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CORRELATION BETWEEN PHYSICO-CHEMICAL PROPERTIES AND COHESIVE BEHAVIOR OF FUROSEMIDE CRYSTAL MODIFICATIONS

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ABSTRACT

This study reports the influence of changes in crystal form, with subsequent changes in physico-chemical properties, on the cohesive properties of furosemide powders. Two known polymorphs and three crystal habits were prepared by changing the crystallisation solvent and velocity. Crystallised products were characterised by their XRD profiles. Powder properties including solid-state photochemical reactivity, particle size and distribution, density, wettability and dissolution were measured. Fine particles of form I, mean size 3 μm, were extremely cohesive, mean size of agglomerates 108 μm, and poorly wettable, contact angle > 90°. Changes in the crystal habit of form I led to the crystallisation of large (mean size > 50 μm) tabular and rod shape, less cohesive but also poorly wettable (contact angle > 90°) particles. These large particles although not cohesive had poor dissolution properties. Milled particles with a mean size of smaller than 10 μm, obtained from the large crystals were again cohesive. The method of preparation of form II produced small plate like crystals, mean size 8 μm, fractionally more wettable, contact angle 75°, and not as cohesive, mean size agglomerates 25 μm. Milling to a mean size of 4 μm increased the cohesive properties because the mean size of agglomerates was then 53 μm. Different crystal habits of form I did not show a difference in degradation during the nucleation period, mean rate constant 1.4×10^{-2} h^{-1}, and the growth period, mean rate constant 2.4×10^{-2} h^{-1}. In summary crystal modification improved the wettabillity and cohesive properties of furosemide particles without changing the solid-state stability of the drug. The dissolution properties of larger less cohesive particles were however poor and milling, to increase the surface area available for dissolution, increased the cohesive properties of particles.

INTRODUCTION

In practice, the primary particles of micronised powders - particle size > 20 μm - will adhere to one another due to surface forces forming secondary particles, agglomerates and aggregates.[1] Normally the synthesis of drugs concludes with a

crystallisation procedure which may determine the physico-chemical properties, in particular the agglomeration or cohesive behaviour, of the drug substance. The properties of such crystallised materials are the result of relative rates of nucleation, growth and agglomeration, and the structure of growth and agglomeration units.[2]

Very high super saturation give very small growth units and promote the growth of amorphous particles. Polymorphism is the ability of a solid to crystallise in more than one distinct crystal species.[3] However, changes in the outer appearance of crystalline solids may also lead to crystal habit differences. Habit bears upon the overall shape of the crystal but also reflects internal structure changes, e.g. polymorphs and solvates.[4] Different crystal configurations are associated with different energies, and therefore one configuration may have significantly different properties from another. Crystal modification can lead to differences in solid-state reactivity[5] and because of surface changes, for instance surface roughness, can decrease or increase the cohesive properties of a powder.[6] These changes depend on a number of factors such as storage conditions, particle size, etc.[7]

In this study two known polymorphs and a number of crystal habits of furosemide were prepared and the physico-chemical properties of the particles namely, solid-state photochemical stability, particle size and distribution, density, wettability and dissolution were determined and used to assess the cohesive behaviour as a function of crystal form.

MATERIALS AND METHODS

Materials

Furosemide was generously supplied by Lennons Pty. Ltd. (South Africa). Either HPLC or reagent grade chemicals and solvents, and water fit for chromatography were used.

Preparation of Crystal Modifications

Polymorph I[8] was furosemide as supplied by the supplier, figure 1(a). Polymorph II, figure 1(b), was obtained from an acetone solution, evaporated to dryness under reduced pressure.[9] Different crystal habits of polymorphic form I were prepared as follows:

1. Long flat needles were obtained from a hot saturated solution in n-butanol, rapidly cooled in an acetone dry ice bath to -20 °C, figure 1(c).
2. Tabular crystals connected at the base to form coalesced structures were obtained from a solution in an acetone / dimethyl sulphoxide mixture allowed to crystallise at room temperature, figure 1(d).
3. Very long tabular needles were crystallised from a saturated acetone solution cooled rapidly in an ice bath, figure 1(e).

X-ray powder diffractograms, figure 2, were used to characterise the different crystal form. Samples of the recrystallised particles, figure 1(b - e), were milled with a Retsch model 5657 (Haan, Germany) high speed mill. Milling was repeated three times.

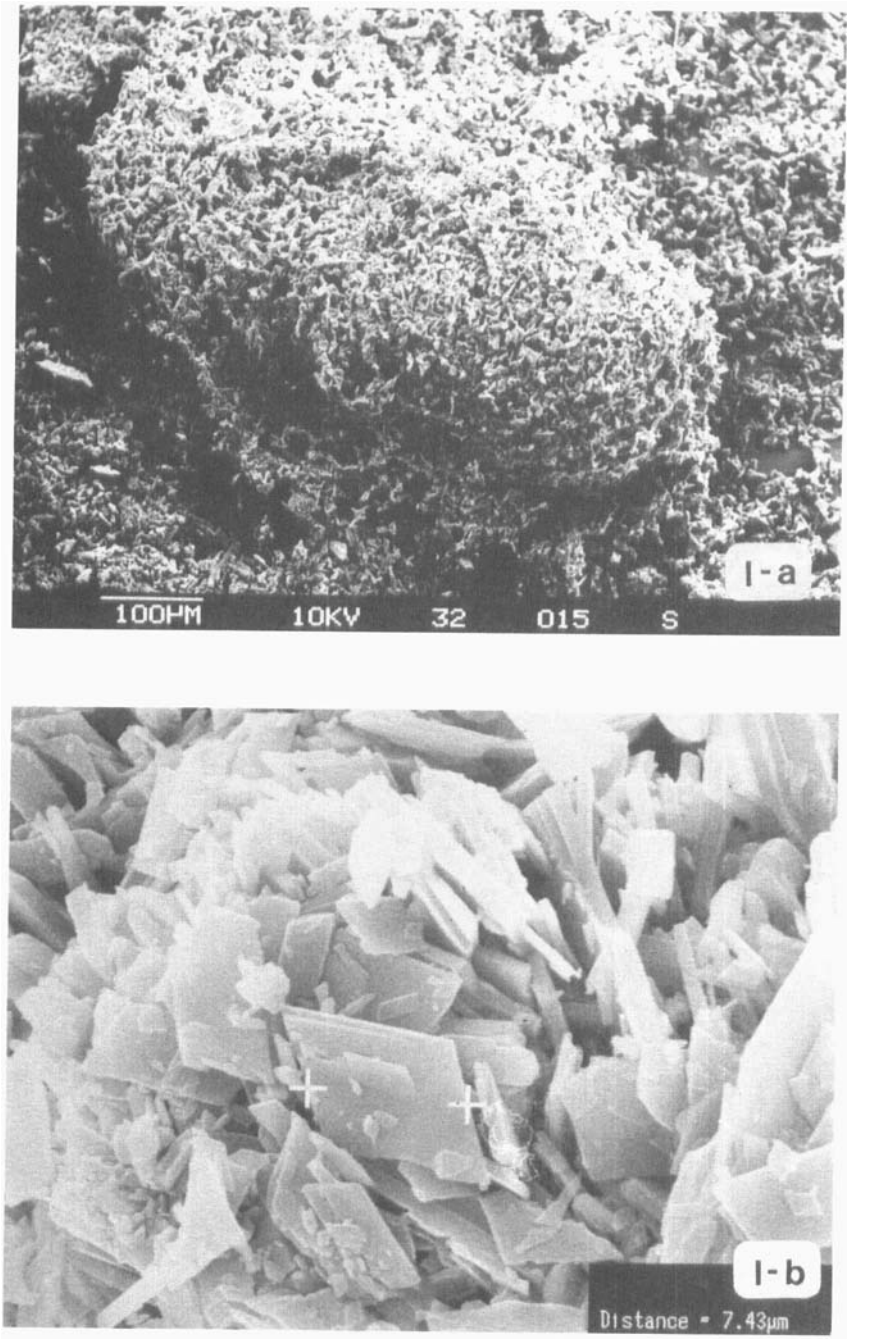

FIGURE 1

Scanning electron micrographs of furosemide polymorph I (a), polymorph II (b), crystal habits of polymorph I, form I-A (c), form I-B (d) and form I-C (e) and form I-A after being milled (f).

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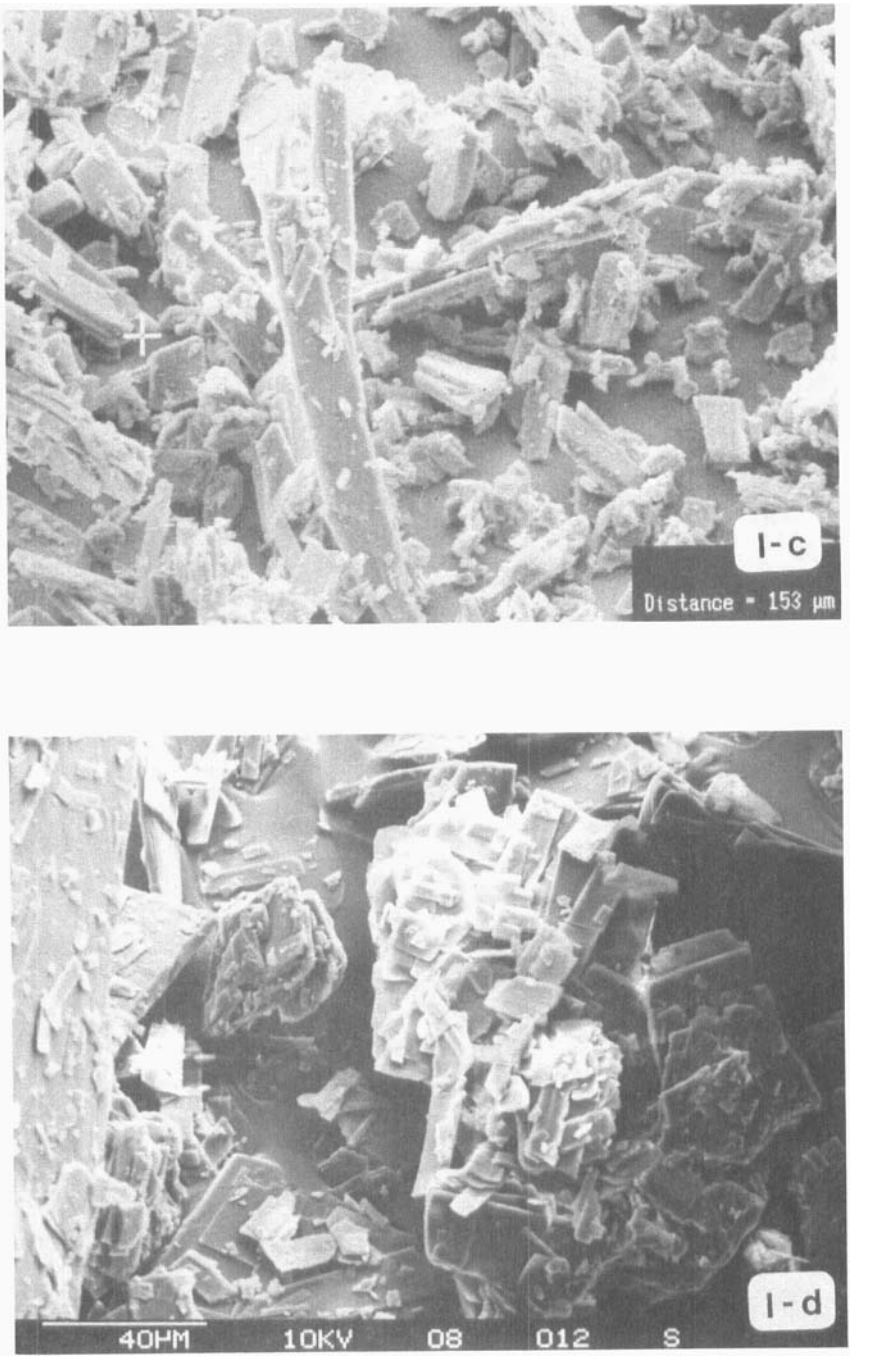
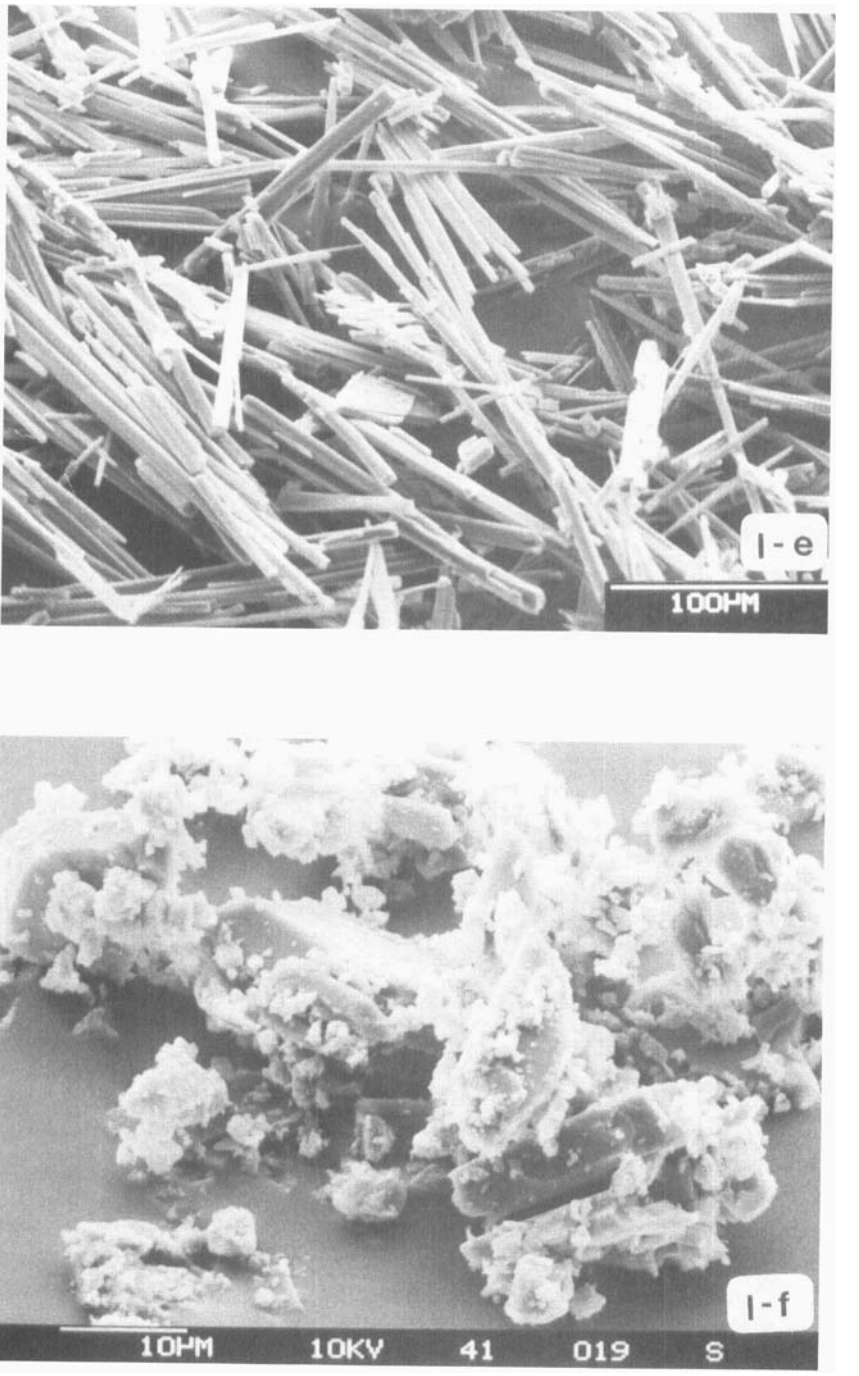


FIGURE 1. Continued



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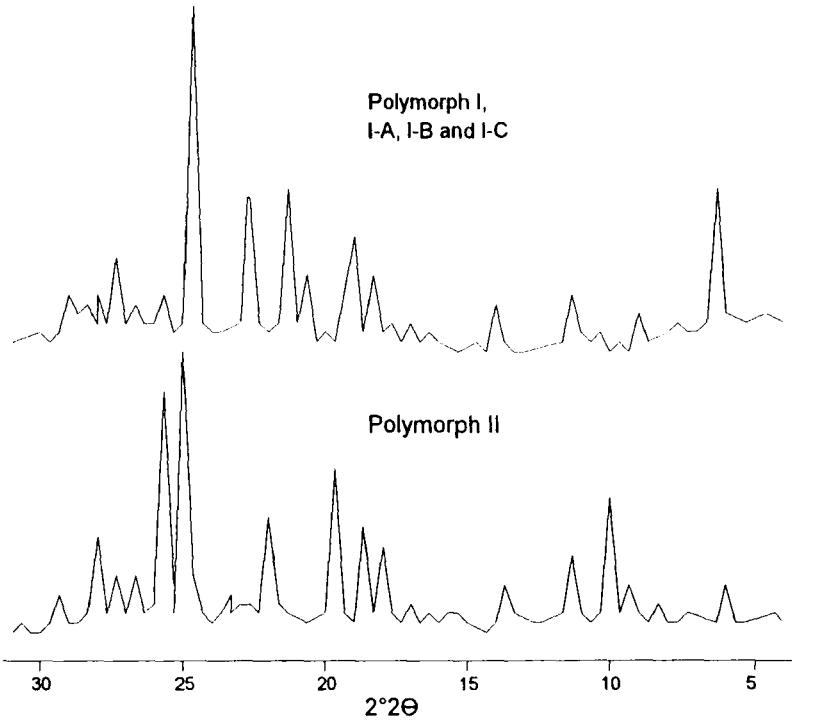

FIGURE 2
X-ray powder diffraction profiles of furosemide crystal modifications.

An example of the product of milling is shown in figure 1(f). Milling did not cause crystal modification because the powder X-ray diffraction profiles stayed the same.

Particle Size Analysis

The particle size was measured with a particles in liquid method using a dual discipline analysis technique integrating laser diffraction and image analysis (Galai-Cis-1, Israel). Concentrated homogeneous suspensions were prepared by lightly shaking suspended powders with a mechanical shaker (agglomerates) or sonication in an ultrasonic bath (dispersed particles).[10] Both membrane filtered solutions saturated with the drug and saturated solutions containing 0.01 gL^{-1} polyoxyethylene sorbitan monooleate were used as dispersing solutions.[10] Results presented throughout are the mean of five individual measurements and particle size distributions are the relative frequency distributions by volume.[11]

Dissolution Measurements

The powder dissolution of samples prepared as for the particle size analysis were measured with a rotating bottle apparatus.[12] The advantage of this method is that it

prevents agglomerates of cohesive particles from floating on the dissolution medium. Samples were placed in a 200 cm^3 amber glass bottle containing 200 cm^3 dissolution medium. The dissolution medium was an acetate buffer pH 4.6.[13] Bottles were rotated at 20 rpm for predetermined times, removed and a sample taken through a 2 μm porous membrane filter. The remaining content of the bottle was transferred to a volumetric flask and suitably diluted. From the UV absorbance of samples measured at 271 nm the amount dissolved was calculated and dissolution profiles constructed. The dissolution of agglomerates and dispersed particles, samples prepared as for particle size analysis, were measured.

Density Measurements

An indirect method to measure the cohesiveness of a powder from bulk density is to calculate the percentage compressibility (C) used to evaluate the flow properties of powders.[14]

$$C = (Dt\text{-}Dp)/Dt \times 100 \quad \ldots\ldots\ldots (1)$$

where Dt is the tapped density and Dp the poured or fluffed density. Powders with a compressibility of > 28 % have extremely poor flow properties and are classified as cohesive.[15] To measure the density change a known powder mass was placed in a calibrated glass cylinder and the cylinder mechanically tapped until no change in the volume could be detected. The true density was measured using an air comparison pycnometer (Model 930, Beckman, USA). Presented values are the mean of five determinations.

Contact Angle Measurements

To lower the interfacial tension, surfactants (wetting agents) are used.[16] The most popular approach to obtain an indirect contact angle for powders is to prepare a compressed disc and to observe a small drop of liquid on the surface. Powder discs were compressed on a RIIC ring press used for compressing discs for infrared spectroscopy. For each powder three discs were prepared and the contact angle of the dispersing solutions measured. Results are the mean of fifteen measurements per disc.

Photochemical Stability

Three samples, 5 g, each of the powdered crystal modifications, particle size between 0-100 μm, were kept either in clear glass containers (petri dishes) directly in sunlight, or in amber glass containers in the dark, under normal atmospheric conditions.[5] The powder was so distributed in the container as to ensure the maximum surface area was exposed to irradiation. At predetermined intervals ± 100 mg samples were removed and the furosemide and 4-chloro-5-sulphamoylanthranilic acid (CSA) content measured using a method described by De Villiers *et al.*[17] CSA was prepared according to the method of Rowbotham *et al.*[18] and identified from its IR spectrum. Analytical plots of peak area against analyte concentration were rectilinear, relevant data are summarised in table 1. Results are the mean of five determinations.

TABLE 1
Statistical data for the HPLC analysis of furosemide and CSA.

Compound	Y-intercept	Standard error of Y-intercept	Slope	Standard error of slope	Correlation coefficient
Furosemide	-1368	1	5504001	25	0.9999
CSA	-706	6	2780455	643	0.9998

Calculations

A computer program (Qautro Pro) was used to treat the fraction degraded, calculated from HPLC peak areas, versus time data, according to an apparent bilateral first order degradation process that was described by a power law dependence ($n = 2$) of the fraction decomposed (α) on time (t) for the nucleation period and first order kinetic degradation with an asymptote, for the growth and deceleration period.[17]

RESULTS & DISCUSSION

Assessment of Cohesive Behaviour

No uniform behaviour of the powders could be detected when examining the appearance of the micronised, recrystallised or milled, furosemide powders. However, scanning electron micrographs of the micronised furosemide powder, figure 1, showed that the powder contained agglomerates of particles with varying sizes. Furthermore, estimation of the cohesive properties of the powders, indicated by the percentage compressibility larger than 28 % (equation 1), showed that the micronised furosemide powders were extremely cohesive (C > 30 % listed in table 2 and 3). Agglomeration was also indicated by the large difference in particle size of agglomerates and dispersed particles listed in table 2 and 3.

Particle Size and Size Distribution of Cohesive Powders

Fine particles of form I, mean size 3 μm, were extremely cohesive, mean size of agglomerates 108 μm, and poorly wettable, contact angle > 90°, see table 2 and 3. Changes in the crystal habit of form I led to the crystallisation of large (mean size > 50 μm) tabular and rod shape, less cohesive but also poorly wettable (contact angle > 90°) particles. The method of preparation of form II produced small plate like crystals, mean size 8 μm, fractionally more wettable, contact angle 75°, and not as cohesive, mean size agglomerates 25 μm. Powders were completely wet by the surfactant solution, contact angle not measurable, used to prepared suspensions of dispersed particles.

TABLE 2
Powder properties of the recrystallised crystal modifications

Crystal Form	Density	C	Particle Size		Contact Angle
			Agglomerates	Dispersed	
	(gcm^{-3})	(%)	(μm)	(μm)	(°)
I	1.65	34	108	3	91
I-A	1.66	15	151	148	90
I-B	1.65	28	27	19	92
I-C	1.65	31	300	43	93
II	1.62	33	25	8	75

TABLE 3
Powder properties of the milled crystal modifications

Form	Density	C	Particle Size		Contact Angle
			Agglomerates	Dispersed	
	(gcm^{-3})	(%)	(μm)	(μm)	(°)
I	1.65	32	111	3	92
I-A	1.64	36	123	11	90
I-B	1.66	34	135	8	91
I-C	1.63	33	146	12	94
II	1.60	32	53	4	78

Effect of Size Reduction on Cohesive Behaviour

Scanning electron photomicrographs, figure 1(f), showed that repeated grinding of large recrystallised furosemide particles produced small particles, but these particles adhered to larger particles to form agglomerates. In table 3 the change in mean particle size of milled particles, suspended by sonication[10] in a saturated aqueous solution, are listed. Milling reduced the particle size but increased cohesion between small particles completely alleviated any advantage gained by size reduction. Milling to a mean size of 4 μm also increased the cohesive properties of form II because the mean size of agglomerates was now 3 μm, see difference in particle size listed in table 2 and 3.

Dissolution Properties of Cohesive Powders

The dissolution rate of the agglomerated powders and suspensions prepared in a saturated furosemide solution containing 0.01 gL^{-1} polyoxyethylene sorbitan monooleate and made in an ultrasonic bath, were measured in an acetate buffer pH 4.6. Large particles, although not cohesive, had poor dissolution properties, figure 3(a). Dispersion of agglomerates improved the dissolution properties, figure 3(b). Milled particles with a mean particle size < 10 μm, prepared from the large crystals, were again cohesive with poor dissolution properties, see difference in dissolution profiles shown in figure 4(a) and 4(b).

Effect of Crystal Modification on Solid-State Photochemical Stability

The apparent first order solid-state photolytic degradation of the three crystal habits of furosemide form I, fitted to the hypothesis proposed by De Villiers *et al.*[17], is shown in figure 5. The first order rate constants according to the "power law" (k_n) and Prout-Tompkins equation (k_g), "power law" factor (n), regression coefficients (R) and maximum fraction degraded (α_m) are listed in table 4.[17]

Most photochemical changes are complex in that it involve subsequent reactions of the molecules or free radicals formed by photolytic degradation. After exposing furosemide to sunlight CSA is found in significant concentrations in samples taken from different polymorphic forms[5]. Although different polymorphic forms may exhibit different photochemical stability[5] the degradation of crystal habit changes of form I, both during the nucleation and growth periods, were not significantly different. This was illustrated by the rate constants listed in table 4 and degradation process shown in figure 5.

CONCLUSIONS

Microfine furosemide particles (form I and form II) were extremely cohesive. Slow dissolution as a result of poor wettability could be overcome by using form II which showed increased wettability and was approximately 1.6 times more soluble. Changes in crystal habit of form I of furosemide led to the crystallisation of large, tabular, less cohesive particles, form I-A, but large particles, although not cohesive had poor dissolution characteristics. When milled to below 20 μm, these particles were again cohesive with poor dissolution properties.

The solid-state photolytic degradation of the furosemide powder samples, exposed to sunlight, followed apparent first order kinetics as described by a model consisting of a nucleation and growth period, with eventual deceleration as it reached a maximum fraction degraded. From results obtained, after fitting fractions CSA formed against time exposed, it was clear that crystal habit changes of form I did not significantly change the solid-state photochemical reactivity of furosemide.

In summary the cohesive behaviour of furosemide powders depended on solid-state properties i.e., polymorphic form, crystal habit but mainly particle size. However, the

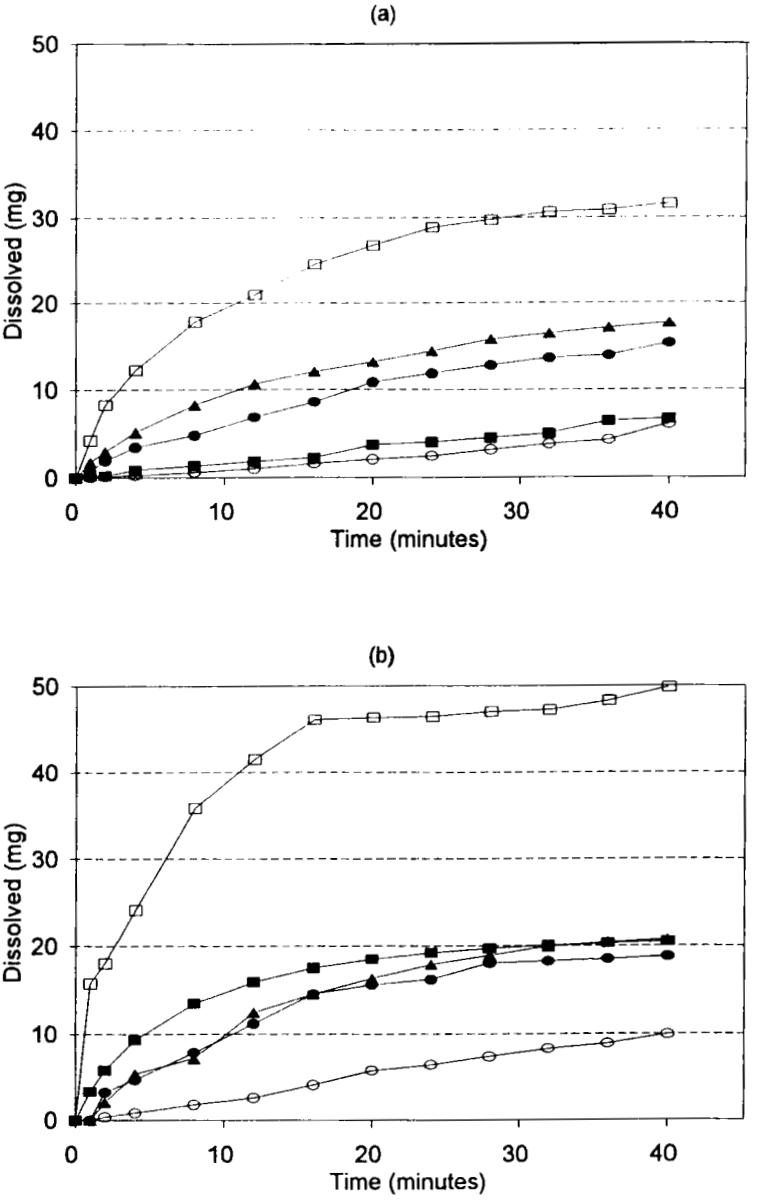

FIGURE 3

Dissolution profiles of crystal modifications (a) agglomerates and (b) dispersed particles: ■ = Form I; □ = Form II; O = Form I-A; Δ = Form I-B; ● = Form I-C.

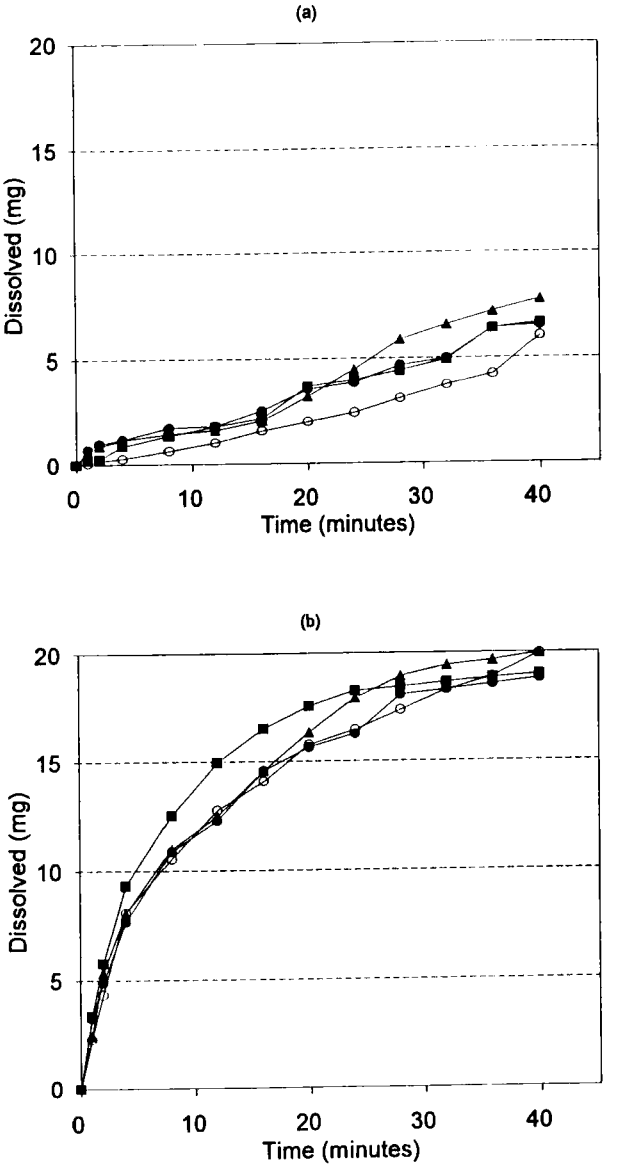

FIGURE 4

Dissolution profiles of milled crystal modifications (a) agglomerates and (b) dispersed particles: ■ = Form I; O = Form I-A; Δ = Form I-B; • = Form I-C.

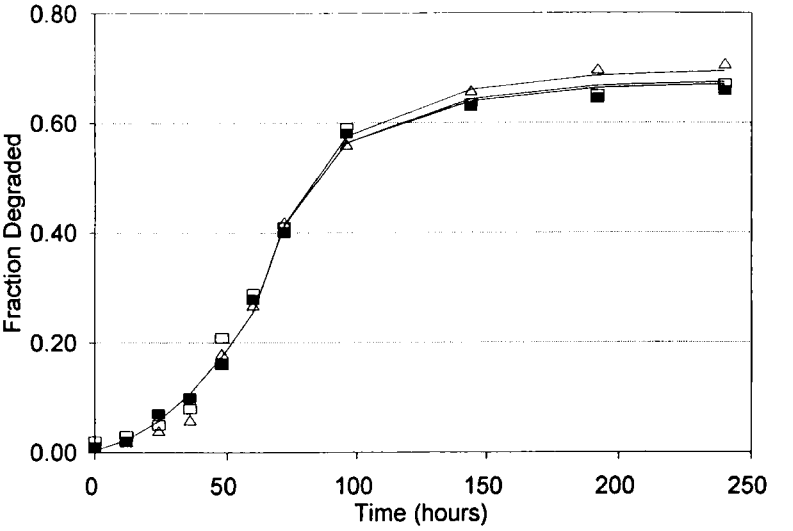

FIGURE 5

Apparent first order bilateral kinetic degradation of crystal habits of polymorph I when exposed to direct sunlight: (■) form I-A, (□) form I-B and (Δ) form I-C. The lines represent the best fit and the markers the mean measured values.

TABLE 4

First order rate constants (k_n and k_g), "power law" factor (n), maximum fraction CSA measured (α_m) and regression coefficients (R) for the solid-state photolytic formation of CSA from three crystal habits of form I of furosemide.

Crystal Form	$k_n \times 10^{-2}$ (h^{-1})	n	R	$k_g \times 10^{-2}$ (h^{-1})	α_m	R
I-A	1.4	2	0.989	2.1	0.68	0.978
I-B	1.4	2	0.997	2.4	0.67	0.992
I-C	1.5	2	0.995	2.6	0.69	0.983

usual specifications for powdered drugs and excipients pay no or scant attention to the crystallographic state. Therefore different samples of chemically identical substances which completely fulfil specifications may have very different physico-chemical properties.

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