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Correlation between wettability and dissolution rate of pharmaceutical powders *

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Summary

Quotients of the 'effective' surface areas (A_{ef}) and the boundary layer thickness (d) are calculated from initial dissolution rates of pharmaceutical powders in 2-propanol/water mixtures by taking the corresponding solubilities and diffusion coefficients into account. These quotients A_{ef}/d are correlated with the contact angles of the drug against the solvent mixtures. Increasing wettability results in an evident increase of the 'effective' surface area which in turn leads to a higher dissolution rate. The correlations found for several examined drugs are quite similar. Studies on surfactant solutions instead of 2-propanol/water mixtures principally show the same results. Obviously the complete wetting of the drug surface ($A_{ef} = 100\%$) is achieved by contact angles of about 40 degrees in contrast to the commonly accepted value of zero degrees for spreading wetting. Assuming complete wetting, calculated values of the boundary layer are comparable to literature data.

Introduction

It is well known that improving the wettability of a drug leads to less agglomeration of drug particles in contact with the liquid. Thus the dissolution rate of the drug powder is increased because the surface area which is definitely wetted by the solvent is greater. According to the Noyes-Whitney/Nerst-Brunner equation (Eqn. 1) the kinetics of the dissolution rate is zero order if sink conditions are maintained and a constant drug surface area is assumed in spite of dissolution:

$$\frac{dm}{dt} = \frac{D \cdot A_{ef}}{d} \cdot c_s = k \cdot c_s = k_0 \qquad (1)$$

where dm/dt is the dissolution rate of the drug, D is the diffusion coefficient, d is the thickness of the liquid boundary layer, c_s is the solubility and A_{ef} is the 'effective' surface area (Finholt, 1974; Goldberg, 1974). A_{ef} can be calculated from dissolution rate constants k ($k = k_0/c_s$) by means of D and d (Eqn. 1). k-values can be obtained from the slopes k_0 of initially linear plots of dissolved drug versus time. It is important to stress that for a given solvent A_{ef} depends on the wettability of the drug powder.

A_{ef} for different solvents is correlated with the wettability of the drug characterized by the con-

* Dedicated to Paul Reisen, president of the International Association for Pharmaceutical Technology, on the occasion of his 60th birthday.

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tact angles against the corresponding solvents which are obtained by means of the Sessile Drop technique (Ohm and Lippold, 1985). It is assumed that this correlation characterizes quantitatively the relation between the wettability and the dissolution rate of pharmaceutical powders.

Materials and Methods

Substances

Chloramphenicol palmitate polymorph A Gruppo Lepetit (Milano); phenacetin, salicylamide and theophylline Merck (Darmstadt); amidopyrine, phenazone and chloramphenicol Bayer (Leverkusen). Purity is checked by differential thermoanalysis. 2-Propanol analytical grade Merck (Darmstadt); sodium dodecylsulphate Texapon K 12 Henkel Dehydag (Düsseldorf).

Contact angle measurement

The contact angles are determined by the Sessile Drop technique (cf. Johnson and Dettre, 1969), device by Lorentzen and Wettres (Stockholm). The measurement is carried out at $20 \pm 1°C$ immediately after placing the drop on the surface of the compacted powder. Compaction of the powder: hand hydraulic press Perkin Elmer (Überlingen), pressure: 11.3×10^8 Pa, weight of the compact: 300 mg; the liquid is not saturated with the drug. More details are given by Ohm and Lippold (1985).

Specific surface area of the pharmaceutical powders

The determination of the drug specific surface areas was carried out by an AREAmeter II Ströhlein (Düsseldorf) after storing the pharmaceutical powder in a pure nitrogen atmosphere at temperatures well below the melting point. The temperature of storage was changed in order to check the complete desorption of molecules from the surface area of the drug. No sample assayed showed a greater specific surface area at higher storage temperatures. Both carbon powder possessing a specific surface area of 74 ± 2 m^2/g and quartz powder, W 10 Quarzwerke (Frechen), possessing a surface of 0.1 m^2/g, were used as standards. In order to achieve a reliable decrease in pressure, large amounts of powder had to be used for measurement. In those cases the volume of powders was compensated in the reference container by glass spheres. Consequently new constants for the determination of the specific surface area had to be calculated (Haul and Dümbgen, 1960; Johne and Severin, 1965; Rath, 1971; Lippold and Lippold, 1973). Specific surface areas obtained in this manner and by means of the AREAmeter nomogramme are listed in Table 1. The difference between the values determined by these two methods is insignificant.

TABLE 1

SPECIFIC SURFACE AREAS OF PHARMACEUTICAL POWDERS (m^2/g)

Drug	Gas adsorption method correction of the volume	Nomogramme
CPA	0.82	0.88
salicylamide	0.50	0.46
phenacetin	0.48	0.46
chloramphenicol	0.66	0.70
theophylline	1.99	2.04
amidopyrine	–	0.58
phenazone	0.25	0.36

Diffusion coefficients

The diffusion coefficients are obtained by means of the diaphragm cell technique introduced by Stokes (1950). Temperature: $20 \pm 1°C$. The diffusion media are degassed by ultrasonics, Sonifier Cell Disruptor B 15 Branson (Schwäbisch Gmünd). The concentration used for the experiments is 2.5×10^{-3} mol/l; time of diffusion: 48 h (if necessary 72 h). The cell constant is obtained by using nicotinic acid methyl ester: $D = 0.81 \times 10^{-5}$ cm^2/s at $25 \pm 1°C$ (Cadman et al., 1981). More details are given by Ohm (1984). The experimentally determined diffusion coefficients (D_{exp}) are listed in Table 2. The diffusion coefficients of the drugs are quite similar to each other.

Using the Stokes-Einstein equation, diffusion coefficients can be calculated by means of the partial molal volumes (Flynn et al., 1974). For the drugs examined the volume of the drug molecules is assumed to be larger compared with the volume of a water molecule. Calculated diffusion coefficients are listed in Table 2, too. A correction

TABLE 2

EXPERIMENTALLY DETERMINED AND CALCULATED DIFFUSION COEFFICIENTS (D_{exp} AND D_{calc}) OF DRUGS IN WATER AT 20 ± 1°C

Drug	D_{exp} (10^5 cm^2/s) mean (minimum–maximum)	D_{calc} (10^5 cm^2/s)
CPA	–	0.38
salicylamide	0.76 (0.60–0.90)	0.65
phenacetin	0.63 (0.55–0.70)	0.56
chloramphenicol	0.60 (0.51–0.66)	0.51
theophylline	0.63 (0.55–0.71)	0.67
amidopyrine	0.39 (0.33–0.46)	0.52
phenazone	0.74 (0.51–0.91)	0.57
nicotinic acid-methylester	0.81 [a]	0.77

[a] Value taken from Cadman et al. (1981).

considering the non-spherical shape of the molecules is not carried out, which means that a tolerance of about 10% has to be taken into account. In case of CPA it might be greater. Diffusion coefficients calculated in this way (D_{calc}) are similar to those obtained experimentally (D_{exp}).

The influence on the diffusion coefficient of salicylamide by increasing the 2-propanol concentration is studied, too. According to the Stokes-Einstein equation the diffusion coefficient decreases because the viscosity of 2-propanol/water mixtures is increased up to a volume ratio of about 50% (cf. Ohm, 1984). Values of D_{exp}, D_{calc} and of diffusion coefficients calculated by Eqn. 2, inserting the D_{exp}-water values, are listed in Table 3:

$$D_I \cdot \frac{1}{\eta_W} = D_W \cdot \frac{1}{\eta_I} \qquad (2)$$

where η is the viscosity of the diffusion medium, D is the diffusion coefficient, the indices W and I stand for the diffusion media water respectively 2-propanol/water mixtures. For the other drugs the diffusion coefficients in 2-propanol/water mixtures are calculated by means of Eqn. 2. Viscosity of 2-propanol/water mixtures and of sodium dodecylsulphate solutions are determined by a Höppler viscosimeter Haake (Karlsruhe).

Solubility

Solubility of the drugs at 20 ± 1°C is determined spectrophotometrically. Samples are assayed after 72 h via a sintered glass filter (porosity 4). In case of CPA the determination of the solubility as well as the dissolution rate is carried out by means of high-pressure liquid chromatography (HPLC) Hewlett Packard 1088 A (Frankfurt).

Dissolution rate

Apparatus

The dissolution rate of the drug powders is studied in the paddle apparatus USP XX 72 RL Hanson Research (Northridge, U.S.A.). In between the stirrer and the edge of the vessels samples are assayed continuously at medium level via glass sintered filters (porosity 2) with glass wool in front of it. After measurement by a spectrophotometer PMQ III Zeiss (Oberkochen) samples are pumped into the vessel again via glass tubes (diameter: 3 mm) which end 1 cm under the surface of the liquid. The solvent is degassed by ultrasonics. The temperature is 20 ± 1°C, agitation speed 100 min^{-1} and the solvent volume is 1 litre. Thus sink conditions are valid for the drugs studied until 20% of the dose used in the experiment is

TABLE 3

DIFFUSION COEFFICIENTS (10^5 cm^2/s) OF SALICYLAMIDE IN 2-PROPANOL/WATER MIXTURES AT 20 ± 1°C

2-Propanol (%)	Viscosity (mPas)	D_{exp} mean (minimum–maximum)	D_{calc} (Eqn. 2)	D_{calc} (Flynn et al., 1974)
0	1.00	0.76 (0.60–0.90)	0.76	0.65
5	1.18	0.67 (0.64–0.70)	0.65	0.55
10	1.47	0.61 (0.42–0.77)	0.52	0.44
20	2.09	0.47 (0.30–0.66)	0.36	0.31
30	2.75	0.43 (0.30–0.53)	0.28	0.24

dissolved. The only exception is CPA. Furthermore dissolution rate of CPA is analyzed discontinuously by taking samples through a sintered glass filter (porosity 4).

All tubes leading to the spectrophotometer and back have equal length and consist of PTFE. The tubes inside the pump consist of a modified PVC Tygon Norton (Northridge, U.S.A.). Pumping speed is constant 12.8 ml/min.

The pharmaceutical powder is placed in a plastic tube on a movable pusher that closes and opens the tube. After generating vibrations, the pusher is put aside — thus the tube is opened. Then the powder passes a 1 mm sieve which disperses larger agglomerates. This sieve is placed 1 cm above the solvent surface in between stirrer and the edge of the vessel (Ohm, 1984). The method which allows a standardized placing of the powder on the liquid is comparable to those of other authors (Efentakis and Fell, 1980; Kaneniwa and Watari, 1974; Reddy et al., 1976; Schäfer, 1980). The experiments are carried out with powder samples possessing the same surface area of 0.1 m^2. Therefore sample weights vary from 50 to 250 mg.

Evaluation

It is assumed that dissolution rates of the pharmaceutical powders follow zero-order kinetics until 20% of the used dose is dissolved. The only exception is CPA as its solubility is extremely low (the zero-order kinetics is not applicable if sink conditions are no longer granted).

Mixing and dilution processes in the tubes leading to the spectrophotometer are additional parameters to be considered in case of high dissolution rates. This is caused by the fact that transport is faster in the interior of a tube than near to its edge (Poiseuille-flow); additionally turbulent flow may occur too. Thus a drug solution pumped through a tube is transported and diluted at the same time. The dilution processes are assumed to be describable by first-order kinetics. Experimental dissolution graphs are evaluated in respect to those mixing processes. Two methods are used: a graphical one by comparison with simulated zero-order kinetics (graph comparison method) and a mathematical one (Ohm, 1984; Baumgarten et al., in press).

In respect to the graph comparison method experimentally obtained concentration/time graphs with given k_0-values are required. They are generated by pumping a concentrated drug solution into the vessel. This method allows a determination of unknown k_0-values up to relatively high dissolution rates. In case of extremely high dissolution rates, e.g. phenacetin-2-propanol/water 25 and 30% (v/v), k_0, however, can only be roughly estimated. Combinations of drug/solvent where most of the individual experiments do not show lower increases in concentration than those increases obtained after pouring a solution of a drug on the solvent in the vessel (20% of the dose used in dissolution experiments) are not evaluated. This means that, even if the mixing processes discussed above are considered, the dissolution of drug powders can be followed only up to ranges of a fairly good wettability (contact angles of about 40 degrees).

As to the mathematical evaluation of mixing processes, k_0-values of more than 3.5 mg/s are only estimated values as a calculation is impossible without risking considerable mistakes.

Results and Discussion

In Fig. 1 quotients of A_{ef}/d in dependence on the contact angles are shown in a semilogarithmic plot. In case of low contact angles (good wettability) the quotients A_{ef}/d were evaluated graphically. Quotients determined in this way are very close to those obtained mathematically (Ohm, 1984). With decreasing contact angles, the quotients A_{ef}/d are increasing evidently (exception: CPA). The correlation seems to be linear. Whether A_{ef} or d is the parameter which determines this correlation is discussed below.

The value of the boundary layer thickness d depending mainly on the agitation rate (Bircumshaw and Riddiford, 1952) should almost be constant under the experimental conditions chosen in these studies (constant agitation speed). Consequently it is assumed that A_{ef} is the parameter mainly responsible for the increased dissolution rate constant k of hydrophobic drug powders when the surface tension of the dissolution medium is

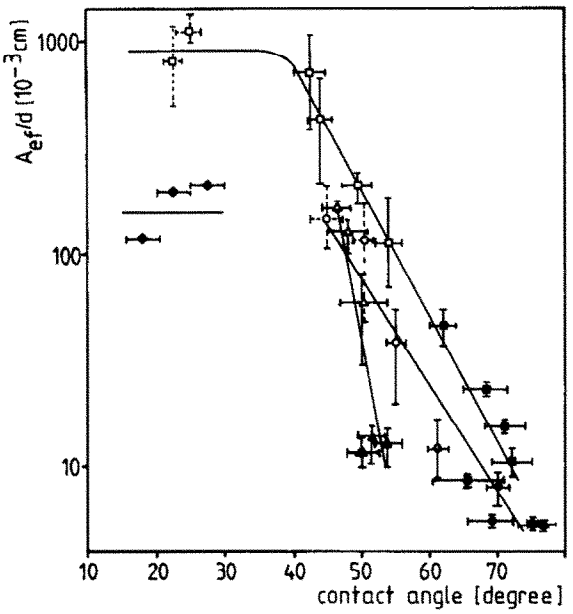

Fig. 1. Quotients of the effective surface area and the boundary layer thickness (A_{ef}/d) in dependence on the contact angle; 2-propanol/water mixtures. Filled symbols: values of k_0 are obtained without correction, open symbols: values of k_0 are obtained by means of graphical correction. Dashed lines: value is considered to be relatively unreliable. Contact angles: mean ± S.D., A_{ef}/d: mean, minimum/maximum value. Phenacetin (□), salicylamide (○), chloramphenicol (△), chloramphenicol palmitate polymorph A (◇).

lowered. Even if agitation speed is varied between 75 and 150 min^{-1}, A_{ef}/d-quotients only rise to a factor between 1.5 and 3.5 (Ohm, 1984, similar results are given by Levy, 1963). The increase in A_{ef}/d caused by varying the solvents (water to 2-propanol/water mixtures), however, is characterized by a factor of 63 in case of phenacetin, a factor of 23 in case of salicylamide and in case of chloramphenicol by a factor of 17.

The drugs possessing fairly good wettability, like theophylline, amidopyrine, and phenazone, dissolve so fast in water that their concentration/time graphs increase as quickly as if drugs which are already dissolved are poured on the dissolution medium (dose 20%). Thus an evaluation of k-values is impossible for hydrophilic drugs. Nevertheless, this observation confirms the fact that the effective surface area A_{ef} of hydrophilic drug powders is about 100%.

'Critical contact angle'

Decreasing contact angles of pharmaceutical powders with good wettability seem not to be followed by an increase of A_{ef}. This assumption holds for the experimental data of CPA, too. The range of contact angles studied in case of CPA does not show any alteration in A_{ef} (Fig. 1) which means that the dissolution rate is not increased by lower contact angles in this region. In the case of phenacetin, a plateau seems to be achieved for contact angles, too. The corresponding values, however, are connected with considerable errors (cf. discussion above). An error in the range of a factor 5–9 is, however, quite impossible. This factor refers to a continuing linear increase in A_{ef}/d versus contact angle graphs. Assuming a continually linear relationship of A_{ef}/d versus contact angle (Fig. 1), in case of spreading conditions (contact angle = 0 degrees) A_{ef}/d values follow which are quite unrealistic if the surface area of the powder samples used is considered (0.1 m^2). If d is estimated to be about 0.003 cm (cf. Bircumshaw and Riddiford, 1952; Langenbucher, 1974; Patel, 1984) phenacetin and salicylamide will have surfaces of about 7–60 m^2 (in case of chloramphenicol the areas are even higher). Vice versa, boundary layers will be smaller than those developing at extremely high agitation speeds (cf. Levy, 1963) if they are calculated on the basis of the experimentally determined powder surface areas of 0.1 m^2. In contrast to this, realistic values of about 5.8×10^{-3} cm (CPA) and 0.9×10^{-3} cm (phenacetin) are achieved, if d is calculated from the plateaus in Fig. 1 by means of the used powder surface area.

Thus, if the contact angle of a pharmaceutical powder is 40 degrees or below this value, dissolution rates result which are obviously not influenced by a decrease in the effective surface area caused by the agglomeration of the drug particles. Therefore it is assumed that in case of contact angles below 40 degrees the velocity of the solvent penetration into the powder agglomerates suffices to disperse the agglomerates at once. Consequently powders then possess an effective surface area of 100%. The angle of 40 degrees mentioned above is empirically required for complete wetting of the material used for contact lenses by physiological

salt solution, too (Kreiner, 1980). According to the term 'critical surface tension' introduced by Zisman (1964) which defines the value necessary for complete wetting, the value of 40 degrees is referred to as 'critical angle'. Another 'critical angle' was already defined by Parfitt and Wharton (1972) when they studied the relation between contact angle and dispersibility (sensitivity to dispersing effects) of graphon and titanium dioxide in surfactant solutions. For a certain minimum of dispersibility these authors indicate a value of 80 ± 12 degrees as a limit which means a better wettability can be observed for the first time at this angle: now the liquid starts penetrating into the powder agglomerates. For drugs which are difficult to wet a similar behaviour is expected in these studies and is indicated in case of salicylamide because the graph (Fig. 1) is flattening for high contact angles.

In all, further studies will have to prove whether the critical angle found in this study is evident in all cases and thus referable to other systems, e.g. gastric juice. A variation of the critical angle in dependence on experimental conditions, e.g. agitation speed, particle size and distribution of the powders used, is to be expected as well. Thus the wetting of agglomerates depends on their structure (Heertjes and Witvoet, 1970).

Discussion of the graphs

The parameters discussed above can also be used for explaining the differences in the characteristics of the individual graphs (Fig. 1). This means that slope differences are probably due to different particle sizes and distributions. In order to explain the different plateaus, a variation of d in dependence on the particle shape (Bircumshaw and Riddiford, 1952) should be taken into consideration. Further possible explanations are f.e. errors in the diffusion coefficients applied and the use of the specific powder surface area determined by gas adsorption in the place of the actual maximum surface area available for dissolution. Thus it can be concluded that surface roughness of the particles is sort of covered by the boundary layer and resulting from this the actual surface area of the dissolving particles no longer corresponds to the surface area of the boundary layer (Levy, 1963). The factors mentioned above may be responsible for the observed differences of the drugs in Fig. 1. Their influence was not investigated.

Despite the observed differences in all, a similar behavior of the investigated common drug powders becomes evident. Therefore a correlation of general validity between the wetted surface area and the contact angles seems to exist.

Dissolution rate in surfactant solutions

In order to examine whether the relation between wettability and dissolution rate proved for 2-propanol/water mixtures is also valid for different systems, dissolution studies with salicylamide in surfactant solutions (sodium dodecylsulphate SDS) are carried out. Only concentrations below the critical micelle concentration (CMC) are used. If there is foam on the liquid surface it is removed. Assuming c_s and D to be constant, A_{ef}/d-values which are graphically obtained as well as calcu-

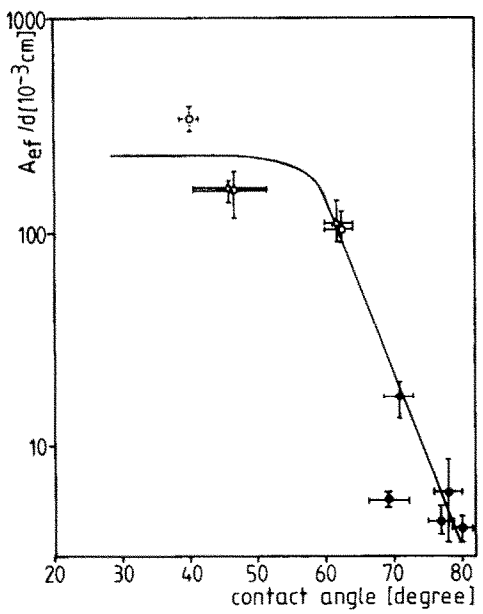

Fig. 2. Quotients of the effective surface area and the boundary layer thickness (A_{ef}/d) in dependence on the contact angle of salicylamide; sodium dodecylsulphate solutions. Filled symbols: values of k_0 are obtained without correction, (○) values corrected by mathematical means, (△) values corrected by graphical means. Dashed lines: value is considered to be relatively unreliable. Contact angle: mean ± S.D., A_{ef}/d: mean, minimum/maximum value.

lated are shown in dependence on the concentration of SDS in Fig. 2. In this case a graph first steeply increasing, then flattening to a plateau is also observed. The plateau of A_{ef}/d is found at about 220×10^{-3} cm and is thus comparable to values in 2-propanol/water mixtures. Consequently a similar value is also obtained for the thickness of the boundary layer (about 4.5×10^{-3} cm).

The critical angle for salicylamide in SDS is found, however, at about 55 degrees and is thus clearly higher than for 2-propanol/water mixtures. Where concentrations of 0.05 and 0.1% (62 and 71 degrees, respectively) are concerned, the determination of the contact angle is problematic because of its 'drifting', i.e. contact angles with respect to time are decreasing more than proportionally due to the adjustment of equilibrium concerning adsorption processes (Lippold and Ohm, 1985; Ohm, 1984). Up to now it has not been proved whether the used contact angles which were directly measured are also valid for the actual angle determining the dissolution rates in SDS solutions. If 'true angles' (time = 0) are estimated by extrapolation of the drift, a critical angle of about 50 degrees follows. These estimated values most probably better describe the wettability of salicylamide in SDS solutions than angles directly measured. Nevertheless further studies elucidating this problem are necessary.

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References

Baumgarten, E., Ohm, A. and Lippold, B.C., Pharm. Ind., Bestimmung schnell ablaufender Wirkstofffreisetzungen in kontinuierlich arbeitenden Meßsystemen (USP-Paddle-Apparat und DAC-Durchflußzelle), in press.

Bircumshaw, L.L. and Riddiford, A.C., Transport control in heterogeneous reactions. Quart. Rev., 6 (1952) 157–185.

Cadman, A.D., Fleming, R. and Guy, R., Diffusion coefficient determination using a filter-paper diaphragma cell technique. J. Pharm. Pharmacol., 33 (1981) 121–123.

Efentakis, E. and Fell, J.T., The wetting and dissolution rates of aspirin powder in surfactant solutions. Acta Pharm. Technol., 27 (1981) 33–35.

Finholt, P., Influence of formulation on dissolution rate. In L.J. Leeson and J.T. Carstensen (Eds.), Dissolution Technology, Acad. Pharm. Sci., Washington, 1974.

Flynn, G.L., Yalkowsky, S.H. and Roseman, T.J., Mass transport phenomena and models: theoretical concepts. J. Pharm. Sci., 63 (1974) 479–510.

Goldberg, A.G., Methods of increasing dissolution rates. In L.J. Leeson and J.T. Carstensen (Eds.), Dissolution Technology, Acad. Pharm. Sci., Washington, 1974.

Haul, R. and Dümbgen, G., Vereinfachte Methode zur Messung von Oberflächengrössen durch Gasadsorption. Chemie-Ing.-Techn., 32 (1960) 349–354, 586–589.

Heertjes, P.M. and Witvoet, W.C., Some aspects of the wetting of powders. Powder Technol., 3 (1969/1970) 339–343.

Johne, R. and Severin, D., Die Oberflächenmessung mit dem Areameter. Chemie-Ing. Techn., 37 (1965) 57–61.

Johnson, R.E. and Dettre, R.H., Wettability and contact angles. In E. Matijević (Ed.), Surface and Colloid Science, Vol. 2, Wiley Interscience, New York, 1969, pp. 85–153.

Kaneniwa, N. and Watari, N., Dissolution of slightly soluble drugs. I. Influence of particle size on dissolution behavior. Chem. Pharm. Bull., 22 (1974) 1699–1705.

Kreiner, C., Kontaktlinsen-Chemie, Median-Verlag, Heidelberg, 1980, p. 86.

Kreiner, C., Correspondence, Adatomed, München.

Langenbucher, F., Material and method parameters in dissolution rate studies. Pharm. Acta. Helv., 49 (1974) 187–192.

Levy, G., Effect of certain tablet formulation factors on dissolution rate of the active ingredient. I. J. Pharm. Sci., 52 (1963) 1039–1046.

Lippold, B.C. and Lippold, B.H., Physikalisch-chemisches Verhalten von Polymethacrylsäurederivaten. Pharm. Ind., 35 (1973) 729–732.

Lippold, B.C. and Ohm, A., Beeinflussung der Benetzung von Arzneistoffen durch Tenside, Polymere und Magensaft. Acta Pharm. Technol., in press.

Ohm, A., Untersuchungen zur Benetzung und Lösungsgeschwindigkeit von Arzneistoffpartikeln, Ph.D. Thesis, Düsseldorf, 1984.

Ohm, A. and Lippold, B.C., Charakterisierung der Benetzbarkeit von Arzneistoffpulvern mit Hilfe der Sessile Drop-Technik, Pharm. Ind., 47 (1985) 661–664.

Parfitt, G.D. and Wharton, D.G., The dispersion of rutile powder in aqueous surfactant solutions. J. Colloid Interface Sci., 38 (1972) 431–439.

Patel, D.C., Fox, J.L. and Higuchi, W.I., Physical model approach in the study of the transport of alkyl amines across a silicone rubber membrane in a two-chamber diffusion cell. J. Pharm. Sci., 73 (1984) 1028–1034.

Rath, R., Oberflächenbestimmung mit dem Areameter. Staub-Reinhalt. Luft, 31 (1971) 320–322.

Reddy, R.K., Khalil, S.A. and Gouda, M.W., Effect of dioctyl sodium sulfosuccinate and Poloxamer 188 on dissolution and intestinal absorption of sulfadiazine and sulfisoxazole in rats. J. Pharm. Sci., 65 (1976) 115–118.

Schäfer, U., Lösungsgeschwindigkeit und effektive Oberfläche von Phenobarbitalpulvern in Abhängigkeit von der Methode, der Korngröße und dem Hilfsstoffzusatz, Ph.D. Thesis, Saarbrücken, 1980.

Stokes, R., An improved diaphragm-cell for diffusion studies and some tests of the method. J. Am. Chem. Soc., 72 (1950) 763–767.

Zisman, W.A., Wettability and Adhesion, Advances in Chem. Series 43, Am. Chem. Soc., Washington, DC, 1964.