evaporate the CH_3OH until dryness using a rotavapour, at a pressure of 0.9 bar. After dryness, 1 ml of HPLC-H_2O was added to the evaporating flasks and shaken until all lactose or lactose and SCG was dissolved (aqueous solution A). All samples (solutions and standard) were filtered through a 0.45 μm membrane filter prior to injection on the HPLC system. The average of 3 replicates of each sample was taken in order to obtain the SCG and/or lactose concentration. If a mixture of both SCG and lactose was studied, the latter was analysed as before and the SCG as follows: 50 μl of the aqueous solution A is placed into a 25 ml volumetric flask and the volume completed with phosphate buffer pH = 7.4. This solution is analysed by UV spectrophotometry according to Braun et al. [9]. If absorption readings were outside the calibration range, the assay was repeated using only 25 μl aliquot diluted to 25 ml.

References

1 Reynolds, J. E. F.: Martindale – The Extra Pharmacopoeia, 31. Ed., p. 1445, Royal Pharmaceutical Society of Great Britain, London 1996
2 Goodhart, F. W.; in. Wade, A.; Welle, P. J. (Eds.): Handbook of Pharmaceutical Excipients, Lactose monography, 2. Ed., p. 252, American Pharmaceutical Association, Washington and The Pharmaceutical Press, London, 1994
3 Fuller, R. W.; Collier, J. G.. J. Pharm. Pharmacol. **35**, 289 (1983)
4 Segall, A.; Vitale, F.; Ricci, R.; Giancaspro, G.; Pizzorno, M. T.: Drug Dev. Ind. Pharm. **23**, 839 (1997)
5 Radulovic, D.; Kocic-Pesic, V.; Pecanac, D.; Zivanovic, L.: Farmaco **49**, 375 (1994)
6 Ugrinovits, M.: Chromatographie **13**, 386 (1980)
7 Narinesingh, D.; Stoute, V. A.; Davis, G.; Ngo, T. T.: Anal. Biochem. **194**, 16 (1991)
8 Bakken, A. P.; Hill Jr., C. G.; Amundson, C. H.: Biotech. and Bioeng. **39**, 408 (1992)
9 Braun, M. A.; Oschmann, R.; Schmidt, P. C.: Int. J. Pharm. **135**, 53 (1996)
10 Yang, M. T.; Milligan, L. P.; Mathison, G. W.: J. Chrom. **209**, 316 (1981)

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Controlled drug release from coherent systems Part 1: Liberation from hydrocarbon gels

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One of the basic tasks of modern pharmaceutical technology is to control drug release. The drug release from coherent systems for external use (ointments, gels, etc.) is influenced by a great number of factors such as vehicle composition, the state of drug distribution, or the structure of the drug/vehicle boundary surface [1–6].

The aim of our experimental work was to perform a detailed study on the relationships between the properties of the drug and drug release. We intended to determine which properties accelerate drug release and which make it slow and prolonged. The following drug properties were studied: (i) the suspended or dissolved state of the drug, (ii) the solubilization of the drug, (iii) the microencapsulation of the drug and (iv) entering the drug into a molecular capsule – into an inclusion complex. Salicyclic acid (SA) was found to be suitable for the examinations. In each experimental series the base was constant so that the relationship between the drug and liberation could be studied. This paper will present the results of liberation obtained with hydrocarbon base.

The Fig. shows the time course of this process. Based on the liberated drug vs. diffusion time functions the process can be described with a power function in which the exponent is about 0.5:

$$Q = Q_0 t^{ma},$$

where Q is the quantity of the liberated drug, Q_0 is liberation at time 0 ($Q_0 \approx 0$), m is the rate constant of the process, a ≈ 0.5.

The correlation coefficient (r) and the values of factors a and m are summarized in the Table. Calculations were made to determine two other constants from the equation; the time required for the liberation of 1000 μg SA and the quantity of SA liberated in 12 h.

The power function gives an exact description of the kinetics of the process, r is invariably between 0.9–1, while the value of a is around 0.5.

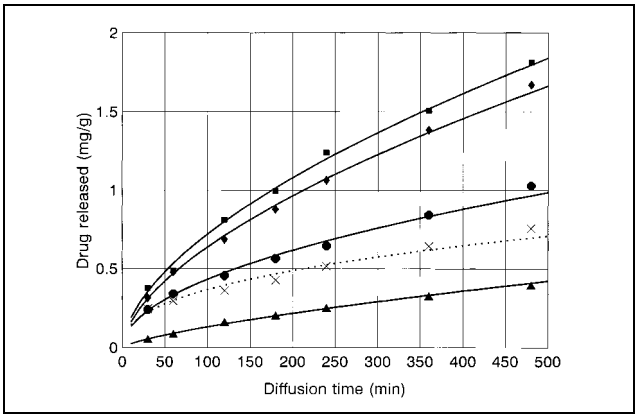

Fig.: Release of salicylic acid from white petrolatum
× SA in suspended state,
◆ SA in dissolved state,
▲ SA in inclusion complex (α-cyclodextrin, physical mixture),
■ SA in solubilized state (surfactant: Cremophor A 25),
● SA in microencapsulated form (covering agent: carboxy-methylcellulose sodium)

Table: Characteristics of drug release based on Eq. $Q = Q_0 t^{am}$

State of active ingredient	Characteristics of liberation process				
	Correlation coefficient r	Exponent of equation a	Rate of release m 10^{-2}	Time required for liberation of 1000 µg SA (h)	Quantity of SA liberated in 12 h (mg)
SA in suspended state	0.985	0.412	3.55	19.21	0.82
SA in dissolved state	0.999	0.596	8.20	3.55	2.06
SA in solubilized state	0.995	0.581	8.87	2.95	2.26
SA in inclusion complex (PM)[a]	0.998	0.517	2.08	43.55	0.54
SA in inclusion complex (SD)[a]	0.994	0.410	0.47	741	0.13
SA in inclusion complex (PM)[b]	0.991	0.505	0.83	151	0.28
SA in inclusion complex (SD)[b]	0.994	0.502	0.48	671	0.16
SA in microencapsulated form[c]	0.995	0.459	3.57	13.96	0.94
SA in microencapsulated form[d]	0.996	0.435	3.66	10.79	1.19
SA in microencapsulated form[e]	0.994	0.511	4.67	8.59	2.34

[a] inclusion complex was formed with α-cyclodextrin
[b] inclusion complex was formed with RAMEB (randomly methylated β-cyclodextrin)
[c] covering agent: methylcellulose
[d] covering agent: hydroxyethylcellulose
[e] covering agent: carboxymethylcellulose sodium

The elements of drug release are as follows: dissolution, diffusion of the dissolved molecules and their distribution between phases of various polarities [1]. Liberation was considerably increased by solubilization and dissolution. This increase can be explained by the major increase in the quantity of the dissolved molecules, therefore the role of dissolution is emphasized in the process of liberation. The increase is considerably smaller in the case of microencapsulation probably due to the fact that although the rate of dissolution was increased by the polymeric coat on the surface, the extent of drug dissolution was not enhanced. The three polymeric coats were found to increase liberation to various extents. The greatest effect was exerted by carboxymethylcellulose sodium, the second best was hydroxyethyl cellulose and the smallest effect was observed with the use of methylcellulose.

Inclusion complexes were found to decrease and to prolong liberation considerably. Liberation from inclusion complexes prepared with different technologies showed a characteristic difference: the physical mixture (PM) was liberated quickly, while the spray-dried product (SD) had prolonged liberation.

Experimental

1. Materials

The particle size of salicylic acid (SA) (Ph. Hg. VII) was between 0.2 to 0.1 mm. The ethanolic solution of SA was used for dissolved distribution, solubilization was carried out with Cremophor A25 (BASF). Solubilization was performed with method 3 described in our previous paper [7]. The inclusion complexes were made with the method of Kata and Selmeczi [8], using α-cyclodextrine and RAMEB (Cyclolab, Hungary). Microencapsulation was carried out with spray-drying (NIRO Atomizer, Denmark), the produced film coat was studied with electron microscope. The vehicle was white petrolatum (Ph. Hg. VII) containing 1 w/w% of SA.

2. Method

Drug release was studied with a Hanson's vertical cell (Hanson model 57-6M Diffusion Cell Test System, Hanson Research Corporation, USA). The mean values were calculated from 6 parallel measurements. The relative standard deviation range was 2.5–6%. The SA content was measured spectrophotometrically.

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References

1 Barry, B. W.: Dermatological Formulation, Percutaneous Absorption, p. 127 New York and Basel, 1983
2 Trotta, M.; Morel, S.; Gasco, M. R.: Pharmazie **52**, 50 (1997)
3 Erős, I.; Takács-Wormsdorff, T.: Pharmazie **52**, 311 (1997)
4 Neubert, R.; Golas, S.; Frixel, M.: Pharmazie **52**, 728 (1997)
5 Löffler, U.; Voss, Ch.; Moest, Th.: Pharmazie **53**, 180 (1998)
6 Loftoson, T.; Másson, M.; Sigurdsson, H. H.; Magnússon, P.; LeGoffic, F.: Pharmazie **53**, 137 (1988)
7 Erős, I.; Sánta, Zs.: Pharmazie **53**, 109 (1998)
8 Kata, M.; Selmeczi, B.: J. Inc. Phenomena **5**, 39 (1987)

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