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The importance of chain length on the wettability and solubility of organic homologs

Susan Forster [1], Graham Buckton [1] and Anthony E Beezer [2]

[1] *Department of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX (U.K.)*
and [2] *Department of Chemistry, University of Kent, Canterbury (U.K.)*

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Summary

The solubilities of an homologous series of compounds (alkyl *p*-hydroxybenzoates) were measured in hexane and water at 298 K. The hexane solubilities followed a trend that could be predicted by the melting points, but the aqueous solubilities showed a linear decrease with increasing alkyl chain length, until the chain was over 4 carbon units long, then the effect of adding extra methylene groups was significantly lower. With both solvents the effect on solubility was small after the chain exceeded 5 (±1) carbon units in length. This phenomenon is explained on the basis that the side chain has greater rotational freedom about C-C bonds as it extends beyond five carbons. The freedom of movement will potentially influence the crystal packing (due to the increased possibility for different orientations and conformations) and hence the hexane solubility results, and the orientation of the molecules that are to be dispersed in the solvent (thus the aqueous solubility). Chain lengths of 2–5 showed no significant variation in aqueous contact angle for the powders. The contact angle did increase slightly above a chain length of 6 carbons. The results indicate that the crystal packing is influenced by chain length and that for chain lengths up to five carbons, the chain is not all present in the crystal surface (no increase in contact angles). For wettability and solubility there is a critical point at a chain length of 5 (±1) carbons where the physical properties of the alkyl *p*-hydroxybenzoates change. Although molecular structure affects both solubility and wettability, there is no direct correlation between these two properties, wettability of the powder being influenced only by the proportions of chemical groupings that are present at the surface of the crystal.

Introduction

Before a drug can be absorbed into the body from the gastro-intestinal tract, usually it must be in solution. A prerequisite of a drug going into solution is that it should be first wetted by the liquid phase and then dissolved. A classical model for the solution process is that the solvent molecules must cover the surface of the solute, there must be a breaking of solute/solute bonds at the surface of the solute, a breaking of solvent/solvent bonds to form a cavity and then an inclusion of the solute molecule in the cavity, i.e. a formation of solvent/solute bonds. The complex nature of this process is such that the enthalpy of solution may be very small, being a sum of interactions which may be almost equal and opposite. The

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Correspondence: G. Buckton, Dept of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, U.K.

interesting factor is whether one step of the process involves a large activation barrier and is in effect the limiting step in dissolution.

In work published to date, much interest has been shown in the studies of structure/property * relationships for solubility, but the role of wettability has not been adequately investigated. There is a clear need to develop an understanding of the inter-relationship between the wettability and solubility of molecules, with a view to understanding whether there is a structure/property link for wettability and, if so, whether the structural features that control wetting are the same as those that control solubility.

In a previous study (Lippold and Ohm, 1986) attempts have been made to link wettability to dissolution rate, this is not the aim of the study reported here. In this work the relationship between equilibrium solubility, wettability and structure will be examined.

The effect of chemical variation on powder wettability

There has been very little work presented on how the wetting of a powder will alter with changes in the molecular structure of a series of (related) compounds. Storey (1986) considered the relationship between computer predicted models of molecular structure and the thermodynamics of aqueous immersion. Electron densities and frontier electron densities were calculated for a series of imidazoles as an indication of the hydrogen bonding potential for the molecules. The frontier electron densities were divided by the energy of the highest occupied molecular orbital for each molecule to give a normalised index for comparison, this is referred to as the superdelocalisability index (SI). It was found that a good correlation existed between SI and a function of the enthalpy of immersion. It was concluded that a structure/property relationship existed for wettability and thus theoretically, the wetting behaviour of a new molecule could be predicted from data obtained on existing compounds.

Work has been undertaken on the wettability and solubility of some substituted barbituric acids (Buckton and Beezer, 1989) to investigate the possibility of structural links for these two properties. The structure/property relationships were shown to exist by use of compensation analysis. This technique looks for correlations between two different thermodynamic parameters (usually enthalpy as a function of entropy, but a better approach is to use the enthalpy/free energy domain (Tomlinson, 1983)). The ranking of the powders in a linear compensation plot demonstrated that wetting, by water, is most favoured for butobarbitone, followed by phenobarbitone, pentobarbitone with amylobarbitone being the most hydrophobic (Buckton and Beezer, 1988, 1989). The ranking obtained for solubility from the enthalpy/free energy plot reveals a different ordering of the compounds with phenobarbitone and butobarbitone being at opposite extremes of the solubility plot. The results suggest that the solubility and perhaps the wettability have a structure/property link, but that the structural features that control solubility are not the same as those that control wettability. The implications of this finding are significant as it may be possible to alter one portion of a molecule slightly to improve either the wetting or the solution behaviour of the compound to optimise the performance. It was these considerations that prompted the current study.

The effect of chemical variation on solubility

Yalkowsky et al. (1972) studied the solubility of alkyl *p*-aminobenzoates in solvents including water and hexane. The solubility in water showed a decrease with increasing chain length, this relationship fitted two straight lines, one for side chains of 1–4 carbon units, and the other for the longer chains. The hexane solubility data showed a linear rise from 1 to 4 carbons, a further rise to 5, then an oscillatory decline in solubility with increasing chain length.

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* The term property is being used in place of the more usual activity, as activity is often taken as synonymous with biological response. It will be demonstrated below that any one series of powders can have independent, non-correlated changes in properties (i.e. wettability and solubility), but both may be structurally related, and neither necessarily have to be directly correlated with biological response.

In the current study, a homologous series of compounds, the alkyl *p*-hydroxybenzoates, have been investigated. Certain of these compounds are used as preservatives in pharmaceuticals. The purpose of the work presented in this paper is to examine the properties of a homologous series of powders to investigate how wettability and solubility change as a function of chain length.

Materials and Methods

Samples of alkyl *p*-hydroxybenzoates, from methyl to decyl inclusive, were obtained from Nipa (methyl to butyl) and Apin Chemicals Ltd (higher chain lengths) (Nipa and Apin Chemicals are essentially the same suppliers) and were used in their as received form. The water used was from a reverse osmosis system and was found to have a surface tension of 72 mN/m. Hexane was Hipersolv (BDH).

The solubility of the powders was determined in water and hexane, by equilibrating excess powder in the liquid until such time as the UV absorbance reading of a filtered sample was the same on three successive days. The experiments were undertaken at 25 ± 0.1°C. The results that are quoted are averages of nine separate determinations. The solubility of the pentyl derivative was not measured, because of its tendency to 'oil out' in water. The melting points of the powders were determined by use of differential scanning calorimetry (Perkin Elmer, 1B).

The wettability was assessed by use of a Wilhelmy plate technique (Zajic and Buckton, 1990). This consists of an electro-microbalance from which a thin compressed plate of powder was suspended. The powder plate was prepared in a rectangular highly polished stainless steel punch and die, which could be dismantled by unbolting to allow easy removal of the formed plate. The die had nominal dimensions of 1 cm × 5 cm and a 10 tonne force was applied to the punch to prepare the compacts. An average thickness for the compacts was in the order of 2–3 mm.

The test liquid, in this case water, was held in a clean clear glass dish and was gradually raised to contact the powder plate, by use of a motor driven platform. When the plate and the liquid make contact, a force was registered on a chart recorder, and it was possible to correct this force displacement to a true displacement reading using the method described previously (Zajic and Buckton, 1990). The contact angle for the liquid (of known surface tension) and the plate can be determined using the equation:

$$\cos\theta = \frac{fg}{p\gamma} \qquad (1)$$

where f is the corrected force on the plate at the time of immersion, g is the acceleration due to gravity, p is the perimeter of the plate and γ is the surface tension of the liquid. Results are quoted as an average of at least three separate beams of powder, each of which was measured six times.

Results and Discussion

The data obtained for the melting points of the alkyl *p*-hydroxybenzoates are presented in Fig. 1. These follow a trend similar to that observed by Yalkowsky et al. (1972) for the melting points of the alkyl *p*-aminobenzoates. There is a fall in melting point as the side chain is increased from methyl to pentyl. After the minimum value the melting points rise in a non-linear manner as the length of the side chain is increased from the pentyl to the decyl derivative.

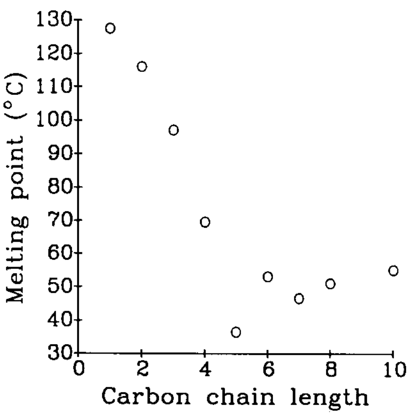

Fig. 1. The melting points of the alkyl *p*-hydroxybenzoates as a function of the number of carbon atoms in the alkyl chain.

If breaking of the crystal lattice is the dominant factor in the solution process, it would be expected that the solubility could be predicted by use of the melting point data, i.e. solubility would reach a maximum at the same region where the melting point data shows a minimum (on the basis that the minimum melting point implies a weakly bonded crystal and thus easier disruption).

The solubility in hexane (Fig. 2) shows a trend in which the solubility rises until the chain length is 5 or 6 carbon units, then the solubility decreases. The exception to this trend is the methyl derivative which is not a typical member of the series. This sort of solubility profile is approximately as would be predicted on the basis of melting point; thus it can be assumed that when the alkyl *p*-hydroxybenzoates are dissolved in such a nonaqueous solvent, the process is limited by the ease of disruption of the crystal lattice, and the accommodation of the solute into the solvent is not a controlling step.

The aqueous solubilities of the alkyl *p*-hydroxybenzoates (Fig. 3) follow an entirely different trend to those in hexane (Fig. 2). The semilogarithmic plot (Fig. 3) reveals a linear decrease in aqueous solubility until a chain length of about 4–5 carbon units, the higher carbon chains show a further decrease, which apparently exhibits an oscillatory fluctuation, and which has a more shallow gradient than the short chain results. There is insufficient data to allow judgement about oscillatory behaviour in the higher chain lengths; odd/even oscillation in properties has been reported for the solubilities of *p*-aminobenzoates (with alkyl chain lengths greater than six) in hexane (Yalkowsky et al., 1972). The results reported by Yalkowsky et al. (1972) for the aqueous solubility of the alkyl *p*-aminobenzoates were similar in that a break was observed at a chain length of 4 carbon units, however, in that instance the results followed two distinct linear relationship with the long chains exhibiting the steeper gradient.

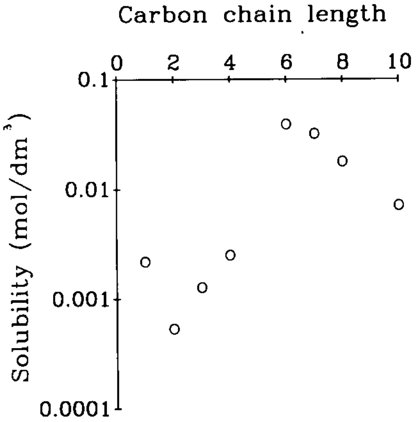

Fig. 2. The solubility of the alkyl *p*-hydroxybenzoates in hexane, as a function of the number of carbon atoms in the alkyl chain.

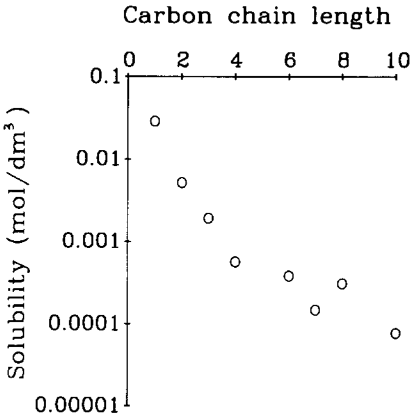

Fig. 3. The aqueous solubility of the alkyl *p*-hydroxybenzoates, as a function of the number of carbon atoms in the alkyl chain.

As the aqueous solubility relationship is not similar to the melting point or hexane solubility trends, it must be concluded that the dispersion of solute molecules in the water is a major barrier to the solution process. This is indicative of a hydrophobic repulsion between the solute molecule and the solvent. The interaction between a dissolved hydrophobic molecule and water is not necessarily the same as that between the solid surface and water, because the powder surface may not exhibit all the functional groups that are present on the molecule (depending on crystal packing arrangements).

Fig. 4 shows the contact angle for water on the alkyl *p*-hydroxybenzoates, as determined by the Wilhelmy plate technique. The samples that were studied were the methyl to heptyl derivatives, as these could be formed into coherent plates. The methyl derivative has a very low contact angle,

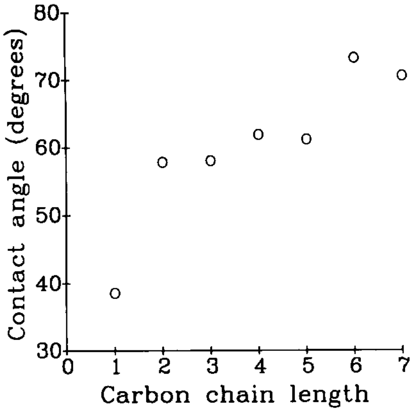

Fig. 4. The contact angles of water on the alkyl *p*-hydroxybenzoates, as a function of the number of carbon atoms in the alkyl chain.

significantly different to the other samples; presumably this compound is behaving in a manner similar to the parent molecule. For the ethyl to pentyl derivatives, the results are indistinguishable. The standard deviations for the contact angle results, for methyl through to heptyl respectively were: 7.9, 5.1, 5.8, 4.4, 4.7, 3.3, and 5.3. The size of the standard deviations reflects the difficulty encountered in compaction of the powders. It is well known that rough surfaces exhibit large contact angle hysteresis, and variability of results. The hexyl and heptyl derivatives, however, have contact angles that are higher than those obtained for ethyl to pentyl, once again demonstrating a break in physical properties as a function of chain length.

General discussion

In a recent publication (Beezer et al., 1990) the Gibbs free energies of solution of the hydroxybenzoates were reported in various solvents. The data showed that the contribution to the free energy of solution per methylene group was not markedly dependent on solvent for chain lengths greater than 6, but for the short chains there was a striking dependence on solvent type. It can reasonably be assumed that the longer chain lengths have greater freedom of movement, and thus they can fold to expose the smallest possible non-favourable face to the solvent. The shorter chains (up to approx. 5 carbon length) have comparatively little freedom of movement, thus the striking influence of each additional methylene group.

The results presented above reveal significant information about the compounds and their interactions with solvents. Firstly, for the compounds to dissolve in hexane, the most important aspect is the disruption of the crystal lattice; subsequent solute/solvent distribution is not hindered greatly. Secondly, when water is the solvent, the accommodation of the solute in the solvent must be significant because the melting points do not bear any relationship to the aqueous solubilities. With this aqueous solution process, there is a fall in solubility with increased chain length; this shows that as the chain gets longer it becomes harder to accommodate the solute within the solvent structure. However, the longer chain lengths have greater freedom of movement, and thus the effect per methylene group is smaller than for the small (more rigid) substituents. It might be expected that this fall in aqueous solubility would be mirrored by a similar rise in hydrophobicity; this is not the case. The wettability of the compounds seems to be very similar until a chain length of six is exceeded, after which the powders are more hydrophobic. Thus the effect of adding methylene groups to the shorter side chains (less than 5–6 carbons) is minimal, implying that only part, and indeed perhaps only a constant part, of the side chain is present in the powder surface. For the longer chains, the aqueous wettability of the powder is reduced, and it may be that the increased freedom of movement that exists within the molecule during crystallisation, allows more of the side chain to be present in the surface of these powders.

Conclusions

The conclusions that can be drawn from this work are that, the crystal lattice energy and the structure of the solute molecule are both important in controlling solubility, as it is the liberated molecule that will have to be accommodated in the solvent. Wettability, however, is controlled by the structure of the exposed surface groups of the crystal, which may or may not reflect the total structure of the molecule.

There is not a simple relationship between wettability and solubility. It is possible that for many compounds total molecular structure will correlate with solubility, but that only part of the structure will affect wettability. Thus a different structure (or partial structure) property relationship may exist for both properties. The implication of this hypothesis is that physical manipulation of a crystal may significantly alter wettability, whilst retaining similar solubility. The increased wettability would aid dissolution rate and may improve bioavailability.

All the physical properties show a break in their trends at a chain length of 5 (±1) carbon units.

More research is under way into the relationship between the physical properties of powders.

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References

Beezer, A.E., Buckton, G., Forster, S., Park, W.-B. and Rimmer, G.J., Solution thermodynamics of 4-hydroxybenzoates in water, 95% ethanol/water, octan-1-ol and hexane. *Thermochim. Acta*, (1991) in press.

Buckton, G. and Beezer, A.E., A microcalorimetric study of powder surface energetics. *Int. J. Pharm.*, 41 (1988) 139–145.

Buckton, G. and Beezer, A.E., Structure-activity relationships for solubility and wettability of a number of substituted barbituric acids. *Thermochim. Acta*, 138 (1989) 319–326.

Lippold, B.C. and Ohm, A., Correlation between wettability and dissolution rate of pharmaceutical powders. *Int. J. Pharm.*, 28 (1986) 67–74.

Storey, D.E., Correlation between the thermodynamics of aqueous immersion and molecular structure. *J. Pharm. Pharmacol.*, 38 (1986) 6P.

Tomlinson, E., Enthalpy-entropy compensation analysis of pharmaceutical, biochemical and biological systems. *Int. J. Pharm.*, 13 (1983) 115–144.

Yalkowsky, S.H., Flynn, G.L. and Slunick, T.G., Importance of chain length on physicochemical and crystalline properties of organic homologs. *J. Pharm. Sci.*, 61 (1972) 852–857.

Zajic, L. and Buckton, G., The use of surface energy values to predict optimum binder selection for granulations. *Int. J. Pharm.*, 59 (1990) 155–164.