J. Pharm. Pharmacol. 1985, 37: 455–460
Received September 26, 1984

The effect of the surface free energy of pharmaceutical tablets on liquid penetration

MARIA DE LOURDES COSTA AND ADAM BASZKIN*

*Laboratoire de Pharmacie Galénique et de Biopharmacie, Faculté de Pharmacie, Université Paris XI, rue Jean-Baptiste Clément, 92290 Châtenay-Malabry, France and *Physico-Chimie de Surfaces et des Membranes, Equipe de Recherche du CNRS associée à l'Université Paris V, UER Biomédicale, 45 rue des Saints-Pères, 75270 Paris cedex 06, France*

The surface free energies (γ_{SV}) of the integral and partial tablet formulations of an antiarrhythmic drug—cibenzoline succinate, have been assessed by contact angle measurements using high-viscosity polyols and Neumann's equation of state. Independent measurements of penetration for these liquids into the tablets yielded pore size values through the use of the Washburn equation. The role of different constituents of the formulations are analysed in terms of their influence upon the free surface energy of the tablets and penetration rates. The relation between (γ_{SV}) and penetration rates yields for a series of liquids two threshold values: $(\gamma_{SV})_s$ 'start' and $(\gamma_{SV})_r$, 'rapid', which define respectively the beginning of the measurable penetration and the rapid penetration.

The wetting of tablets is an initial step in the process of drug dissolution. This process is followed by penetration of the liquid into capillaries of the tablet.

If the rate of penetration of the liquid through a tablet is limited by unfavourable surface energies, disintegration or dissolution of the tablet is poor. To overcome these difficulties several solutions are proposed. The use of surfactants and diluents to decrease the hydrophobicity of the solid drug and/or the reduction of particle size to increase surface area and facilitate penetration are the most common techniques (Singh et al 1968; Finholt 1974; Zografi & Tam 1976; Lerk et al 1978; Mohammad & Fell 1983).

In spite of numerous investigations in this field, a reliable methodology that can be used to determine the surface energies of pharmaceutical tablets on a quantitative basis is still needed.

Estimation of the surface energies of pharmaceutical powders may be made through contact angle measurements using the relation between this angle and the solid surface free energy (γ_{SV}), liquid surface tension (γ_{LV}) and their interfacial free energy (γ_{SL}).

The main difficulty with direct contact angle measurements on compressed powders is that the liquid drop penetrates the tablet so that the measured angle varies with time always leading to an underevalued result and the dissolution of a drug by the liquid may occur. To overcome these problems the saturated solutions of a drug or a tablet constituent in the liquids have been used by several authors (Singh et al 1968; Zografi & Tam 1976; Doelker et al 1981). However such saturated liquids may have different surface tension values from the pure liquids, and adsorption of a dissolved constituent at the solid–liquid interface may take place when a liquid drop is placed on a solid surface. The same phenomenon may occur when liquid mixtures are used to determine contact angles (Harder et al 1970; Fell & Efentakis 1978; Liao & Zatz 1979). Here again a preferential adsorption of one of these liquids at the liquid–solid interface may take place. These phenomena may lead to erroneous estimates of (γ_S) values.

To allow for the penetration of liquids due to the porosity of the compact, some authors measured maximum height of a drop of a saturated solution formed on a presaturated compact of the material (Mohammad & Fell 1983; Fell & Efentakis 1978; Lerk et al 1976). This method suffers, however, from the fact that receding contact angles, not representative for surface free energy estimation, are measured and also that a uniform saturation of a solid by a liquid is difficult to obtain.

The purpose of the present investigation was to estimate the free surface energies of compacts (γ_{SV}) from Neumann's equation of state (Neumann et al 1974). A homologous series of pure liquids of high viscosities (polyols) and low penetration rates was used to measure the advancing contact angles on various compacts.

An additional objective was to study the penetration rates of the used liquids through the compacts and to establish the direct relation between these rates and (γ_{SV}) values using Washburn's equation (Washburn 1921).

* Correspondence.

Table 1. Composition of integral and partial tablets formulations.

Symbol	Cibenzoline succinate	Lactose	Pevikon (PVC)	Talc	Magnesium stearate
F_{21}	190 mg 51·36%	132 mg 35·6%	37 mg 10%	7·3 mg 2%	3·7 mg 1%
F_2	—	—	37 mg 77%	7·3 mg 15·2%	3·7 mg 7·7%
F_4	—	132 mg 73·33%	37 mg 20·56%	7·3 mg 4·06%	3·7 mg 2·06%
F_6	190 mg 52·92%	132 mg 36·77%	37 mg 10·31%	—	—
F_7	190 mg 52·32%	132 mg 36·39%	37 mg 10·20%	—	3·7 mg 1·02%
F_8	190 mg 51·87%	132 mg 36·04%	37 mg 10·10%	7·3 mg 1·99%	—

The influence of each component of a pharmaceutical mixture on the (γ_{SV}) value and on the penetration of liquids can thus be determined.

MATERIALS AND METHODS

Materials

The tablets contain an antiarrhythmic drug–cibenzoline succinate. Table 1 summarizes the composition of the integral and partial tablet formulations. Cibenzoline succinate is a product of the UPSA laboratory (France). All other components used in tablet formulation are from Prolabo (France).

Liquids

All liquids used for contact angle measurements and penetration studies were Fluka analytical grade. They were used as received without further purification. Table 2 summarizes some of their physical properties. Triple-distilled water was used for penetration studies.

Table 2. Some physical properties of the liquids used for contact angle and penetration rate measurement.

Liquid	Viscosity η (cp)	Density d_4^{20}	Surface tension γ (mN m^{-1})
Ethylene glycol	19·9	1·113	48·9
Polyethylene glycol 200 (carbowax)	60	1·12	48·3
1,3-Propandiol	527	1·053	49·2
1,4-Butandiol	997	1·014	47·4
Glycerol	1490	1·23	63·7

All glassware in contact with these liquids was thoroughly cleaned with a freshly prepared strong sulphochromic mixture and then well rinsed with the triple-distilled water and dried. The test of the cleanliness of the glassware was its complete wetting by water.

Preparation of compacts

For all formulations the powders were wetted by methylene chloride before they were mixed in a mortar. The mass was then passed through an Erweka granulator (type F.G.S.) equipped with a 1 mm mesh screen. The resulting granules were dried at 50 °C in a drying room and passed once again through the same Erweka granulator. The material was finally sieved and only the 125–800 μm sieve fraction was used to prepare the compacts. For the formulations in which magnesium stearate and talc were used they were added non-wetted to the granules after the first granulation.

Tablets were prepared by compression in an alternative Frogerais machine type A0 equipped with a die of diameter 12 mm and plane faced punches. Before each compression the punches and the die were cleaned with ethanol and acetone.

Tablet hardness as determined by a crushing apparatus was always 100 N except in a few cases where the tablets were prepared with the single components only. In these cases tablet hardness was less than 100 N.

Liquid penetration studies

Liquid penetration characteristics were determined by modification of the technique described by Liao & Zatz (1979) and shown in Fig. 1. A glass frit (pore size 20 μm) was fitted into the glass tube (2 cm in diameter) about 1 cm above the bottom. Two large slits (0·6 cm in width) were cut in the glass from the frit to the bottom of the tube. The tube was placed in a glass container (volume 25 ml, diameter 3·6 cm) filled with a liquid used for the penetration rate measurements. The lateral slits prevent air bubbles from being trapped between the liquid and the glass frit.

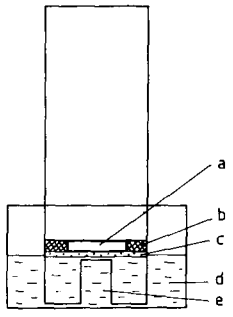

FIG. 1. Apparatus for penetration rate measurements. (a) tablet; (b) paraffin ring; (c) glass frit; (d) penetrating liquid; (e) slit in tube.

The tablets were coated with a molten paraffin on their side walls, inserted into the tubes and placed on the glass frit surfaces. This technique ensured that the studied liquid penetrated the exposed tablet face by capillary ascension, rather than by the rise between the side of tablet and the wall of the tube.

A uniform layer of a dye (Bleu Soluble W 6002, Wackherr, France) was spread on top of the tablets. The appearance of a colour on a whole surface of the tablet is considered as the end point of the penetration experiment.

Contact angle measurements

Contact angles were measured by a drop-on-plate method employing a device built by Société Bouty, Paris. The apparatus was used for extensive studies of polymer surface energetics (Baszkin & Ter-Minassian-Saraga 1974; Baszkin et al 1976a, b) and consists of the following parts: (a) The dark room chamber, double enclosed, thermostatted by means of an external liquid circuit. The chamber has two opposite windows and is installed on a plate which may be moved in two horizontal directions at right angles. The sample holder inside the chamber is fixed above a small dish filled with liquid. This allows saturation of the air phase with the vapour and thus avoids evaporation of the liquid drop during the measurement. (b) An exterior screw permits rotation of the sample holder and measurement of contact angles on various sites of the sample surface. (c) A microsyringe fixed at the top of the chamber by means of which a liquid drop of known volume may be placed on the surface of a tablet. The microsyringe may be displaced in two opposite directions, thus ensuring deposition of the drop along the surface of the sample. (d) A cathetometer with ×15 magnification, equipped with a goniometer that provides the contact angles.

The advancing contact angles of sessile drops were measured directly. The volume of the drop was 6 μl and the measurements were carried out at room temperature (20 °C). The advancing contact angles for the liquids used in this study were generally independent of time in the range of 1–10 min. Readings, therefore, were made 2–3 min after placement of the drop on the surface. Before the measurement, the tablet surface was brushed with a camel hair brush to remove loose powder or any material which might have contaminated the surface and could affect the contact angle. The reproductibility of contact angle values was better than 3°; the reported values are the mean values of at least six measurements on different tablets of the same formulation.

RESULTS

Table 3 lists the mean contact angle values for the tablet formulations indicated in Table 1 measured with the liquids listed in Table 2.

Table 3. Mean contact angles θ_A of liquids (polyols) on tablet formulations.

	Ethylene glycol	Poly-ethylene glycol 200	1,3-Prop-andiol	1,4-But-andiol	Glycerol
F_{21}	56	60	63	60·5	75
F_2	84	78	87·5	87	103
F_4	86	84	86	87	102
F_6	18	18	22	21	55
F_7	59·2	58	55	60	76·7
F_8	16·8	20·8	20·3	12·5	47

Table 4. Penetration rates (1/t) of polyols through tablets ($cm\ s^{-1} \times 10^{-6}$).*

	Ethylene glycol	Poly-ethylene glycol 200	1,3-Prop-andiol	1,4-But-andiol	Glycerol
F_{21}	30·2	12	7·5	6·3	5·5
F_4	15·9	10·5	8·97	5·06	3·64
F_6	574	295	211	212	191·0
F_7	55·8	29·6	21·9	20·2	19·7
F_8	406	217	139	115	97·9

* All results are the average values of at least three separate measurements.

In Table 4 are represented the results of penetration experiments. Retention is defined as a time (t) per unit length of tablet for liquid ascension through the tablet. Penetration is 1/t. When t is small, penetration is high.

The results in Tables 3 and 4 show that the values of contact angle on a given tablet surface are essentially sensitive to the surface tension of the liquid, while penetration mainly depends on the viscosity of the liquid.

DISCUSSION

Surface energies of tablet formulations

Lerk et al (1976) have reported that contact angle values on pharmaceutical solids are independent of particle size in the range 125–850 μm. However, mixed pharmaceutical surfaces, as it has been shown for dicalcium phosphate dihydrate—aspirin compacts (Lerk et al 1976) and for phenobarbitone—emcompress mixtures (Mohammad & Fell 1983), may exhibit a preferential enrichment of the surface of one component of the mixture composition over the other. Such a situation generally occurs when the particle size increases. For high speed milled mixtures the measured contact angle obeys the linear relation defined by Cassie (1948).

$$f \cos \theta_1 + (1 - f) \cos \theta_2 = \cos \theta_{12}$$

where θ_{12} is the contact angle of the liquid on a mixed surface, θ_1 and θ_2 are respectively contact angles on solids 1 and 2 and f and (1 − f) surface fractions of component 1 and 2.

For our system three points should be noted in view of the above considerations. (i) For all formulations the particle size of the main components was maintained in the range of 125–800 μm. (ii) The amounts of talc and magnesium stearate added to granules are believed to be too small to alter their initial size. Also no particle aggregation can be anticipated by the addition of these components as their role in formulation processing is to improve the flow properties of the powder. (iii) For a multicomponent system it is difficult to predict or to measure whether the contact angles are proportional to the fraction of the surface occupied by each solid, they represent however a value for the mixture as it is used.

To calculate the free surface energies (γ_{SV}) of the integral and partial formulation we have used the equation of state proposed by Neumann and initially used for the determination of (γ_{SV}) of polymers (Neumann et al 1974). Later this equation was also successfully used to calculate the surface energies of living cells (Van Oss et al 1975) and protein deposits (Van Oss et al 1981).

$$\cos \theta_e = \frac{(0{\cdot}015\,\gamma_{SV} - 2{\cdot}00)\sqrt{\gamma_{SV}{\cdot}\gamma_{LV}} + \gamma_{LV}}{\gamma_{LV}(0{\cdot}015\sqrt{\gamma_{SV}{\cdot}\gamma_{LV}} - 1)}$$

where (γ_{SV}) and (γ_{LV}) are respectively the free surface energy of a solid and of a liquid (surface tension) and θ_e the equilibrium contact angle which can be approximated by the advancing contact angle (θ_A). From this equation the (γ_{SV}) values were calculated with the help of a computer program based upon that which was used by Neumann et al (1974). They are listed in Table 5. The (γ_{SV}) values obtained with different liquids on all tablet formulations are reasonably constant. This constancy indicates that the corresponding contact angles are thermodynamically significant; specifically they are not influenced by roughness of the tablet surfaces and liquid penetration. Fig. 2 is the graphical representation of the results summarized in Table 5.

Table 5. Surface free energies (γ_{SV}) of Tablet formulations (mN m^{-1}).

	Ethylene glycol	Poly-ethylene glycol 200	1,3-Propandiol	1,4-Butandiol	Glycerol	Mean value ±σn − 1
F_{21}	31·4	29·1	28·2	28·5	31·5	29·7 ± 1·6
F_2	18·3	20·4	16·9	16·3	16·04	17·6 ± 1·8
F_4	17·4	18·0	17·5	16·3	16·6	17·2 ± 0·7
F_6	46·6	46·0	45·8	44·4	42·8	45·2 ± 1·5
F_7	30·0	30·0	32·1	28·5	31·0	30·3 ± 1·3
F_8	46·9	45·3	46·3	46·3	47·3	46·4 ± 0·8

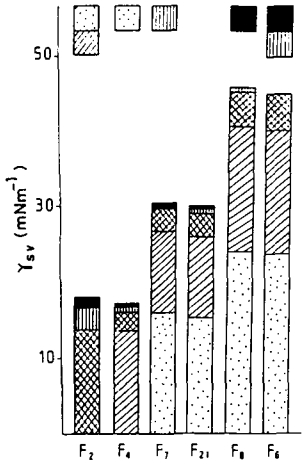

FIG. 2. Free surface energies of tablet formulations. The height of each portion of the column is the constituent percentage in the fomulation. The squares above the columns show the constituents which are missing in tablet formulation. The numbers represent tablet formulations. Hatching code as in Fig. 4.

The hydrophobic character of formulations is ensured by the presence of magnesium stearate; when magnesium is not included in the formulation of tablets (F_6 and F_8) the (γ_{SV}) increases. When F_2 and F_4 are compared, it can be seen that the increase in the hydrophobicity is essentially due to the absence of the drug (it seems that lactose has little or no effect on the γ_{SV} value of the compact). The comparison of the integral tablet (F_{21}) with the F_7 formulation shows that the presence of talc does not change the surface energy of the formulation. An analogous conclusion was made by Harder et al (1970).

All these results indicate that the constituents making up the integral tablet formulation play a part in modifying the compacts' surface energies.

Pore size of tablet formulations

From the results summarized in Table 4 and the equation of Washburn (1921), the average pore radius for each tablet formulation can be calculated.

Washburn's equation may be written as:

$$\frac{L^2}{t} = \frac{R.\gamma_{LV}.\cos\theta}{2\eta}$$

where L is the distance of penetration of the liquid (tablet depth), t is the time required, R is the average pore radius, η is the liquid viscosity and θ the contact angle of the penetrating liquid on a given solid.

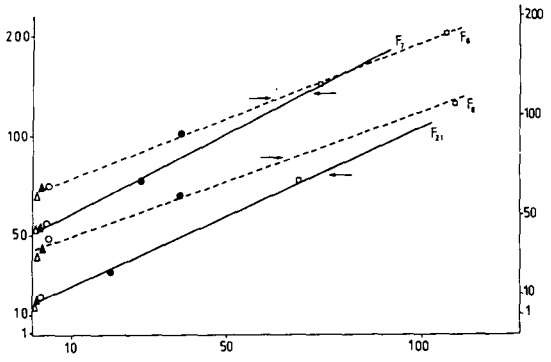

FIG. 3. Penetration of liquids through the tablet formulations. △ Glycerol; ▲ 1,4-Butandiol; ○ 1,3-Propandiol; ● Polyethyleneglycol 200; □ Ethylene glycol. Abscissa, γ_{LV} cos $\theta/2\eta$ (cm s^{-1}); Left ordinate, $L^2/t \times 10^{-7}$ (cm^2 s^{-1}); Right ordinate, $L^2/t \times 10^{-6}$ (cm^2 s^{-1}).

If we plot L^2/t versus γ_{LV} cos $\theta/2\eta$ (Fig. 3) using the data from Tables 2, 3 and 4, a series of linear relations is obtained for the tablet formulations. The slopes of these lines give the pore radii of the compacts. Fig. 4 is a graphical representation of the variation of pore size of the compacts with their composition. The most striking observation which can be deduced from Fig. 4. is that the absence of magnesium stearate in a compact formulation substantially increases the pore size and consequently the penetration rates. The role of talc can be seen when comparing F_8 and F_6 as well as F_{21} and F_7. In both cases the absence of talc increases the pore size. However it is clear that the magnesium stearate role in decreasing pore size is predominant.

The addition of magnesium stearate to tablet formulation lowers the pore size 7–8 times more than the addition of talc. This effect was already observed by Ahmed & Enever (1978) in their study of

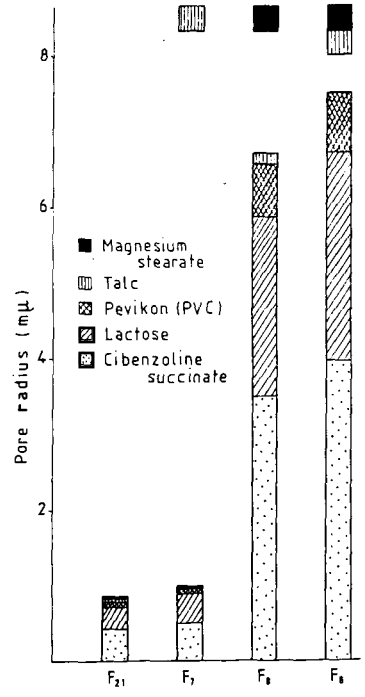

FIG. 4. Pore size of tablet formulations.

biological availability of sulphadiazine tablet formulations. Comparison of F_2 and F_4 makes clear that magnesium stearate is responsible both for the decrease of pore size and (γ_{SV}). Its influence on pore size is however much greater than on (γ_{SV}). These remarks are in agreement with previous findings (Harder et al 1970; Ahmed & Enever 1978).

Relations between (γ_{SV}) and penetration rates

When the penetration rates of the liquids through the partial and/or integral tablets are plotted vs their surface free energies (γ_{SV}) the relation as illustrated in Fig. 5 is obtained. This curve clearly shows that for the F_2 and F_4 formulations the penetration of all liquids is zero (full retention) in this study. The threshold $(\gamma_{SV})_s$, 'start', is approximately 30 mN m^{-1} and corresponds to the (γ_{SV}) value of other formulations. The $(\gamma_{SV})_s$, 'start', represents the surface free energy of the solid for which the penetration is measurable in less than 12 h. In the (γ_{SV}) range of 30–46 mN ml^{-1} the liquid penetration is slow. The second threshold $(\gamma_{SV})_r$, 'rapid' is obtained by extrapolation of the steep linear part of the curve to the abcissa. The $(\gamma_{SV})_r$ is the surface free energy of the solid for which the rate of penetration is less than 1 h.

The $(\gamma_{SV})_s$ and $(\gamma_{SV})_r$ are representative for a given series of liquids on the tablets. Each series of liquids

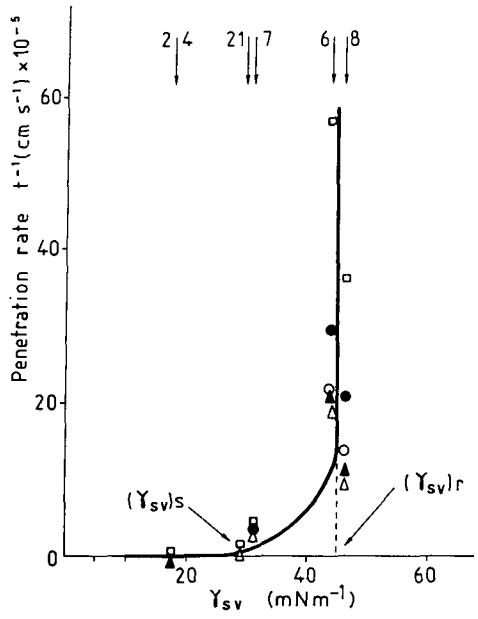

FIG. 5. Relations beween surface free energy (γ_{SV}) of tablet formulations and penetration rate of liquids. Symbols as in Fig. 3. Numbers and arrows indicate (γ_{SV}) of tablet formulation. $(\gamma_{SV})_s$—start and $(\gamma_{SV})_r$—rapid (terms explained in the discussion section).

will yield a specific $(\gamma_{SV})_s$ and $(\gamma_{SV})_r$ on the tablets studied. The physical meanings of $(\gamma_{SV})_s$ and $(\gamma_{SV})_r$ are respectively the absence of penetration for the γ_{SV} values lower than $(\gamma_{SV})_s$; and rapid liquid penetration through all the solids having γ_{SV} values higher than $(\gamma_{SV})_r$. The significance of $(\gamma_{SV})_s$ and $(\gamma_{SV})_r$ is similar to the critical surface tension (γ_C) introduced by Zisman (1963) to describe the wetting properties of a solid surface. However, $(\gamma_{SV})_s$ and $(\gamma_{SV})_r$ are obtained through penetration experiments and they characterize the penetration of liquids. They can thus be interpreted in terms of the close relation which exists between the surface tension and viscosity of the liquids, their capacity to wet the solid and the pore size of the tablet.

The $(\gamma_{SV})_r$ value obtained for our system (46 mN m^{-1}) corresponds to the mean surface tension for most of the polyols studied (except glycerol). The penetration rate increases with the viscosity decrease. This is demonstrated by the position of the liquids on the steep part of the curve. The higher the position of the liquid the lower is its viscosity and the greater is its penetration rate.

If it were possible to make tablet formulations having $(\gamma_{SV}) > 46$ mN m^{-1}, the penetration rate for glycerol would be represented by points somewhere in this region. The (γ_{SV}) value for the integral formulation (30 mN m^{-1}) corresponds to $(\gamma_{SV})_s$ for the polyol series.

CONCLUSION

Surface free energies of tablet formulations were determined using a family of polyols of various viscosities and surface tensions. These liquids of low penetration rates through tablets, provided a reasonable approach to the determination of tablet (γ_{SV}) values by means of the Neumann equation. Jointly with penetration experiments, carried out separately, a relation between (γ_{SV}) and the rates of penetration was found. This yielded two threshold values of penetration $(\gamma_{SV})_s$, 'start', and $(\gamma_{SV})_r$, 'rapid'.

Acknowledgements

The authors thank Mr M. Deyme for the computer programme used for θ_{SV} calculations.

REFERENCES

Ahmed, M., Enever, R. P. (1978) Pharm. Acta Helv. 53: 358–364

Baszkin, A., Ter-Minassian-Saraga, L. (1974) Polymer 15: 759–780

Baszkin, A., Nishino, M., Ter-Minassian-Saraga, L. (1976a) J. Colloid & Interface Sci. 54: 317–328

Baszkin, A., Deyme, M., Nishino, M., Ter-Minassian-Saraga, L. (1976b) Progr. Colloid & Polymer Sci. 61: 97–108

Cassie, A. B. D. (1948) Discussions Faraday Soc. 3: 11–16

Doelker, E., Doelker, C., Mordier, D. (1981) J. Pharm. Belg. 36: 404–411

Fell, J. T., Efentakis, E. (1978) J. Pharm. Pharmacol. 30: 358–541

Finholt, P. (1974) in: Leeson, L. J., Carstensen, J. T. (eds) Dissolution Technology. A PhA Academy of Pharmaceutical Sciences, Washington D.C., pp. 106–118

Harder, S. W., Zuck, D. A., Wood, J. A. (1970) J. Pharm. Sci. 59: 1787–1792

Lerk, C. F., Schoonen, A. J. M., Fell, J. T. (1976) Ibid. 65: 843–847

Lerk, C. G., Lagas, M., Fell, J. T., Nauta, P. (1978) Ibid. 67: 935–939

Liao, W., Zatz, J. L. (1979) Ibid. 68: 488–494

Mohammad, H. A. H., Fell, J. T. (1983) Int. J. Pharm. 17: 39–46

Neumann, A. W., Good, R. J., Hope, C. J., Sejpal, M. (1974) J. Colloid & Interface Sci. 49: 291–304

Singh, P., Desai, S. J., Simonelli, A. P., Higuchi, W. I. (1968) J. Pharm. Sci. 57: 217–226

Van Oss, C. J., Gillman, C. F., Neumann, A. W. (1975) in: Marcel Dekker Inc. (ed.) Phagocytic Engulfment and Cell Adhesiveness as Cellular Surface Phenomena. Vol. 2, NY, pp. 11–19

Van Oss, C. J., Absolom, D. R., Neumann, A. W., Zing, W. (1981) Biochim. Biophys. Acta 670: 64–73

Washburn, E. W. (1921) Phys. Rev. 17: 273–283

Zisman, W. A. (1963) in: Gould, R. F. (ed.) Contact Angle Wettability and Adhesion, American Chemical Society, Series 43, Washington DC, pp 1–51

Zografi, G., Tam, S. S. (1976) J. Pharm. Sci. 65: 1145–1149