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Surface analysis of pharmaceutical powders: X-ray photoelectron spectroscopy (XPS) related to powder wettability

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Summary

Selected barbiturate powders (barbitone, butobarbitone, phenobarbitone and pentobarbitone) have been investigated using XPS. Where possible, samples were studied in the powdered and compacted form. The results indicated that the entire molecule was exhibited in the surface of the samples, irrespective of whether the sample was free powder or a compact. Various published results relating to the wettability of these barbiturates are reported. There is very poor correlation between results obtained by different methods, and also between the surface analysis and the wettability data. The surface energies of powders are known to vary following different physical treatments. One process which is thought to alter contact angles is that of compaction (ironically an essential part of many contact angle measuring methods). The surface analysis results demonstrate that these changes in surface energies are not as a result of changes in the chemical composition of the surface. XPS does not provide information concerning the orientation of the molecules in the samples. The fact that all of the molecule is exhibited does not mean that the hydrophobic portion of each molecule will have the same hindrance towards interactions with water molecules. Finally, the need for further fundamental investigations of techniques for assessing contact angles is highlighted.

Introduction

In recent publications (e.g. Davies et al., 1990) the use of methods of surface analysis (XPS or (static) secondary ion mass spectroscopy (S)SIMS) has been considered for some systems of pharmaceutical interest. Surface analysis techniques seem to be most suited to studies of polymeric films, or smooth faces of dosage forms and are particularly valuable in investigations of, for example, the integrity of film coatings.

Studies on the surface properties of microfine powders are problematic as smooth flat surfaces do not exist. This difficulty results in problems when attempting to assess the wettability of a powder. However, a knowledge of the wettability of pharmaceutical powders is of importance in a great many areas including the preparation, use and stability of dosage forms: these include the wet granulation of powders prior to tabletting, the adhesion of film coating polymers to tablets, the

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dispersion and aggregation of powders in suspension systems and the dissolution rate of solid oral dosage forms. In a number of publications (e.g. Rowe 1989), it has been demonstrated that the surface energetics of powders can be used to predict, and thus optimise, the interactions of components of a dosage form. Predictions based on surface energetics may become more widely used during formulation optimisation, and therefore, it is vital that the method of assessing surface energy (wettability) is considered and validated.

There are numerous methods of assessing the wettability of powders, all of which have either practical or theoretical difficulties. In a recent review (Buckton, 1990), the advantages and disadvantages of the different techniques of assessing wettability have been discussed; these will be outlined briefly below. There are two approaches to the determination of a contact angle of a liquid on a powder; these are to allow a liquid to penetrate a loosely packed powder bed (and to compare the results to those for a perfectly wetting (zero contact angle) liquid) (after Washburn (1921) often using the method of Studebaker and Snow, 1955) or alternatively, to measure a contact angle on a compacted powder bed.

Liquid penetration experiments are generally based on the assumption of a model of a bundle of parallel capillaries, this has been criticised by many authors both theoretically (e.g. Yang et al., 1988) and due to the practical difficulties involved, including the problems in choosing a perfectly wetting liquid and the use of binary liquid mixtures for hydrophobic powders (Buckton and Newton, 1986a). Prior to the work of Yang et al. (1988), which brings the use of the Washburn equation into disrepute, several workers have suggested adaptations to liquid penetration experiments (e.g. Carli and Simioni, 1979) or alternative models for the system (e.g. Levine and Neale, 1975).

Compressed powder systems provide a smooth (or relatively smooth) surface on which a contact angle can be measured. The major criticism of this approach (Buckton and Newton, 1986b) is that the process of forming a compact can alter the surface, perhaps by plastic deformation, such that the angle is measured on a different surface to that which is of interest (viz. the powder). Having accepted this criticism it should be noted that this is the most commonly used method of assessing powder wettability.

Alternatives to contact angle measurement include the assessment of powder/water interactions by calorimetry (adsorption or immersion) and by vacuum microbalances (see Buckton, 1990). The partitioning behaviour of a drug between water and another solvent (conventionally octan-1-ol) is also used as a measure of the molecule's hydrophilic/lipophilic balance, this is generally expressed as the logarithm of the partition coefficient (log P).

Data obtained for the wettability of powders will vary depending upon the method (and perhaps the experimental conditions that are) used. Often there will not even be a similar rank order of wettabilities for powders if their contact angles are assessed using different methods. The implications of this are that predictions based on contact angles are only as reliable as the contact angle measurement method.

The purpose of this study is to consider wettability data for some model compounds, and to compare these data with information obtained by using surface analysis (XPS), with a view to exploring any correlations.

XPS is a method by which the surface of the sample is bombarded with X-rays, and the energy of the emitted photo-electron is measured using a suitable electron energy analyzer. The technique allows quantification of the surface composition (unlike (S)SIMS which is essentially qualitative). The depth of sample which is analyzed is dependent upon the angle of the incident X-ray beam, and typically can be in the range of 3–10 nm of the sample surface.

The choice of model drugs

A considerable amount of data exist to describe the wettability of certain barbiturates. This includes published partition coefficients, contact angles obtained by liquid penetration, sessile drops and dynamic techniques and thermodynamic functions of adsorption (see Table 1). Barbitone, butobarbitone, phenobarbitone and pentobarbitone were selected for study, as they cover a range

TABLE 1

Published data that relate to the wettability of some barbiturates

	Barbitone	Buto-barbitone	Pheno-barbitone	Pento-barbitone
Contact angles (°)				
a	78	88	91	
b	62	56	70	84
c	87	78	64 [1]	
d	47	42	53	
Partitioning (ln P)				
e	−0.31	1.78	1.39	
f	−1.51	1.70	1.41	
Thermodynamics ($\Delta_{ads}S$) (J/mol per K)				
g	–	−334.9	−348.3	−355.4
h	–	−144.0	−156.7	−171.5
Adsorption rate (s^{-1}) ($\times 10^3$)				
i	–	9.94	6.67	7.0

a, liquid penetration (Buckton and Newton, 1986a); b, sessile drop advancing angles (Buckton and Newton, 1986b); c, sessile drop, equilibrium angles (Lerk et al., 1977; except [1] Mohammed (1983)); d, dynamic angles (Young and Buckton, 1990); e, calculated and f, measured value (Pinal and Yalkowsky, 1987); g, isosteric and h, calorimetric entropies of adsorption (Buckton and Beezer, 1988); i, calorimetric apparent first-order rate constant for the adsorption of water vapour (Buckton and Beezer, 1988).

of wettabilities (barbitone and butobarbitone are comparatively easy to disperse in water, phenobarbitone can be dispersed with considerable effort, and pentobarbitone is very poorly wetted by water).

Materials and Methods

The barbiturates were from the same batches that were used in previous studies (e.g. Buckton and Newton, 1986a,b; Buckton et al., 1986; and Buckton and Beezer, 1988). The structures of the barbiturates are outlined in Table 2.

Spectra were acquired using a Kratos ES 300 electron spectrometer fitted with a hemispherical electrostatic electron analyzer. An incident beam of Al KL X-radiation was used to excite photoelectron emissions from the sample surface. Samples were investigated either as free powder or as a compressed compact. Pentobarbitone was not suitable for study as a free powder, as static charging caused it to disperse in the instrument. The powdered samples (which were tightly packed, but not compacted, into a holding boat) were tilted at an angle of 30° from the horizontal, which would result in a study of approx. 0–100 nm of material. For the compacts, it was possible to tilt the sample without it being lost from the holder, and thus it could be tilted at an angle of 70° to the horizontal, resulting in a study of the first 0 to between 1 and 3 nm depth of the compact, i.e. true surface analysis.

Results

The plots of collected electron intensity as a function of binding energy revealed four main peaks. The binding energies of these peaks were such that they can be ascribed to different species of the molecule, i.e. carbon, oxygen or nitrogen atoms, and C–H or C=O bonds (Table 3).

Discussion

The surface analysis reveals that the surface composition of the powders and the compacts is essentially a reflection of the total composition of the drug molecules. In all cases, the hydrophilic

TABLE 2

The structures of the barbiturates used in this study, expressed as trivial names, proper names, and the structure of the substituent group at position five on the barbituric acid ring

Trivial name	Proper name (suffix: barbituric acid)	R5 group
Barbitone	5,5-Diethyl-	CH_3-CH_2-
Butobarbitone	5-Ethyl-5-butyl-	$CH_3-CH_2-CH_2-CH_2-$
Phenobartirone	5-Ethyl-5-phenyl-	Phenyl ring
Pentobarbitone	5-Ethyl-5-(1-methyl-butyl)-	$CH_3-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$

TABLE 3

The extents of chemical bonding, as determined by binding energy measurement and areas under the curve for each peak (expressed as atomic %), for the powdered (p) and compressed (c) form of each compound.

Peak identity	Atomic %								Relative proportion							
	C=O		C–H		O		N		C=O		C–H		O		N	
	p	c	p	c	p	c	p	c	p	c	p	c	p	c	p	c
Barbitone	20	22	45	39	22	22	13	17	3	3	7	5	3	3	2	2
Butobarbitone	17	19	52	49	19	18	12	13	3	3	9	8	3	3	2	2
Phenobarbitone	15	18	56	52	20	17	12	13	3	3	9	9	3	3	2	2
Pentobarbitone	–	18	–	52	–	17	–	13	–	3	–	9	–	3	–	2

The relative proportion of the different species is presented as a guide, and is correct to the nearest integer.

sites are visible in the surface, i.e. it is possible to access the hydrogen bonding sites that are associated with the ring structure. In some circumstances, notably when the free powder was investigated, there was a higher composition of C–H bonds than would have been expected (i.e. 9 for butobarbitone). This could be due to the preferential existence of the side chains of the molecules in the powder surface, however, the possibility of contamination in the form of hydrocarbons from the instruments vacuum pump oil must also be considered, as must the possibility of contamination during sample preparation and storage. As all samples were stored and used in the same manner, it is probable that the analysis data are an accurate reflection of the true surface volume composition.

The C–H composition was generally lower for the compacts than the free powder. There are two possible explanations for these results, one is that the process of forming the compact results in a change of the surface properties (due to plastic deformation), and the other is that this is the true measure of the surface composition (due to the shallower sampling depth resultant from the lower angle of the incident radiation used for the compacts).

On the basis of the surface analysis data presented in Table 3, it would be reasonable to assume that pentobarbitone and phenobarbitone would be equally the most hydrophobic, and that butobarbitone would be quite similar, with barbitone being distinctly different and notably more hydrophilic. The data in Table 1, however, show a more complicated and confusing situation.

There is little or no correlation between the different sets of data that are presented in Table 1 as assessments of the wettability of these barbiturate powders. The lack of correlation extends to comparisons with the surface analysis data, and to comparisons between the sets of data that are supposed to be assessments of wettability. A number of reasons can be offered for this, including the effect of different polymorphic forms (the barbiturates are known to exist in a number of different forms), and the effect of previous physical treatments (e.g. milling, compaction, etc.) on the surfaces. This concept raises a curious issue: if physical treatments alter surface energetics, do they alter surface composition? For example, are the changes in wettability a result of a reordering of molecules at the interface, or of some other kind of change of energy state? If it is accepted that the formation of a compact will alter the surface energy of a powder (Buckton and Newton, 1986b), due to plastic deformation of the surface, then perhaps a significant difference might be expected in the surface analysis results before and after compaction. Phenobarbitone, for example, was shown to have contact angle values in excess of 100° prior to, but of around 70° following, plastic deformation of its surface during a compaction process (sessile drop method, advancing angle (Buckton and Newton, 1986b)); however, the surface analysis of phenobarbitone shows no significant difference in chemical composition, before, or after compaction. Indeed the only major difference in the surface analysis results following compaction is for barbitone, which is one of the powders for which the contact angle was not found

to change following compaction (Buckton and Newton, 1986b). It is likely, therefore, that rather than producing changes in surface composition (due to reordering of the molecular packing at the interface), that physical treatments 'stress' the existing surface, by deformation, resulting in the same chemical composition, but a different surface energy. This observation for the barbiturates need not, however, be universally true because milling, for example, can alter polymorphic forms and thus presumably can alter surface orientation of molecules. A further problem is that XPS does not provide detail on surface orientation, i.e. there is no way of mapping the surface in terms of ease of access to hydrophilic sites on an atomic (rather than a molecular) level; for example, does the ring structure of phenobarbitone (which is seen in the surface layers) result in a hindrance to approaching water molecules that is the same as, or greater or less than that of the side chain of amylobarbitone? It is possible that changes in orientation and order occur within the surface following physical treatments, which have different surface energies, but which are made up of the same surface chemical composition. It is equally possible that the chemical composition varies for the different faces of the crystals. For example, pentobarbitone, phenobarbitone and butobarbitone all have similar amounts of C–H bonds present in their surfaces (Table 3), but it has been shown that the rate of water sorption to these powders is much more rapid for butobarbitone than the others, which suggests that despite similar chemical composition, the hydrophilic sites are more readily accessible on the butobarbitone crystal than on the others; perhaps the hydrophobic regions on the butobarbitone crystal are concentrated in one region, but on the others there is a more even distribution. It is now possible to use 'small area XPS' to examine small regions of specific crystal faces (less than 80 μm) microscopically, in order to investigate such possibilities (this facility was not available on the instrument to which we had access).

To return to the data in Table 1, the absence of any consistency in rank order and indeed magnitude of the results, is on one level disturbing. It demonstrates the extreme complexity and difficulty involved in obtaining an assessment of the wettability of powders. If contact angle data are to be used to make predictions about product performance, then changes in rank order could result in seriously misleading conclusions. However, the range of results is not entirely surprising, as each value is obtained by a different technique on powders which will be of different ages, and, in some cases, from different suppliers and be in different forms (the last factor being a prerequisite of the measuring techniques). The practical and theoretical limitations of the current methods of assessing the wettability of powders have been outlined above (and presented in more detail in a recent review (Buckton, 1990)), however, the current state of understanding of these techniques remains inadequate if they are to be used to provide reliable data to characterise pharmaceutical systems. A basic problem is the fact that the results of various experimental techniques cannot easily be compared directly, as the sample preparation methods are so critical in conditioning the results that are obtained. More fundamental work is needed in order to investigate the true role of these different experimental methods. A further problem in contact angle measurement stems from the fact that some of the techniques are subjective and as such are open to considerable operator error (Neumann and Good, 1979). Sessile drop techniques, for example, are notorious as experiments from which any one operator can obtain consistent results which are significantly different to the, equally consistent, results of another (due to errors in drawing correct tangents). Dynamic contact angle measurements (using a Wilhelmy plate approach), however, yield a non-ambiguous value which is not so susceptible to operator interpretation errors (it should be remembered, however, that although the result is not open to such error, sample preparation is still a major variable for such experiments, preparation methods must be refined and controlled).

Conclusion

The data that relate to the wettability of the barbiturates, which have been collected together

in this work, demonstrate that all or some of the following may have significant influences on the results: changes in (i) method, (ii) sample history, (iii) sample preparation and (iv) investigator.

Surface analysis, in the form of XPS, has revealed that for each of these barbiturates the entire molecule is present in the analyzed surface volume of the crystal. It is not possible to map the surface, i.e. there is no way of telling where the different functional groups are (e.g. which crystal face), and to what extent they hinder access of water to the hydrophilic ring sites.

Compaction of the powder is thought to change the surface energetics (Buckton and Newton, 1986b), but it does not change the chemical composition of the surface. Thus orientations and energy states change, but not the chemical composition.

The use of XPS has provided interesting information about the surfaces of these powdered systems, however, surface analysis may be of more value (in its own right) when demonstrating the absence of structures from the surface, for example, if on one sample the ring structure had been fully internalised.

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