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Characterization of humidity-dependent changes in crystal properties of a new HMG-CoA reductase inhibitor in support of its dosage form development

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Abstract

Humidity-dependent changes in the crystal properties of the disodium salt of a new HMG-CoA reductase inhibitor (SQ-33600) were characterized using a combination of gravimetric, thermal, and spectral techniques. The drug substance was found to exhibit rapid moisture sorption and/or desorption, depending on the environmental conditions. Three crystalline solid hydrates and one liquid crystalline phase were identified, each having a definite stability over a range of humidity. The drug substance turned amorphous upon wet granulation, and the amorphous phase reconverted to crystalline hydrates upon exposure to 33–75% relative humidity. To avoid physical instability of dosage forms due to phase changes, manufacturing of solid dosage forms by dry processing below 52% relative humidity was recommended. The dissolution of drug from solid dosage forms was observed to be independent of the crystal form of the active.

Key words: HMG-CoA reductase inhibitor; SQ-33600; Crystal properties; Hydrate; Humidity effect; Liquid crystalline phase; Dosage form design

1. Introduction

Many pharmaceutical solids are known to form hydrate species (Byrn, 1982), with more than one hydrate form being stable depending on the crystallization conditions, degree of drying after crystallization, or subsequent exposure to different humidity conditions (Cox et al., 1971; Haleblian, 1975). A particular hydrate form of a compound may also convert to an anhydrous crystalline form, an amorphous form, or other hydrate forms depending on processing conditions the material undergoes during the formulation of dosage forms, or as a result of environmental humidity conditions (Byrn, 1982; Nyqvist and Wadsten, 1984; Puttipipatkhachorn et al., 1990). Any change in crystal properties of a drug may influence its physical and chemical stability, dissolution rate,

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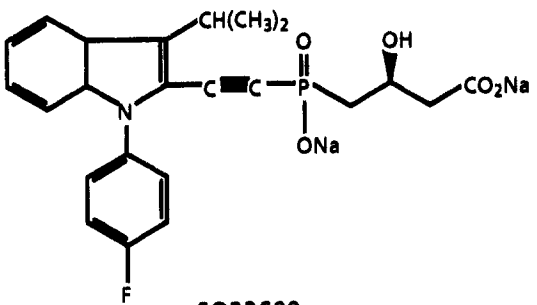
and processability (Ando et al., 1992; Fukumori et al., 1983; Imaizumi et al., 1980; Shefter and Higuchi, 1963; Yamaka et al., 1982). It is important, therefore, that a salt or other chemical form which is relatively nonhygroscopic (and therefore has the least propensity for a humidity-dependent change in crystal form) be selected for dosage form design (Morris et al., 1994).

When a hygroscopic chemical form must be selected for development (because a nonhygroscopic form is not available, or may be unsuitable for other reasons), it is essential that the propensity of the compound to form hydrate, anhydrate, or other forms be characterized. It becomes essential to discover the optimum range of moisture content for the bulk drug substance, and the limits of humidity conditions permissible in the processing environment (Cox et al., 1971).

The present report details how the humidity-dependent changes in crystal forms of SQ-33600, the disodium salt of a novel HMG-CoA reductase inhibitor, was characterized during the development of its solid dosage forms. The structure of this compound is as follows:



SQ33600

2. Experimental

2.1. Materials

SQ-33600 was manufactured by the Chemical Process Development Division of Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ.

2.2. Moisture sorption / desorption studies

Equilibrium moisture contents were determined by storing samples in closed desiccators over saturated aqueous solutions of LiCl, CH_3COOK, $CaCl_2$, $MgCl_2$, K_2CO_3, $Mg(NO_3)_2$, NH_4NO_3, 1:1 NH_4Cl/KNO_3, NaCl, KCl, KNO_3, and K_2SO_4, which maintained relative humidities (R.H.) of 11, 22, 31, 33, 43, 52, 60, 70, 75, 84, 93, and 97%, respectively. Anhydrous $CaSO_4$ (Drierite®, Hammond, OH) provided the 6% R.H. condition. Preliminary experiments demonstrated that although the moisture contents of samples reached equilibrium in less than 24 h, moisture contents were routinely determined after 40–48 h of storage in the desiccators. The moisture contents of various samples were measured either by Karl-Fischer (KF) titration (using a Brinkman 684 coulometer) or by thermogravimetric (TG) analysis. Sample sizes for KF analysis were selected to yield approx. 1000 μg of water. The rate and extent of moisture sorption or desorption under different humidity conditions were also determined by using a Cahn Digital Recording Balance fitted with a system to maintain and monitor specific relative humidity conditions. A description of the apparatus has been reported (Morris et al., 1994). Various salt solutions at room temperature were used to maintain different relative humidity conditions.

2.3. Differential scanning calorimetry (DSC) and thermogravimetric (TG) analyses

To obtain a DSC thermogram, the sample was sealed in an aluminum pan, in which a pinhole was punched in the pan lid. Samples were heated at a rate of 5°C/min from room temperature to about 200°C, using a TA Instruments 2000 Thermal Analyst system. The TG analysis was conducted by heating a 10 mg sample on an open pan in the TG module of the same system at a heating rate of 10°C/min. A 40 ml/min nitrogen purge was maintained during the TG experiments.

2.4. Optical microscopy studies

The particle morphologies of samples of SQ-33600 exposed to various humidity conditions were evaluated using polarizing optical microscopy, on a Nikon Microphot-SA system. 1–2 mg of a sample was mulled in mineral oil on a glass slide, and immobilized with a cover slip. Owing to the relatively fine particle size of the material, most work was conducted at magnifications of 100 and 200×. Polarizing optics were used to study the crystallographic properties of the solids and to identify the possible presence of any amorphous material. The liquid crystalline phase of SQ-33600 was also investigated using polarizing optics.

2.5. Powder X-ray diffraction (XRD) analysis

XRD powder patterns of the samples were recorded using a Phillips APD 3720 powder diffraction system, with a vertical goniometer in the $\theta/2\theta$ geometry. The X-ray generator (model XRG3100) was operated at 45 kV and 40 mA with a copper radiation source. A scintillation detector was used to scan the range between 2 and 32° 2θ. For investigating possible changes in powder patterns due to alterations in relative humidity, the powder pattern of selected samples were recorded after equilibration in a sample holder at a particular humidity for 24–48 h. The top surface of the sample in the holder was completely exposed to the atmosphere, thus presenting no barrier to the diffusion of moisture into the powder bed. In other experiments, variable temperature powder X-ray diffraction (VT-XRD) was used to observe changes in crystallinity which took place upon thermal treatment. For this work, the sample was heated for 4 min in the instrument at a given temperature, and then the powder pattern was obtained at the equilibration temperature. The effect of bulk moisture on samples were obtained by misting the sample in its holder, and subsequently measuring the powder pattern.

2.6. Solid-state ^{13}C-NMR analysis

The solid-state ^{13}C-NMR spectra were obtained on a Bruker AM-250 spectrometer utilizing the ^{13}C resonant frequency of 62.89 MHz (magnetic field strength of 5.87 T). Approx. 500 mg of sample was required to fill the zirconium rotors, which utilized a Kel-F cap. The cross polarization, magic angle spinning (CP/MAS) pulse sequence was used to acquire the qualitative spectra (Yannoni, 1982). The sample was spun at a frequency of 5.0 ± 0.1 kHz and the magic angle setting calibrated by the KBr method (Frye and Maciel, 1982). Each spectrum represents 128 transients acquired under the following conditions: 4K data set zero filled to 16K, spectral width of 20000 Hz, 5 s recycle time, 2 ms contact time, 7.1 μs pulse width for ^{13}C and 5.7 μs for ^{1}H. The Hartmann-Hahn match was optimized by monitoring the ^{13}C intensity vs ^{13}C radiofrequency (rf) field with a spinning adamantane sample. The data set was subjected to an exponential weighting function of 5.0 Hz to improve the signal-to-noise ratio (Ernst, 1965; Ernst and Anderson, 1965). Fourier transformation and phase correction of the FID then produced a frequency domain spectrum. The spectrum was recorded at ambient temperature and the chemical shifts externally referenced to tetramethylsilane [$\delta(CH_3)_4Si = \delta$(adamantane CH_2) − 38.3)].

2.7. Solid-state Fourier transform infrared (FTIR) analysis

Qualitative diffuse reflectance FTIR spectra (DRIFTS) were acquired on a Nicolet model 740 FTIR spectrophotometer, interfaced with a Collector® diffuse reflectance accessory unit (Spectra-Tech, Inc.). A water-cooled globar source was used in conjunction with a Ge/KBr beam-splitter and a narrow-band mercury cadmium telluride (MCT-a) detector cooled with liquid nitrogen. Each spectrum represents 32 co-added scans, obtained at a spectral resolution of 4 cm^{-1}. Variable temperature DRIFTS (VT-DRIFTS) spectra were also recorded between 25 and 185°C by heating samples at 20°C intervals and measuring the spectrum at each temperature point.

2.8. Prototype formulation studies

A series of prototype capsule and tablet formulations were prepared by dry blending and wet

granulation procedures. During the wet granulation method, approx. 22% w/w water was used, which was subsequently removed by drying at approx. 55°C. To obtain high-quality powder patterns, the drug-to-excipient ratio used in prototype formulations used for the XRD studies was 1:2.8, which was much higher than that used (1:10 and 1:15) in the capsule and tablet formulations developed for potential clinical use. To evaluate the dissolution profiles of formulations prepared from the different hydrate phases, testing of 20-mg potency capsules and tablets prepared by dry blending as well as wet granulation (weight per capsule or tablet = 300 mg) was conducted in 0.1 N HCl (pH 1.1), in water, and in pH 7.5 phosphate buffer. All work was conducted at 37°C, using the USP paddle method and a paddle speed of 50 rpm. The drug concentrations in dissolution media were analyzed by an ultraviolet spectral method.

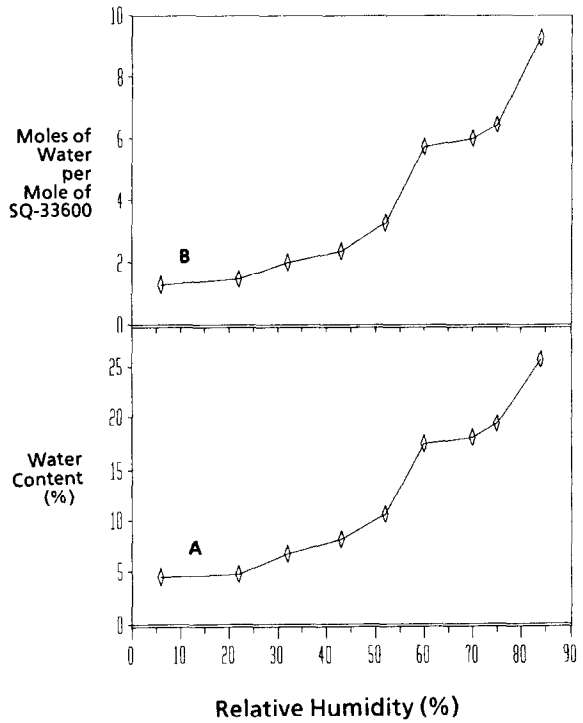


Fig. 1. Water content of SQ-33600, after full equilibration at room temperature with selected controlled humidity conditions. The composition is shown both in terms of (A) the percent water content, and (B) the number of moles of water contained per mole of SQ-33600.

3. Results and discussion

3.1. Moisture sorption / desorption studies

SQ-33600 was found to be hygroscopic, and its moisture content could be varied with changes in ambient humidity. This behavior is shown in Fig. 1, where the average equilibrium moisture contents of three representative lots of SQ-33600 are plotted in units of %w/w water content and in units of mol of water per mol of drug. There was no significant lot-to-lot variation in equilibrium moisture contents at different humidity conditions. During early stages in development, the initial moisture contents of different bulk lots, however, varied from 3.3 to 13.0% w/w, indicating that a control of the initial moisture content of bulk drug substance would be necessary to maintain batch to batch uniformity.

As shown in Fig. 2, the moisture sorption/desorption rates of SQ-33600 were quite rapid. When a sample having an initial moisture content of 8% w/w was exposed to 6% R.H., it lost approx. 5% of its weight in 1 h. The lost water was regained rapidly when the sample was subsequently exposed to higher humidity conditions. Under certain humidity conditions, plateau values in moisture sorption indicating equilibration with ambient humidity conditions were reached in less than 30 min. The short equilibrium process was confirmed by exposing samples to different humidity conditions in desiccators for 7 days, and the moisture content of these samples was not significantly different from that obtained in the moisture balance. Moisture sorption rates at 84% and higher humidity conditions were found to be much slower, with the system requiring at least 24 h to attain full equilibrium. After 24 h of exposure to 84% relative humidity, the powders were observed to shrink and agglomerate. At relative humidities of 93 and 97%, semisolid masses were formed.

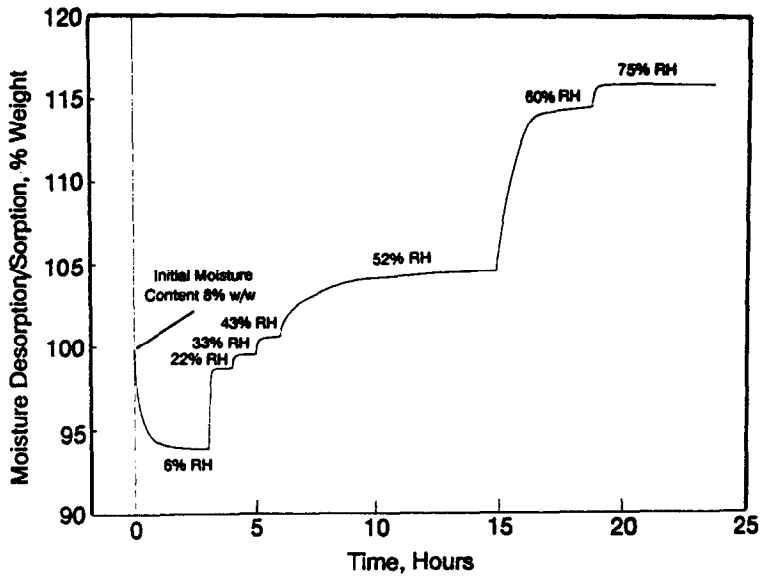


Fig. 2. Room temperature moisture desorption/sorption by SQ-33600 under different relative humidity conditions, as determined by weight loss/gain on a Cahn recording balance.

3.2. Humidity-dependent changes in crystal properties

The influence of humidity conditions on the crystal properties of bulk SQ-33600 drug substance was investigated by DSC, thermogravimetric analysis, powder X-ray diffraction, and solid-state ^{13}C-NMR spectrometry.

The thermal properties of SQ-33600 were significantly different when the material was ex-

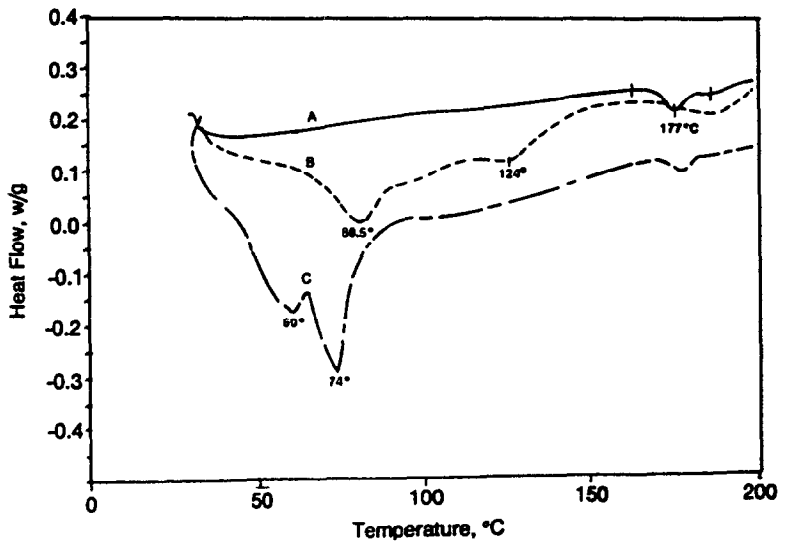


Fig. 3. DSC scans of SQ-33600 samples, exposed to (A) 22%, (B) 43%, and (C) 75% R.H. conditions. The thermograms were obtained at a heating rate of 5°C/min.

posed to less than 22, 33–52, and 60–75% R.H. This behavior is shown in Fig. 3, which contains the DSC thermograms of samples exposed to 22, 43, and 75% R.H. While samples exposed at less than 22% R.H. (which according to the equilibrium moisture studies may contain up to 1.4 mol of water per mol of drug substance) did not exhibit any distinct thermal features below 170°C (curve A, Fig. 3). It is possible that subambient DSC analysis would show more detail, however, this analysis could not be performed at the time. Multiple endotherms between 25 and 150°C, and 25 and 90°C were observed in samples exposed to 33–52% R.H. (curve B, Fig. 3) and 60–75% R.H. (curve C, Fig. 3), respectively. These events were followed by minor endotherms around 175°C, and the samples finally decomposed above 220°C. Through the use of both TG (Fig. 4) and Karl Fischer analyses, it was confirmed that endotherms present in curves B and C at temperatures less than 150°C were indicative of dehydration of the samples. As shown in curve A of Fig. 4, the dehydration of samples exposed to less than 22% R.H. (or which contained less than 5% w/w moisture) proceeded smoothly between room temperature and 150°C, and no plateaus were seen. This behavior may be contrasted with that noted for samples exposed to 33–52% R.H. (curves B and C) or 60–75% R.H. (curves D and E), where sharper changes in TG baselines were seen which agreed closely with the DSC thermal events illustrated in Fig. 3.

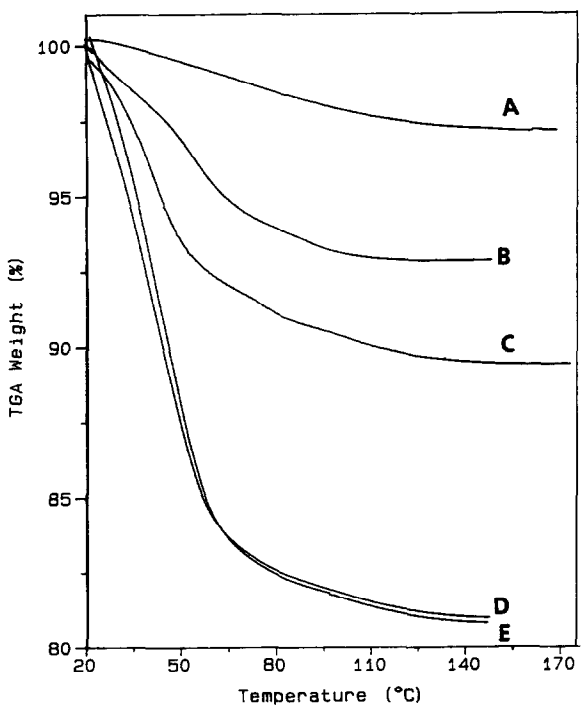


Fig. 4. Thermogravimetric analysis of SQ-33600 samples, (A) containing approx. 3% water, and after this material was exposed to relative humidities of (B) 33%, (C) 52%, (D) 60%, and (E) 75%.

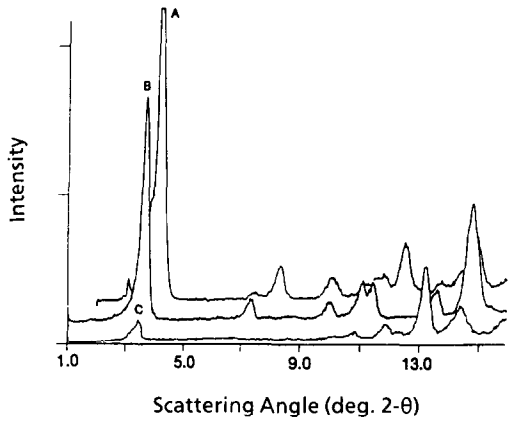


Fig. 5. X-ray powder diffraction patterns of SQ-33600 materials exposed at room temperature to (A) 22%, (B) 43%, and (C) 75% R.H. conditions.

Representative examples of XRD powder patterns on samples exposed to different humidity conditions are shown in Fig. 5. These reveal that several scattering peaks observed in samples exposed to 22% R.H. were lost after equilibration at 43% R.H., while others appeared in their place. Considered together with the DSC data, this trend indicates the formation of a new crystalline hydrate phase after exposure to 43% R.H. The XRD patterns of samples exposed to 33 and 52% R.H. were essentially equivalent to those obtained for the 43% R.H. sample. Slight shifts in peak positions were noted for these materials, but these shifts are most likely due to lattice expansions associated with the water sorption (Cox et al., 1971). Further changes in the XRD pattern were observed in samples exposed to 60–75% R.H. (pattern C in Fig. 5), which indi-

cated the formation of yet another crystalline hydrate species. Powder patterns obtained on materials equilibrated at humidity values exceeding 84% were featureless, indicating that yet another phase transformation could take place at the highest humidity values.

Variable temperature powder XRD experiments were found to be very useful in characterizing the nature of the water lost during the dehydration processes of each crystalline hydrate species. The powder pattern of material exposed at less than 22% R.H. did not change when samples were heated up to 180°C and dehydrated. This finding would suggest that either the water is not incorporated into the crystal lattice or that the dehydration does not cause large enough changes in the lattice parameters to be observed with our experimental variation. The powder patterns of samples exposed to 33, 53, or 75% R.H. were found to change significantly upon dehydration, indicating that the water contained in these hydrate phases was part of the crystal structure.

Based on the information deduced from the DSC thermograms and the XRD powder patterns, it was possible to identify three highly humidity sensitive crystalline phases for bulk SQ-33600. These are specifically characterized into the species existing over certain relative humidity ranges: type I (existing at relative humidities less than 22%), type II (existing in the relative humidity range of 33–52%), and type III (existing over the range of 60–75% R.H.). The semisolid material formed at relative humidity values exceeding 84% must represent a fourth phase that does not exhibit a powder pattern, and, therefore, cannot be classified as a crystalline species.

To further investigate the possible influence which any amorphous phase coexisting with the crystalline phases of SQ-33600 might exert on the hygroscopicity trends, a true amorphous sample was prepared by lyophilization of bulk material. Its moisture sorption and possible conversion to crystalline forms at different humidity conditions was studied. The moisture content of this amorphous solid after its equilibration at 22% R.H. (as determined using the Cahn balance) was 7.1% w/w, as compared to the 5% w/w normally

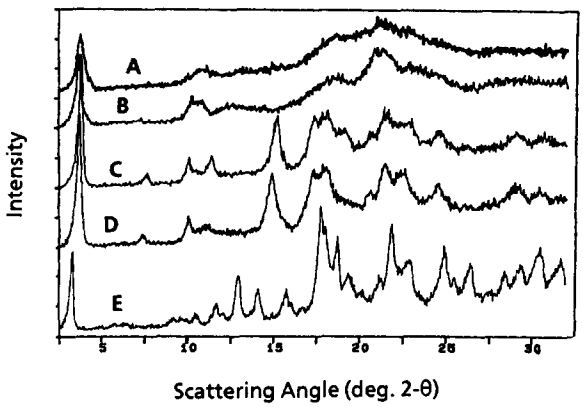


Fig. 6. X-ray powder diffraction patterns of (A) amorphous SQ-33600, and after exposure of this sample to relative humidities of (B) 22%, (C) 33%, (D) 52%, and (E) 75%.

found for type I material. As mentioned above, the DSC and powder XRD results indicate that the type I material is crystalline, and therefore, it is possible that the material exists as a crystalline hydrate. As shown in Fig. 6, the lyophilized material was found to convert to the various crystalline phases upon exposure to 33–75% R.H. conditions for 24 h. These findings provide evidence that the samples studied were largely crystalline although a small amorphous halo was observed in all patterns.

The humidity-dependent changes in the SQ-33600 crystalline phases were further investigated by solid-state ^{13}C-NMR analysis. Fig. 7 shows the solid-state NMR spectra of material initially containing 3.5% w/w moisture, and of samples stored at relative humidities of 31, 52 and 70%. The single carbonyl functional group within SQ-33600 yields the resonances centered at approx. 180 ppm. The material containing 3.5% w/w moisture (type I) exhibited two resonances ($\delta = 178.5$ and 179.9 ppm). The presence of two resonances for one functionality may be attributed to crystallographic splittings or hydrogen bonding effects (Fletton et al., 1987; Etter and Vojta, 1989). Samples exposed to the intermediate R.H. conditions (type II material) display a new carbonyl resonance at 181.5 ppm (Fig. 7B and C). It appears that the sample exposed to 31% R.H. did not fully convert to type II material as indicated by

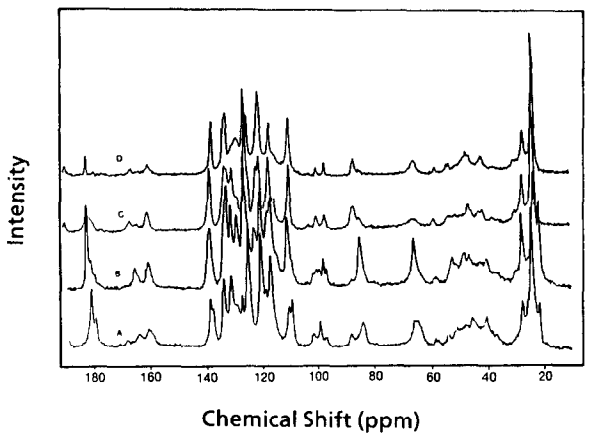


Fig. 7. Solid-state ^{13}C-NMR spectra of SQ-33600 (A) initially containing 3.5% moisture, and after its exposure to (B) 31%, (C) 52%, and (D) 70% R.H. conditions.

the presence of carbonyl resonances at 178.5 and 179.9 ppm which are indicative of type I material. At 52% R.H., almost complete conversion to type II material is noted based upon the single carbonyl resonance at 181.5 ppm. The sample exposed to high humidity (70% R.H., type III material) displayed only a single carbonyl resonance at $\delta = 182.0$ ppm.

In the aromatic region of the NMR spectrum (150–110 ppm), slight spectral differences are noted for the three different forms. Since only slight spectral shifts are measured for the various resonances (typically < 1.0 ppm), the relative orientation of the aromatic portion of the SQ-33600 molecule appears to remain relatively unchanged upon conversion from one pseudopolymorphic form to another. This is not the case for the isopropyl carbon atoms. Significant spectral differences exist upon comparison of the NMR resonances for the methyl and methine carbons from one form to another. The major resonance at 23.8 ppm (assigned to the $-CH_3$ group) in type I material shifts to 22.9 ppm for type II material and 23.5 ppm for type III material. In addition, slight shifts for the methine carbon are noted from one relative humidity condition to another. Based upon the solid-state ^{13}C-NMR results, three distinct pseudopolymorphs exist and it appears that types II and III are fairly similar in their three-dimensional structure.

3.3. Microscopic examination of different phases

It was necessary to establish whether the hygroscopicity of types I, II, or III could be attributed to the presence of an amorphous phase. For example, Saleki-Gerhardt (1993) used mixtures of crystalline and amorphous sucrose to demonstrate that the hygroscopicity of the solid was due to the presence of an amorphous phase. It was particularly important to study the type I material, due to the ambiguity of the DSC events associated with the dehydration processes in the TG thermograms. Samples of SQ-33600 which had been exposed to various humidity conditions (ranging from 6 to 75% R.H. over a period of 7 days) were critically examined using polarizing optical microscopy for the presence of amorphous material. Amorphous material was not evident using the criteria of significant depolarization in the samples stored at relative humidity values less than 75% R.H., although powder XRD patterns clearly exhibit an amorphous halo for these samples. A definite change in material properties was, however, noted for materials stored at 84% R.H. The individual crystallites of SQ-33600 which existed in materials stored under lower humidity conditions were not observed in material stored at relative humidities exceeding 84%. Instead, the material was found to consist of large aggregates of semi-solid. When smeared onto a microscope slide, these aggregate masses exhibited zone birefringence which largely reflected the thickness of the material. This behavior is consistent with that noted for other liquid crystalline phases (McCrone et al., 1984). Recently, Vadas et al. (1991) also reported the formation of a liquid crystalline phase when a crystalline solid was subjected to high humidity.

3.4. Nature of moisture present in the hydrate phases

Infrared spectra, obtained within the high-frequency region, are capable of being used for the characterization of water contained within crystalline solids (Brittain et al., 1988). As shown in Fig. 8, the diffuse reflectance IR spectra of SQ-33600 materials, stored under different hu-

midity conditions, provided additional information as to the nature of moisture present in the different hydrate phases. The sharp absorption band at 3640 cm^{-1} is indicative of the O-H stretching mode associated with either strongly bound or crystalline water. This band is noted even in samples stored under the lowest humidity condition (6% R.H.), indicating that the water contained in type I samples is not characteristic adventitious water. The sharpness of the band is evidence of a bound species even at the lowest levels of moisture content. The bound nature of this water contained in low moisture samples was confirmed by VT-DRIFTS studies. As shown in Fig. 9, the 3640 cm^{-1} peak progressively decreased in intensity upon thermal dehydration, and completely disappeared at a temperature of 145°C. No other spectral features changed during VT experiments confirming the integrity of the SQ-33600 molecule. This finding agrees well with the TG studies carried out on the same sample, which indicated that all water loss was essentially complete by 150°C.

It was not possible to grow crystallographically acceptable crystals of any of the hydrate phases

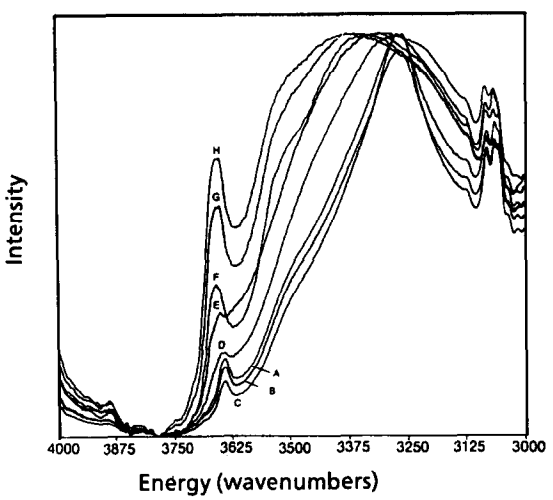


Fig. 8. Diffuse reflectance IR spectra of SQ-33600 displaying the absorption bands due to bound water of hydration after exposure of samples to different relative humidity conditions. Spectra are shown for (A) the initial sample containing 3.5% water, and after its exposure to relative humidities of (B) 6%, (C) 15%, (D) 31%, (E) 43%, (F) 52%, (G) 70%, and (H) 84%.

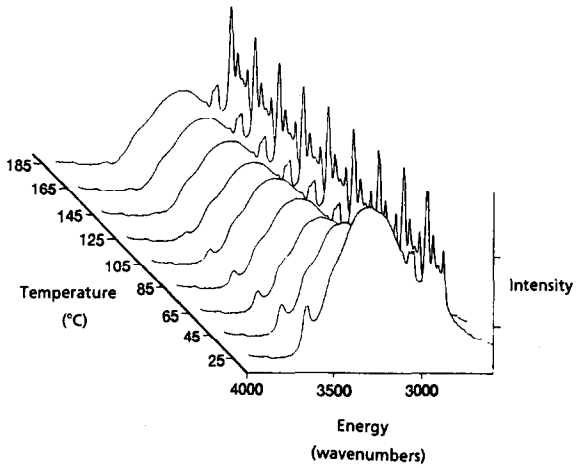


Fig. 9. Variable temperature diffuse reflectance IR spectra of SQ-33600, initially containing 3.5% water.

for single-crystal diffraction work, and consequently the positions of water molecules in the SQ-33600 hydrate phases could not be directly ascertained. However, the available data do permit certain deductions to be made regarding the modes of water binding within the SQ-33600 hydrate phases. These may be summarized as follows:

Type I: This form is characterized by solids containing up to 1.5 mol of water per mol of SQ-33600. The IR data strongly indicate that the water cannot be purely adventitious, even though no DSC endotherm or a change in powder XRD pattern is associated with its loss. It is possible that the water is contained within 'channels' in the solids. The nonspecific desolvation observed in the TG analysis, and the absence of DSC endotherms, may be taken as indicating the presence of noncrystalline water. The IR absorption band at 3640 cm^{-1} is an indication that the water must be bound at some type of localized site. This conclusion is different from that noted for some compounds for which dehydration through channels does dramatically change the crystal structure (Byrn, 1982; Morris and Rodriguez-Hornendo, 1993), but has precedent for others in which dehydration of the channels does not measurably affect the crystal structure as determined

by powder XRD (Pfeiffer et al., 1970; Cox et al., 1971).

Type II: This crystalline phase is formed upon sorption of up to 2 additional mol of water per mol of drug, with the maximum drug-to-water ratio being 1:3.5. All data indicate that the crystal lattice can reversibly expand over this water content range while still maintaining the basic crystal structure.

Type III: This hydrate phase appears to contain an average of 5.5 water molecules per molecule of SQ-33600.

Liquid crystalline phase: At the highest levels of water content a liquid crystalline phase can be formed. This requires the sorption of a relatively large amount of water.

While the crystalline forms of SQ-33600 are distinct, the fact that no exact stoichiometry is maintained over the relative humidity ranges studied leads to the following speculation. One possibility is that any amorphous portion of the sample which does not convert to crystalline material due to prohibitive kinetics contributes to the moisture value. Another possibility is that within the relative humidity ranges specified for the various forms, the hydration continuously varies within lattice channels as observed by Cox et al. (1971) for cromolyn sodium.

3.5. Specification for moisture content

Since any moisture-dependent change in the crystal form of SQ-33600 might adversely influence the processing of its solid dosage forms, it was important that the moisture content of the bulk drug substance was kept within a narrow range. A moisture specification was therefore recommended after consideration of the possible humidity conditions for which the material might encounter under normal processing. A typical manufacturing environment normally ranges from 20 to 50% R.H., and within this humidity range the moisture content of SQ-33600 could vary between 5 and 10.5% w/w. At the approximate midpoint of this range (33–43% R.H.), the moisture content of the material would be predicted to vary between 7 and 8.5% w/w. For this reason, the moisture specification for the bulk drug substance was set at 7–8.5% w/w so that moisture sorption/desorption under typical processing environments would be minimal.

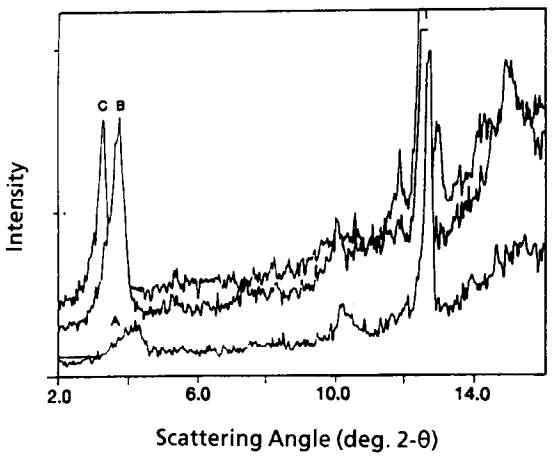


Fig. 10. X-ray powder diffraction patterns, showing the influence of wet granulation on SQ-33600. Powder patterns are shown for (A) material as produced by the process, and after storage of these granules at (B) 52%, (C) and 75% R.H.

3.6. Solid dosage form design considerations

Capsule and tablet dosage forms of SQ-33600 were prepared by wet granulation as well as by dry blending of drug substance with excipients. The powder XRD analysis showed no change in crystallinity in the dry blending procedure, however, the wet granulation of SQ-33600 transformed most of the drug into the amorphous phase (it is possible that this proceeds through a liquid crystalline phase). The wet-granulated amorphous material, however, gradually became crystalline upon exposure to humidity conditions between 33 and 75% R.H. for different lengths of time. Fig. 10 shows the effect of direct exposure of granules to 52 and 75% R.H. for 4 days. The increase in XRD scattering at 3–5° 2θ is indicative of the crystallization of SQ-33600 (there were no interfering peaks from the excipients in this region).

To avoid any physical instability of dosage forms due to crystallization of drug after wet granulation, a dry blending process was adopted for the preparation of SQ-33600 capsules and

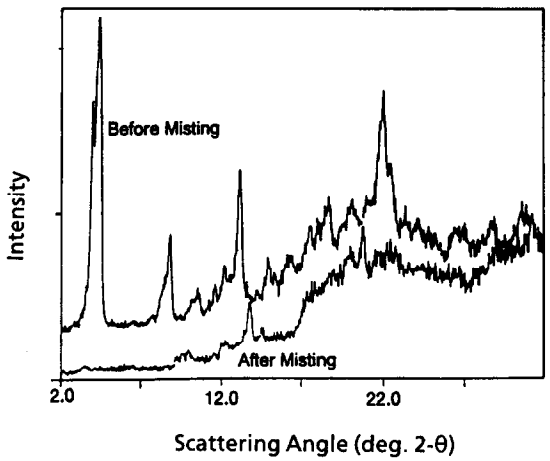


Fig. 11. X-ray powder diffraction patterns, showing the influence of the misting of a SQ-33600 pellet surface by water.

tablets. It was, however, recognized that if the long-term stability of capsules and tablets prepared by the wet granulation method was acceptable, and the bioavailability of amorphous and crystalline forms of the drug were equivalent, a wet granulation process could be used at a later time. The dissolution of capsules and tablets in aqueous media (0.1 N HCl, water, and pH 7.5 phosphate buffer) was not found to be influenced by prolonged (up to 3 months) exposure of both the wet-granulated and the dry-blended formulations to 52 and 75% R.H., although the XRD powder pattern demonstrated that a change in crystal form occurred. This lack of influence of phase composition on dissolution is due to the high intrinsic solubility of SQ-33600 (known to exceed 300 mg/ml in water at room temperature).

To study the possible phase changes on the surface of dissolving dosage forms, the XRD powder pattern of a neat SQ-33600 compact in a XRD sample holder was obtained before and after misting the surface with a spray of water. As seen in Fig. 11, the disappearance of scattering peaks within the 2–5° 2θ range and the loss of most peaks at higher scattering regions indicate that the surface of the material either converted to the amorphous or possibly the liquid crystalline phase after contact with water. Since such a conversion would occur at the dissolving surface of all forms of SQ-33600, it is predicted that the dissolution of all forms of SQ-33600 would be identical. It was therefore concluded that the phase composition of the drug would not significantly influence its dissolution, and that the humidity-dependent change in crystal form would be a factor only in the processing and in the physical stability of formulations.

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