpose water containing hydrophilic ointment DAB 1998 (WHS) [3], with 1% hydrocortisone was used as a model system. It was diluted with the same base (WHS) and other various hydrophilic and lipophilic bases in the ratios 1 : 1, 1 : 2 and 1 : 3. The resulting dilutions were examined for their liberations of hydrocortisone. In addition, the liberation of hydrocortisone from the different hydrophilic and lipophilic bases containing 1% hydrocortisone was tested to reveal the effect of the undiluted bases on liberation.
Furthermore the solubility of hydrocortisone in the different hydrophilic and hydrophobic bases as well as in the diluted formulations was determined to detect its possible influence on drug release.

2. Investigations and results

2.1. Influence of base type on drug liberation

In order to study the influence of base type on drug release various hydrophilic and lipophilic bases were chosen from the German Pharmacopoeia, DAB 1998. They can be classified into the following types:

- anhydrous hydrophilic base: hydrophilic ointment (HS), DAB 1998
- water-containing hydrophilic bases: water-containing hydrophilic ointment (WHS), DAB 1998 and non ionic hydrophilic cream (NHC), DAB 1998
- anhydrous lipophilic base: wool fat ointment (WS), DAB 1998
- water-containing lipophilic base: water containing wool fat ointment (WWS), DAB 1998

The above mentioned cream bases were prepared with 1% hydrocortisone and examined for their drug liberation. The amount of drug released per unit area ($\mu g/cm^2$) was plotted versus the square root of time ($min^{1/2}$).
Figure 1 shows that the liberation rates of WHS (70% water) and NHC (50% water) were very high with no significant difference, followed by HS (anhydrous) with a remarkably low liberation profile. At last WS (anhydrous) and WWS (50% water) showed the lowest liberation rates. This result reveals the great influence of water on drug liberation when incorporated in the hydrophilic bases, while having no effect on liberation from lipophilic bases.

2.2. Influence of dilution on drug liberation

To investigate the effect of dilution on drug liberation, WHS containing 1% hydrocortisone was diluted with the other bases in the relations 1 : 1, 1 : 2 and 1 : 3.
Figures 2 a, b, c, d and e show the effects of diluting WHS in ratios of 1 : 1, 1 : 2 and 1 : 3 with WHS, NHC, HS, WS and WWS, respectively. A linear correlation was obtained with all graphs between the cumulative amount

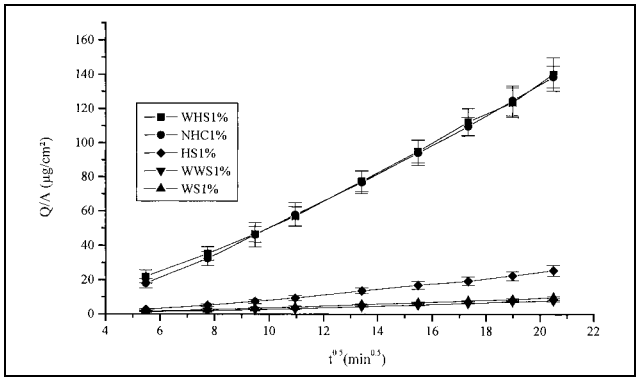
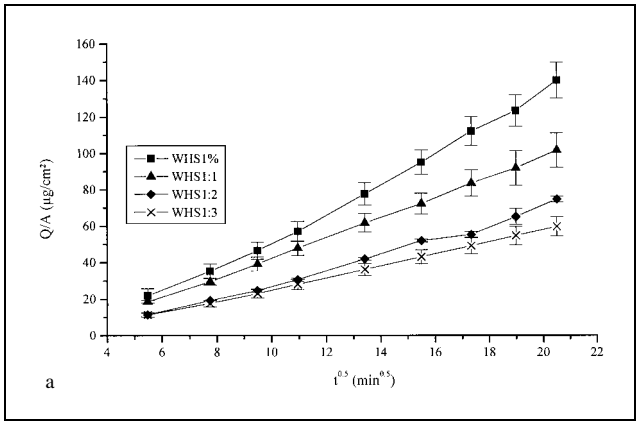
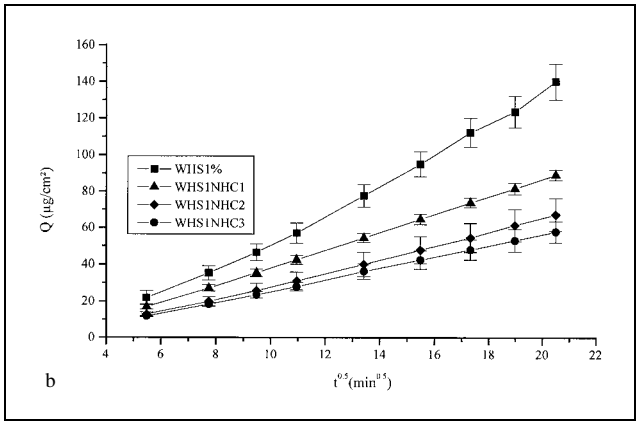
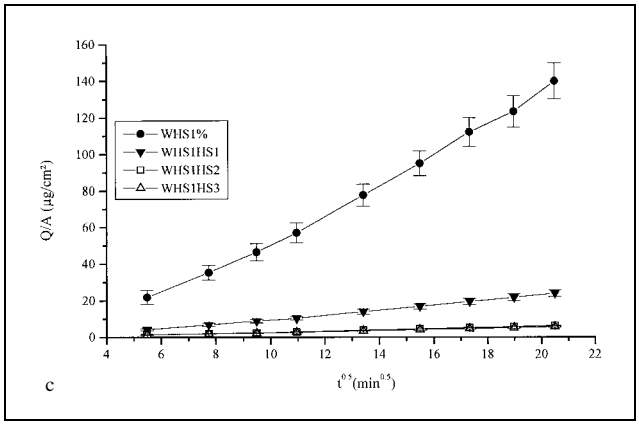
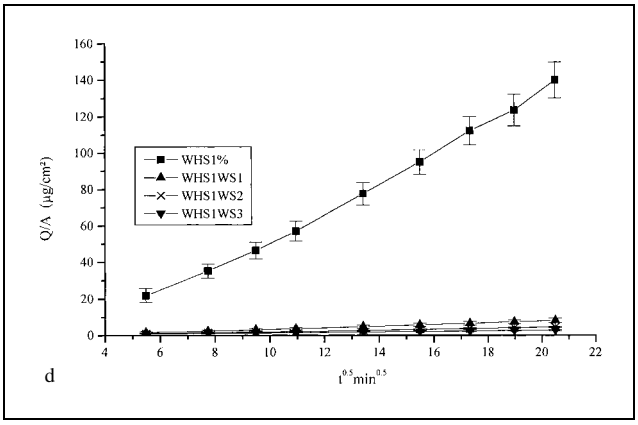


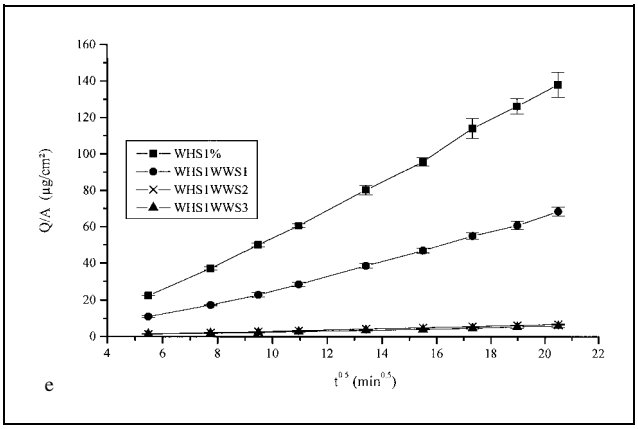
Fig. 1: Release of hydrocortisone from 1% WHS, NHC, HS, WS and WWS (n = 3)











Figs. 2a, b, c, d and e:
Release of hydrocortisone from 1% WHS diluted 1 : 1, 1 : 2 and 1 : 3 with WHS, NHC, HS, WS and WWS respectively (n = 3)

of drug released in µg per contact area in square centimeters and the square root of time. Therefore liberation coefficients could be calculated from the slopes of the graphs (Table 1).

Diluting WHS 1% with WHS resulted in higher liberation rates than expected. With the dilution ratio of 1 : 1 the liberation rate was not reduced to the half but was higher. The same was noticed with the ratios of 1 : 2 and 1 : 3. As WHS 1% was diluted with NHC almost the same phenomenon was observed.

A drop in the liberation of hydrocortisone was noticed upon dilution with HS, even with the ratio 1 : 1, which proves the great influence of water when incorporated in hydrophilic bases.

Diluting WHS 1% with WWS shows an interesting liberation profile. The ratio of 1 : 1 resulted in a reduction in the liberation rate of WHS 1% almost to the half while the dilutions 1 : 2 and 1 : 3 decreased the release of hydrocortisone drastically.

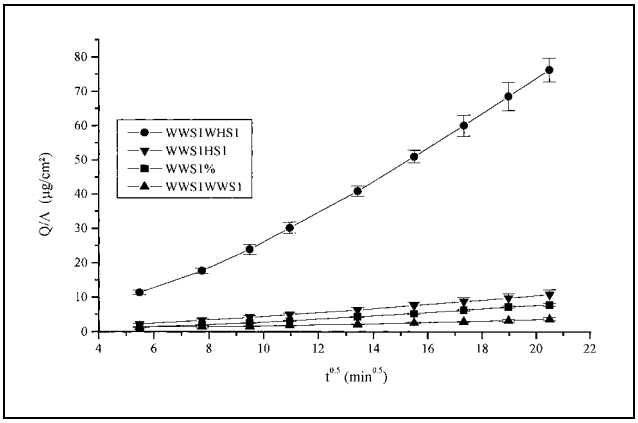


Fig. 3: Release of hydrocortisone from 1% WWS diluted 1 : 1 with WHS, HS and WWS (n = 3)

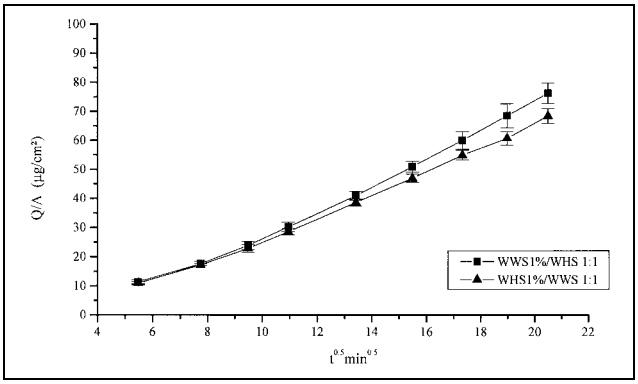


Fig. 4: Release of hydrocortisone from WHS 1% diluted with WWS 1 : 1 and from WWS 1% diluted with WHS 1 : 1 (n = 3)

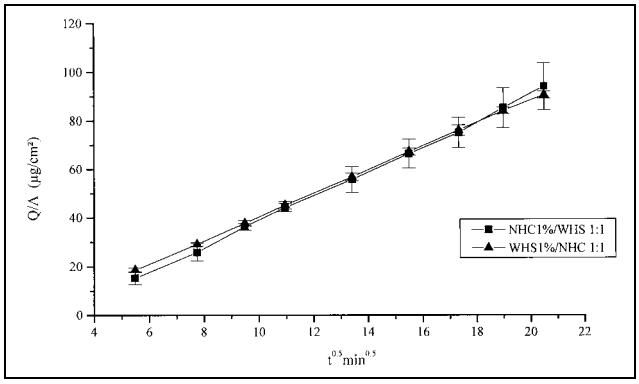


Fig. 5: Release of hydrocortisone from WHS 1% diluted with NHC 1 : 1 and from NHC 1% diluted with WHS 1 : 1 (n = 3)

Using WS as diluting vehicle resulted with all ratios in a very low drug release.

It was also interesting to incorporate the drug into a lipophilic cream base and to investigate the effect on drug release when diluted with the other cream bases. WWS 1% was chosen for this purpose as a model cream. It was diluted in the ratio 1 : 1 with the other bases (Fig. 3). Diluting WWS 1% with WHS resulted in a remarkable increased drug release, inspite of reducing the amount of drug to the half. With HS as dilution medium only a minimal increase in liberation was observed, whereas diluting WWS 1% with the same base reduced the liberation almost to the half. Comparing the systems WHS 1% diluted with WWS 1 : 1 and WWS 1% diluted with WHS 1 : 1 (Fig. 4) revealed no significant difference in their liberation profiles.

The same was noticed with the systems WHS 1%/NHC 1 : 1 and NHC 1%/WHS 1 : 1 (Fig. 5). This means that incorporating the drug in either of the two bases before dilution does not affect drug release from the final formulation.

Table 1: Liberation coefficients calculated from the slopes of the liberation curves of the studied cream bases

Base	Slope of curves ($\mu g/cm^2 \cdot min^{-0.5}$)	Liberation coefficient $cm^2/s \times 10^{-7}$
WS 1%	0.58	0.39
WWS 1%	0.52	0.14
HS 1%	1.63	0.60
NHC 1%	8.66	5.75
WHS 1%	8.63	5.72
WHS/WHS 1 : 1	5.74	5.05
WHS/WHS 1 : 2	4.53	4.76
WHS/WHS 1 : 3	3.29	3.33
WHS/NHC 1 : 1	4.86	3.82
WHS/NHC 1 : 2	3.82	2.99
WHS/NHC 1 : 3	3.02	2.44
WHS/HS 1 : 1	1.43	0.63
WHS/HS 1 : 2	0.35	0.08
WHS/HS 1 : 3	0.33	0.09
WHS/WWS 1 : 1	4.18	9.29
WHS/WWS 1 : 2	0.37	0.15
WHS/WWS 1 : 3	0.38	0.13
WHS/WS 1 : 1	0.48	0.23
WHS/WS 1 : 2	0.26	0.13
WHS/WS 1 : 3	0.14	0.06

2.3. Influence of the solubility of hydrocortisone in the cream base on drug liberation

The solubility of hydrocortisone in all studied formulations is very limited, which means that hydrocortisone is rather suspended in the bases than dissolved, however only the soluble part of the drug is able to diffuse [4]. Therefore, it was important to determine the saturation concentration (Cs) of hydrocortisone in the different bases in order to reveal its possible influence on drug release (Table 2).

WHS and NHC exhibit the greatest solubilizing capacity for hydrocortisone. The solubility of hydrocortisone is decreased to some extent in HS, while being relatively low in WWS and WS. It is obvious that the release of hydrocortisone from the cream bases studied agrees well with the solubility of hydrocortisone in these bases. The release of hydrocortisone thus seems to be dependent on the concentration of dissolved hydrocortisone in the creams.

3. Discussion

Topical creams are heterogeneous systems that contain, in addition to oil components, different amounts of water and various types of emulsifiers. In such complex systems different kinds of interactions may occur between active ingredients and components of the vehicle, which consequently might affect the release and availability of the drug [5].

Table 2: Saturation concentration of hydrocortisone in the different cream bases at 20 °C

Base	Cs (%, m/m)
WHS	0.012%
NHC	0.012%
WHS/NHC 1 : 1	0.012%
WHS/NHC 1 : 2	0.012%
WHS/NHC 1 : 3	0.012%
HS	0.005%
WHS/HS 1 : 1	0.0066%
WHS/HS 1 : 2	0.005%
WHS/HS 1 : 3	0.005%
WWS	0.002%
WHS/WWS 1 : 1	0.0033%
WHS/WWS 1 : 2	0.0027%
WHS/WWS 1 : 3	0.0023%
WS	0.0012%
WHS/WS 1 : 1	0.002%
WHS/WS 1 : 2	0.0015%
WHS/WS 1 : 3	0.0015%

Considering the microstructure of the cream bases and the solubility of hydrocortisone helps to explain the different liberation profiles. WHS as well as NHC are o/w systems having similar microstructures. They consist of 4 phases, a hydrophilic gel phase, a lipophilic gel phase, an aqueous bulk phase and an internal dispersed lipophilic phase [6]. The high liberation rates of both creams are probably due to the fast release of hydrocortisone from the external aqueous phase [7] and the relatively high solubility of hydrocortisone in the bases.

HS is a hydrophilic, anhydrous cream base consisting of a 3-phase system. The solubilization of the drug presumably occurs inside the mixed crystals of emulsifying cetostearyl alcohol [8]. The different results for WHS and HS in context with both the liberation and solubility studies prove the increased solubility of hydrocortisone in the external aqueous phase.

WS is a lipophilic base consisting mainly of white petrolatum (93.5%), in which the wool fat alcohols are partly suspended and partly dissolved. In this base wool fat alcohols act as lyotropic solubilizing agents [8]. The solubility of hydrocortisone in WS is very low, about 10 times lower than that in WHS and NHC and this agrees well with its low liberation rate. No significant difference between WWS and WS concerning their liberation profiles was observed. WWS is a w/o system, the internal phase is the aqueous phase which is incorporated as droplets inside the system [6] having no significant influence on the diffusion and the solubility of hydrocortisone. The diffusion through the external, more viscous, oily phase seems to be the rate limiting step for drug liberation.

As previously mentioned, diluting WHS 1% with the same cream base (WHS) resulted in higher liberation rates than expected for all mixing ratios investigated. As long as the same vehicle was used for the dilution the influence of any variations in structure of the vehicle or in solubility of hydrocortisone is excluded. In WHS 1% as well as in all diluted formulations the drug is suspended to a great extent, but only the dissolved part of the drug can diffuse [4]. Thus the factor influencing the drug release in this case could be the variation in concentration gradient between the suspended and the dissolved drug upon dilution. Almost the same phenomenon was observed for the dilutions of WHS with NHC. This was expected because NHC has a similar microstructure and dissolving capacity for hydrocortisone as WHS.

The great decrease in liberation of hydrocortisone, that was noticed upon dilution of WHS 1% with HS even at the ratio 1 : 1, shows that hydrocortisone is dissolved to a great extent in the external aqueous phase. Decreasing the amount of aqueous phase by dilution with HS therefore affects the drug release negatively.

The dilution of WHS 1% with WWS 1 : 1 resulted in a quite high liberation rate if compared to the dilutions 1 : 2 and 1 : 3, which means that this combination is probably still an o/w system, whereas increasing the amount of WWS in the mixture converts it into a w/o system. This was proven by conductivity and colouring tests. The combination 1 : 1 showed a blue colouration with methylene blue and a conductivity of 94 μS/cm. The combinations 1 : 2 and 1 : 3 gave no blue colour with methylene blue but exhibited a bright red colour with sudan red and a conductivity of just 0.04 μS/cm.

Diluting WHS 1% with WS resulted in all combinations in very low liberation rates which indicate that a phase conversion has taken place already with a dilution ratio of 1 : 1. This was proven with a colouring test using sudan red, which gave a bright red colour for all dilution ratios indicating a lipophilic external phase.

Considering the liberation coefficient of the combination WHS 1%/WWS 1 : 1 we notice that it has a remarkably high value, because of the low saturation concentration of hydrocortisone in this formulation. It will be of further interest to investigate the behaviour of this combination in permeation studies through excised human stratum corneum.

To avoid unexpected incompatibilities influencing drug release upon diluting a cream preparation with another cream base it is necessary to choose a suitable base for the dilution.

This base has to be similar to the original base of the cream with regard to the emulsion type and water content.

4. Experimental

4.1. Materials

Emulsifying cetostearyl alcohol (Henkel, D-Düsseldorf), cetostearyl alcohol (Caesar & Loretz GmbH, D-Hilden), liquid paraffin DAB 10 (Mainland, D-Frankfurt), white petrolatum DAB 10 (Hansen & Rosenthal, D-Hamburg), wool fat alcohol (Caesar & Loretz GmbH, D-Hilden), glycerol 85% (Henry Lamotte GmbH, D-Bremen), Tween® 60 (ICI, UK-Cleveland) and micronized hydrocortisone (Synopharm, D-Hamburg) were used as provided. Water was used in bidistilled quality. For preparation of phosphate buffer pH 7.4, 2.38 g sodium monohydrogenphosphate and 0.19 g potassium dihydrogenphosphate were dissolved in 1000 ml water.

4.2. Methods

4.2.1. Preparation of creams

Creams were prepared according to the instructions of the German Pharmacopoeia DAB, 1998. In order to obtain homogeneous distribution of hydrocortisone within the base and homogeneously diluted formulations a Cito-Unguator® [9, 10] was used. The homogenization was done at 1000 rpm for 2 minutes at room temperature.

4.2.2. Liberation studies

The liberation experiments were carried out in triplicate with a modified Franz diffusion cell [11]. The donor compartment was filled with the cream formulation and phosphate buffer pH 7.4 was used as acceptor. Donor and acceptor were separated from each other by a siliconized Spectrapore membrane MWCO 6000–8000 (Spectrum Medical industries; USA Los Angeles). The Franz cells were mounted in a water bath at 37 °C. Aliquots were taken every 30 min in the first 2 h afterwards every 60 min and replaced by fresh buffer. The duration of the experiment was 7 h. The amount of hydrocortisone in the acceptor medium was analyzed by HPLC. The liberation coefficient was calculated from the slope of the graph of the liberation curve according to the Higuchi equation [12]:

$$Q = A \cdot \sqrt{2 \cdot D_L \cdot C_0 \cdot C_s \cdot t}$$

Q = Cumulative amount of the liberated drug (mg)
A = Diffusion area (cm^2)
C_0 = Starting concentration of the drug in the donor (mg/cm^3)
C_S = Saturation concentration of the drug in the donor (mg/cm^3)
t = Time (s)
D_L = Liberation coefficient (cm^2/s)

4.2.3. HPLC analysis

Analysis was performed by reversed phase chromatography using a column of Hypersil® ODS 5 μm 250 · 4 mm (Grom, D-Herrenberg), the mobile phase was methanol/water (60 : 40) with a flow rate of 1.1 ml/min. The HPLC system consisted of a Beckman System Gold solvent Delivery System 126 and UV detector Beckman System Gold Detector Module 166 (Beckman, D-München). Linear correlation between peak area and hydrocortisone concentrations was obtained within the concentration range of 0.1 μg/ml to 20 μg/ml.

4.2.4. Determination of saturation concentration of hydrocortisone in the cream base

The base was prepared with a definite concentration of hydrocortisone, after having been left for 3 d at room temperature the preparation was examined for the presence of hydrocortisone crystals using a polarizing microscope. If no crystals were detected concentrations were examined, until crystals could be found. The first concentration at which crystals could be detected was taken as concentration at saturation [8].

4.2.5. Determination of density of cream bases

The determination of the density was necessary to convert the concentrations from w/w into w/v in order to fulfil the requirements of the Higuchi equation. The density of the different cream bases was determined using a Beckman Air Comparison Pycnometer 930 (Beckman, D-München).

References

1 Dolder, R.: Pharmazeutische Verfahrenstechnik heute 1, 9 (1980) supplement to Dtsch. Apoth. Ztg. **120** (1980)
2 Wolf, G.: Pharm. Ztg. **133** (14), 24 (1988)
3 Deutsches Arzneibuch 1998, Deutscher Apotheker Verlag Stuttgart & Govi Verlag Frankfurt
4 Preiss, A.; Mehnert, W.; Frömming, K.-H.: Pharmazie **49**, 902 (1994)
5 Niemi, L.; Kahela, P.; Turakka, L.: Acta Pharm. Nordica **1** (1), 23 (1989)
6 Niedner, R.; Ziegenmeyer, J.: Dermatika, Wissenschaftliche Verlagsgesellschaft, Stuttgart 1992
7 Benninger, A.: Dissertation, Entwicklung und Testung eines in-vitro Modells zur Untersuchung der Arzneistoffliberation aus Salben, Saarbrücken 1977
8 Loth, H.; Holla-Benninger, A.; Hailer, M.: Pharm. Ind. **41**, 789 (1979)
9 Alberg, U.; Meschkat, C.; Diesing, M.: Pharm. Ztg. **141**, 2758 (1996)
10 Zobel, H.-P.; Brinkmann, I.; Fröstel, B.; Heim, S.; Müller, C.; Nguyen, T.; Prescher, K.; Zimmer, A.: Pharm. Ztg. **142**, 2944 (1997)
11 Franz, T. J.: J. Invest. Derm. **64**, 190 (1975)
12 Higuchi, W. I.: Pharm. Sci. **56**, 315 (1967)

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Prof. Dr. C. C. Müller-Goymann
Institut für Pharmazeutische Technologie
TU Braunschweig
Mendelssohnstr. 1
D-38106 Braunschweig