ELSEVIER

International Journal of Pharmaceutics 145 (1996) 165–173

international journal of pharmaceutics

The mechanical properties of two forms of primidone predicted from their crystal structures

Robin S. Payne[a,*], Ronald J. Roberts[a], Raymond C. Rowe[a], Mary McPartlin[b], Allan Bashal[b]

[a]*Zeneca Pharmaceuticals, Hurdsfield Industrial Estate, Macclesfield, Cheshire SK10 2NA , UK*
[b]*School of Applied Chemistry, University of North London, 166–220 Holloway Road, London N7 8DB, UK*

Received 15 July 1996; revised 25 September 1996; accepted 27 September 1996

Abstract

Molecular modelling is used to predict the mechanical properties of aspirin and forms A and B of primidone. It is shown that the predictive method gives values which are in good agreement with the experimental ones. The method is therefore of great potential value to those interested in the compaction characteristics of pharmaceutically active compounds, as it obviates the need for measurements which can be difficult to make. Copyright © 1996 Elsevier Science B.V.

Keywords: Molecular modelling; Mechanical property prediction and measurement; Polymorphism

1. Introduction

In the pharmaceutical industry there is a need to understand the performance of powdered material during milling and compaction. This understanding can generally be acquired through a knowledge of the mechanical properties of the compound (Roberts et al., 1989a; Duncan-Hewitt and Weatherly, 1990a,b). Unfortunately, making precise measurements on the small particles present in powders is all but impossible, so the industry relies on mechanical measurements made on beams formed by compaction and on data from instrumented tablet presses. Any convenient theoretical route to mechanical property prediction would therefore be extremely valuable.

The concept of cohesive energy density provides a basis for a relationship between the crystal structure and the mechanical properties of a molecular solid (Roberts et al., 1991). This concept has been applied to pharmaceutical materials with some predictive success. A more fundamental approach is to consider the modelling of molecular mechanics. This provides a route to the

* Corresponding author.

PII S0378-5173(96)04760-6

second derivatives of the lattice energy, with respect to lattice parameters and atomic coordinates and hence to values of mechanical properties (Kitaigorodsky, 1973). Methods of extracting such information from molecular models have existed for some time, but the means to apply them have not been widely available until quite recently. The requirements are basically, ready obtainment of molecular and crystal structure data, access to molecular modelling packages and increased computing power on the desk-top. The primary requirement has largely been achieved, the rate at which crystal structures are solved has increased to such an extent that 80% of the 144 000 entries currently in the Cambridge Structural Database have been made since 1980 (Desiraju, 1989). In addition, methods for solving crystal structures from powder diffraction data are being developed (Cernik et al., 1991; Cheetham, 1993; Delaplane et al., 1993). Success in this field will significantly increase the number of important structures that can be solved and hence used for the derivation of further information. The second requirement has also been met, through advances in computational technology. The power of a 1980 mainframe computer is now available for desktop use, at a relatively small fraction of the original price.

The materials investigated in this study are typical of small to medium sized pharmaceutical molecules. They therefore provide good test cases for a predictive methodology. Aspirin is a sufficiently well studied molecule for the single experimentally known form to have a solved crystal structure and for there to be mechanical property measurements and predictions in the open literature (Florey, 1979; Wheatley, 1964; Kim et al., 1985). In addition, the hydrogen bonds in the crystal structure might be expected to lead to anisotropic mechanical characteristics. These features make it ideal as a means of validating theoretical procedures which we wish to apply to the main target molecule: primidone.

Primidone (Boon et al., 1951) is an anticonvulsant which occurs in two polymorphic forms, A and B (Daley, 1973; Summers and Enever, 1976). The crystal structure of form A has been known for many years and is entered in the Cambridge Structural Database as ref. code EPHPMO (Yeates and Palmer, 1975; Cambridge Crystallographic Data Centre, 1995). The structure of form B has been solved recently and is presented here for the first time. Unit cell details of these two structures are contained in Table 3. The atomic coordinates of the structure solutions are presented in Appendix A. Primidone has a strong propensity to hydrogen bonding and this is reflected in the packing motifs of the crystal structures (a topic which will be addressed again in Section 5 of this paper). The fact that the packing motifs are different in the two forms is apparent in their crystal habits; form A takes on a rhombic shape, whilst form B grows as plates with a very high ratio of plate breadth to thickness, perhaps approaching 1000:1. This source of potential anisotropy leads to difficulties in predicting the milling and compaction behaviour of each form from bulk property measurements.

2. Theory

In this paper, the mechanical properties of the three materials of interest were derived using the second derivative technique. In this methodology, the crystal structure is minimised using the atom–atom potential method (Pertsin and Kitaigorodsky, 1987), with atomic charges calculated ab initio. The quantum mechanics program Gaussian 92 was used for charge calculation (Frisch et al., 1993). The charges were generated from a fit to the electrostatic potential at points selected according to the Merz-Singh-Kollman scheme, using the restricted Hartree-Fock wavefunction formalism and the wavefunction basis set 6-31G** (summary descriptions of, and references to the methodologies and the basis set are given in the manual for Gaussian 92). Following minimisation, a single point energy calculation was performed on the crystal structure. The Drieding 2.21 force field, with Ewald summation was employed in this work (Mayo et al., 1990; Ewald, 1921). The second derivatives of the lattice energy were obtained with respect to the lattice parameters and the atomic coordinates, using the equation:

$$U = U_0 + \sum_i \frac{\delta U}{\partial \varepsilon_i} \varepsilon_i + \tfrac{1}{2} \sum_{ij} \frac{\partial^2 U}{\partial \varepsilon_i \partial \varepsilon_j} \varepsilon_i \varepsilon_j + \cdots \quad (1)$$

where U_0 is the equilibrium energy and ε's are components of strain. The second derivative terms are equal to the components, C_{ij}, of the stiffness matrix **C**.

$$C_{ij} = \frac{\delta^2 U}{\delta \varepsilon_i \delta \varepsilon_j} \quad (2)$$

The compliance matrix **S** is equal to the inverse of the stiffness matrix, i.e. $\mathbf{C}^{-1}$. For crystals of any symmetry, there are two methods of calculating the bulk modulus, B, from the components of the compliance matrix. These are termed the Reuss method:

$$B_r = [S_{11} + S_{22} + S_{33} + 2(S_{31} + S_{21} + S_{32})]^{-1} \quad (3a)$$

and the Voigt method:

$$B_v = \tfrac{1}{9}[C_{11} + C_{22} + C_{33} + 2(C_{31} + C_{21} + C_{32})] \quad (3b)$$

The three orthogonal components of the Young's modulus can be determined from the first three diagonal components of the compliance matrix, as follows:

$$E_x = \frac{1}{S_{11}} \qquad E_y = \frac{1}{S_{22}} \qquad E_z = \frac{1}{S_{33}}$$

3. Experimental

3.1. Materials

Primidone has the chemical name 5-ethyl-5-phenyl-hexahydro-pyrimidine-4,6,dione. The molecular structure of this compound is shown in Fig. 1(i). Primidone form A was obtained from Zeneca Pharmaceuticals. Form B was crystallised from a 0.024 mg/ml solution of primidone in 75% aqueous ethanol. Dissolution was achieved by heating to 65°C, whilst stirring. Stirring was discontinued and the temperature of the solution was reduced to 20°C at an approximate rate of 0.4°C/min. Crystals were isolated initially by filtration and then by vacuum drying at 30°C for 16 h.

Aspirin was obtained from Fluka AG. The molecular structure of aspirin is shown in Fig. 1(ii).

The identities of the three materials were confirmed by obtaining X-ray powder patterns and comparing the positions of the observed reflections with those presented by Florey (1979) and Wheatley (1964). In each case the agreement between the peak positions of the experimental and literature data was good. All three materials were micronised to minimise the effects of preferred orientation.

3.2. Experimental techniques

3.2.1. Single crystal X-ray diffraction

Data were collected from a primidone B crystal of dimensions $0.02 \times 0.38 \times 0.44$ mm, on a Siemens P4 four-circle diffractometer. Graphite

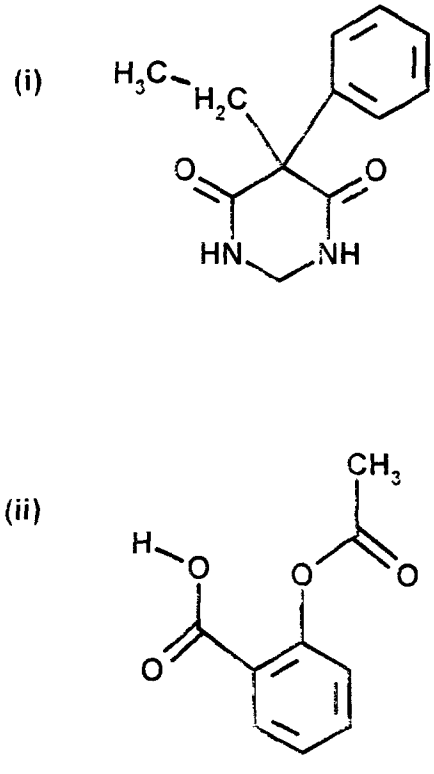

Fig. 1. The molecular structures of (i) primidone and (ii) aspirin.

monochromated Cu-Kα radiation was used (λ = 1.54178 Å) and a θ-2θ scan mode. A total of 2877 reflections were collected in the θ-range 3.21–56.72°. After equivalent reflections were merged 1452 unique ones were obtained. The data was corrected for Lorentz and polarisation effects and for an observed decay of ca. 4.8% as indicated by three reference reflections which were measured periodically during data collection. The structure was solved by direct methods followed by difference Fourier synthesis and refined by full-matrix least squares with the non-hydrogen atoms assigned anisotropic thermal parameters. The hydrogen atoms were located from a difference map. The refinement converged to a good fit factor of $R_1 = 0.0521$ (Siemens Analytical Instruments Inc., 1994).

Primidone B was found to exist in an orthorhombic structure, space group Pbca, with eight molecules in the unit cell. The unit cell parameters are presented in Table 3 of this paper. The atomic co-ordinates of the structure solution are contained in Appendix A.

3.2.2. Property prediction

The prediction of mechanical properties was performed using the molecular modelling suite, Cerius[2] (BIOSYM/Molecular Simulations Inc., 1995).

3.2.3. Mechanical testing

The Young's moduli of the materials were determined using a three point bend test as reported by Roberts et al. (1989b). Beams of length 20 mm and breadth 7 mm, were prepared by compaction, using a rectangular die. The die was lubricated with stearic acid prior to compaction. Compaction was performed uniaxially, using a 150 kN Specac hydraulic press. The final porosities of the beam were determined from the actual thicknesses of the beams.

Modulus measurements were made in a three point test rig, on a Mettler thermomechanical analyser (TMA40), by applying a static load of 0.3 N and a dynamic load of 0.25 N at a frequency of 0.17 Hz. Twenty measurements of specimen displacement were obtained for each sample, to an accuracy of ± 0.005 μm and a mean determined. Any effects of mechanical distortion in the beams were taken into account using a calibration run. Moduli were calculated using the equation:

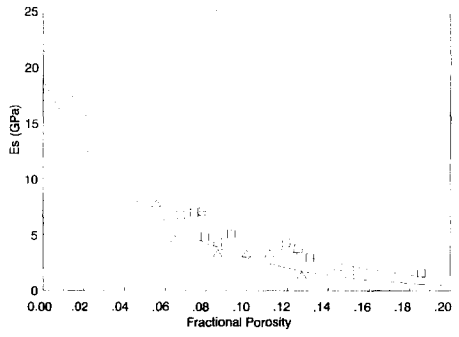

Fig. 2. Experimental Young's moduli (E_s) of the two forms of primidone, plotted against sample porosity (□: primidone B, △: primidone A). The solid and dashed lines represent the exponential fits to the data of form A and B, respectively.

$$E_s = \frac{Fl^3}{4(s-d)t^3w} \tag{4}$$

where F is the dynamic load, l is the distance between beam supports (17 mm), t is the thickness of the beam, w is the width of the beam, s is the flexure at the midpoint and d is the distortion.

The Young's modulus at zero porosity, E_0, was determined by curve fitting to the experimental data, using the exponential relationship proposed by Spriggs (Spriggs, 1961):

$$E_s = E_0 \exp(-bP) \tag{5}$$

where P is the fractional porosity and b is a constant.

4. Results

The experimental data on aspirin presented in this paper were previously reported by Roberts et al. (1991). Fig. 2 contains the previously unreported experimental data for beams of primidone A and B. The details of the exponential fits for all three materials are summarised in Table 1.

The important predicted components of the compliance matrices for aspirin, primidone A and primidone B are contained in Table 2. The corresponding values of the Reuss and Voigt bulk

Table 1
Exponential fits to the mechanical testing data, derived using Eq. (5)

Parameter	Aspirin[a]	Primidone A	Primidone B
E_0 (GPa)	7.45	18.75	21.54
b	−6.84	−18.55	−15.07
Standard error	0.95	0.95	0.93
Correlation coefficient	0.73	0.91	0.93

[a] Data taken from Roberts et al. (1991).

moduli, and the three components of the Young's moduli are displayed in Table 3. This table also contains an experimentally determined value of the bulk modulus of aspirin and the Young's moduli of each of the three materials. The average of the predicted x, y and z components of the Young's moduli are very much comparable with the experimentally determined values.

The errors on the experimental data were estimated from the standard error associated with exponential fits to plots of Young's modulus versus porosity. The values for primidone A and B are quite close to each other, and can only be differentiated at a low confidence limit (approximately 65%). This is despite correlation coefficients for the fitting of Eq. (5) of 0.91 and 0.93, respectively.

Table 2
Important predicted components of the compliance matrices

Compliance component	Aspirin	Primidone A	Primidone B
S_{11}	0.2064	0.0450	0.0437
S_{22}	0.1632	0.0447	0.0429
S_{33}	0.0902	0.1302	0.1000
S_{44}	0.1473	0.0938	0.1032
S_{55}	0.2053	0.3445	0.3135
S_{66}	0.0909	0.0783	0.0753
S_{12}	−0.1314	−0.0122	−0.0133
S_{23}	−0.0313	−0.0291	−0.0233
S_{13}	−0.0309	−0.0074	−0.0073

All values are quoted in GPa^{-1}.

Table 3
Predicted values of mechanical properties

Modulus	Aspirin	Primidone A	Primidone B
B_r	13.80	8.15	10.15
E_r	10.45	13.90	15.56
B_v	14.47	12.28	13.44
E_v	16.11	20.54	20.99
E_x	4.84	22.19	22.88
E_y	6.13	22.37	23.28
E_z	11.08	7.68	10.00
E_{mean}	7.35	17.41	18.72
E_{exp}	7.4 ± 0.3[a]	18.7 ± 0.5	21.5 ± 0.8

All values are quoted in GPa. An average was taken over the predicted E_x, E_y and E_z components of the Young's moduli, to give E_{mean} for comparison with the experimental modulus (E_{exp}).
[a] Data taken from Roberts et al. (1991).

5. Discussion

The correspondence between the predicted and measured values of mean Young's modulus is very good. The predictions for primidone A and B indicate that it would be difficult to differentiate between these materials experimentally and this is indeed the case. However, the two forms of primidone are predicted to be much stiffer than aspirin and again, this is supported by the experimental data. These differences in mechanical properties result from the hydrogen bond motifs associated with each structure. Aspirin molecules exist as dimers in the solid state, having a carboxylic acid group and hence one hydrogen bond acceptor and one nearby hydrogen bond donor (see Fig. 1(i)). These dimers are arranged in pairs of sheets, each pair at an angle of ca. 58° to each other. However, being based on dimers, the hydrogen bond motif does not confer extended strength to the crystal lattice much beyond that expected from general non-bonded interactions. The energy associated with hydrogen bonds is 3.7 kJ/mol.

Primidone has two acceptors and two donor groups per molecule and these are arranged so that one donor and one acceptor appear on each side of the molecules approximate line of mirror symmetry (see Fig. 1(i)). In primidone A each molecule is attached to two others by two hydro-

gen bonds. The hydrogen bonding motif takes the form of parallel ribbons of double hydrogen bonds which run through the structure, approximately in the $x-y$ plane. The energy associated with this arrangement of bonds is 6.2 kJ/mol. In primidone B each molecule is attached to four others by single hydrogen bonds. This means that the hydrogen bonds describe rippled planes which lie in parallel, approximately coinciding with the $x-y$ plane. The hydrogen bond energy is 4.4 kJ/mol. Each form of primidone therefore contains extended hydrogen bonding patterns which confer considerable resistance to forces applied in the planes of the extended motifs.

In the case of primidone B, the experimentally measured value is significantly higher than the value predicted by the mean of the x, y and z predicted components of the Young's modulus. Despite the fact that the materials were micronised, the most likely explanation for this result is a tendency for plate-like crystals to preferentially orient their major axes into the plane of a beam during compression. The longest axes associated with the crystal habit coincide with the fastest growth directions during crystallisation and so are likely to be associated with the addition of molecules to the surfaces at which hydrogen bond acceptors and donors are exposed. As a consequence, three-point bending, which is known to apply tension to a beam at the surface opposite the central point, preferentially works in the $x-y$ plane of primidone B. The moduli in this plane are greater than the average of the three components, so the experimental value is found to be higher than that obtained by prediction (E_{mean}). Preferred orientation is less likely to play a role in the experimental measurements for aspirin and primidone A, since they exist as more equiaxed crystals.

Despite the apparent success of the predictions presented in this paper, it is worth mentioning some sources of error in the method used. In the predictive process, the crystal structures were minimised before the mechanical property prediction was performed by lattice dynamics. Minimisation is said to be necessary for a number of reasons.

(1) The crystal structures suffer from experimental errors in their interatomic distances and angles. These would be removed if the force-field represents the true values with more precision than can be achieved experimentally.
(2) Crystal structures are usually, as in this case, obtained at room temperature and the basic atom–atom potential method applies to 0 K. The method only provides a calculation of the enthalpy of a system, and not its entropy. As a consequence, it cannot provide information about the effects of temperature on free energy.
(3) It ensures that all forces and torques on the molecules are in equilibrium according to the force-field, before the dynamics of the crystal lattice are investigated (Williams, 1982).

Whilst the crystal structure solution is subject to experimental error, molecular geometries generated by a force-field associated with the atom–atom potential method will also be in error. This results from the fact that it was impractical to incorporate more parameters in the equations and that a limited number of molecules could be used for parameterisation. To paraphrase the authors of the Dreiding force-field, a lack of accuracy for a particular subset of molecules is compensated for by the speed with which reasonable results can be obtained for a large number of molecules (Mayo et al., 1990). The force-field was tested against 76 crystal structures, yielding root mean square errors of 0.035 Å in bond lengths, 3.2° in angles and 8.9° in torsions. A combination of experimental and force-field inaccuracy will lead to errors in mechanical property prediction. In some cases a crystal structure may contain a degree of disorder. The structure determined by X-ray diffraction then represents a mean of the structures present. In these cases the minimised structure may best represent one of the structures present and so the mechanical property prediction may differ from the experimentally determined value.

It is clearly true that the atom–atom approach does not consider the effect of temperature on the crystal structure, but the results will be most applicable to the temperature at which the structures used for force-field parameterisation were determined. In the case of the Dreiding force-field, room temperature crystal structures were part of the parameterisation process and so it should operate well for many such structures.

The stresses mentioned by Williams (1982) arise from a difference between the experimental geometry of the molecules and the geometry preferred by the force-field. Clearly, these discrepancies should be removed before the effects of distorting the lattice on the energy of the system are calculated. However, this does not mean that the minimised structure is closer to the true crystal structure than that determined by experiment. As previously stated, the force-field will be in error for specific molecules.

The coulombic interaction is a major component of the energy of a crystal, sometimes approaching 60% of the total. This interaction has been dealt with by assigning atomic point charges to the atom–atom model. Unfortunately, such charges are very sensitive to the conformation of the molecule upon which they are calculated. Thus charges calculated for the crystal structure are not those that would be derived for the minimised structure. Clearly, an iterative process of charge derivation and minimisation would be required to obtain the best charges for the structure upon which mechanical property prediction was attempted. This would be time-consuming and it is doubtful whether there would be a noticeable improvement in the final result when compared with experiment.

Dreiding 2.21 was chosen for this study on the basis that it contains explicit hydrogen bonding terms and that these were expected to be particularly important for aspirin and primidone. The question of whether a particular force-field is appropriate for a molecular system is best checked by comparing the packing energy of minimised structures with their measured heats of sublimation (Gavezzotti and Filippini, 1994). Appropriateness can also be checked by comparing the lattice parameters of the minimised structure with the experimental values. Ideally, the minimised values should be within $\approx 5\%$ of the experimental ones. Since enthalpies of sublimation are not available to us for the materials studied here, we can only use the lattice parameter comparison to assess the appropriateness of the force-field. The data is presented in Table 4. It can be seen that the differences between the parameters for the experimental and minimised structures are of the order of 5%. Hence we can assume that the force-field provides a reasonable description of these molecular systems.

Table 4
The lattice parameters of the experimental and minimised experimental structures of aspirin, primidone A and primidone B

Compound	a	b	c	β	ρ
Aspirin[a]	11.43	6.59	11.40	95.68	1.401
Aspirin[b]	11.42	6.69	11.22	95.04	1.402
Primidone A[c]	12.25	7.09	14.80	117.82	1.276
Primidone A[b]	11.62	7.43	14.27	112.53	1.274
Primidone B	10.27	7.92	27.54	—	1.296
Primidone B[b]	10.38	7.69	28.33	—	1.282

The unit cell dimensions are given in Angstroms, β in degrees and the density ρ, in g/cm^3. Aspirin and primidone A have monoclinic structures (space group $P2_1/c$), whilst primidone B is orthorhombic (space group Pbca). Only cell angles which differ from 90° are explicitly noted.

[a] Unit cell data taken from Kim et al. (1985). Atomic positions obtained from the Cambridge Structural Database, using the program QUEST3D (Cambridge Crystallographic Data Centre, 1995).

[b] Denotes values which correspond to the minimised crystal structure.

[c] Unit cell data taken from Yeates and Palmer (1975). Atomic positions obtained from the Cambridge Structural Database, using the program QUEST3D (Cambridge Crystallographic Data Centre, 1995).

The final likely source of error in the predictive methodology arises from the truncated expansion of Eq. (1). Unfortunately, it is difficult to estimate the relative importance of the sources of error described above. However, it is possible to state that the errors involved in the cases of aspirin and primidone appear to be small and that the results reported in this paper offer encouragement for the wider application of this predictive methodology.

6. Conclusions

The method of predicting the mechanical properties of organic compounds described in this paper has proven successful for aspirin, primidone A and primidone B. This methodology is clearly of value to the pharmaceutical industry, where the use of materials as fine powders makes it difficult to perform mechanical property measurements.

Acknowledgements

The technical assistance of J.G. Barker is gratefully acknowledged. The Authors are also grateful to Dr R. Docherty of Zeneca Specialties, and Dr S. Maginn of BIOSYM/Molecular Simulations for their constructive comments.

Appendix A. The crystal structure solution of primidone B

Wavelength of radiation: 1.54178 ÅR_1 = 0.0521Space group: PbcaUnit cell dimensions in Angstrom units: a, 10.2660; b, 7.9150; and c, 27.5357.

Atomic positions within the unit cell:

Atom number	Atom type	x	y	z
1	C	−0.05651	0.25332	0.15833
2	C	−0.17049	0.20203	0.18086
3	C	−0.20955	0.27068	0.22461
4	C	−0.13444	0.39082	0.24727
5	C	−0.02039	0.44256	0.22565
6	C	0.01839	0.37556	0.18175
7	C	−0.02000	−0.18282	0.11793
8	C	0.02370	0.32263	0.07344
9	C	0.06728	0.26013	0.02414
10	C	−0.12172	0.07536	0.08750
11	C	−0.01807	0.18082	0.10947
12	C	0.11241	0.07463	0.11889
13	O	−0.21368	0.14607	0.06704
14	O	0.21858	0.14388	0.12563
15	N	0.10152	−0.09162	0.11949
16	N	−0.11736	−0.09096	0.09154
17	H	0.17740	−0.15450	0.12370
18	H	−0.18900	−0.15510	0.07750
19	H	−0.22178	0.11966	0.16622
20	H	−0.28711	0.23540	0.23882
21	H	−0.16037	0.43657	0.27684
22	H	0.03109	0.52359	0.24081
23	H	0.09555	0.41241	0.16758
24	H	−0.00622	−0.29167	0.10258
25	H	−0.05034	−0.20275	0.15079
26	H	−0.05193	0.39461	0.06921
27	H	0.09262	0.39111	0.08734
28	H	0.10253	0.35267	0.00583
29	H	−0.00587	0.21323	0.00711
30	H	0.13286	0.17482	0.02819

References

BIOSYM/Molecular Simulations, *Cerius*^{2}, Release 2.0, 16 New England Executive Park, Burlington, USA, MA 01803, 1995.

Boon, W.R., Carrington, H.C. and Vasey, C.H. (Imperial Chemical Industries Ltd., England) *US Patent No. 2 578 847*, 18 Dec. 1951.

Cambridge Crystallographic Data Centre, *QUEST3D*, Union Road, Cambridge, England, CB2 1EZ, 1995.

Cernik, R.J., Cheetham, A.K., Prout, C.K., Watkin, D.J., Wilkinson, A.P. and Willis, B.T.M., The structure of cimetidine ($C_{10}H_{16}N_6S$) solved from synchrotron-radiation x-ray powder diffraction data. *J. Appl. Cryst.*, 24 (1991) 222–226.

Cheetham, A.K., Ab initio structure solution with powder diffraction data. In Young, R.A. (Ed.), *The Rietveld Method*, Oxford University Press, Oxford, 1993, pp. 276–292.

Daley, R.D., Primidone. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances*, Vol. 2, Academic Press, New York, 1973, pp. 409–437.

Delaplane, R.G., David, W.I.F., Ibberson, R.M. and Wilson, C.C., The ab initio crystal structure determination of α-malonic acid from neutron powder diffraction data. *Chem. Phys. Letts.*, 201 (1993) 75–78.

Desiraju, G.R., *Crystal Engineering: The Design of Organic Solids*, Elsevier, Oxford, 1989, pp. 68–69.

Duncan-Hewitt, W.C. and Weatherly, G.C., Modeling the uniaxial compaction of pharmaceutical powders using the mechanical properties of single crystals I: ductile materials. *J. Pharm. Sci.*, 79 (1990a) 147–152.

Duncan-Hewitt, W.C. and Weatherly, G.C., Modeling the uniaxial compaction of pharmaceutical powders using the mechanical properties of single crystals II: brittle materials. *J. Pharm. Sci.*, 79 (1990b) 273–278.

Ewald, P.P., Die berechnung optischerund elektrostatischer gitterpotentiale. *Annalender Physik*, 64 (1921) 253-287.

Florey, K., Aspirin. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances*, Vol. 8, Academic Press, New York, 1979, pp. 1–40.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Gill, P.M.W., Johnson, B.G., Wong, M.W., Foresman, J.B., Robb, M.A., Head-Gordan, M., Replogle, E.S., Gomperts, R., Andres, J.L., Raghavachari, K., Binkley, J.S., Gonzalez, C., Martin, R.L., Fox, D.J., Defrees, D.J., Baker, J., Stewart, J.J.P., Pople, J.A., *Gaussian 92/DFT, Revision G.1*, Gaussian Inc., Pittsburgh PA, 1993.

Gavezzotti, A. and Filippini, G. J., Geometry of the intermolecular X–H....Y (X,Y = N,O) hydrogen bond and the calibration of the empirical hydrogen bond potentials. *Phys. Chem.*, 98 (1994) 4831–4837.

Kim, Y., Machida, K., Taga, T. and Osaki, K., Structure redetermination and packing analysis of aspirin crystal. *Chem. Pharm. Bull.*, 33 (1985) 2641–2647.

Kitaigorodsky, A.I., *Molecular Crystals and Molecules*, Academic Press, London, 1973, pp. 325–328.

Mayo, S.L., Olafson, B.D. and Goddard, W.A., DREIDING: a generic force field for molecular simulations. *J. Phys. Chem.*, 94 (1990) 8897–8909.

Pertsin, A.J. and Kitaigorodsky, A.I., The lattice at equilibrium. In Pertsin, A.J. and Kitaigorodsky, A.I., *The Atom–Atom Potential Method*, Springer, Berlin, 1987, pp. 149–157.

Roberts, R.J., Rowe, R.C. and Kendall, K., Brittle-ductile transitions in die compaction of sodium chloride. *Chem. Eng. Sci.*, 44 (1989a) 1647–1651.

Roberts, R.J., Rowe, R.C. and P. York., A dynamic mechanical method for the determination of the Young's modulus of powdered drugs and excipients. *J. Pharm. Pharmacol.*, 41 (1989b) Suppl. 30P.

Roberts, R.J., Rowe, R.C. and York, P., The relationship between Young's modulus of elasticity of organic solids and their molecular structure. *Powder Technology*, 65 (1991) 139–146.

Siemens Analytical Instruments Inc., *SHELXTL-PC, Version 5.0*, Madison, WI, 1994.

Spriggs, R.M., Expression for effect of porosity on elastic modulus of polycrystalline refractory materials, particularly aluminium oxide. *J. Am. Ceram. Soc.*, 44 (1961) 628–629.

Summers, M.P. and Enever, R.P., Prepartion and properties of solid dispersion system containing citric acid and primidone. *J. Pharm. Sci.*, 65 (1976) 1613–1617.

Wheatley, P.J.,The crystal and molecular structure of aspirin. *J. Chem. Soc.*, Part 4, (1964), 6036–6048.

Williams, D.E., Conformational analysis. In Metzger, R.M. (Ed.) *Crystal Cohesion and Conformational Energies*, Springer, Berlin, 1982, p. 41–63.

Yeates, D.G.R. and Palmer, R.A., The crystal structure of primidone. *Acta Cryst. B*, 31 (1975) 1077–1082.