Liquid penetration as a method of assessing the wettability and surface energy of pharmaceutical powders

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The use of a liquid penetration technique to assess the wettability and surface energy of a series of barbiturates, including the use of bicomponent systems, has been critically evaluated. Values of apparent contact angles (θ) obtained using the Washburn relationship (1921) and the Carli & Simioni correction (1979) were found to reflect the practically derived wettability of the powders. Values of γc obtained from modified Zisman plots and from Neumann's equation of state did not realistically describe the surface energies of the powders. The nature of alcohol–water mixtures has been examined to assist elucidation of the theoretical problems associated with the technique and to offer a possible explanation for the inadequacies of the surface energy results.

The wettability of pharmaceutical powders is of importance in formulation, production, and dissolution of many pharmaceutical products. Wettability is often described in terms of a contact angle (θ), which is understood to represent an equilibrium of energies at a three phase interface. Fox & Zisman (1952) suggested that contact angles obtained for a series of liquids, preferably homologous, of known surface energy could be extrapolated to a value of surface energy which corresponds to a zero contact angle. This value will be the minimum surface tension of a liquid which would spread on the solid surface, and is known as the critical surface tension of the solid (γc). Good (1980) suggested that $\cos \theta$ as a function of $\gamma_{LV}^{-\frac{1}{2}}$ was of greater theoretical significance and that this approach should replace that of Fox & Zisman (1952).

Ward & Neumann (1974) and Neumann et al (1974) developed an equation of state which allowed the surface energy of a low energy solid to be determined from a single contact angle formed by a liquid which is chemically inert with respect to the solid, and whose surface tension is known. These workers postulated that this method should be valid for materials with values of γc up to that of the surface tension of water, which should cover the range of values for most solids.

If data for the wettability of a number of liquids are available, it is possible to obtain a value of γc from a modified Zisman plot, and an average value of γc from Neumann's equation of state. If these results prove comparable, it is reasonable to assume

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that the values of θ are of sound thermodynamic basis; equally the opposite is true.

We have noted that when a powder is to be used in an uncompressed form, liquid penetration seems to present the most logical choice of method of assessing wettability currently available (Buckton & Newton 1985). We further noted that, if water does not penetrate the powder bed, the use of binary liquid mixtures allows extrapolations to a value of θ for water and the production of modified Zisman plots yielding values of γc which appear to be in the correct order of magnitude for a hydrophobic powder (amylobarbitone). However, theoretical reservations were expressed about the technique. The present work extends these concepts to related powders with differing degrees of hydrophobicity.

MATERIALS AND METHODS

Experiments were carried out on five barbiturates: amylobarbitone BP (Eli Lilly), barbitone (Fisons), butobarbitone BP (May and Baker), pentobarbitone BP (Grinsted), and phenobarbitone BP (May and Baker). Whilst particle size does not affect values of θ obtained by this method (Mohammed 1983), the median surface volume diameters obtained from a Coulter Counter TAII were 76·0, 79·5, 32·0, 55·0 and 83·5 μm, respectively.

The liquid penetration method of Studebaker & Snow (1955) was used and the perfectly wetting liquid was assigned as previously described (Buckton & Newton 1985). All the liquids, which were of BDH AnalaR grade or equivalent, were saturated with the appropriate barbiturate before use. Penetration

times were measured on 6–10 replicate beds of each powder, each bed being packed to a 3·5 cm depth. The packing of the tubes was as reported by Studebaker & Snow (1955). Whenever the liquid passage was not uniform, poor packing was suspected and the result rejected. However, when the solvent front flowed evenly, the gradients of l² as a function of t were reproducible (see Discussion) and it would appear that good reproducibility of packing has occurred. The liquids used for amylobarbitone, and results obtained, were those previously reported (Buckton & Newton 1985). For the other powders the liquids used were triple-distilled water, hexane, cyclohexane, toluene, a series of straight chain alcohols (ethanol to hexan-1-ol) and binary liquid mixtures of ethanol–water and propan-2-ol–water of various mole fractions of alcohol. The exceptions to this were the butobarbitone, where excessive solubility in pure solvents limited the selection to water, hexane and the two binary liquid mixture systems, and pentobarbitone and phenobarbitone where water would not penetrate. The viscosities of the saturated solutions were measured with a U-tube viscometer in a thermostatted water bath at 20 °C. Their densities were measured with a Parr digital densitometer (DMA 35). Surface tensions were measured with a Wilhelmy plate on a torsion balance (Whites Electronics) and results were averages of at least five determinations.

Values of θ were obtained as described by Buckton & Newton (1985) and will be referred to as Washburn values (θw). The contact angle has also been determined according to the correction suggested by Carli & Simioni (1979) as the assumption made by Washburn (1921) that l² is proportional to t is not always valid. Thus the relationship lᵐ as a function of t was obtained from a double logarithmic plot of distance of penetration as a function of time as previously described (Buckton & Newton 1985). The corresponding value of θ will be ascribed θs.

RESULTS

Some representative values of cos θw and the surface tensions of the saturated liquids, are presented in Table 1, and those for cos θs in Table 2.

The values of θw and θs obtained for penetration of water into barbitone and butobarbitone, and for extrapolation of both binary liquid systems on all five powders to zero alcohol content as previously demonstrated (Buckton & Newton 1985), are presented in Table 3.

Determinations of γc

The values of cos θ used to obtain γc are generally equilibrium contact angles, however, it is clear that the contact angle obtained from liquid penetration will be an advancing contact angle. Neumann & Good (1972) and Neumann (1974) have shown that advancing contact angles can reflect the equilibrium contact angle of the most hydrophobic portion of the surface, and as this will be the area that will determine the ultimate wettability of the solid, it follows that taking the advancing contact angle as the equilibrium contact angle can be valid.

The results previously published for amylobarbitone (Buckton & Newton 1985) are of the same form

Table 1. The values of cos θw and the surface tensions (γ_{LV}) of selected penetrating liquids, for barbitone (Ba), butobarbitone (Bu), pentobarbitone (Pe) and phenobarbitone (Ph). (Amylobarbitone results as previously published, Buckton & Newton 1985.)

	Ba		Bu		Pe		Ph	
	γ_{LV}	cos θw	γ_{LV}	cos θw	γ_{LV}	cos θw	γ_{LV}	cos θw
Cyclohexane	27·1	0·746	b	b	26·1	0·874	26·9	1·000
Hexane	19·9	0·894	18·4	0·029	20·3	0·827	20·0	0·833
Toluene	30·6	0·697	b	b	30·0	0·792	30·0	0·749
Ethanol	24·5	0·985	b	b	24·9	1·000	24·8	0·604
Propan-1-ol	26·2	2·403	b	b	26·2	0·905	26·2	0·848
Butan-1-ol	27·0	0·836	b	b	26·5	0·831	26·9	0·656
Pentan-1-ol	27·0	0·820	b	b	27·1	0·835	27·5	0·712
Hexan-1-ol	28·0	0·963	b	b	28·0	0·887	27·7	0·858
20% Propan-2-ol	35·4	1·000	33·3	0·255	35·0	0·694	35·0	0·905
15% Propan-2-ol	38·7	0·757	38·6	0·167	35·0	0·694	29·9	0·994
10% Propan-2-ol	43·6	0·714	40·5	0·125	43·5	0·250	44·3	0·485
5% Propan-2-ol	51·3	0·486	46·3	0·083	a	a	51·6	0·256
20% Ethanol	41·1	0·695	40·7	0·191	42·5	0·415	35·1	0·598
15% Ethanol	43·2	0·612	43 3	0·141	45·7	0·273	38·6	0·433
10% Ethanol	46·8	0·548	44·0	0·116	50·5	0·120	41·0	0·254

a Would not penetrate.
b High solubility resulted in high viscosity and no penetration.

Table 2. The values of cos θs obtained for a selection of saturated liquids with amylobarbitone (A), barbitone (Ba), butobarbitone (Bu), pentobarbitone (Pe) and phenobarbitone (Ph).

	A	Ba	Bu	Pe	Ph
Cyclohexane	0·583	0·757	b	0·741	0·466
Hexane	0·759	0·317	0·106	0·701	0·185
Toluene	0·866	0 247	b	0·672	0·753
Ethanol	0·763	1·000	b	0·777	0·528
Propan-1-ol	0·725	0·755	b	1·000	0·848
Butan-l-ol	0·910	0·849	b	0·704	0·660
Pentan-1-ol	0·728	0·832	b	0·766	0·717
Hexan-1-ol	0·789	0·256	b	0·776	0·741
20% Propan-2-ol	0·374	0·372	0·255	0·601	0·714
15% Propan-2-ol	0·195	0·286	0·167	0·398	0·606
10% Propan-2-ol	0·089	0·159	0·110	0·212	0·335
5% Propan-2-ol	a	0·111	0 084	a	0·150
20% Ethanol	0·177	0·352	0·191	0·361	0·359
15% Ethanol	0·112	0·307	0·126	0·239	0·359
10% Ethanol	0·065	0·198	0·103	0·110	0·244

a Would not penetrate.
b High solubility resulted in high viscosity and no penetration.

as those obtained for barbitone, butobarbitone, pentobarbitone and phenobarbitone. In all cases the straight chain alcohols would not produce a modified Zisman plot, but the two alcohol–water dilution series each produced their own distinct relationships yielding two distinct values of γc for each powder. It is surprising, especially in view of the work of Bleier (1983), and others, who have obtained a single straight line for liquids which do not fit a homologous series, that the pure liquids do not fit the straight line and that the alcohol–water dilution series each form their own line rather than forming one extrapolation.

The values of γc obtained from extrapolation of the values of θw obtained from the Washburn equation are assigned γcw, and those from the Carli & Simioni (1979) correction γcs. Both sets of values are presented in Table 4.

The use of Neumann's equation of state

$$\gamma_{SL} = f(\gamma_{SV} \cdot \gamma_{LV}) \quad (1)$$

together with Young's equation

$$\cos \theta = (\gamma_{SV} - \gamma_{SL})/\gamma_{LV} \quad (2)$$

(where the variables γ_{SV}, γ_{SL}, γ_{LV} are the relative interfacial tensions between the solid/vapour, solid/liquid, and liquid/vapour states, respectively) provides two equations relating four variables. If γ_{LV} and θ are known it is possible to obtain γ_{SV} and γ_{SL}.

The method outlined by Taylor (1984) for use of a programmable calculator to implement the equation of state was adapted for use on an Apple microcomputer. The method involved is to treat γ_{SV} as an adjustable parameter, then to assume arbitary values of γ_{SV}, thus from equation (2) it is possible to compute hypothetical values of γ_{SL} using the values of γ_{LV} and cos θ. A set of values of Φ, which is known as Good's interaction parameter, and is obtained from

$$\Phi = (\gamma_{SV} + \gamma_{LV} - \gamma_{SL})/\sqrt{\gamma_{SV} \cdot \gamma_{LV}} \quad (3)$$

are calculated, and Φ is expressed as a function of γ_{SL}. Then different values of γ_{SV} are selected until an intercept of 1·00 on the Φ axis is obtained. Finally the intercept $\gamma_{SL} = 0$ is determined and from equation 3 using the experimentally determined value of γ_{LV}; the value of γ_{SV} can be obtained; if the vapour pressure of the solid is assumed to be negligible this becomes γc.

The values of γcw and γcs were determined for each liquid on each powder. Mean values are quoted together with the standard deviations in Table 5.

DISCUSSION

The results obtained proved to be reproducible and yielded straight lines for l² as a function of t, with correlation coefficients in the region of 0·999, consequently it would appear that the fundamental

Table 3. Directly determined contact angles for water and values of θ obtained from extrapolation to 0% alcohol using the Washburn (1921) assumption (θw) and the Carli & Simioni (1979) correction (θs).

Powder	θw			θs		
	Propan-2-ol extrapolation	Ethanol extrapolation	Water	Propan-2-ol extrapolation	Ethanol extrapolation	Water
Amylobarbitone	102·8	99·5	b	101·8	101·2	b
Barbitone	a	73·4	78·2	87·3	85·5	88·6
Butobarbitone	87·8	88·4	87·9	88·5	88·8	88·5
Pentobarbitone	101·2	99·7	b	99 2	97·5	b
Phenobarbitone	87·3	94·9	b	92·9	95·2	b

a Values non-linear, extrapolation not possible.
b Water would not penetrate sample.

Table 4. Values of γc obtained from modified Zisman plots.

Powder	γcw (mN m⁻¹)		γcs (mN m⁻¹)	
	Ethanol extrapolation	Propan-2-ol extrapolation	Ethanol extrapolation	Propan-2-ol extrapolation
Amylo-barbitone	26·7	27·8	27·9	27·7
Barbitone	33·9	34·8	15·8	18·4
Butobarbitone	19·4	15·5	18·0	17·9
Pentobarbitone	31·4	29·7	28·7	26·5
Phenobarbitone	30·3	31·7	28·2	29·6

Table 5. Mean values of γc, and standard deviations obtained from Neumann's equation of state.

Powder	γcw (mN m⁻¹)	s.d.	γcs (mN m⁻¹)	s.d.
Amylobarbitone	19·8	3·84	18·6	3·45
Barbitone	19·3	3·90	25·8	5·93
Butobarbitone	16·0	4·56	16·4	4 26
Pentobarbitone	20·8	2·55	22·9	2·67
Phenobarbitone	20·9	5·25	23·8	4·41

Washburn relationship does apply for all the liquids studied. A typical example of the reproducibility of l^2 as a function of t is that of 25% propan-2-ol penetrating into phenobarbitone, where the mean gradient was 0·1022 with s.d. 0·0021. The gradients of the double logarithmic plots of penetration as a function of time were not always 0·5 (range 0·48 to 0·78), and thus it was possible to correct the results as suggested by Carli & Simioni (1979). The corrected values for the apparent contact angle with water are in the same rank order as the original values and are numerically in the same order of magnitude. It is clear from simple empirical tests, such as attempting to immerse the powder in water, that amylobarbitone and pentobarbitone are the most hydrophobic of the powders, followed by phenobarbitone then butobarbitone and finally barbitone which is the most hydrophilic. This apparent rank order is reflected in the values of θ obtained.

The values of γc obtained by the two methods do not produce a similar rank order to that of the empirical tests or the values of θ obtained. There is no similarity between γc obtained from modified Zisman plots and γc from Neumann's equation of state, furthermore the results corrected as suggested by Carli & Simioni (1979) are significantly different to those derived from Washburn values. The obvious implication is that the values of γc do not adequately reflect the wettability of the powder.

Fell & Efentakis (1978) found that values of γc calculated from methanol–water dilutions did not reflect the true surface energy of a selection of powders. The explanation that these workers proposed was that adsorption of the methanol from the mixture had occurred, giving rise to the methyl groups effectively replacing the surface of the solid. While this suggestion is logical, and while the values of γc obtained by Fell & Efentakis (1978) also appear to be unrelated to the wettability of the powder, their proposal does not resolve the matter as values of θ of realistic magnitude can be calculated from the results. This clearly shows that the hydrophobic nature of the surface has been assessed to some extent. It is clear, however, that the possible effects of the binary liquid mixture must be carefully considered.

The nature of alcohol–water mixtures is complex (Rowlinson 1969), but it is clear that a structured solution is formed when ethanol and water are mixed. This is demonstrated by the relationship between viscosity and mole fraction of ethanol in the liquid (Cook 1978) where a maximum exists at a mole fraction of about 0·22 of ethanol. The heat of mixing curve reported by Franks & Ives (1966) for the same system shows a minimum at the same mole fraction of ethanol. At low mole fractions of ethanol the system is thought to exist in a similar form to that of pure water, that is a tetrahedral configuration. The few alcohol molecules are accommodated interstitially in the lattice. As the mole fraction of ethanol is increased, a point is reached where the alcohol molecules cannot be accommodated and the water lattice is disturbed. Steric hindrance ensures that only one lone pair of electrons on the ethanol molecule is available. Thus a tetrahedral configuration is not possible. Effectively, polymers are produced by hydrogen bonding, resulting in structural rigidity due to hindrance of rotation. This explains the effects already mentioned, with the mole fraction of ethanol of 0·22 in the liquid being the point of maximum hydrogen bonding. This is supported by the work of Good (1973) who showed that polar forces in the liquid mixtures reached a minimum at a mole fraction of about 0·22.

All the ethanol–water mixtures used here were of less than 0·22 mole fraction of ethanol in the liquid, as this is the region which allows for extrapolation. However, Cook (1978) studied the wetting of a sample of griseofulvin using the liquid penetration technique of Studebaker & Snow (1955) with a large range of mole fractions of ethanol. The results are reproduced in Fig. 1, together with the values of cos θ replotted as a function of mole fraction of ethanol in the vapour phase. It is clear that a linear relationship exists between cos θ and mole fraction of ethanol in the vapour phase up to a value of about 0·6. The relationship between mole fraction and
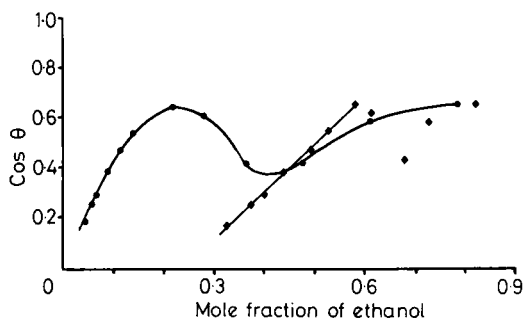
FIG. 1. Cos θ as a function of mole fraction of ethanol. ● = liquid phase (after Cook 1978); ◆ = vapour phase.

FIG. 3. The relationship between the mole fraction of ethanol in the vapour and the mole fraction of ethanol in the liquid phase of an ethanol–water mixture.

cos θ in the liquid phase is curved. This can be related to the vapour having a different composition to the liquid. Fig. 2 demonstrates the difference in ethanol composition between liquid and vapour expressed as a percentage, and Fig. 3 as a mole fraction. The straight line portion of Fig. 1 for cos θ as a function of mole fraction of ethanol deviates above a mole fraction of 0·583 in the vapour phase, which is equivalent to a 40% (0·207 mole fraction) ethanol–water mixture, and from Figs 2 and 3 this can be seen to be just at the beginning of the point of inflection. It is reasonable to postulate that below this mole fraction, the penetration of liquid is aided by the relatively high concentration of ethanol in the vapour, whilst above this mole fraction the properties of the ethanol in the mixture limit its evaporation, and thus the penetration is not so readily aided.
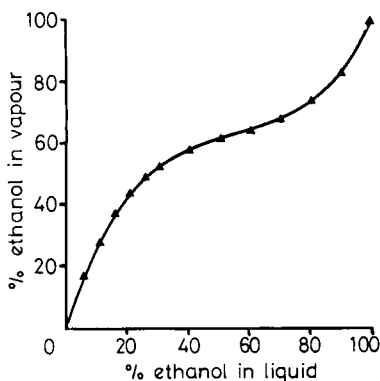
This shows that the minimum observed for ethanol at a mole fraction of about 0·2 is displaced for methanol and propanol. This minimum is thought to indicate the point where the polar forces reach a minimum and the liquid mixture structure changes from water-like to alcohol-like.

Another problem with the liquid penetration technique is, because it is dynamic there can be no certainty that the vapour, irrespective of its composition, is in equilibrium with the powder. Failure of such an equilibrium would mean that a true contact angle was not being measured.

CONCLUSIONS

The true nature of the penetration process remains unquantified. When considering the many theoretical limitations of this technique, it is not surprising that values of γc cannot be obtained to reflect the hydrophobic/hydrophilic nature of the powders. It is perhaps more surprising that a technique which appears to be theoretically invalid is practically so useful.

Liquid penetration studies using alcohol–water mixtures yield a value of θ which is: (1) in the correct order of magnitude to quantify the wettability of the powder, (2) reproducible, (3) consistent with respect to two different alcohol–water series. The major problem is that the value of θ is not of sufficient thermodynamic basis to determine surface energy parameters of the powder. This could be due to one or more of the following: (1) the presence of preferential adsorption of one component of the liquid mixture by the solid, (2) the failure of the vapour to be in equilibrium with the powder, (3) the variation in the composition of the vapour with respect to the liquid.

FIG. 2. The relationship between the % ethanol in the vapour and the % ethanol in the liquid phase of an ethanol–water mixture. Values from International Critical Tables 1933.

This process can be regarded as being the same for other alcohol series, as indicated by the heat of mixing effect demonstrated by Franks & Ives (1966).
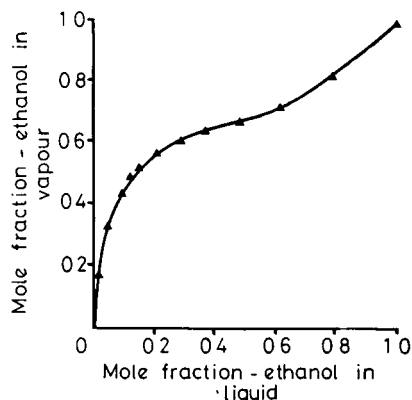
The conclusion must be drawn that this technique has potential for major practical application as an empirical assessment of wettability, but offers limited value to fundamental theoretical assessment of the wetting process.

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