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The effects of disordered structure on the solubility and dissolution rates of some hydrophilic, sparingly soluble drugs

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Abstract

The effects of experimental design on the apparent solubility of two sparingly soluble hydrophilic compounds (barium sulphate and calcium carbonate) were studied in this paper. The apparent solubility appeared to be primarily dependent on the amount of solute added to the solvent in each experiment, increasing with increased amounts. This effect seems to be due to the existence of a peripheral disordered layer. However physico-chemical methods used in the present study were not able to unambiguously verify the existence of any disorder in the solid state structure of the drugs. At higher proportions of solute to solvent, the solubility reached a plateau corresponding to the solubility of the disordered or amorphous molecular form of the material. Milling the powders caused the plateau to be reached at lower proportions of solute to solvent, since this further disordered the surface of the drug particles. It was also found that the apparent solubility of the drugs tested decreased after storage at high relative humidities. A model for describing the effects of a disordered surface layer of varying thickness and continuity on the solubility of a substance is presented. This model may be used as a method for detection of minute amount of disorder, where no other technique is capable of detecting the disordered structure. It is suggested that recrystallisation of the material occurs via slow solid-state transition at the surface of the drug particle; this would slowly reduce the apparent solubility of the substance at the plateau level to the thermodynamically stable value. A biphasic dissolution rate profile was obtained. The solubility of the disordered surface of the particles appeared to be the rate-determining factor during the initial dissolution phase, while the solubility of the crystalline core was the rate-determining factor during the final slower phase. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

1.1. Solubility and apparent solubility

Comparison of preformulation studies in the literature is often confusing because of contradictory solubility data reported for some sparingly soluble drugs. From a thermodynamic or chemical point of view, each substance has only one solubility value at a specific temperature, pressure and volume. This value is defined as the saturated concentration of the substance in solution when it is in equilibrium with its most stable solid state structure.

In the literature, the term ‘solubility’ is often used loosely to mean the metastable or dynamic solubility, rather than the solubility at this thermodynamically stable state. The term ‘apparent solubility’ is used throughout this paper for the metastable or dynamic solubility of the materials (i.e. supersaturated states with different degree of supersaturation). The apparent or metastable solubility, i.e. the concentration of the material in solution at apparent equilibrium (supersaturation), decreases to the level of the true or thermodynamically stable solubility, after an infinite equilibrium time. This paper endeavours to evaluate some of the possible reasons behind such a variety of solubility values for a given substance in the literature.

It should be noted that the term ‘apparent solubility’ has also been used in the literature to discuss a change in solubility due to ionic interaction. The result of such interionic interactions may be that the actual or effective number of ions is no longer the same as that calculated based on the concentration of the solution. This is the reason why sometimes it is necessary to replace concentration with activity, which is the effective concentration. However in the present study the experimental design (the choice of buffer and salts) was such that the ion effect was negligible. Thus the term apparent solubility used here refers to a deviation from the thermodynamic stability which is caused due to the existence of disordered structure.

On the other hand the solubility of sparingly soluble salts is often expressed or discussed in

terms of the solubility product, which is an equilibrium constant describing the equilibrium between a sparingly soluble compound and a saturated solution of its ions. The numerical value of the solubility product of a salt can thus be regarded as a quantitative statement of the limit of solubility of the salt.

1.2. The concept of mechanical activation and deactivation

Disruption of the physical order of the molecules of a material which is initially well ordered structurally (i.e. purely crystalline) as a result of mechanical or chemical activation has been reported frequently in the literature (Haleblian et al., 1971; Hersey and Krycer, 1980). Technological and processing operations can also cause mechanical activation of some materials (Hüttenrauch, 1988). These changes will affect the chemical or physical reactivity and thus the dissolution characteristics (Chiou and Kyle, 1979; Gubskaya et al., 1995) of the material.

It is therefore important to study the mechanisms involved in the physico-chemical activation, and consequent alteration in the dissolution behaviour, of sparingly soluble solid structures. As the majority of the studies in this field have been conducted using hydrophobic drugs, it is also of interest to study the behaviour of more hydrophilic compounds.

Materials rendered to amorphous state (disordered) are often metastable. At favourable condition (evaluated temperature and/or humidity) they might convert to ordered form (crystalline state), i.e. a process of deactivation. Absorbed moisture can act as a plastisizer to cause increased molecular mobility. The subsequent result could be recrystallisation or deactivation (Ahlneck and Zeografi, 1990).

1.3. The dissolution process

The dissolution process of solids in liquids has been described by Hildebrand and Scott (1950) and Scatchard (1931) as involving three steps: (1) the removal of a molecule from the solute; (2) creation of a hole in the solvent; and (3) insertion

of the solute molecule into the solvent (i.e. solute–solvent interaction). This interaction between the solute and the solvent is obviously dependent on the physical and chemical nature of the two participating molecules.

The processes involved in the dissolution of hydrophobic materials, which have low aqueous solubility, will differ from those affecting the dissolution of hydrophilic substances. The amount of energy required to remove a molecule of a sparingly soluble drug from the solute particle is lower for a hydrophobic drug than for a hydrophilic drug (such as those composed of inorganic salts). The intermolecular bonds in inorganic salts are so strong that a large amount of energy is required to disassociate the discrete molecules. However, when the individual solute molecules are liberated, a hydrophilic salt molecule (or ion) is more likely to interact with water than a hydrophobic drug molecule. Thus, the main factor affecting the solubility and dissolution of a hydrophobic drug is the limited energy released when a drug molecule is bonded to the solvent (Florence and Attwood, 1981). Conversely, the main barrier to dissolution of a sparingly soluble hydrophilic substance appears to be disruption of the strong intermolecular forces.

1.4. The concept of an external disordered surface layer

It has been suggested that the surface of the particles becomes energised or destabilised during milling (Hüttenrauch, 1983), creating an external disordered (amorphous) layer around a crystalline core (Elamin et al., 1994). The presence of this layer is thought to increase the apparent equilibrium solubility of the material. Thus, the equilibrium solubility of materials with a layer of amorphous material on the surface of the particles will be a function of the amount of material added to the solvent until a plateau is reached; this plateau will correspond to the apparent solubility of the amorphous form of the material. Elamin et al. (1994) confirmed this hypothesis for a hydrophobic drug, griseofulvin, where 15 min of milling the drug in a mortar resulted in an increase in apparent solubility of approximately 30%.

A schematic representation of the influence of the amount of solute added to the solvent on the apparent solubility of materials containing an external disordered layer is shown in Fig. 1.

If only a small amount of material is added to the solvent, a substantial proportion of the disor-

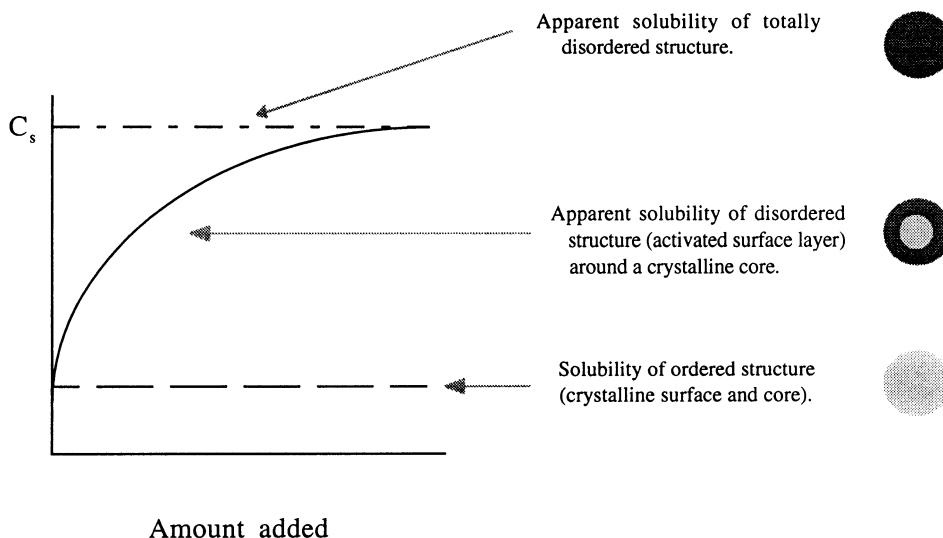


Fig. 1. Solubility (C_s) of a material with totally crystalline, totally disordered and disordered surface structure, respectively, as a function of the amount of material added in the solubility test.

dered external layer of the sample will be dissolved, exposing a new solid/liquid interface consisting mainly of crystalline solid structure. The solubility of the material will thus then be determined mainly by this crystalline surface. Conversely, as larger amounts of material are added to the solvent, the solubility of the drug will increase progressively since more amorphous material will be available, until the solution becomes saturated.

It is, however, important to realise that this increase in solubility is an increase in the metastable or apparent solubility. The apparent solubility will then gradually decrease to the solubility of the crystalline or most thermodynamically stable phase. The kinetics of this recrystallization process are thought to involve either a slow solid-state transition on the surface of the particle (Rodriguez-Hornedo et al., 1992; Elamin et al., 1994) or diffusion of drug molecules from the metastable solution back to the surface of the particles to form a crystalline structure. The importance of nucleation and crystal growth has also been discussed in the literature in this context (Beckmann and Otto, 1996).

Higuchi et al. (1979) claimed that heterogeneity in the energy of the surface molecules may also affect the solubility of a compound. Cracks or other defects on the surface of crystals would thus affect solubility. Higuchi et al. presented a similar hypothesis to that described by Elamin et al. (1994). They suggested that, when a large excess of solid material is added to the solvent, the observed solubility will be related to the thermodynamic activity of the most highly energised component; the solution may therefore be considered supersaturated with respect to the most stable crystal form. They also suggested that the recrystallization rate, i.e. the rate at which the supersaturated solution returns to normal, would be extremely slow because of the very low concentrations of solute in solution.

It should be mentioned that such relationship between the apparent solubility of a material and the amount of material added to the solvent may also exist if the material contains a relatively high proportion of impurities. For example it was reported (Higuchi et al., 1979; Grant and Higuchi,

1990) that the solubility of a crystalline solid containing 10% soluble impurity, was increased linearly as a function of amount added.

1.5. The salting-in and salting-out effects

The solubility of electrolytes may also be influenced by the presence of other ions. The effect of ionic strength and common ions have been discussed briefly in the literature. One of the most emphasised phenomena are the salting-in and salting-out effects which are described by the Debye–Hückel limiting law:

$$-\log \gamma_{\pm} = z_+ z_- A I^{1/2} \quad (1)$$

where γ_{\pm} is the mean ionic activity coefficient; z_+ and z_- are the valences of each ion; A is a constant whose value is determined by the dielectric constant and the temperature ($A = 0.509$ in water at 297 K); and I is the total ionic strength defined by:

$$I = 1/2 \sum (m z^2) \quad (2)$$

where m and z are the molality and the charge of the ion in the medium (Florence and Attwood, 1981). The following equation has been described in the literature (Chang, 1981) to relate the solubility of a salt to the ionic strength of the solution in water:

$$\log S/S^0 = 0.509 |z_+ z_-| I^{1/2} \quad (3)$$

where S and S^0 are the apparent and thermodynamic solubilities in mol l^{-1} .

1.6. The small-particle phenomenon

It has also been postulated that the surface curvature of the dissolving particles will influence solubility. The basic theory derives from the classical Gibbs–Kelvin equation which, when adapted to the solubility of solids, is known as the Ostwald–Freundlich equation:

$$-\Delta(\Delta G) = RT \ln(S/S_0) = (2\gamma V)/r \quad (4)$$

where $\Delta(\Delta G)$ is the difference in the free energy of a solution of small and large particles; S and S^0 are the solubility of a spherical particle of radius

r and the solubility of a noncurved solute surface ($r \rightarrow \infty$), respectively; V is the molar volume of the solute; γ is the solid–liquid interfacial tension; R is the universal gas constant; T is the absolute temperature; and r is the particle radius.

Eq. (4) is valid for particles that have a very large surface to volume ratio and is of practical importance only for particles smaller than $0.1 \mu\text{m}$ in diameter (Florence and Attwood, 1981).

It has also been claimed (Mukerjee, 1972) that the surface of finely divided solids may be less regularly crystalline and more amorphous than that of well-grown crystals.

There are thus different reasons behind deviations from the thermodynamically stable solubility. Factors such as impurities, ion effect, particle size and crystal structure are some of the factors which may lead to such deviations.

The objective of this paper was to examine how changes in the amount of material added to a solvent can cause an apparent change in the solubility of some poorly soluble inorganic hydrophilic drugs and to discuss the role of disordered external particle structure in this context. The effect of disordered structure was also investigated on dissolution rate. Additionally, the effects of both relative humidity (as an environmental factor) and milling (as an example of a widely used method of pharmaceutical preparation) on the equilibrium solubility were studied.

2. Materials

2.1. Test materials

Barium sulphate extra pure (Barium sulfate puriss, batch no. 1.1433-250, Merck, Germany, distributed in Sweden by Kebo, Sweden) and calcium carbonate precipitated (batch no. 414A86 5266, Art. 2066, Merck, Germany, distributed in Sweden by Kebo) were used in the experiments. These samples are referred to as untreated or original materials when used as supplied. They were both of analytical grade and the purity was stated to be at least 99%. In the case of CaCO_3 , according to the suppliers guaranty certificate, the maximum content of impurities was as follows:

(Cl) 0.001%, (SO_4) 0.01%, (N) 0.001%, (Pb) 0.0005% (Cu) 0.0005%, (Fe) 0.001%, (Mg) 0.05%, (Sr) 0.1%, (Ba) 0.005%, (Na) 0.2% and (K) 0.01%. The maximum content of impurities for BaSO_4 was as follows: $\text{PO}_4 < 0.005\%$, heavy metals (as Pb) $< 0.001\%$ and arsenic (As) $< 0.00008\%$.

The degree of order of these test materials could not be directly analysed and was therefore deduced. It was assumed that the materials were not totally crystalline and had an activated or disordered surface, as discussed in more detail below.

2.2. Dissolution medium (blank)

The dissolution medium was prepared using PBS-Buffer tablets (EC Diagnostics AB, Sweden). One tablet was dissolved in 1 l ultra pure deionized water (milli. Q UF Plus, Millipore, France) and resulted in a buffer solution, (pH 7.4) containing 0.01 M phosphate buffer (NaH_2PO_4), 0.14 M NaCl, 0.003 M KCl. The dissolution medium also contained 0.01% w/w Tween 80. The ionic strength of the medium was 0.153 and there were no Ba^{2+} or Ca^{2+} ions detectable in this solution.

3. Methods

3.1. Storage of test materials at different relative humidities

In order to study the effect of relative humidity on crystal structure and solubility, a thin layer of each substance was placed in petri dishes in a desiccator with a saturated solution of P_2O_5 (0% relative humidity (RH)) at approximately 23°C . The samples were then removed to another desiccator containing saturated K_2SO_4 or NaCl solution (corresponding to 97 and 75% RH, respectively). The samples were stored at 97% RH for up to 9 months and at 75% RH for up to 12 months before further analysis. Samples stored at 97% RH were used for all experiments except differential scanning calorimetry (DSC) measurements. The weight of salt and volume of solution used in the experiments were based on the guidelines reported by Nyquist (1983).

3.2. Mechanical activation of test materials

In order to study the effect of mechanical activation of the material on its apparent solubility, the samples of BaSO₄ and CaCO₃ were milled in a Mortar grinder (Mortar grinder, type KMI, Germany) for up to 7 and 13 min, respectively.

3.3. Primary characterisation of the test materials

3.3.1. Particle size analysis

Analysis of the size of the particles was carried out using a Coulter Multisizer II. The material was dispersed to the dissolution medium. This medium (1 l in each case) was saturated over a period of 24 h with the respective material and then filtered through a 0.22 μm polycarbonate membrane filter (using a vacuum pump) before particle size measurement in order to obtain a particle free saturated medium.

Stock suspensions of each material were then prepared (using these saturated particle free mediums as dispersing mediums) and ultra-sonicated. An amount of stock suspension was added to 200 ml particle free saturated medium so that the final amount did not cause a coincident error greater than 5%. The number of particles was determined in 256 channels using capillary tubes of specific diameters. The choice of capillary tube was dependent on the size distribution of each material (see Table 1). The tubes were calibrated using Dynospheres (Dyno particles AS, Norway) of specific sizes. The size distribution of the particles and the mean volume diameter by weight of test materials were then calculated. The results presented are the means of three measurements.

3.3.2. Apparent particle density

The apparent particle density (British Standard, 1958) of the samples was determined by gas pycnometry (AccuPyc 1330), using helium gas. The samples were washed with helium gas 30 times before starting the experiment. Each value is the mean of at least ten measurements.

3.3.3. External powder surface area

The external particle surface area for each of the samples was determined by permeametry. A

Blaine apparatus (Blaine, 1943) was used. Because of the fine particle size of the test materials, the results obtained from these experiments were corrected for slip flow (Alderborn et al., 1985). The results presented are the means of three measurements.

3.3.4. Estimation of particle shape

Scanning electron microscopy (SEM) was used to estimate the surface morphology and particle shape. The samples were examined in a JEOL JSM-T330 scanning microscope, using an acceleration voltage of 15 kV. The calcium carbonate samples were coated with a thin layer of gold for 10–15 min and the barium sulphate samples were coated for 25 min.

The particle shape was also determined quantitatively using the surface shape factor (α_s), (Nystrom et al., 1985). However, the geometric mean diameter by weight, obtained from the Coulter experiments, was used in these calculations instead of the harmonic mean diameter by weight, because of limitations in the computer program used in this study. The results are presented in Table 1.

3.3.5. X-ray powder diffraction

Diffraction patterns were obtained for all samples using a Philips X'pert MPD diffractometer, using Cu K α radiation at 40 kV 50 mA. The samples were scanned in steps of 0.02° from 5° to 60° (2θ) with a rate of 1 s per step, using a zero background sample holder.

3.3.6. Differential scanning calorimetry (DSC)

Samples of 10–15 mg were placed in open silver pans and scanned at a rate of 10°C/min in a differential scanning calorimeter (Seiko DSC 320, Japan) to monitor the thermal properties of the materials in the temperature range 20–1300°C. Both untreated samples and those stored at 75% RH for 1 year were investigated using DSC.

3.4. Solubility determination

The solubility of the material was studied as a function of the amount of material added to the solvent in all cases.

Table 1
Primary characteristics of test materials

Material	Particle size (μm) ^a	Orifice size (μm)	Covering range (μm)	Apparent particle density (g/cm^3) ^b	Density (literature value)	Surface area (m^2/g) ^c	Surface shape factor ^d
Barium sulphate							
Untreated	3.9	30	0.6–18	4.34	4.2–4.5 ^e	2.2	19.1
After milling	2.0	30	0.6–18	4.41		2.8	13.1
After storage at 97% RH ^f	3.1	30	0.6–18	4.49		2.1	15.1
Calcium carbonate							
Untreated	16.5	140	2.8–80.4	2.67	2.71 ^g	0.3	5.8
After milling	5.1	30	0.6–18	2.73		2.3	16.5
After storage at 97% RH ^f	14.8	140	2.8–80.4	2.68		0.3	5.9

^a Geometric mean volume diameters by weight were used due to the approximate log-normal size distribution of the materials.

^b Determined by a Helium gas pycnometer (AccuPyc 1330).

^c Determined by permeometry (Blaine, 1943).

^d In these calculations the geometric mean volume diameter was used instead of the harmonic mean diameter.

^e The Merck Index, 1996.

^f This quality was obtained after storage of the untreated (original) quality at 97% RH for 9 months.

^g McGraw-Hill Encyclopaedia of Science and Technology, vol. 3, 1987.

3.4.1. Sample preparation

In all cases a series of suspensions of known concentration (in the range 20–23000 $\mu\text{g/ml}$) was prepared using the dissolution medium. The choice of the buffer and the buffer concentration gave a constant pH (7.4) which was not affected by amount of sample added to the medium in the concentration range used in the present study.

All the suspensions were stirred at ambient temperature ($23^\circ\text{C} \pm 1$) for up to 1 day. The suspensions (25–50 ml) were then centrifuged at a rotation speed of 2500 rpm for 10 min and the supernatants were removed for further analysis as described below.

3.4.2. Analysis of Ca^{2+} concentration by atomic absorption spectrophotometry

A Perkin-Elmer atomic spectroscopy instrument, equipped with a calcium-magnesium hollow cathode lamp and an air acetylene flame, was used to determine the concentration of CaCO_3 in each solution (the apparent solubility). All the experiments were carried out at a wave length of 422.5 nm. A standard curve was constructed by plotting absorbance versus known concentrations (2–20 $\mu\text{g/ml}$) of a Ca^{2+} standard solution [$\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$]. The concentration of calcium ions in each test solution was then determined. Mean values of three experiments are presented.

3.4.3. Analysis of Ba^{2+} concentration by induced coupled plasma atomic emission spectrometry (ICP-AES)

Induced coupled plasma atomic emission spectrometry (ICP-AES) was used to determine the concentration of barium sulphate in each test solution. Standard solutions in the concentration range 0.2–2 $\mu\text{g/ml}$ were prepared. Barium emission was then measured in an argon plasma at 455.403 nm using a Spectroflame (Spectro, Germany). Mean values from three experiments are presented for untreated barium sulphate, and mean values from two experiments are presented for milled and stored barium sulphate.

3.4.4. Influence of stirring and equilibrium time on apparent solubility

It has been claimed that the time taken to reach saturation in a dissolution experiment is approximately proportional to the excess of solid material present, i.e. the larger the excess, the faster the saturation rate (Higuchi et al., 1979). In order to study whether the differences in equilibrium solubility were a factor of time (i.e. whether true saturation is achieved more rapidly if higher amounts of material are added to the solvent because smaller amounts require longer time to reach saturation equilibrium), the effect of stirring on the apparent solubility of calcium carbonate was studied. Two concentrations of calcium carbonate were chosen (15 and 20000 $\mu\text{g/ml}$) and the suspensions were studied over 10 days, at a constant stirring rate. The amounts of calcium carbonate added to the solvent were chosen to correspond to the lowest and highest apparent solubility values (3 and 15 $\mu\text{g/ml}$, respectively). Specific amounts of the powder were thus added to 250 ml volumetric flasks and sufficient solvent was added to give the final concentrations. The amount of sample dissolved was characterised in 10 ml samples of the suspension at specific time intervals using an atomic absorption spectrophotometer as described above. Presented results are the means of two experiments.

3.4.5. Evaluation of the mechanism behind transformation from apparent solubility to thermodynamically stable solubility

In order to investigate the mechanism behind the recrystallisation of the samples, the influence of stirring on the apparent solubility was studied. Thus, four suspensions containing 20000 μg of untreated CaCO_3 per ml of solvent were prepared. All suspensions were stirred under ambient conditions for 48 h. At this point, the stirring was stopped in two of the suspensions and continued in the other two. During the experiment, 10 ml samples were analysed at specific time intervals. The amount dissolved was then determined as described above. This experiment was continued over 6 days and was carried out only for untreated calcium carbonate. Presented results are the means of two experiments.

3.5. Estimation of the ionic strength of the solution

Since all the impurities of CaCO_3 and BaSO_4 , respectively (listed in Section 2) are ionic in nature, their effect on solubility would be expected to be more limited due to a possible change in the ionic strength of the solution. If the ionic strength is increased sufficiently, the solubility of the test materials would be increased. This effect which is known as salting-in effect was investigated here for CaCO_3 .

The ionic strength of the solution was calculated from Eq. (2) for the lowest (26 $\mu\text{g/ml}$) and highest (20000 $\mu\text{g/ml}$) amounts of CaCO_3 added to the medium. The apparent solubility values used for these calculations were 0.48×10^4 M (4.75 $\mu\text{g/ml}$) and 1.5×10^{-4} M (15.11 $\mu\text{g/ml}$), respectively.

Knowing the percentage amount of impurities, the concentration of impurities and thus their contribution to the ionic strength of the solution, was calculated in each case. (In these calculations only the ionic impurities with a concentration greater than 0.01% were considered.) The total ionic strength of the solution was thus calculated as shown in Table 3.

3.6. Dissolution rate determination

Dissolution rate studies were carried out on a Coulter Multisizer II according to the method described by Nyström et al. (1985). This experiment was only conducted for untreated calcium carbonate. A stock suspension (5000 $\mu\text{g/ml}$) was prepared and ultra-sonicated. A certain amount of the suspension was then added to 300 ml particle free dissolution medium. The concentration of the substance in the dissolution medium at the starting time of dissolution process was thus equal to 1.5 $\mu\text{g/ml}$. The dissolution process was followed over 30 min, during which 75% of sample was dissolved. The capillary tube used had an aperture of 140 μm in diameter. The amount of calcium carbonate added resulted in sink conditions with respect to the highest apparent solubility value (15 $\mu\text{g/ml}$) and was also lower than the lowest solubility value (3 $\mu\text{g/ml}$). The mean di-

ameter of the CaCO_3 particles as a function of dissolution time was calculated. Presented data are mean values of two measurements.

4. Results and discussion

4.1. Primary characteristics of test materials

4.1.1. Surface morphology

Considering the SEM photomicrographs (Fig. 2a) the particles of calcium carbonate could be described as strongly bonded aggregates of smaller primary particles or crystals (Ek et al., 1994). This figure also shows that the surfaces of the crystals were not perfectly ordered. The surface seemed to be broken or damaged in most of the particles and small crystals and colloidal particles adhered to the surface of larger particles. In some of the untreated calcium carbonate particles dislocations could be seen. There were no obvious differences between the crystalline view of calcium carbonate before storage at 97% RH and that seen after storage. However, storage appeared to result in the formation of larger aggregates of primary particles or crystals (Fig. 2b). As shown in Fig. 2c, milled CaCO_3 consisted of very fine particles which adhered to the surface of coarser particles.

SEM photomicrographs of barium sulphate samples are shown in Fig. 3. The particles were very fine, although irregular in shape. Untreated barium sulphate showed a tendency toward aggregation. The particle surface did not appear to be crystalline when viewed under the microscope.

After storage at 97% RH (Fig. 3b), some of the primary particles seemed to have fused together to form larger aggregates, probably because of absorption of water and crystal growth.

4.1.2. Size, shape and surface area properties

According to the particle size analysis (Table 1), all samples were fine particulate with a log-normal size distribution. In general, the sizes of barium sulphate particles were less polydisperse than those of calcium carbonate. The barium sulphate samples had a greater surface area and the particles were of a more irregular shape (Table 1).

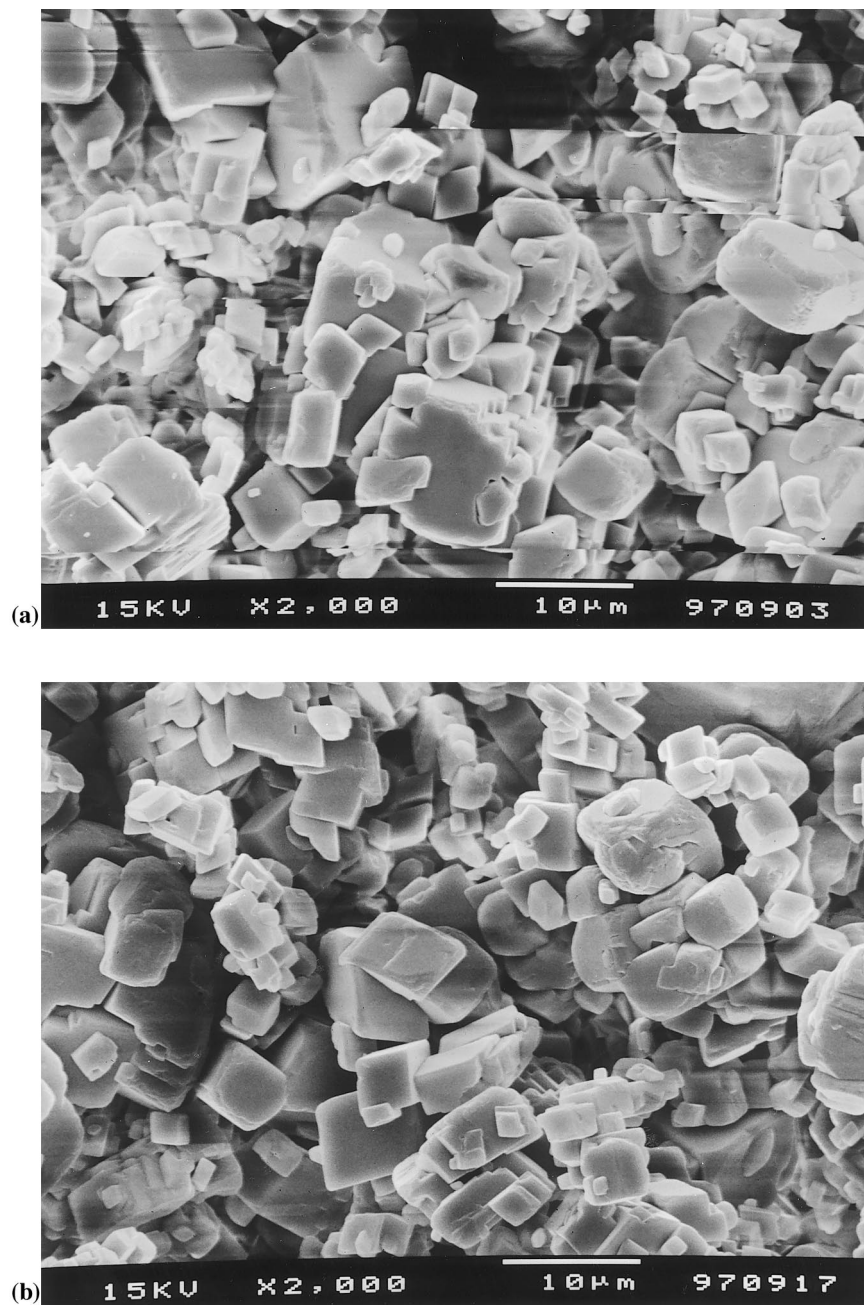


Fig. 2. Scanning electron microscopy photo-micrographs of calcium carbonate: (a) untreated; (b) stored at 97% RH; and (c) milled.

Untreated calcium carbonate particles were relatively isodiametrical ($\alpha_s = 5.8$) with a rather small external surface area ($0.3 \text{ m}^2/\text{g}$). Storage of these particles at high relative humidity did not

lead to any significant change in the primary characteristics. However, milling of calcium carbonate caused a significant reduction in particle size (from mean 16.5 to $5.1 \mu\text{m}$), accompanied by

an increase in surface area (to 2.3 m²/g), caused by fragmentation of secondary particles to primary particles due to milling. From the calculated shape factor (Table 1), it was concluded that the particles became much more irregular after milling.

4.1.3. Density

The density of the tested materials was high and in agreement with those in the literature (Table 1), confirming that the test materials possessed a compact structure. There was, however, a notable difference between the density of BaSO₄ before and after storage at 97% RH. The sample seemed to become more dense and more ordered after storage under these conditions (Table 1).

4.2. Solid state characteristics of test materials

4.2.1. X-ray powder diffraction

According to the literature there are six different forms of calcium carbonate: three anhydrous crystalline polymorphs (calcite, aragonite and vaterite) and three hydrated forms (a crystalline monohydrate, a crystalline hexahydrate and ‘col-

loidal’ or amorphous calcium carbonate) (Clarkson et al., 1992; Kojima et al., 1994). It is widely accepted that calcite is the most stable of the calcium carbonate polymorphs (Harker, 1987).

According to X-ray diffraction analysis (Fig. 4) all samples were highly crystalline and pure. Calcium carbonate was in the form of calcite with a hexagonal-rhombohedral crystal system and barium sulphate was in the form of barite with an orthorhombic crystal system. No change was detectable in the crystal structure of the samples after milling or storage at 97% RH. Since the untreated CaCO₃ was in the form of calcite before and after the dissolution test, there was no evidence for inter-polymorphic conversions or degradation occurring during the dissolution of calcite. In addition, these results also confirmed that there were no potential for the precipitation of Ca²⁺ as another salt form.

4.2.2. Differential scanning calorimetry, DSC

DSC was not able to detect any phase transition in calcium carbonate samples as these samples were decomposed at about 689–769°C to CaO and CO₂. The decomposition temperature of

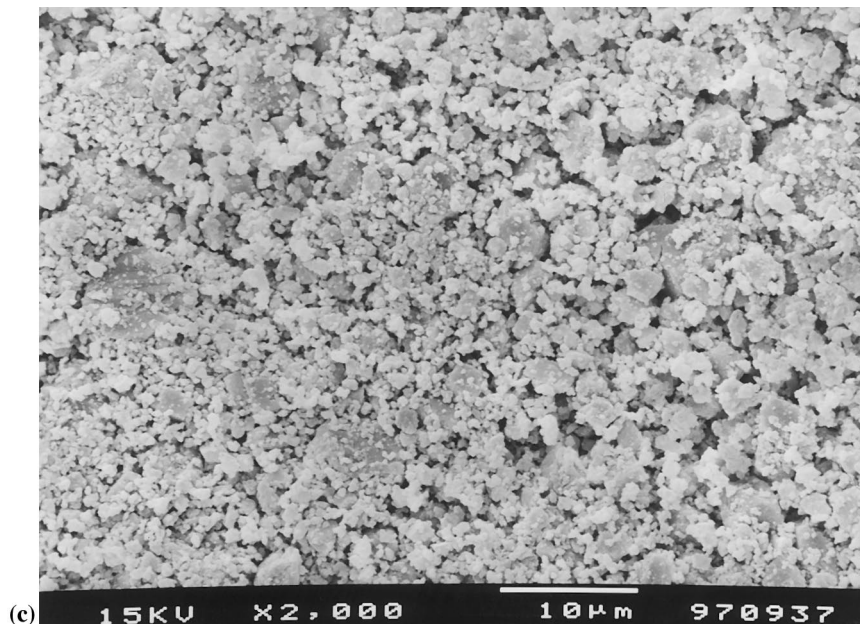


Fig. 2. (Continued)

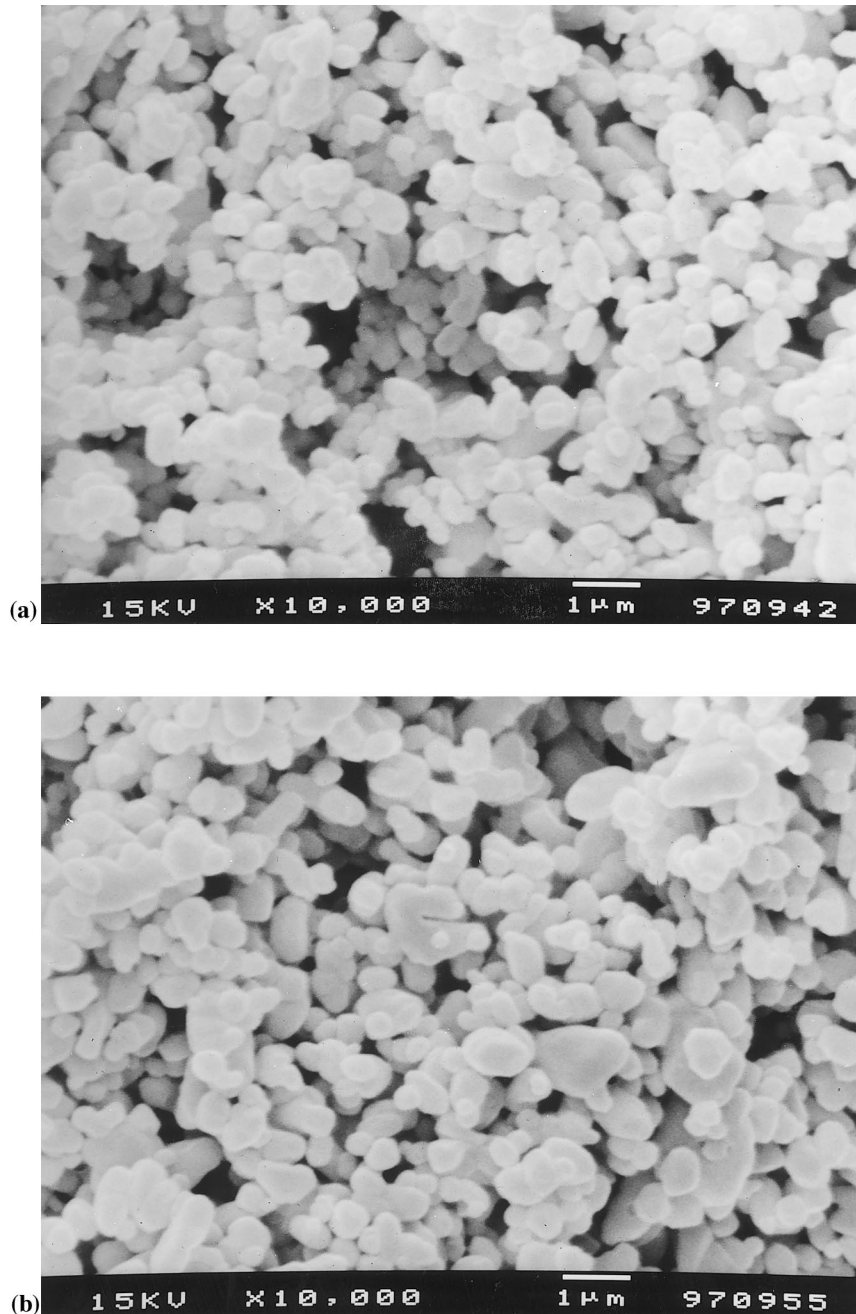


Fig. 3. Scanning electron microscopy photo-micrographs of barium sulphate: (a) untreated; (b) stored at 97% RH; and (c) milled.

calcite was thus lower than that reported in the literature (The Merck Index gives the decomposition temperature as for calcite, i.e. 825°C). Thus it seems that the form of calcite used in these exper-

iments was less stable than the totally ordered form referred to in the literature. In the case of barium sulphate, transition to the monoclinic form occurred at about 1110°C, just before melt-

ing at about 1157°C. However, it should be noted that Saleki-Gerhardt et al. (1994) suggest that the amount of disorder would have to be above or about 10% of the total amount of the material in order to be detectable by DSC or X-ray diffraction techniques.

4.2.3. Summary of the solid state structure of the test materials

It is purposed in this study that all tested materials seemed to have activated or disordered surfaces, although the degree of disorder differed among them. As the background of the untreated test materials is not known, it is not clear at this stage why these samples were disordered.

The physico-chemical methods used in the present study were not able to unambiguously verify the existence of any disorder or any difference in the solid state structure of the test materials. The assumption of the existence of a peripheral disordered layer is mainly based on the solubility results. Nonetheless, collective sum of the results of DSC, density measurements and the SEM micrographs indicate the presence of disordered or amorphous material on the surfaces of

the particles. Further, the reduction in the apparent solubility after storage of powder at high relative humidity could indirectly indicate that a very slow recrystallisation process is occurring. (As it is known that disordered material absorbs water vapour and recrystallises under storage at high relative humidity (Ahlneck and Zeografi, 1990; Sebhatu et al., 1994).) The reason that such a recrystallisation process is very slow, may be that only a thin molecular layer of the surface of the particles is in contact with the vapour inside the desicator and thus in equilibrium. Meanwhile, the internal core of the particles remains intact and is not substantially affected by the environment. Hence the substantial change in the measured physico-chemical properties of CaCO_3 seen here was not achieved just by changing the relative humidity. It seems that if complete surface recrystallization is desired, parameters such as temperature should have also been changed. Similar behaviour has been reported for other pharmaceutical excipients, emphasising the effect of temperature on crystallisation rate under different RH (Dalton and Hancock, 1997). Further investigation of this matter was not within the scope of the present study.

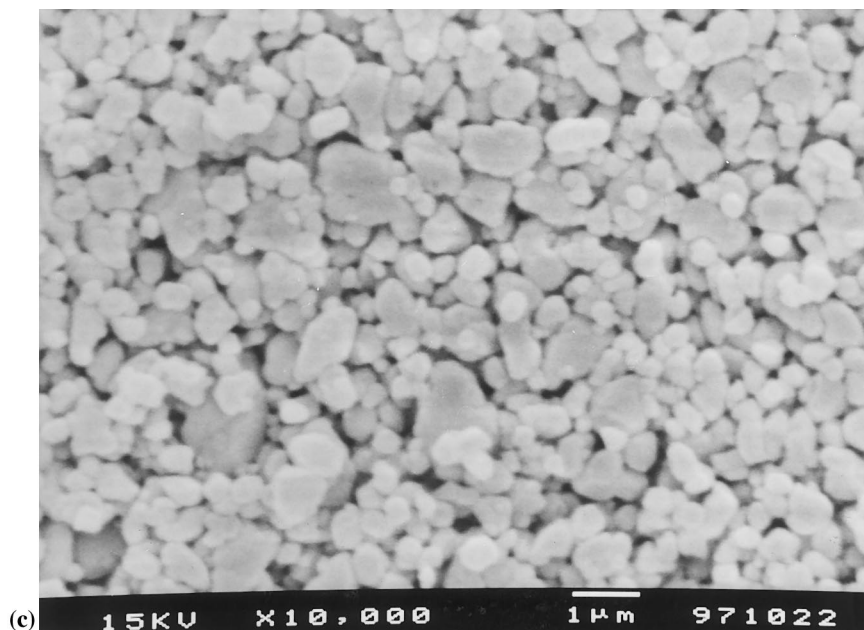


Fig. 3. (Continued)

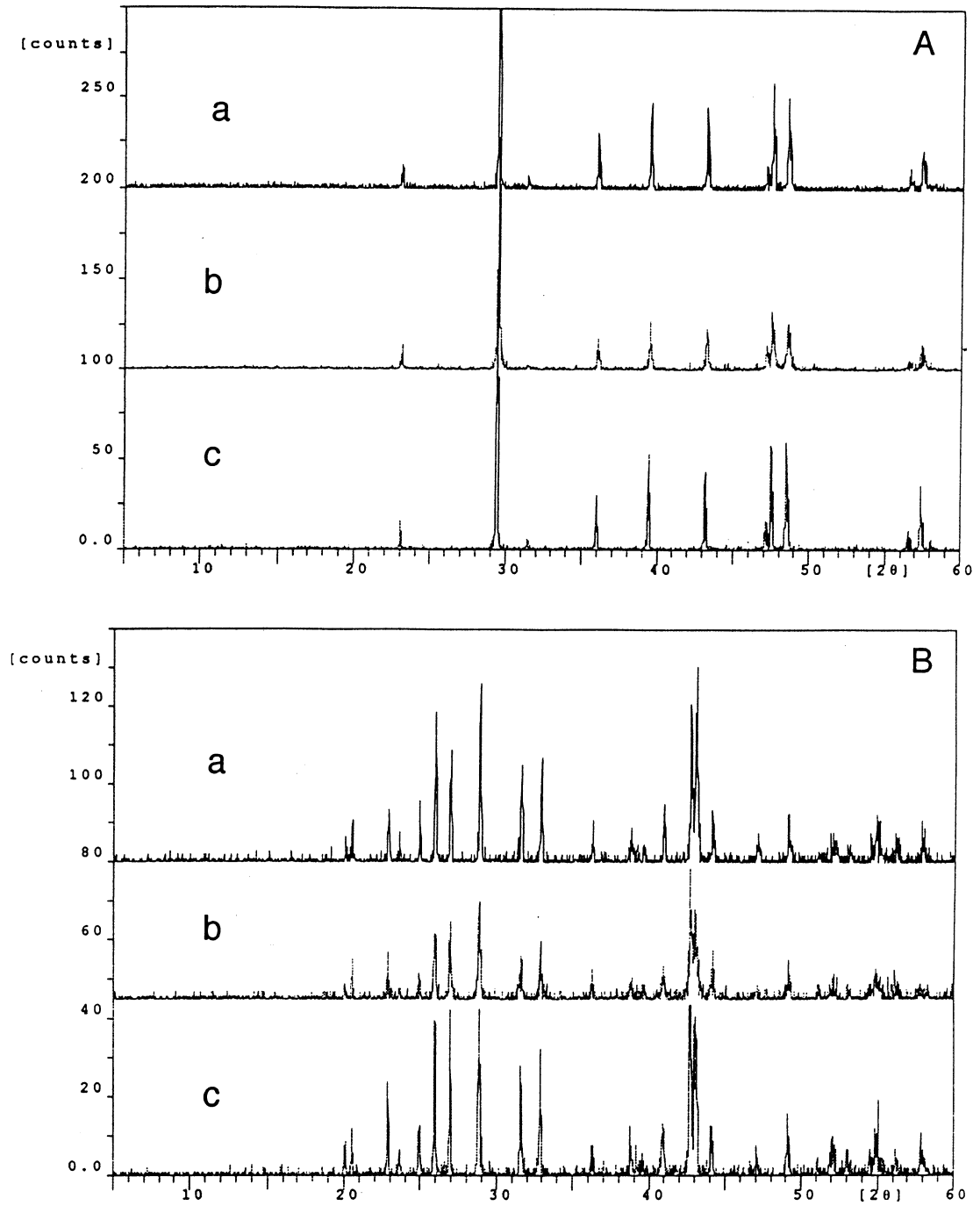


Fig. 4. X-ray diffraction patterns for calcium carbonate (A) and barium sulphate (B) samples. (a) Stored at 97% RH; (b) milled; and (c) untreated.

4.3. Solubility characteristics of test materials

4.3.1. Apparent equilibrium solubility as a function of amount of material added to the solvent

The solubility of calcite differs in the literature (Table 2). The results of this study indicate that the amount of material added to the dissolution medium determines the actual resulting apparent equilibrium solubility. Generally, the apparent solubility of the tested material increased as a function of the amount added to the solvent until a plateau was reached, at which point the solution seemed to be in metastable equilibrium. An approximately 5-fold increase in the apparent equilibrium solubility of the untreated calcium carbonate and barium sulphate was obtained as the amount of material was increased (Figs. 5 and 6).

Very large amounts of each of the test materials were required to reach the plateau level. In all cases the amount of material required to be added to the solvent was at least 10 times greater than the concentration dissolved at apparent equi-

Table 2
Reported solubility values at 25°C

Material	Solubility ^a	
	($\mu\text{g/ml}$)	mol/l
Calcite	0.50	5.01×10^{-6}
	0.50	5.00×10^{-6}
	0.63	6.30×10^{-6}
	6.76	6.76×10^{-5}
	10.2	1.02×10^{-4}
	13.5	1.35×10^{-4}
	14.0	1.40×10^{-4} ^b
	14.8	1.48×10^{-4}
Amorphous CaCO_3	66.0	0.66×10^{-3}
	813	8.13×10^{-3}
Barite	2.50	1.07×10^{-5}

^a These values are based on a summary, and were reported as limiting solubility values, by Gal et al. (1996), unless otherwise stated.

^b Encyclopaedia of Chemical Technology (Kirk-Othmer, 1964).

^c Recalculated data from the Merck Index (The Merck Index, 1996).

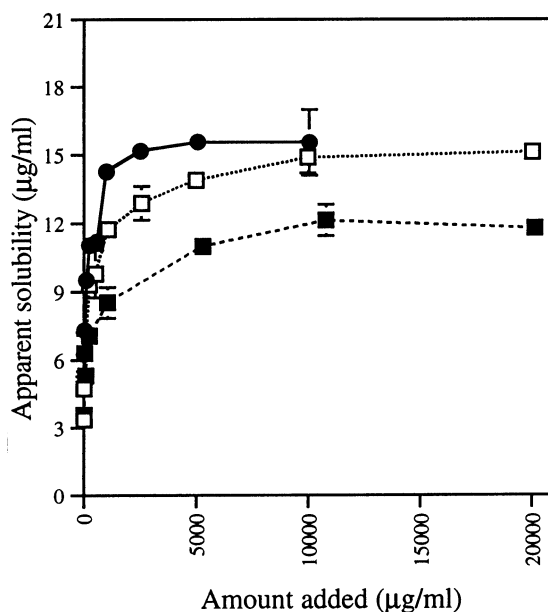


Fig. 5. Apparent solubility profile of calcium carbonate after milling and storage at 97% RH compared to the original profile as a function of amount added (at 23°C and pH 7.4), (bars = standard deviation). Symbols: ●, milled; □, untreated; ■, stored at 97% RH.

librium, and in most cases the amount required to reach the plateau was at least 100–300 times greater than equilibrium solubility. As mentioned above, this increase in the apparent equilibrium solubility may have been caused by: (a) the existence of impurities (Grant and Higuchi, 1990); (b) the salting-in effect and ionic strength; (c) small colloidal particles ($< 0.1 \mu\text{m}$) (according to Eq. (4)); or (d) heterogeneity in the energy content of the test materials, i.e. the existence of disordered structures (Higuchi et al., 1979; Elamin et al., 1994).

The results listed in Table 3, demonstrate that the amount of ions present in the CaCO_3 solutions (in the form of impurities or solute) has a minor effect (at the highest addition) or no effect at all (at the lowest addition) on the total ionic strength of the solution. The total ionic strength of the solution was increased from minimum 0.153 to maximum 0.162 as the amount of salts in the solution was increased. According to the calculated S/S^0 values (Table 3), this increase in

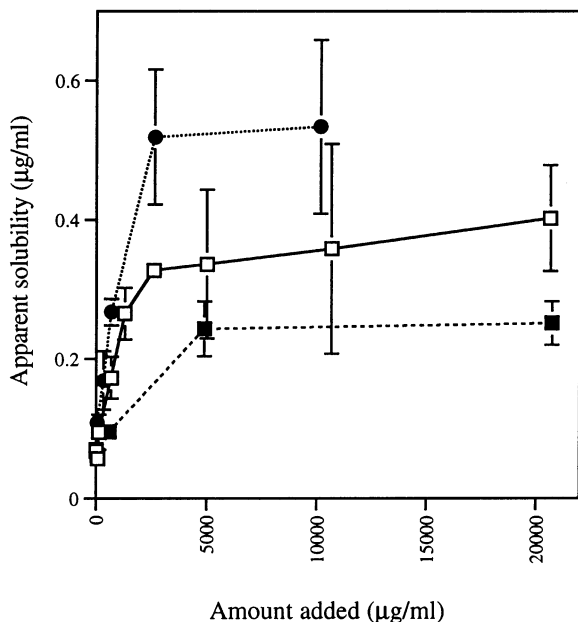


Fig. 6. Apparent solubility profile of barium sulphate after milling and storage at 97% RH compared to the original profile, as a function of the amount added (at 23°C and pH 7.4), (bars = standard deviation). Symbols: ●, milled; □, untreated; ■, stored at 97% RH).

ionic strength is not sufficient to explain the solubility enhancement observed during the experiments. The calculated S/S^0 values (based on Eq. (3)) were almost constant (6.3 and 6.6, respectively) and independent of the amount of solute added to the medium.

Table 3
The ionic strength (I) values for CaCO_3 solutions

	Ionic strength ^a		Specification
	26 ($\mu\text{g/ml}$) ^b	20 000 ($\mu\text{g/ml}$) ^c	
Medium (blank) ^d	0.153	0.153	NaH_2PO_4 , NaCl, KCl
Impurities	2.34×10^{-5}	8.85×10^{-3}	Na^+ , K^+ , Sr^{2+} , Mg^{2+} , SO_4^{2-}
Calcium carbonate	0.048×10^{-4}	1.5×10^{-4}	CaCO_3
Total	0.153 ^e	0.162 ^f	$\Delta I = 0.009$

^a Calculated according to Eq 2.

^b The lowest amount added.

^c The highest amount added.

^d Phosphate buffer (pH 7.4), 0.09% NaCl, 0.01% Tween 80.

^e $\text{Log } S/S^0 = 0.80$ and $S/S^0 = 6.3$ (according to Eq. 3).

^f $\text{Log } S/S^0 = 0.82$ and $S/S^0 = 6.6$ (according to Eq. 3).

The same argument may be applied to BaSO_4 . However, in this case the level of impurities was less than 0.01%. Therefore their influence on the ionic strength of the solution did not seem to be significant and was assumed to be negligible.

Another phenomenon which is usually brought in to discussion, is the common ion-effect. According to this rule which is based on the Le Chatelier's principle, if a common ion is added to a solution, the equilibrium will be shifted to the left (i.e. the salt will precipitate). As far as the results of the present study are concerned a more detailed discussion around the common-ion effect does not seem to be necessary. First, there are no common ions present in the solutions (i.e. there are no impurities in the form of Ba^{2+} and SO_4^{2-} in BaSO_4 solutions or Ca^{2+} and CO_3^{2-} in CaCO_3 solutions). Second, the results presented, mainly show an enhancement in the apparent solubility rather than a reduction.

Further, the volume size distribution data did not reveal any substantial contribution of colloidal particles by weight. Thus, the existence of an external disordered layer around the crystals of CaCO_3 and BaSO_4 seems to be a reasonable explanation for the increase in apparent solubility.

In fact, the existence of a single skeletal element composed of crystalline calcite in one layer and stable amorphous CaCO_3 in another has been reported recently (Aizenberg et al., 1996). The spicules on the calcareous sponge *Clathrina* are composed of such a combination.

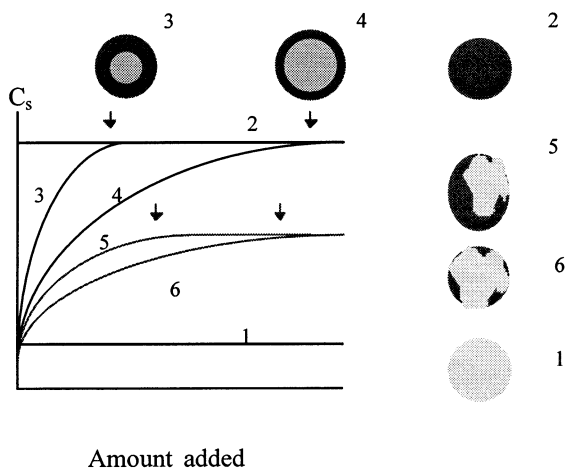


Fig. 7. A schematic figure, illustrating some of the possible plateau levels obtained for apparent solubility of a drug, as a function of the amount added and the degree of disorder. 1: totally ordered; 2: totally disordered; 3 and 4: crystalline core surrounded by a thick or thin disordered layer, respectively; 5 and 6: the surface is not continuously disordered. C_s : apparent solubility.

4.3.2. Mechanisms behind different solubility plateau values

As illustrated in Fig. 5, two plateau levels were distinguishable for calcium carbonate: one for the untreated and milled samples and one for the sample stored at high relative humidity. The upper limit for the solubility of calcium carbonate seems to be around $15 \mu\text{g/ml}$, irrespective of particle size or degree of disorder (Fig. 5).

Moreover, as illustrated in Fig. 6, three plateau levels were distinguishable for BaSO_4 : one for untreated barium sulphate, a higher level for the sample that had been milled, and a lower level after storage of the powder at high relative humidity (97% RH).

If the plateau level is assumed to correspond to the solubility of the totally disordered structure, the existence of several plateau levels for a given material requires further explanation.

In an attempt to elucidate this matter, a schematic figure has been developed (Fig. 7). It is assumed that there are several plateau levels for every substance. The existence of two independent plateau values (corresponding to the minimum and maximum solubility values) was demon-

strated above in Fig. 1. Similarly examples 1 and 2 in Fig. 7 are hypothesised to occur when the structure of the compound is either totally ordered (crystalline) or totally disordered (amorphous), i.e. this situation will occur independently of the amount of material added to the solvent.

However, when the crystalline and amorphous phases coexist, the plateau level (or the apparent equilibrium solubility) for a substance is affected by the ratio of amorphous to crystalline phases on the particle surface. In this case the apparent solubility is dependent on the amount of material added to the solvent.

When the degree of disorder is much higher than is required to form a saturated metastable solution, the peripheral surfaces of the particles remain disordered, enclosing the totally crystalline core (cases 3 and 4). In this case, the apparent equilibrium solubility would be determined solely by the disordered phase and would approach that seen with a totally amorphous drug structure.

If (cases 5 and 6) the surface is partly crystalline and partly amorphous, some areas of crystalline structure will be exposed even if high amounts of solute are added, and the plateau value will be intermediate between those of the purely crystalline (profile 1) and the purely amorphous (profile 2) states. Thus, the solution will be simultaneously in equilibrium with the crystalline and disordered surfaces.

Thus, in the same way that there are different solubility values for different crystalline polymorphs, there seem to be different apparent solubility values for solids with different degrees of surface disorder.

4.3.3. The effects of stirring and equilibrium time on solubility determination

The different values seen in these experiments for the apparent solubility of the same material after different amounts of the material had been added to the solvent did not appear to be a function of the equilibrium kinetics. As shown in Fig. 8, the solubility of calcium carbonate after $15 \mu\text{g/ml}$ was added to the solvent was constant at about $3 \mu\text{g/ml}$ over 10 days of constant stirring. However, if the solubility of calcium carbonate had been $12\text{--}15 \mu\text{g/ml}$, as it was when higher

amounts (above 10000 $\mu\text{g/ml}$) were added, the entire amount added (15 $\mu\text{g/ml}$) would have been dissolved after such an extended period of stirring. Since this did not occur, it can be assumed that there were two distinguishable levels of solubility: 3 $\mu\text{g/ml}$, approaching the true solubility, for the more ordered structure and 12–15 $\mu\text{g/ml}$, or the apparent metastable solubility, for the disordered phase.

In one experiment in this paper, 20000 $\mu\text{g/ml}$ of calcium carbonate was added to the solution. In this case, equilibrium was established after 2–4 days, instead of 1 day as was seen in corresponding experiments (Fig. 8). Possible explanations for this difference include the lower stirring rate and different stirring equipment.

4.3.4. The specific effect of mechanical activation

It has been shown (Figs. 6 and 9a) that not only did milling increase the plateau value for the apparent solubility of barium sulphate (Fig. 6)

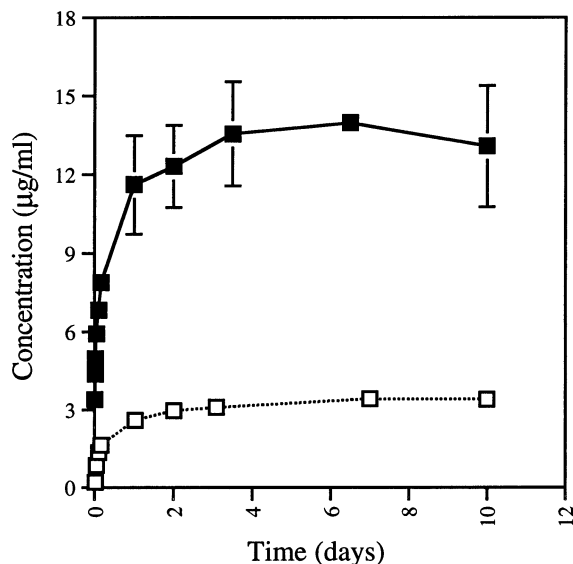


Fig. 8. The effect of stirring time on the equilibrium concentration of untreated calcium carbonate for the lowest (15 $\mu\text{g/ml}$) and the largest (20000 $\mu\text{g/ml}$) amount added (pH 7.4 and 23°C). Symbols: \square , 15 $\mu\text{g/ml}$ and \blacksquare , 20000 $\mu\text{g/ml}$. In this experiment 250 ml volumetric flasks were used (bars = standard deviation).

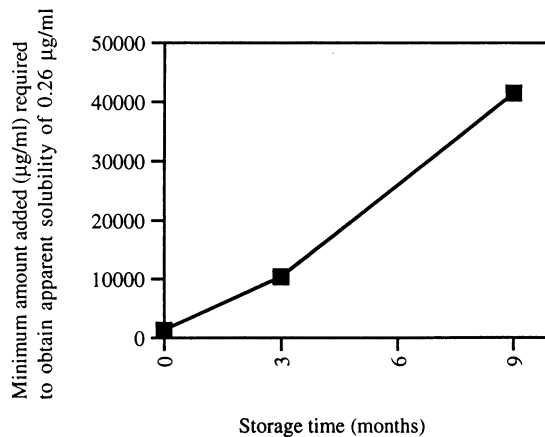
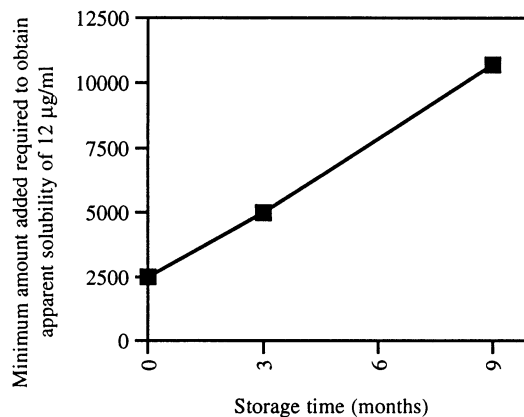
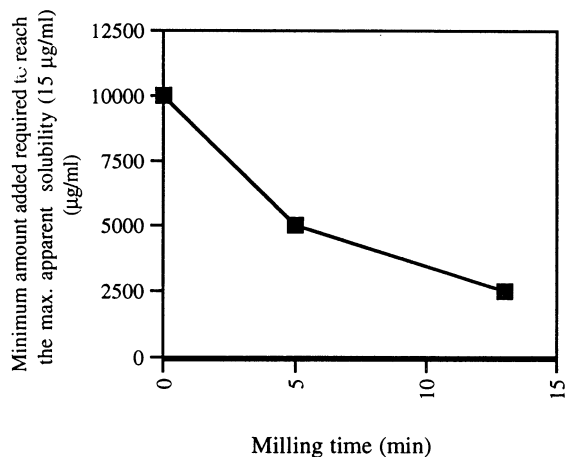


Fig. 9.

but it also caused the plateau level for both materials to be reached on the addition of lower amounts of material to the solvent than were necessary without milling. Fig. 9a shows the effect of milling time on the minimum amount of calcium carbonate required in the solvent in order to reach the plateau.

It is shown that the amount of material required in the solvent in order to reach the plateau is 4-fold less after 13 min milling (i.e. 2500 $\mu\text{g}/\text{ml}$ instead of 10000 $\mu\text{g}/\text{ml}$). This effect appears to be a result of mechanical activation and surface disruption of the test materials. In fact, the degree of disorder appears to be a function of milling time (Ahmed et al., 1996). The thickness of the disordered layer is therefore an important factor in determining the equilibrium rate. This is illustrated in Fig. 7, where a difference may be seen between profiles 3 and 4, and 5 and 6, respectively. The thicker the disordered layer, the less material is required to reach equilibrium (and thus the plateau value). When the thickness of a continuous disordered layer is increased (see profiles 3 and 4, Fig. 7), the plateau corresponding to the solubility of a totally amorphous structure is established with less excess material in the solvent. When the disordered layer is discontinuous (see profiles 5 and 6, Fig. 7), the apparent equilibrium level is intermediate between the plateau level when the material is totally crystalline and when it is totally amorphous.

4.3.5. The specific effect of humidity

Storage of the powders not only reduced the concentration at which the plateau occurred but

also affected the kinetics of the process when the powder was stored at high relative humidity. In Fig. 9b, it can be seen that the amount of calcium carbonate required in the solvent to reach an apparent solubility of 12 $\mu\text{g}/\text{ml}$ was greater after storage of the powder at 97% RH. This suggests that the powder contained less of the amorphous phase after storage under these conditions. The same result was seen with barium sulphate (Fig. 9c).

4.3.6. Evaluation of the mechanism behind transformation from disordered structure to ordered thermodynamically stable structure

The concentration of the solution at equilibrium will decrease after a period of time to the level equivalent to the solubility of the most stable crystalline form.

The duration of the period of increased (metastable) solubility is generally thought to be controlled by the rate of nucleation and, thus, the rate of growth of the more stable phase (Clarkson et al., 1992). Many researchers have based their data analysis on the assumption that the processes of dissolution of the metastable form and crystallisation of the stable form are both diffusion controlled. The surface area available for growth and the stirring rate of the system would then be rate-determining factors for the transformation process to the stable, crystalline form.

Rodriguez-Hornedo et al. (1992), however, suggested that polymorphic phase transformations are dependent on supersaturation of the solvent and are independent of the stirring rate. They discuss the mechanisms behind the phase change in terms of a surface phase transition process, i.e. transformation in the solid state. The results reported recently by Elamin et al. (1994) on the transformation of disordered griseofulvin to the crystalline form support the latter explanation.

As shown in Fig. 10, the apparent solubility of calcium carbonate obtained after addition of 20000 $\mu\text{g}/\text{ml}$ was constant and stable up to 6 days (i.e. as long as it was monitored in this test), for both the unstirred and stirred suspensions. In this case, an excess amount of solid calcium carbonate was present in the medium. It thus seems that the recrystallisation rate of calcium carbonate is controlled by a surface solid-state transition mecha-

Fig. 9. (a) Effect of milling time on the degree of disorder of calcium carbonate, and thus the minimum amount added required to reach the plateau. Increase in degree of disorder is accompanied by a decrease in the required amount added. (b) The effect of storage time at 97% RH on the degree of disorder of calcium carbonate, and thus the minimum amount added required to obtain an apparent solubility of 12 $\mu\text{g}/\text{ml}$. Decrease in degree of disorder is accompanied by an increase in the minimum amount required to obtain this value. (c) The effect of storage time at 97% RH on the degree of disorder of barium sulphate, and thus the minimum amount added required to obtain an apparent solubility of 0.26 $\mu\text{g}/\text{ml}$. Decrease in degree of disorder is accompanied by an increase in the minimum amount required to obtain this value.

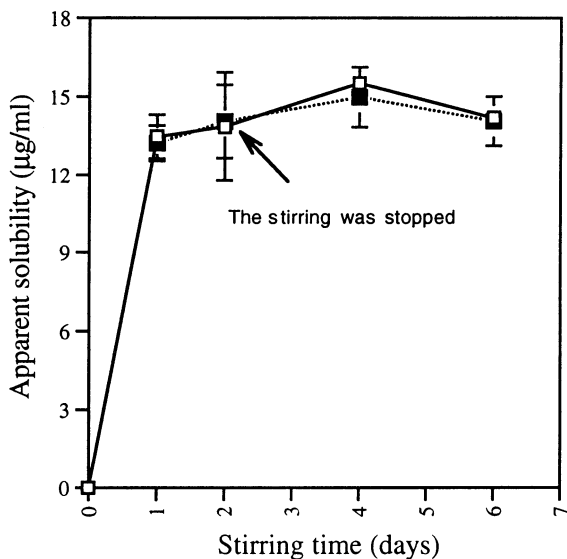


Fig. 10. The effect of stirring on the apparent equilibrium solubility of a suspension of untreated calcium carbonate (20000 $\mu\text{g/ml}$) at 23°C and pH 7.4. Symbols: ■, continuous stirring and □, stirring was stopped after 2 days (bars = standard deviation). In this experiment 250 ml volumetric flasks were used.

nism. This would appear to be valid as long as the pH and temperature of the system are kept constant and controlled.

4.4. Dissolution rate

Results from dissolution experiments with calcium carbonate are presented in Fig. 11.

The dissolution profiles of calcium carbonate, expressed both as the amount of material dissolved and as the surface specific dissolution rate (G), as a function of time are presented in Fig. 11 (a and b, respectively). The dissolution process appeared to follow a biphasic pattern (Fig. 11a). It is suggested that during the initial stage the disordered surface of the calcium carbonate is rapidly dissolved to expose the crystalline core, which is subsequently dissolved at a slower rate.

In Fig. 11c the changes in remaining weight^{1/3} was studied as a function of dissolution time, in order to apply the cube root law (Hixon and Crowell, 1931). As the cube root law represents a dissolution rate which is normalised for the de-

crease in surface area as a function of time and thus can be used in order to calculate rate constants.

When sink condition is applied the cube root law can be written as:

$$W_t^{1/3} = W_0^{1/3} - Kt \quad (5)$$

where W_t denoted the remaining weight of solid at time $t = 0$, and K represents the dissolution rate constant ($\text{weight}^{1/3} \cdot \text{time}^{-1}$). A plot of $W_t^{1/3}$ vs t should yield a straight line with intercept $W_0^{1/3}$ and slope K (Anderberg and Nyström, 1990).

As it can be seen from Fig. 11c, the tested calcium carbonate followed the cube root law fairly well, provided the profile is described as a biphasic plot. For both phases there was a linear relationship between $W^{1/3}$ and t (Fig. 11c). During the first phase the dissolution rate was extremely fast and the rate constant (K) was approximately five times of that obtained from the second phase. This relative difference correlates well with the ratio of the apparent solubility value of disordered to ordered phase (i.e. $15/3 \mu\text{g/ml} = 5$). Thus the apparent solubility of the activated surface will affect the initial dissolution rate, while the final (dominating) stage will be mainly determined by the solubility of the ordered crystalline phase.

Furthermore, the changes in the mean particle size by weight (d_{wg}), during the dissolution process are plotted vs time in Fig. 11d. These data are in good agreement with the particle size analysis result presented in Table 1 for untreated calcium carbonate. It is also shown that the mean particle size was moderately reduced from 13.1 to 10.6 during the dissolution, which is in accordance with previously published data (Anderberg and Nyström, 1990).

5. Conclusions

This study has examined the solubility and dissolution of two solid hydrophilic materials. In all the experiments, the solubility of the materials increased as the amount of material added to the dissolution medium was increased, until a plateau was reached. This phenomenon was probably the

result of an external disordered or amorphous layer on the particles of calcium carbonate and barium sulphate.

The solubility of both compounds increased dramatically as a function of the amount of material added to the dissolution medium, reaching a plateau at five times the solubility of the pure crystalline compound (seen at stable equilibrium). This is in agreement with the results reported for griseofulvin by Elamin et al. (1994). As the previ-

ous treatment of the test materials is unknown, it is assumed that such peripheral disorder is caused by precipitation or milling. Therefore it can be concluded that the apparent solubility of all materials, especially those with a small mean particle size, may be affected by the amount of material added to the dissolution medium.

Milling the powders caused the plateau to be reached at lower proportions of solute to solvent, since this further disordered the surface of the

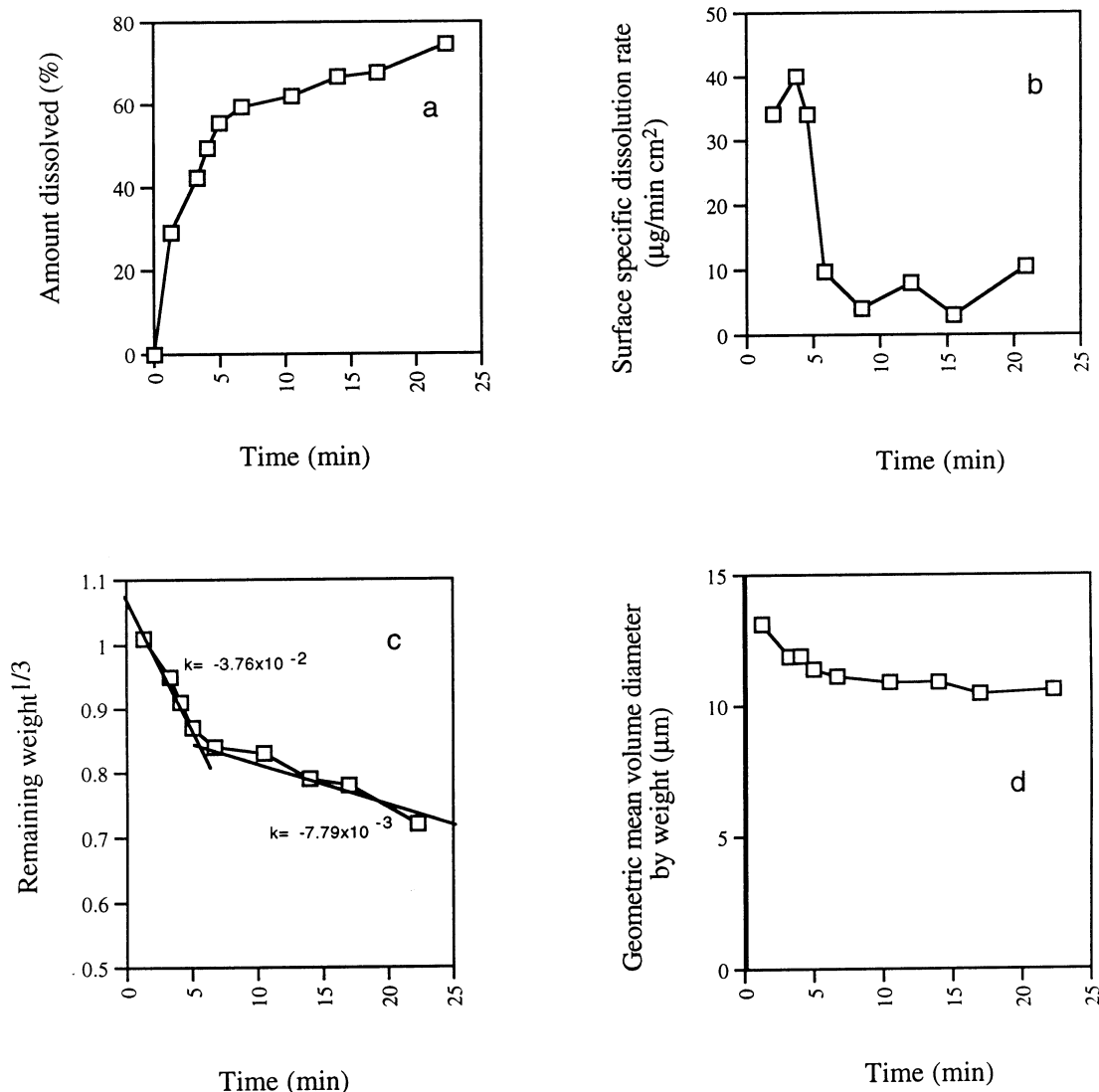


Fig. 11. Dissolution profile of untreated calcium carbonate by time at pH 7.4 and 23°C, expressed as (a) amount dissolved; (b) the surface specific dissolution rate; (c) the cube root law; and (d) the mean particle diameter by weight.

drug particles. A model for describing the effects of a disordered surface layer of varying thickness and continuity on the solubility of a substance is presented. It was also found that the solubility of the drugs tested decreased after storage at high relative humidities.

Since the rate at which the solution was stirred appeared not to affect the recrystallisation rate, it is concluded that the recrystallization of calcium carbonate or barium sulphate is not diffusion controlled. It is suggested that the process of recrystallisation was the result of a slow surface solid-state transition and that this would result in a very slow reduction in the apparent solubility plateau level down to the thermodynamically stable value.

The dissolution rate profile of untreated calcium carbonate consisted of two main phases. The solubility of the disordered fraction appeared to be the rate-determining factor during the first short phase while the solubility of the crystalline state affected the second (dominating) phase.

It is concluded that the investigation of the relationship between equilibrium solubility, the amount of solute added to the solvent and the proportion of disordered or amorphous structures on the surface of the particles will provide valuable information which can be used to predict and control the solubility and dissolution behaviour of sparingly soluble hydrophilic drugs.

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