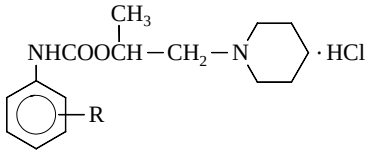
Table: Studied substances, their rate constants of alkaline hydrolysis and activation parameters



1: 2-OC_6H_{13}
2: 2-OC_7H_{15}
3: 3-OC_7H_{15}
4: 4-OC_7H_{15}

Compd.	Temp. (°C)	$k \cdot 10^5$ ($s^{-1} \cdot l \cdot mol^{-1}$)	$t_{1/2}$ (h)	n	r	F	s	a	b
1	60	3.297 ± 0.135	59	11	0.990	462.8	0.00488	0.0029	0.00504
	65	5.890 ± 0.244	33	11	0.992	581.6	0.00819	−0.0110	0.00898
	70	9.612 ± 0.282	20	10	0.997	1163	0.00780	−0.0104	0.01465
	75	14.21 ± 0.401	14	10	0.997	1254	0.01111	−0.0160	0.02165
2	60	3.118 ± 0.141	63	7	0.995	488.7	0.00227	−0.0016	0.00475
	65	5.651 ± 0.115	35	10	0.998	2420	0.00318	−0.0026	0.00861
	70	8.948 ± 0.275	22	6	0.998	1060	0.00350	−0.0036	0.01364
	75	12.53 ± 0.502	16	7	0.996	623.8	0.01708	−0.0086	0.01910
3	60	4.509 ± 0.089	44	12	0.998	2649	0.00685	−0.0108	0.00675
	65	7.691 ± 0.283	26	16	0.991	735.4	0.01658	−0.0187	0.01134
	70	11.06 ± 0.433	18	13	0.992	653.0	0.01114	−0.0124	0.01632
	75	15.73 ± 0.806	13	11	0.988	380.4	0.02388	−0.0241	0.02330
4	60	3.179 ± 0.121	64	16	0.990	694.0	0.01055	−0.0096	0.00467
	65	3.820 ± 0.185	53	12	0.987	383.1	0.01091	0.0053	0.00561
	70	5.136 ± 0.214	38	14	0.990	572.9	0.01297	−0.0124	0.00795
	75	6.369 ± 0.296	32	8	0.994	462.7	0.00851	−0.0022	0.00944

	E_A ($kJ \cdot mol^{-1}$)	ΔH^+ ($kJ \cdot mol^{-1}$)	ΔS^+ ($J \cdot K^{-1} \cdot mol^{-1}$)
1	94.0 ± 4.9	91.7 ± 4.6	−56.1 ± 13.6
2	89.4 ± 7.0	86.6 ± 7.1	−71.7 ± 20.7
3	74.4 ± 2.5	71.6 ± 2.5	−113.4 ± 7.3
4	45.9 ± 3.0	43.1 ± 3.0	−202.9 ± 8.7

lic buffers at pH 7; basic media have an infavourable influence on its stability in solution.

Experimental

The alkaline hydrolysis of the studied substances was carried out in aqueous-ethanolic NaOH (0.1 $mol \cdot l^{-1}$) in closed flasks tempered in an ultrathermostat at 60.0, 65.0, 70.0 and 75.0 ± 0.2 °C. The buffer solutions at pH 7.0, 8.0 and 9.0 possessed an amount of NaOH in the concentration of 0.0115 $mol \cdot l^{-1}$, 0.0291 $mol \cdot l^{-1}$ and 0.0461 $mol \cdot l^{-1}$, respectively. The ionic strength of buffers was 0.1 $mol \cdot l^{-1}$. Hydrolysis was carried out at 70.0 ± 0.2 °C. The C_2H_5OH concentration was 50% (v/v). The concentration of the studied substances was 0.001 $mol \cdot l^{-1}$. The concentration of the corresponding alkyloxyaniline, produced by the reaction, was determined spectrophotometrically [7], (spectrophotometer Specol 11, Carl Zeiss Jena, Germany). Rate constants of alkaline hydrolysis were calculated using the kinetic equation of the second order. Values of E_A were determined by the Arrhenius equation. Values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were determined by the Eyring equation [8].

Technical cooperation: Miss M. Makýšová.
The work was supported by grant 1/5008/98 of Ministry of Education of Slovak Republic.

References

1 Pokorná, M.; Čižmárik, J.; Sedlárová, E.; Račanská, E.: Česk. a Slov. Farm, in press
2 Čižmárik, J.; Borovanský, A.; Švec, P.: Acta Fac. Pharm. Univ. Comenianae **29**, 53 (1976)
3 Beneš, L.; Švec, P.; Kozlovský, J.; Borovanský, A.: Českoslov. Farm. **27**, 167 (1978)
4 Stankovičová, M.; Bachratá, M.; Bezáková, Ž.; Blešová, M.; Čižmárik, J.; Borovanský, A.: Českoslov. Farm. **36**, 9 (1987)
5 Stankovičová, M.; Čižmárik, J.; Pešák, M.: Chem. Zvesti **32**, 86 (1978)
6 Wells, J. I. in: Pharmaceutical Preformulation Study the Physicochemical Properties of Drug Substances, p. 152, Ellis Horwood Ltd. Publisher Chichester 1988
7 Stankovičová, M.; Kučárová, M.; Pešák, M.: Chem. Zvesti **29**, 227 (1975)
8 Treindl, L.: Chemická kinetika, p. 22, 73. Slovenské pedagogické nakladatel'stvo, Bratislava 1990

Received July 20, 1998
Accepted August 19, 1998

Doc. RNDr. Mária Stankovičová, CSc.
Odbojárov 10
832 32 Bratislava
Slovakia

Department of Industrial Pharmacy[1], College of Pharmacy, University of Cincinnati, Cincinnati OH, USA, and Department of Pharmaceutical Technology[2], Institute of Pharmacy, University of Leipzig, Leipzig, Germany

Effect of curing and storage on fluid-bed granules

A. Sakr[1], O. Neumerkel[2] and W. Süss[2]

Aqueous colloidal polymer dispersions (latexes or pseudolatexes) have been developed as an alternative to organic polymer solutions for the coating of solid dosage forms [1–3]. So films or coatings of water-insoluble polymers can be prepared without toxic organic solvents.

During coating of solid dosage forms with an aqueous polymer dispersion, coalescence of the colloidal polymer particles into a homogeneous film is often incomplete. To overcome this problem, it is recommended to expose the product to elevated temperatures (curing) [4, 5].

The objective of this work was to study the influence of storage time and temperature on granules, coated with a commercial ethylcellulose pseudolatex, Aquacoat®.

Oven-curing of new coated theophylline granules at 70 °C decreased the released amount of drug of about a quarter

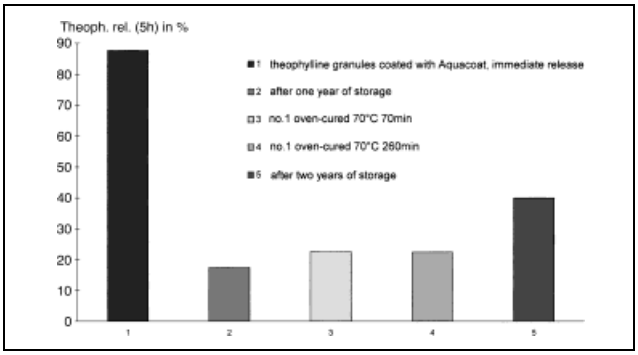


Fig. 1: Effect of storage and curing on theophylline release from coated granules

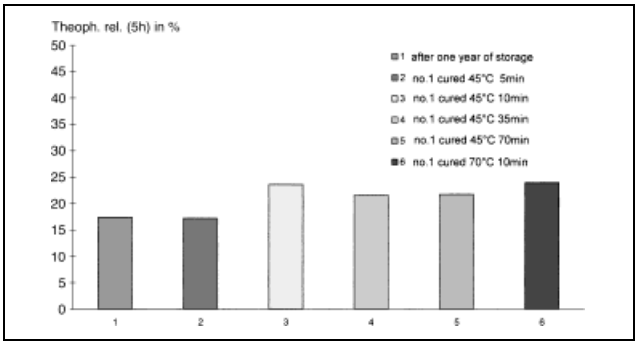


Fig. 2: Effect of storage and curing time on theophylline release from one year old coated granules

within five hours. The curing times of 70 min and 260 min caused no significant differences in drug release pattern.

Under normal conditions of storage (room temperature and humidity) the released amount of theophylline from coated granules within five hours was after one year about five times less than the released amount of new coated theophylline granules. After two years of storage (same conditions), surprisingly the released amount of drug within five hours was half of the release of the new coated granules (Fig. 1). This effect may be caused by aging of the material.

As can be seen in Fig. 2, oven-curing of the one year old granules did not show an effect by 45 °C and 5 min. By 45 °C and 10, 35 and 70 min, the theophylline release was slightly increased as well as at 70 °C and 10 min.

Experimental

A powder mixture of Emcocel® 50M (microcrystalline cellulose, Mendell Co. Inc., Carmel, NY, USA), theophylline (China), lactose hydrous (Sheffield Products, Norwich, NY, USA) and Ac-Di-Sol® (croscarmellose sodium, FMC Corporation, Newark, DE, USA) was used to produce granules in a fluid-bed rotor granulator (GPCG1, Glatt Air Techniques, Ramsey, NJ, USA) while continuously spraying a binder solution of 2.5% Plasdone® K-29/32 (polyvinylpyrrolidon, ISP Technologies Inc., Wayne, NJ, USA). After drying in the rotor granulator to a humidity of 2–4% the granules over 0.85 mm and under 1.7 mm were coated in the same granulator with a mixture of Aquacoat® (ethylcellulose aqueous dispersion, FMC Corporation, Newark, DE, USA) and 30% dibutyl sebacate (Sigma Chemical Co., St. Louis, MO, USA). The thickness of the layer was 4 mg/cm^2.

The dissolution test was made by USP basket-apparatus at 37 °C and 50 rpm. The medium was 900 ml of water. Samples were measured by UV spectrophotometry (Beckmann DU-70, Beckmann Inc., Fullerton, CA, USA).

The moisture content was determined using an automated gravimetric moisture content analyzer (Computrac, Max-50, Arizona Instruments, Tempe, AZ, USA).

The content uniformity was examined and the USP requirements were met for all batches.

References

1 Steuernagel, C. R.; in: McGinity, J. W. (ed.): Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, p. 1, Dekker, New York 1989
2 Lehmann, K.; in: McGinity, J. W. (ed.): Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, p. 153, Dekker, New York 1989
3 Seitz, J. A.; in: Swarbrick, J.; Boylan, J. C. (eds.): Encyclopedia of Pharmaceutical Technology, Vol. 1, p. 337, Dekker, New York 1988
4 Bodmeier, R.; Paeratakul, O.: Drug Dev. Ind. Pharm. **20**, 1517 (1994)
5 Hutchings, D.; Kuzmak, B.; Sakr, A.: Pharm. Res. **11**, 1474 (1994)

Received September 18, 1998
Accepted September 28, 1998

Prof. Dr. W. Süß
University of Leipzig
Dept. of Pharmazeutical Technology
Schönauer Straße 160
D-04207 Leipzig

School of Pharmacy[1], Kaohsiung Medical College, Kaohsiung, and Graduate Institute of Pharmaceutical Sciences[2], Taipei Medical College, Taipei, Taiwan

Effect of adhesive and drug reservoir on *in vitro* transdermal delivery of nicotine

J.-Y. Fang[1,2], S.-S. Chen[1], P.-C. Wu[1] and Y.-H. Tsai[1]

Transdermal delivery of drugs from polymeric devices has been around for over a decade and significant advances have been made in this field [1]. A complete design of a transdermal device or patch incorporates a drug-loaded matrix or reservoir totally covered by a rate-controlling membrane. The entire skin-contacting surface of the patch is coated with an adhesive [2]. Accordingly the topical permeability of a drug depends on the rate of release from its formulated product including drug reservoir, membrane and adhesive. The purpose of this investigation was to evaluate the influence of adhesive and drug reservoir on *in vitro* permeability of nicotine as a model drug. Transdermal delivery of nicotine into the systemic circulation has been shown to facilitate tobacco withdrawl by mitigating or even preventing abstinence symptoms and diminishing craving [3, 4]. Both natural rubber and silicone are used as the base of adhesive to determine the permeation of nicotine *in vitro*. A polysulfone hydrophobic membrane is employed as the rate-controlling membrane because of the good wetting of the membrane by the aqueous fluid beneath it [5]. In the drug reservoir of the *in vitro* diffusion cell, nicotine was incorporated into the hydrogel formulations including Carbopol polymer (polyacrylic acid), methylcellulose (MC) and hydroxypropyl cellulose (HPC).

Various nicotine loading amounts are incorporated into pH 7.0 McIlvaine buffer for the *in vitro* permeation study through a polysulfone membrane combined with natural rubber or silicone adhesive. The profile of nicotine flux and the permeability coefficient is shown in the Table. There is an ascendant trend for nicotine to increase its flux from the nicotine concentration of 3 to 9% either through a natural rubber adhesive or through a silicone adhesive. After the calculation of the correlation coefficient between the drug concentration of 3 to 9% and flux, a linear relationship ($r = 0.999$ for natural rubber; $r = 0.998$ for silicone adhesive) was observed. No significant difference was found between the flux from drug re-