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The use of molecular orbital indices to predict the surface properties of pharmaceutical powders

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Abstract

The electron density, frontier electron density and superdelocalisability indices have been calculated for the total molecular structures, and the parts of the molecules which are anticipated to be involved in hydrogen bonding interactions. The models used comprised of an homologous series (alkyl *p*-hydroxybenzoates), materials related by a common ring structure, but with differing substituents (imidazoles), and three related comparatively large molecular weight drugs (HMG-CoA reductase inhibitors). Surface energies were determined from contact angle data with water, using Neumann's equation of state. No relationship was seen between data for total molecular orbital indices for the molecules and measured contact angles or derived surface energies. However, when the hydrogen bonding atoms of the molecules were selected, a good linear correlation was observed for all three types of molecule between superdelocalisability and both contact angle and surface energy. This is expected as the hydrogen bonding regions are probably especially important in interactions with water. Two (of 16) molecules were outliers from the general relationship. These were one of the HMG-CoA reductase inhibitors and methyl *p*-hydroxybenzoate. It is possible that the high molecular weight of the first of these molecules was the cause of an error in calculation of the molecular orbital indices (due to optimisation to a secondary minimum). For the methyl *p*-hydroxybenzoate, there are considerable data in the literature to indicate that this material has idiosyncratic properties. Its curious behaviour is examined with consideration to possible crystal packing energy differences over other members in the series. The data presented here give encouragement that the surface properties of a wide range of different materials may be predicted from molecular structure, however, there are inevitable outliers which will mean that predictions will have to be confirmed with practical observations, until modelling approaches have been developed further and adequately validated.

Keywords: Molecular orbital indices; Electron density; Frontier electron density; Superdelocalisability; Hydrogen bonding; Contact angle; Surface energy

1. Introduction

The ability to predict physical properties from molecular structure has obvious advantages, when considering the formulation of dosage forms.

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Work in this area to predict (without measurement) the surface properties of pharmaceutical powders falls into three categories: (a) determination of the surface free energy of a solid or liquid from parachor values (Quayle, 1953); (b) calculation of surface energies from solubility parameters; and (c) calculation of molecular orbital indices.

Comparatively few studies have attempted to link calculations of molecular structure to physical properties of pharmaceuticals. However, Storey (1986) elucidated a relationship between various thermodynamic parameters of aqueous immersion and two molecular orbital indices, frontier electron density, Σf_r and superdelocalisability index, ΣSI. Knowledge of this relationship enables the prediction of wettability from molecular structure.

It is necessary to know the density of the powders under consideration to calculate surface energies from parachor and solubility parameters. Therefore, the method used by Storey (1986), offers a small advantage. Consequently, it was decided to investigate the use of this approach to see if any correlation existed with measured contact angles or calculated surface energies for powders of three structural types, namely, the alkyl *p*-hydroxybenzoates, which are an homologous series, differing by sequential addition of a methylene group to an alkyl side chain; the imidazoles, related by having differing substituents on a common ring structure; and the HMG-CoA reductase inhibitors, which are examples of comparatively high molecular weight drugs, which may be expected to present difficulties for computer optimisation of structure.

Three molecular orbital indices will be considered here, these are electron density (q_r), frontier electron density (f_r) and superdelocalisability index (SI_r). Each of these is considered below.

2. Methods

2.1. Choice of computational chemistry methods

To determine the molecular orbital indices for the three groups of model compounds selected, it was first necessary to calculate their minimum energy conformation. This may be carried out using molecular mechanics, or force field calculations, or molecular orbital theories, where molecular energies are calculated using schroedinger's equation. This equation can be solved with the introduction of some approximations (semi-empirical) or with no approximations at all (ab-initio).

Although the molecular mechanics approach is considered accurate for the determination of the minimum energy conformation for small molecules, it is not very accurate for larger molecules. In addition, the information provided by molecular mechanics calculations is not sufficient to enable properties such as electron density, frontier electron density and superdelocalisability index to be calculated. Therefore, only computational chemistry programs using molecular orbital theory were considered.

An excellent overview of the most widely used computational chemistry packages is given in Clark, 1985. Many factors need to be considered when choosing a suitable package. It is important that the program selected is appropriate for the compounds under investigation. Most programs are only suitable for a restricted number of elements. For example, the semi-empirical theory of modified neglect of differential overlap (MNDO), available in the MOPAC program, can only be used for compounds containing the following elements: H, Be, B, C, N, O, F, Al, Si, P, S, Cl, Br, and I.

Programs using ab-initio calculations are the most accurate and therefore, in theory, would be expected to be the most appropriate. However, ab-initio methods may not be feasible for larger molecules due to the enormous amount of computer processor time and disk space required. Consequently, semi-empirical methods are generally considered to be more suitable, for practical reasons, particularly when large molecules are being studied. For this work, only semi-empirical methods were feasible due to the size of the HMG-CoA reductase inhibitors. MOPAC, a combined package of MINDO/3 (Bingham et al., 1975) and MNDO (Dewar and Thiel, 1977a), was utilised for this study. By comparing heat of for-

mation values calculated by these two theories with experimental values for a large number of molecules, Dewar and Thiel (1977b) were able to confirm the superiority of MNDO over MINDO/3. Therefore, MNDO molecular orbital theory was selected for this work.

2.2. Calculation of the minimum energy conformation.

Initially, the molecular structure was imputed into the computer. The structure was defined by means of a Z-matrix. This defined the position of every atom in the molecule in terms of bond lengths, bond angles and dihedral angles.

The Z-matrix was then edited, using data (i.e., bond lengths, bond angles and dihedral angles) obtained from the Cambridge Data Base for molecules with similar structures to the alkyl *p*-hydroxybenzoates (Lee, 1983) and the HMG-CoA reductase inhibitors (Sato et al., 1984). This ensured that the starting geometry was close to a minimum energy conformation and therefore, the molecule was more likely to be optimised to the global minimum, rather than a local minimum energy conformation.

The computational time to optimise large molecules can be quite considerable and during the process of optimisation atoms may overlap, which results in termination of the calculation. The HMG-CoA reductase inhibitors are large molecules and therefore, each molecule was split into three portions, a naphthalene ring, a lactone ring and a butanoic side chain. These fragments were optimised separately and then merged together. The molecule was then optimised as a whole.

The alkyl *p*-hydroxybenzoates and imidazoles are much smaller molecules and therefore, the process of splitting the molecule into fragments was unnecessary.

As described previously, the molecular geometry is input in the form of a Z-matrix. This information is used to calculate Cartesian co-ordinates of the atoms. The total number of electrons and molecular orbital occupancies are then determined and atomic orbitals are assigned to each nucleus. The program then produces an initial guess or trial set of molecular orbitals to use as a starting point for the self-consistent field (SCF) calculations. In general, semi-empirical programs divide electrons evenly amongst the atomic orbitals and allow the SCF procedure to find more realistic molecular orbitals. This initial guess is used as the starting point for an iterative SCF treatment, to eventually optimise on the lowest electronic energy. This is often referred to as the linear combination of atomic orbitals (LCAO) formalism.

Once the calculation has converged and the minimum energy conformation has been found, the program starts the population analysis. This involves calculation of eigenvectors, eigenvalues and electron densities. This information is compiled and used to calculate the molecular orbital indices.

2.3. Calculation of the molecular orbital indices

The molecular orbital indices were calculated in three different ways,

1. adding up the contributions from ALL atoms in each molecule,
2. adding up the contributions from the atoms which are known hydrogen bonding atoms.
3. adding up the contributions of the atoms of the functional groups which are known to be able to hydrogen bond, e.g., NO_2, COOH, etc. The selected atoms for the alkyl *p*-hydroxybenzoates, imidazoles and HMG-CoA reductase inhibitors are shown in Fig. 1, Figs. 2 and 3, respectively.

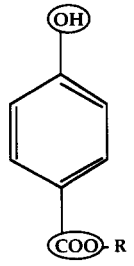


Fig. 1. General structure of the alkyl *p*-hydroxybenzoates, with the atoms which were used for the HB+ calculations (see Table 3) highlighted.

2.4. Electron density.

This describes the charge associated with an atom, r and can be calculated using Eq. 1:

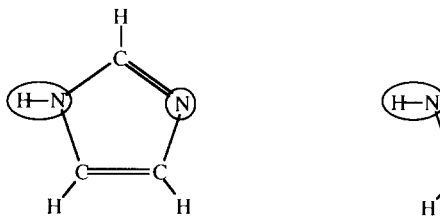
$$q_r = \Sigma 2C_{ir}^2 \quad (1)$$

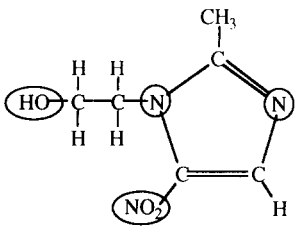
where C_{ir} is the coefficient (eigenvector) of the atomic orbital, i in the atom, r.

To understand the significance of the electron density, a definition of the coefficients, C, shall be given, using a hydrogen molecule as an example. Hydrogen (H_2) consists of one occupied molecular orbital, ψ, which contains two electrons. The hydrogen molecule consists of two atomic orbitals ψ_a and ψ_b, each in the vicinity of the two nuclei of the two hydrogen atoms, referred to here as 'a' and 'b'. It is likely that each atomic orbital, ψ_a and ψ_b contains one electron, in the vicinity of their nuclei.

$$\psi = C_a\psi_a + C_b\psi_b \quad (2)$$

The coefficients, C_a and C_b, weight the contributions from the atomic orbitals ψ_a and ψ_b. The value of ψ^2 represents the probability of finding an electron in a region of space. The probability of finding an electron in a molecular orbital is 1.





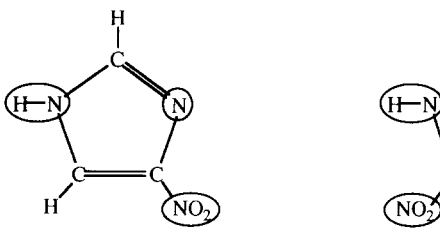


Fig. 2. General structure of the imidazoles, with the atoms which were used for the HB+ calculations (see Table 3) highlighted.

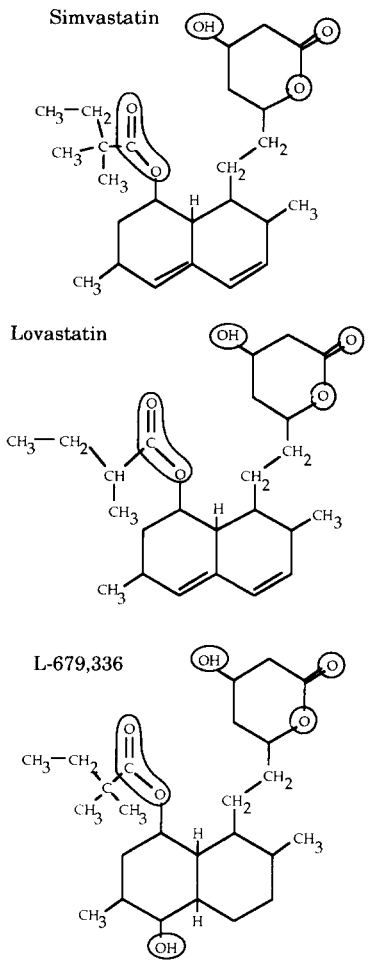


Fig. 3. General structure of the HMG-CoA reductase inhibitors, with the atoms which were used for the HB+ calculations (see Table 3) highlighted.

The coefficients for ψ_a and ψ_b are the same, because the molecule is symmetrical, consisting of two hydrogen atoms. Eq. 3 provides a more general expression to describe a molecular orbital, ψ.

$$\psi = C_a\psi_a + C_b\psi_b ....C_n\psi_n \quad (3)$$

The total electron density, Σq_r was calculated by adding up the electron densities for all the atoms. The total electron density for all hydrogen bonding atoms, $\Sigma q_{r(HB)}$ was calculated by adding up all the individual electron densities for all hydrogen bonding atoms, and $\Sigma q_{r(HB+)}$ for all the atoms in hydrogen bonding functional groups (see Fig. 1–3).

2.5. Frontier electron density

This is the charge associated with the orbitals which contain the *least* tightly bound electrons, called the frontier orbitals or the highest occupied molecular orbitals (HOMO), it can be calculated as shown in Eq. 4:

$$f_r = \Sigma_f 2C_{fr}^2 \quad (4)$$

where C_{fr} is the eigenvector of the frontier orbital, f, in atom, r. The frontier electron density for each atom, f_r, was calculated using Eq. 4. A basic computer program was written to allow easy calculation of the frontier electron densities for all the molecules. The frontier electron densities over all atoms, Σf_r, were calculated by adding together f_r for every atom in the molecule. Values of $\Sigma f_{r(HB)}$ were calculated by adding together f_r for all the hydrogen bonding atoms in the molecule, and $\Sigma f_{r(HB+)}$ is the sum of f_r for atoms in the hydrogen bonding functional groups.

2.6. Superdelocalisability index (SI)

This is a measure of the electron availability of an atom. It represents the electron density of an atom, r, in a molecular orbital, j, divided by the energy (or eigenvalue, E) of the molecular orbital which allows comparison of the electron availability of the atom with those in other molecules. The SI is calculated according to Eq. 5:

$$SI_r = 2\Sigma\left(C_{ji}^2/E_j\right) \quad (5)$$

The superdelocalisability index was developed by Fukui et al. (1954), to predict the probability of a reaction occurring at a given atomic centre of a molecule. The greater, the positive value of SI, the more likely it is that a reaction will take place (Fukui et al., 1954). Subsequently, SI_{HOMO} (Eq.

Table 1
Total molecular orbital indices

Material	Σq_r (total)	Σf_r (total)	ΣSI_r (total)	ΣSI_{HOMO} (total)	ΣSI_{LUMO} (total)
HBA	52.00	2.000	−2.2937	−0.2099	−2.8457
Methyl PHB	58.00	2.000	−2.4763	−0.2113	−3.1651
Ethyl PHB	64.00	2.000	−2.6697	−0.2116	−4.9712
Propyl PHB	70.00	2.000	−2.8694	−0.2115	−5.0473
Butyl PHB	38.00	2.000	−3.0795	−0.2156	−9.9510
Benzyl PHB	80.00	2.000	−3.5339	−0.2100	−5.0592
Hexyl PHB	88.00	2.000	−3.5154	−0.2157	−9.9886
Heptyl PHB	94.00	2.000	−3.7550	−0.2156	−10.1019
Imidazole (I)	26.00	2.000	−1.1765	−0.2202	2.1977
2-Methyl I	32.00	2.000	−1.3603	−0.2175	2.3776
Metronidazole	50.00	2.000	−2.0081	−0.2169	2.7108
4-Nitro I	42.00	2.000	−1.8492	−0.1886	−1.4410
2-Methyl-5-nitro I	48.00	2.000	−2.0415	−0.1920	−2.7479
Simvastatin	168.00	2.000	−6.4517	−0.2166	7.0194
Lovastatin	162.00	2.000	−6.2512	−0.2165	7.3372
L-679-336	178.00	2.000	−6.6659	−0.1720	1.9568

Table 2
Molecular orbital indices for the hydrogen bonding atoms only

Material	Σq_r(HB)	ΣSI_r(HB)
HBA	19.6481	−0.920
Methyl PHB	19.7171	−0.934
Ethyl PHB	19.6808	−0.926
Propyl PHB	19.6826	−0.926
Butyl PHB	19.7396	−0.926
Benzyl PHB	19.6131	−0.915
Hexyl PHB	19.7398	−0.926
Heptyl PHB	19.7398	−0.926
Simvastatin	32.4594	−1.572
Lovastatin	32.4451	−1.565
L-679-336	41.6029	−1.886

NB: (1) Only two columns are shown, which reveal that considering only hydrogen bonding atoms does not discriminate between molecules in the homologous series. (2) The data for the imidazoles in Table 3 are for hydrogen bonding atoms only, but have been presented with the HB+ data as they have been used in the correlations in the figures. The reason why the imidazole data do not change between Tables 2 and 3 is that there are no non-hydrogen bonding atoms in hydrogen bonding functional groups for the imidazoles (unlike the alkyl *p*-hydroxybenzoates which have COO).

6) and SI_{LUMO} (Eq. 7) (where LUMO is lowest unoccupied molecular orbital) were developed by Brown and Simas (1982), to describe the likelihood of an electrophilic or nucleophilic reaction occurring at a particular atomic centre in a molecule.

$$SI_{r,HOMO} = 2\Sigma\left(C^2_{i,HOMO}/E_{HOMO}\right) \quad (6)$$

$$SI_{r,LUMO} = 2\Sigma\left(C^2_{i,LUMO}/E_{LUMO}\right) \quad (7)$$

For the compounds included in this study it was not necessary to calculate the total superdelocalisability indices for all atoms in each molecule, ΣSI_{total}, as this was obtained from a data file generated from MOPAC for each molecule. Values for $\Sigma SI_{total(HB)}$ and $\Sigma SI_{total(HB+)}$ were obtained by adding together the individual superdelocalisability indices for the appropriate atoms. For imidazole, $\Sigma SI_{total(HB)}$ was calculated by adding together the superdelocalisabilities for atoms 1(N), 3(N) and 9(H). Similar files were also obtained for SI_{HOMO} and SI_{LUMO} to enable ΣSI_{HOMO}, ΣSI_{LUMO}, $\Sigma SI_{HOMO(HB)}$ and $\Sigma SI_{LUMO(HB)}$ to be calculated.

2.7. Measurement of surface properties

The materials used are as listed in Table 1. The alkyl *p*-hydroxy benzoates were obtained from Apin, and the HMG-CoA reductase inhibitors were a gift of MSD Research Laboratories, UK. Contact angles were measured for wa-

Table 3
Molecular orbital indices for atoms in functional groups involved in hydrogen bonding (i.e., those highlighted in Fig. 1–3)

Material	Σq_r(HB+)	Σf_r(HB+)	ΣSI_r(HB+)	ΣSI_{HOMO}(HB+)	ΣSI_{LUMO}(HB+)
HBA	23.2694	0.2762	−1.055	−0.036	−0.293
Methyl PHB	23.3035	0.3404	−1.068	−0.036	−0.345
Ethyl PHB	23.2756	0.3066	−1.060	−0.031	−0.240
Propyl PHB	23.2781	0.3078	−1.060	−0.032	−0.248
Butyl PHB	23.3205	0.2963	−1.058	−0.031	−0.441
Benzyl PHB	23.2106	0.2151	−1.049	−0.021	−0.224
Hexyl PHB	23.3205	0.2961	−1.493	−0.031	−0.480
Heptyl PHB	23.3206	0.2966	−1.733	−0.031	−0.479
Imidazole (I)	11.2262	0.4446	−0.560	−0.012	0.489
2-Methyl I	11.4302	0.1412	−0.559	−0.013	0.598
Metronidazole	17.6203	0.1130	−0.869	−0.014	0.621
4-Nitro I	28.3484	0.2364	−1.305	−0.018	−0.720
2-Methyl-5-nitro I	28.2929	0.2207	−1.315	−0.021	−1.385
Simvastatin	39.7359	0.0029	−1.572	0.000	0.001
Lovastatin	39.7288	0.0029	−1.565	0.000	0.000
L-679-336	46.8790	0.6908	−1.886	−0.064	0.713

ter on the *p*-hydroxybenzoate and HMG-CoA reductase inhibitor powders, by compacting the powders into a thin plate, in a rectangular punch and die. The plates were then removed and used in a Wilhelmy plate apparatus (Cahn DCA) (for further experimental details see Zajic and Buckton, 1990). The contact angle was obtained from an extrapolated buoyancy slope for the advancing data. The imidazole results were taken from the literature (Storey, 1986).

Surface energies were calculated using Neumann's equation of state (Ward and Neumann, 1974), using an adaptation of the computer programme devised by Taylor (1984).

3. Results and discussion

The total molecular orbital indices and molecular orbital indices for all hydrogen bonding atoms calculated, are shown in Tables 1 and 2, respectively, whilst those for the atoms that have been indicated in Fig. 1–3 are shown in Table 3.

As expected the total electron density, Σq_r, has a value of twice the number of filled levels or occupied molecular orbitals for each molecule. For example imidazole has 13 filled levels and since each molecular orbital contains two electrons, the electron density is 26. Similarly the total frontier electron density, Σf_r, has a value of 2 since there are two electrons in the HOMO in each molecule (this provides a good internal check that the calculations are correct).

As expected, there is no correlation between these molecular orbital indices and the surface properties. This is because these values represent the electron availability over each molecule as a whole, rather than the electron availability of the atomic centres most likely to be involved in hydrogen bonding. It is well known that hydrogen bonding is not the only process which occurs in liquid/powder interactions. However, polar liquids such as water are of interest for most pharmaceutical systems, therefore, selection of atoms involved in hydrogen bonding was considered most appropriate.

Regarding the atoms which were selected as hydrogen bonders (nitrogen and oxygen atoms and OH groups only), the summed values for these atoms (Table 2) did not correlate with surface energy data. It is notable that the summed values for these atoms are essentially the same for each of the alkyl *p*-hydroxybenzoates, a situation which differs totally when the adjoining carbon atom (in the COO group) is considered (Table 3). The importance of the carbon in reflecting the influence of the remainder of the molecule is very clear from these data.

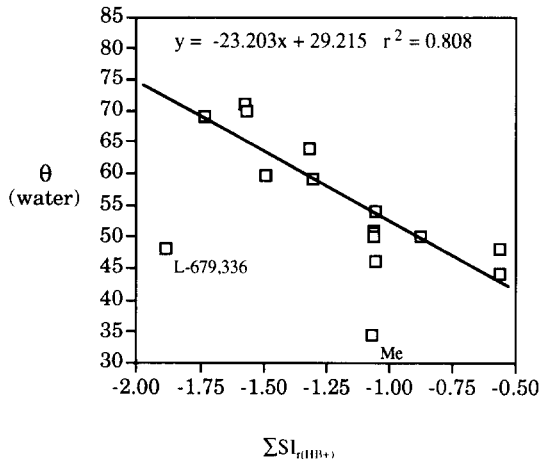


Fig. 4. Relationship between the superdelocalisability index for functional groups involved in hydrogen bonding and the contact angle with water, for the 16 molecules from the three different series of compounds.

There is no relationship between $\Sigma q_{r(HB+)}$ and $\Sigma f_{r(HB+)}$ and contact angle, θ against water or surface energy, γ_{sv}. However, there is a relationship between θ and γ_{sv}, and $\Sigma SI_{r(HB+)}$ (see Figs. 4 and 5). This is consistent with the findings of Storey (1986) who reported a correlation between ΣSI and several thermodynamic parameters of aqueous immersion, for the imidazoles.

The relationship is quite clear throughout the three groups of powders (with the exception of methyl *p*-hydroxybenzoate and L-679,336) and allows calculation of θ and γ_{sv} from the molecular structure of a material using Eq. 8 and 9, respectively.

$$\theta = -23.203\Sigma SI_r(HB+) + 29.215 \quad (8)$$

$$\gamma_{SV} = 13.381\Sigma SI_r(HB+) + 64.504 \quad (9)$$

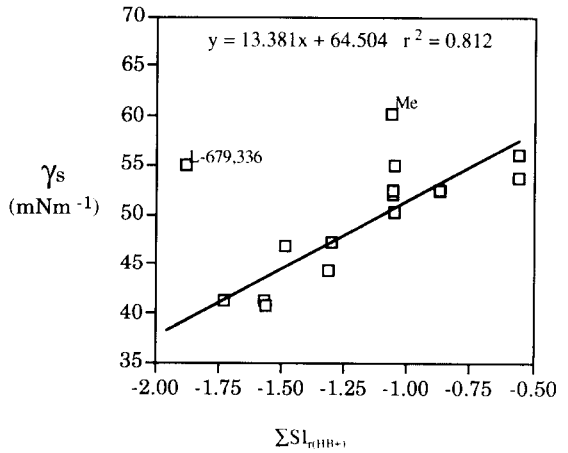


Fig. 5. Relationship between the superdelocalisability index for the functional groups involved in hydrogen bonding and the calculated surface energy of the solids, for the 16 molecules from the three different series of compounds.

Knowledge of such relationships may prove useful for predicting the wettability of pharmaceutical powders at an early stage during formulation development. However, it is necessary to be aware of the assumptions and/or limitations of this study. Most pharmaceutical materials are crystalline in nature. Therefore, orientation of molecules must be such that all atoms involved in hydrogen bonding are represented in direct proportion to their occurrence in each individual molecule, over the entire crystal surface; this will not always be the case. It is notable that polymorphic transitions may result in different surface properties, and thus deviation from predicted results. However, this limitation may not be too significant, as measured surface properties tend not to differ drastically for different polymorphic forms (unpublished data). A further limitation in predicting surface properties of powders is that Buckton et al. (1988) reported that previous history of a powder can have a substantial effect on θ. The major influence of processing may be to produce amorphous material at the powder surface (Briggner et al., 1994), and thus allow preferential orientation of surface molecules, thus altering the net surface energy. Therefore, this approach may only be suitable for powders which have been processed in a similar manner.

Since it is well recognised that the previous history can have major effects on the surface properties of pharmaceutical powders it is surprising, and at the same time extremely encouraging, that a relationship between $\Sigma SI_{r(HB+)}$ and measured surface properties was found. This is particularly true considering that three quite different groups of drug compounds were used.

The deviation from the common relationship (Fig. 4 and 5) for methyl *p*-hydroxybenzoate and L-679,336 could be due to several reasons. In the case of L-679,336, one possibility is that the size of the molecule is such that MNDO was unable to find the correct minimum energy conformation, and that the value obtained was a secondary minimum conformation. An alternative explanation, which would also hold for methyl *p*-hydroxybenzoate, is that these compounds are unique in their respective series in that they have additional intermolecular hydrogen bonds. Two different types of intermolecular hydrogen bonds are possible in methyl *p*-hydroxybenzoate, due to the small size of the methyl substituent (compared to only one intermolecular hydrogen bond in the higher molecular weight members), in perpendicular directions in the crystal and there is no pi stacking. The surface energy of methyl-p-hydroxybenzoates is idiosyncratic in relation to the other members of the homologous series (Forster et al., 1991; Sheridan et al., 1994). Several of the mechanical properties, namely the fracture toughness, critical stress intensity factor, and critical strain energy release rate, are greater for methyl *p*-hydroxybenzoate than would be expected by comparison with 4-hydroxybenzoic acid and other homologs of the alkyl *p*-hydroxybenzoate series (Newton et al., 1993). Similarly, only one inter-molecular hydrogen bond exists in simvastatin and lovastatin (unpublished data), but because there are two OH donors and two carbonyl receptors in L-679, 336 two inter-molecular hydrogen bonds exist.

The crystal unit cell structures for methyl *p*-hydroxybenzoate and L-679,336 are, therefore, different from the other members in their respective series which may well lead to an unequal distribution of hydrogen bonding groups on the crystal surface. Since the $\Sigma SI_{r(HB+)}$ values for each molecule are proportional to the square of

the molecular orbital coefficients, those groups with high coefficient values contribute significantly to the overall $SI_{r(HB+)}$ value.

Therefore, although theoretical methods (i.e., use of solubility parameters and superdelocalisability indices) of predicting surface energies may be useful for many pharmaceutical powders, it must be emphasised that they have limitations for some materials. This indicates that data obtained by theoretical methods offer a valuable initial indication of expected behaviour, which may often prove to be reliable. However, theoretical considerations should, at this stage, not be used as a substitute for experimental data, obtained from contact angle measurements, for example.

4. Conclusions

A relationship between $\Sigma SI_{r(HB+)}$ and both contact angle against water and surface energy has been elucidated. Knowledge of such a relationship should prove useful for the prediction of surface properties from molecular structure of new drug compounds. It should, however, be emphasised that there are exceptions to this relationship, as there are with other theoretical methods of predicting surface properties, such as the use of solubility parameters. The early success of this approach provides encouragement to further refine and extend the database.

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