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Characterisation of the surface energetics of milled dl-propranolol hydrochloride using inverse gas chromatography and molecular modelling

P. York [a,*], M.D. Ticehurst [1,a], J.C. Osborn [a], R.J. Roberts [b], R.C. Rowe [b]

[a] *Drug Delivery Group, School of Pharmacy, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK*
[b] *Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 2NA, UK*

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Abstract

Inverse gas chromatography (IGC) has been successfully used to characterise the nature of the surface of samples of dl-propranolol hydrochloride which have been produced under conditions of increasing milling intensity. It has been shown that the surface becomes increasingly more energetic as indicated by an increase in the dispersive component of the surface free energy and more electron donating as indicated by the adsorption of tetrahydrofuran and dichloromethane. Both effects increase until at a critical particle size a plateau is reached with no further change with a reduction in particle size. The critical particle size coincides with the brittle ductile transition determined previously by mechanical measurement. Molecular modelling was used to predict which surfaces would predominate by making use of calculations of attachment energies. The face which had the lowest attachment was postulated to be the plane which predominately fractures during high intensity milling. Visualisation showed that the π-electron rich naphthalene moiety of dl-propranolol hydrochloride dominated this surface supporting the data from IGC.

Keywords: Attachment energies; Fracture planes; Inverse gas chromatography; Milling; Surface free energy

1. Introduction

Inverse gas chromatography (IGC) has recently been shown to be a sensitive technique for measuring the surface properties of pharmaceutical powders (Ticehurst et al., 1994, 1996). Milling is known to cause profound changes to the surface

* Corresponding author.
[1] Present address: Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK.

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of powders exposing new surfaces, creating lattice defects and in some cases producing partially or totally amorphous material (Florence and Salole, 1976; Egawa et al., 1992; Briggner et al., 1994). The identity of the new surfaces created by milling will depend on how the particles fracture. For some powders this may be along preferred shear planes within the crystal lattice. Preferred shear planes have been predicted for some materials (Roberts et al., 1994) using attachment energies derived from the predictions of crystal morphology (Clydesdale et al., 1997).

In this study a range of techniques, including IGC has been used to confirm the nature of the surfaces generated when dl-propranolol hydrochloride was jet milled (micronised). Molecular modelling has then been used to determine attachment energies and to identify molecular groups that might be exposed at the surface and thus relate this to the nature of the surface determined from IGC measurements.

2. Theory—attachment energies

The major habit faces can be predicted using the growth morphology model (Hartman, 1973; Hartman and Bennema, 1980; Berkovitch-Yellin, 1985). The calculation of the slice energy (E_{sl}) and attachment energy (E_{att}) forms the foundation of the approach. The slice energy is the energy released on the formation of a growth slice of thickness d_{hkl}, while the attachment energy is defined as the fraction of the total energy (E_{latt}) released on the attachment of this slice to a growing surface (Eq. (1)).

$$E_{att} = E_{latt} - E_{sl} \quad (1)$$

In this model the attachment energy (E_{att}) of a molecular layer on each possible crystal face is calculated and the rate of growth of that face is assumed to be proportional to this energy. Crystal faces that have the lowest magnitude attachment energies dominate the crystal habit. In calculating the attachment energy of a face, it is necessary to determine the most likely growth slice by cutting the unit cell so as to obtain the molecular layer which is most weakly bound to the crystal face. This growth slice has the smallest attachment energy and also the largest slice energy (i.e. the largest cohesive energy within the slice) of all possible molecular layers which could be obtained by cleaving the crystal parallel to a given face. The functional groups exposed on the face will be those found at the boundary of the growth slice.

3. Materials and methods

3.1. Materials

The milled and parent unmilled dl-propranolol hydrochloride batches were donated by Zeneca Pharmaceuticals (Cheshire, UK). Probes employed for IGC were pentane (Aldrich, Milwaukee, WI), hexane (Sigma, St. Louis, MO), heptane (Sigma), octane (Aldrich), nonane (Aldrich), acetone (Aldrich), diethylether (May and Baker, Essex, UK), ethyl acetate (R.P. Normapur, Manchester, UK), dichloromethane (Aldrich) and tetrahydrofuran (Rathburn Chemicals, Peebleshire, UK).

3.2. Thermal analysis

Enthalpy of melting of the samples was measured using differential scanning calorimetry performed on a Perkin-Elmer series 7 at a heating rate of 10°C/min over the range 25–225°C.

3.3. Surface area measurement

Multipoint analysis of N_2 adsorption on a Flowsorb 2300, applying the BET equation (Braunauer et al., 1938) was used to determine the surface area of the powders. Prior to the determination of specific surface area the powders were preconditioned at 40°C for 16 h under 30% N_2/70% He.

3.4. Inverse gas chromatography

Full details of the IGC equipment and experimental procedure can be found in Ticehurst et al. (1994). The columns were packed with between 0.5 and 5 g of dl-propranolol hydrochloride pow-

der and up to four separate columns were used for each sample. The surface thermodynamic properties of the powders, the dispersive component of surface free energy (γ_s^D) and specific component of the free energy of adsorption ($-\Delta G_A^{SP}$), were determined according to the method of Schultz and Lavielle (1989).

3.5. Computational methodology

Molecular modelling techniques have been employed to determine the functional groups of the dl-propranolol hydrochloride molecule (Fig. 1) which are most likely to be exposed on crystal surfaces. The first step in this process is to obtain the crystal structure of dl-propranolol hydrochloride from the Cambridge Database having a reference code PROPDL10 (see also Ammon et al., 1977). dl-propranolol hydrochloride is monoclinic having space group $P2_1/c$, $a = 14.017$ Å, $b = 8.285$ Å, $c = 14.005$ Å, $\beta = 98.76°$, $Z = 4$. In addition the hydroxyl in the region of hydrochloride is disordered and this can be in two configurations. Both these two configurations were examined (Fig. 1a and b).

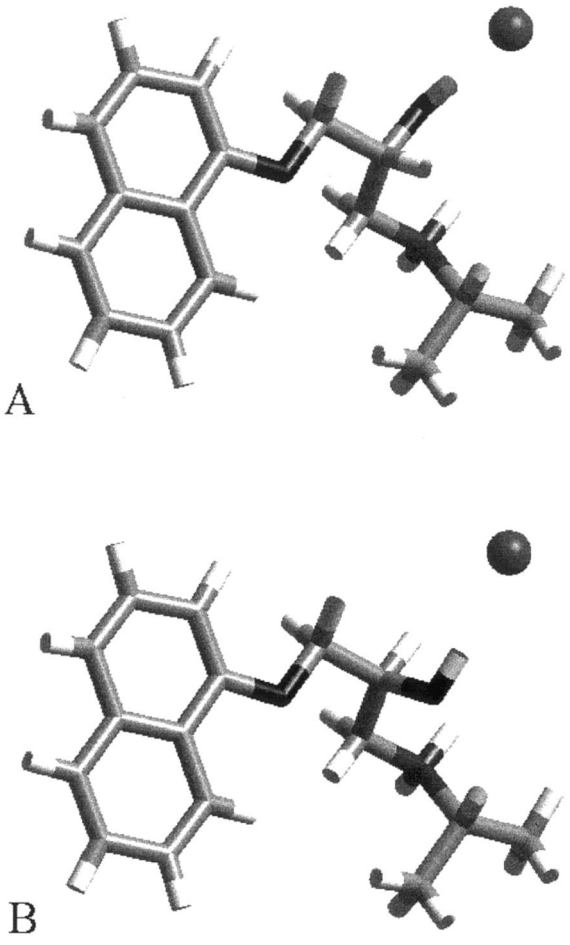

Fig. 1. Molecular conformation of dl-propranolol hydrochloride as in the crystal structure for Configuration A and B.

The hydrogen atom in the hydroxyl group was not located by single crystal X-ray diffraction (Ammon et al., 1977) and therefore it was assigned a standard bond angle and assumed to point towards the closest chloride ion. Furthermore, all other hydrogen covalent bond lengths were adjusted to correspond to what would be expected if the bond lengths were determined by high quality neutron diffraction structures (lengths tabulated by Allen et al., 1987). Apart from the normalisation of the hydrogen atom positions, the experimental crystal structure was used for all calculations without prior structure optimisation (e.g. minimisation of the total energy).

The electrostatic interactions around an isolated molecule were determined by ab initio molecular orbital calculations at the Hartree-Fock 6-31G** level, using GAMESS molecular orbital package (Schmidt et al., 1993). Point charges were assigned to each atom so as best to reproduce the electrostatic potential distribution, using the CHELPG least-squares fitting scheme for determining such charges (Breneman and Wiberg, 1990). Electrostatic potential-derived charges of this nature have been found to be effective in calculating electrostatic contributions to the energy in molecular modelling.

The van der Waals interactions were modelled using Buckingham (exponential-6) potentials taken from the DREIDING molecular modelling force field (Mayo et al., 1990). No special hydrogen-bond potentials were used. The only hydrogen bonds present in dl-propranolol hydrochloride are those in which the chloride ion is the acceptor and it is considered that these interactions will be adequately represented by the electrostatic potentials.

Table 1
Particulate characteristics of unprocessed and micronised batches of dl-propranolol hydrochloride

Batch	Continuation method	Median particle size (μm)	Specific surface area (m^2/g)	Enthalpy of melting (J/g)
PA	None	74.7	0.41 ± 0.01	126
PMA1	Jet mill	21.2	1.44 ± 0.02	123
PMA2	Jet mill	14.1	2.29 ± 0.01	127
PMA3	Jet mill	8.3	3.15 ± 0.04	124
PMA4	Jet mill	6.6	5.16 ± 0.14	125

The attachment and slice energies were calculated using the MARVIN surface modelling program (Gay and Rohl, 1995) which incorporates two-dimensional Ewald summation to calculate the electrostatic component to the energy. Since there are significant long range electrostatic interactions due to the ionic nature of hydrochloride salt this program can best model these interactions.

Visualisation of crystal structures, surfaces and morphology of dl-propranolol hydrochloride was performed using Cerius[2] (Molecular Simulations, 1995).

4. Results and discussion

4.1. IGC measurements

The particulate and bulk properties of the four jet milled and the parent unmilled dl-propranolol hydrochloride batches are presented in Table 1. As expected the median particle size was found to be inversely proportional to the nitrogen specific surface area, which suggests little agglomeration of the powder post milling. The heat of fusion of all five batches including the unmilled sample of dl-propranolol hydrochloride are relatively consistent and therefore independent of milling intensity, indicating that the bulk crystallinity of dl-propranolol hydrochloride is not being influenced by the comminution process.

Values of the dispersive component to the surface free energy (γ_s^D) determined by IGC for the five batches of dl-propranolol hydrochloride are plotted against their median particle size (from Table 1) in Fig. 2. This indicates that as particle size decreases during milling the surface of the powder is becoming increasingly more energetic until a critical point is reached where there is a plateau followed by a small fall in magnitude for the finest powder (PMA4). It should be noted that the start of this plateau region corresponds with the brittle ductile transition or critical particle size (d_{crit}) found previously by Roberts (1991). This was determined as 15.8 μm by compaction measurements on milled/micronised dl-propranolol hydrochloride powders of similar particle sizes to those used here. At this point the material changes from one that is predominantly brittle to one that is predominantly ductile. Below this particle size no fragmentation should take place provided that the forces are compressive in nature. It is thought that the mechanism of size reduction below this point is one of particle attrition rather than fragmentation along the major cleavage planes.

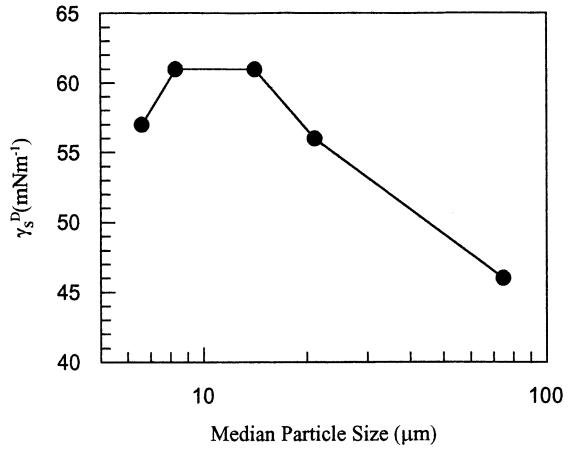

Fig. 2. Dispersive component of surface free energy (γ_s^D) versus median particle size of dl-propranolol hydrochloride.

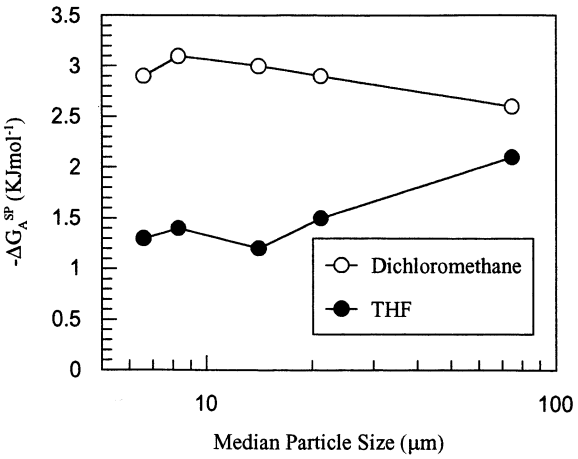

Fig. 3. The specific component of the free energy of adsorption ($-\Delta G_A^{SP}$) of dichloromethane (electron accepting) and THF (electron donating) versus median particle size of dl-propranolol hydrochloride.

Size reduction processes that occur below this point are associated with mainly attrition rather than fracture of specific crystal planes. The plateau region (Fig. 2) where the dispersive interactions are essentially constant implies that the new surfaces exposed due to these attrition processes have only minor effect on the measured dispersive surface energetics. This might be indicative that the groups at the surface are the same when new surfaces are exposed or that the surfaces have become aged due to surface restructuring (e.g. the surface is unstable and will adjust itself to achieve a minimum total surface free energy). It must be remembered that the IGC measurements were carried out quite some time after milling and therefore surface ageing is a probability.

The magnitude of the specific interactions, $-\Delta G_A^{SP}$ also show interesting trends for the electron donating probe, tetrahydrofuran (THF) and the electron accepting probe, dichloromethane as shown in Fig. 3. Both reflect an increase in the electron donation of the surface of milled dl-propranolol as the intensity of milling (reduction in particle size) proceeds. It is interesting to note that for the finest powder sample (6.6 μm) the material seems to have a slight reduction in electron donation properties of the surface as indicated by the dichloromethane probe, although for the THF probe there is a slight indication that for particle sizes smaller than the critical particle size there is a tendency for the surface to become slightly more electron accepting. This might mean that other groups of the molecule are being exposed at the surface. However, the major component of that surface are groups that are electron donating.

4.2. Computational results

The major habit faces of dl-propranolol hydrochloride were determined using MARVIN (Gay and Rohl, 1995), the habit for configuration A is shown in Fig. 4 (the habit was visualised

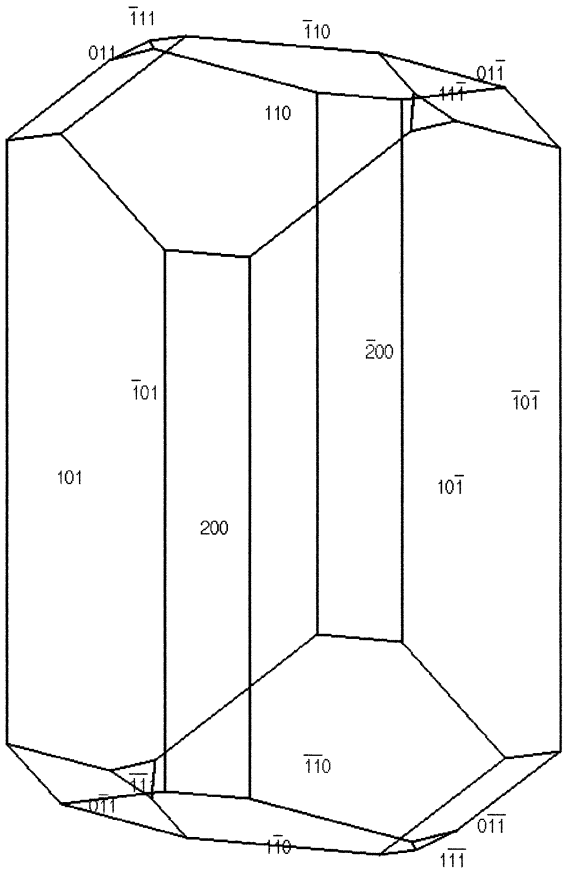

Fig. 4. Morphology of dl-propranolol hydrochloride for Configuration A, with attachment energies from MARVIN and Cerius^2 visualisation.

Table 2
Attachment (E_{att}) and slice energies (E_{sl}) calculated using MARVIN, where MARVIN (A) and MARVIN (B) are the values for dl-propranolol hydrochloride Configuration A and B, respectively

hkl	MARVIN (A)		MARVIN (B)	
	E_{att} (kJ/mol)	E_{sl} (kJ/mol)	E_{att} (kJ/mol)	E_{sl} (kJ/mol)
$10\bar{1}$	−65	−649	−65	−654
101	−85	−630	−92	−627
200	−91	−624	−84	−636
$30\bar{1}$	−118	−597	−111	−609
002	−131	−584	−139	−580
110	−143	−572	−128	−591
011	−163	−552	−149	−571

using Cerius[2] with the attachment energy data from MARVIN). The predicted habit for configuration B showed little difference to that in Fig. 4 with the exception of slightly more dominant (200) surface and this is reflected in the attachment energies in Table 2. This indicates that the disorder in the hydroxyl group does not grossly affect the energetics of the system. Lattice energies determined by using the MARVIN software (Gay and Rohl, 1995) for configurations A and B were −715 and −719 kJ/mol, respectively.

Comparison of the habit (Fig. 4) predicted by the MARVIN software (Gay and Rohl, 1995) to that from scanning electron micrographs (Fig. 5) on the unmilled sample (PA) shows some similarities in crystal shape and crystal surfaces, indicating the model used is reasonably accurate. The differences are probably due to the effects of solvent and this aspect has been recently examined for ε-caprolactam (Roberts et al., 1996) using HABIT95 (Clydesdale et al., 1996) which was unavailable at the time of this work.

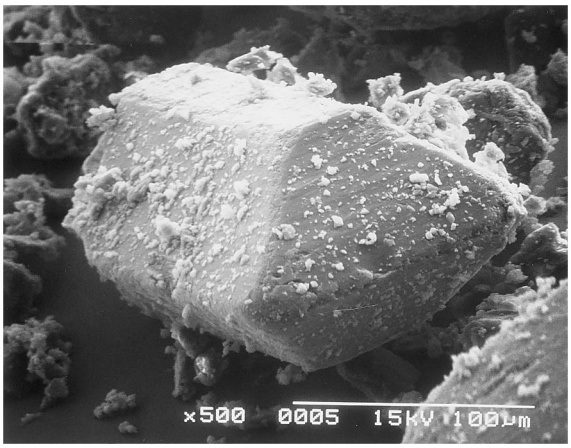

Fig. 5. Scanning electron micrograph of a crystal of dl-propranolol hydrochloride taken from the unmilled sample.

The most dominant face and the one with the lowest attachment energy (Table 2) is the $(10\bar{1})$ face, it is therefore predicted that this will be the major fracture plane of the crystal. Visualisation of this $(10\bar{1})$ face (Fig. 6) using Cerius[2] (Molecular Simulations, 1995) indicates that the naphthalene moiety of the dl-propranolol hydrochloride dominates this surface, indicating that this surface will be electron rich due to the π-electron cloud of the naphthalene ring. If this surface is increasingly exposed due to an increase intensity of milling then we might expect the surfaces produced to become more electron donating. This corresponds to the surface character measured by IGC measurements using the two solvents as surface probes. It should be noted that, as discussed above, attrition might become more dominant as milling intensity increases and therefore other surfaces might become available. The next two lowest energy faces based on attachment energies are the (200) and (101) faces (Table 2). Visualisation of these two faces indicates that hydroxyl group as well as the electron donating groups naphthalene and chloride ion are present, which might support this hypothesis.

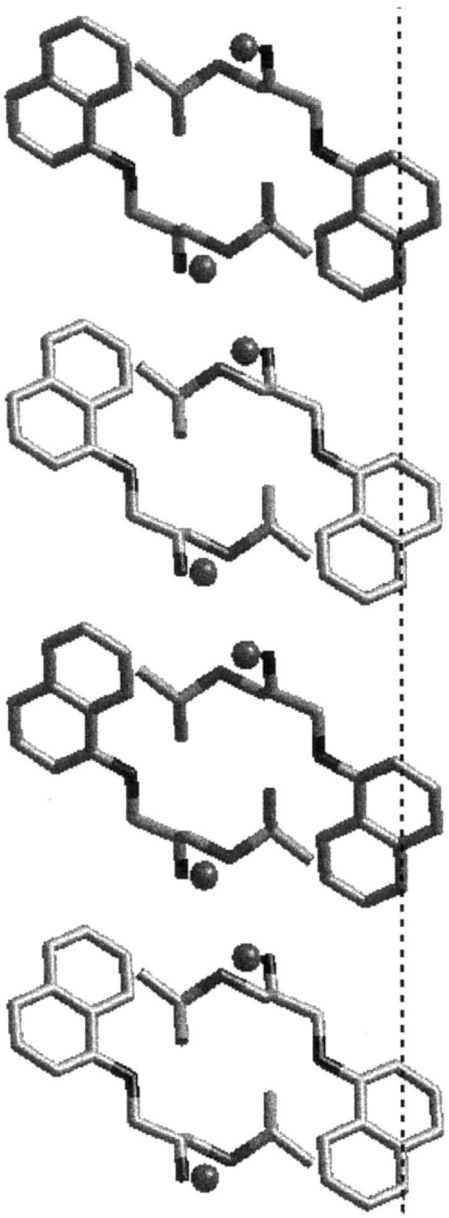

Fig. 6. The (10$\bar{1}$) surface of dl-propranolol hydrochloride showing two unit cells, with H atoms removed for clarity.

5. Conclusions

The concept of using molecular modelling to confirm the nature of the surfaces exposed during milling has been successfully applied to dl-propranolol hydrochloride and found to support the experimental data from IGC measurements.

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