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International Journal of Pharmaceutics 137 (1996) 21–31

international journal of pharmaceutics

Effects of excess enantiomer on the crystal properties of a racemic compound: ephedrinium 2-naphthalenesulfonate

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Received 25 August 1995; revised 11 November 1995; accepted 15 November 1995

Abstract

A small enantiomeric excess in the crystallization medium during the crystal growth of the racemic compound, (±)-ephedrinium 2-naphthalenesulfonate, (±)-EN, is found to become partially incorporated into the racemic crystals. The small enantiomeric excess (guest) in a racemic compound (host) may disrupt the crystal lattice, leading to changes in the thermodynamic properties and intrinsic dissolution rate of the host crystals. This hypothesis was tested by growing crystals of (±)-EN from aqueous media containing various excess quantities of either enantiomer and the resulting crystals were analyzed by a stereoselective HPLC method. The melting point phase diagram of (±)-EN was determined and the extent of solid solution formation was 0.029 mole fraction of either enantiomer of EN in the racemic compound of EN at 25°C. The segregation coefficient was found to be about 0.078, lower than 0.15 for a homochiral host (Duddu, S.P. et al., *Int. J. Pharm.*, 94 (1994) 171–179), suggesting that (±)-EN with higher symmetric packing has a lower tendency to take up excess enantiomer into its host crystals. The melting point and the heat of fusion of the crystals were measured by differential scanning calorimetry. Increasing amounts (0–5%) of guest incorporated into the host gave approximately linear decreases in the melting point, enthalpy of fusion and entropy of fusion. The disruption index was on the order of 5, which is comparable with that for non-isomeric doping of organic crystals, but much lower than that of 20 for doping (−)-EN with (+)-EN (Duddu, S.P. et al., *Int. J. Pharm.*, 94 (1994) 171–179). The intrinsic dissolution rate reached a maximum value at low levels (0.015–0.03 mole fraction) of doping corresponding to solid solution formation, and then decreased to the original value at higher levels of doping corresponding to the formation of a separate phase. Thus, a small excess of either enantiomer in the racemic compound significantly changes the thermodynamic properties and the intrinsic dissolution rate of (±)-EN. These results may have implications for other racemic drugs.

Keywords: Chiral impurity; Crystallization; Disruption index; Intrinsic dissolution rate; Solid solution; Racemic compound

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SSDI 0378-5173(95)04395-0

1. Introduction

Even the most carefully grown and purified molecular crystals inevitably contain residual impurities (Wright, 1987). For chiral drugs, this problem is particularly apparent, because it is often difficult to separate the residual undesirable chiral isomers (Jacques et al., 1981). During crystal growth, the chiral impurity may be first adsorbed onto certain surface sites of the crystals and may eventually become occluded into the crystal lattice (Addadi et al., 1986; Weissbuch et al., 1991). The occlusion of impurity molecules at low concentrations results in the formation of a solid solution (Weissbuch et al., 1995). At higher impurity concentrations the conjugate terminal solid solution may co-crystallize, resulting in a separate phase which influences the properties of the crystalline material differently. Depending on the nature and extent of disorder induced by the chiral impurities, the behavior of crystalline chiral compounds can be significantly modified, which often manifests itself as batch-to-batch variations in pharmaceutical raw materials. Thus, a thorough understanding of the nature of the enantiomeric interaction is essential for the development of effective and reliable formulations of chiral drugs.

More than one half of the commercial drugs available worldwide have chiral center(s) (Stinson, 1993; Millership and Fitzpatrick, 1993). Approximately one half of chiral drugs are marketed as racemic forms, usually termed racemates, and half as pure stereoisomers; the latter are predominantly natural products and only 10% are synthetic drugs (Borman, 1990; Testa and Targer, 1990). Although there is a growing trend in the past few years to develop enantiomerically pure forms because of their therapeutic advantages, many chiral drugs are still available as racemic forms. It is generally believed that crystallization from a racemic solution is likely to produce a racemic compound, because it has relatively high stability (often higher melting point) and has more choices to crystallize in one of the common symmetric space groups (Brock and Dunitz, 1994). Indeed, racemic compounds or true racemates (Brittain, 1990), in which the opposite enantiomers are paired up to form a new crystal lattice, are the dominant species (> 90%) among crystalline racemic drugs and may be difficult to resolve.

The chiral impurity can be either the opposite enantiomer in a homochiral crystal, or an excess of either enantiomer in a racemic compound. A schematic phase diagram of a racemic compound is depicted as Fig. 1a, in which the zone of

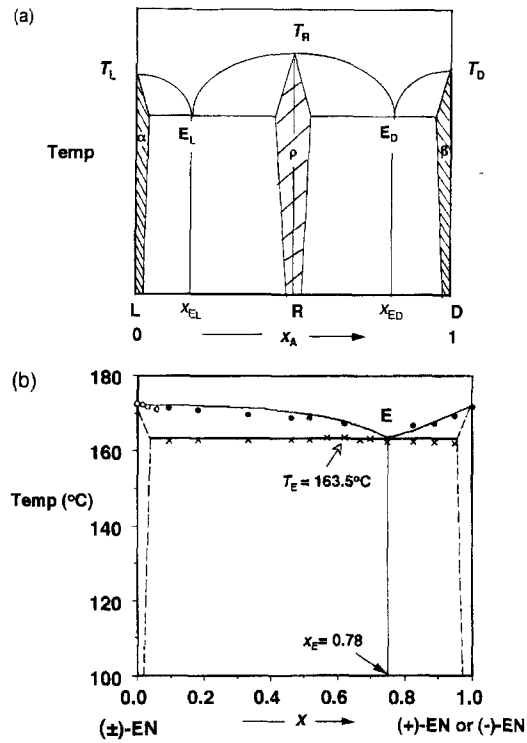

Fig. 1. (a) Schematic melting point phase diagram of binary mixtures of two enantiomers, D and L, for which the racemic species is a racemic compound. E_D and E_L are the eutectic points of the R-D and R-L regions, respectively, and x_{E_D} and x_{E_L} are their corresponding eutectic compositions. α, β and ρ are the solid solutions in the regions of the corresponding pure phases, L, D and R, respectively. (b) Experimental melting point phase diagram of binary mixtures of (+)-EN or (−)-EN and (±)-EN. E is the eutectic point of melting temperature T_E and composition x_E. The liquidus line was calculated from Eqs. (A1) and (A2). The solid circles and the open circles represent the melting points of the physical mixtures of two enantiomers and the doped crystals, respectively, whereas the crosses are the eutectic temperatures of the physical mixtures. The dotted lines indicate the hypothetical solid phase boundary.

miscibility in the solid state, i.e. a solid solution, is shown by the shaded areas. Although these solid solution regions may be narrow, they are often representative of many so-called 'pure' materials (98–99.9%), because the experimental delineation of these zones is rarely possible for practical reasons. The terminal solid solutions at the two end regions, α and β, are the respective homochiral crystals containing a trace of the opposite enantiomer (an enantiomeric impurity). The central hatched area, ρ, in the vicinity of the racemic compound (the center line), represents the racemic compound containing a small enantiomeric excess in solid solution. Goldberg et al. (1965, 1966a,b) and Allen and Kwan (1969) have shown that solid solution formation in drug-carrier systems produces significant increases in dissolution rate, and provides a useful means of increasing the instantaneous solubility and absorption of poorly soluble drugs.

The effects of an enantiomeric impurity (i.e. solid solution α and β) has been investigated in the homochiral salts, (*SS*)-(+)-pseudoephedrinium salicylate and (*RS*)-(−)-ephedrinium 2-naphthalenesulfonate by Duddu (1993) and Duddu et al. (1994, 1995). These studies have demonstrated that traces (as low as 0.0025 mole fraction) of the enantiomeric impurity cause significant changes in the physicochemical properties of the pure enantiomers.

If a racemic compound takes up a small excess of one enantiomer as chiral impurity (i.e. solid solution ρ) during crystallization, the nature and concentration of the defects may change and the disorder in the crystal lattice may increase, perhaps resulting in a change of the physicochemical properties of the racemic compound. Hence, using a model compound, (±)-ephedrinium 2-naphthalenesulfonate, (±)-EN, the present work aims to investigate the effects of an excess enantiomer as a chiral impurity on its crystal properties by determining: (1) the extent of uptake of the chiral impurity into crystals of the racemic compound, (±)-EN; (2) the location of the occluded impurity, the formation of a solid solution with the host and/or a separate phase on the surface or as microcrystallites in the crystal; (3) the effect on thermodynamic properties, such as melting point, enthalpy of fusion and entropy of fusion, of the host crystals by the presence of a chiral impurity; (4) the changes of dissolution behavior, particularly the intrinsic dissolution rate, of the host crystals.

2. Materials and methods

2.1. Materials

(*RS*)-(−)- and (*SR*)-(+)-ephedrine hydrochloride were obtained from Sigma Chemical Company (St. Louis, MO). Sodium 2-naphthalenesulfonate, was obtained from Eastman Kodak Chemical Company (Rochester, NY). The formation of the model salts can be expressed by the following preparative reactions in aqueous solution:

$$(+)\text{-}E^+ + Cl^- + Na^+ + N^- \quad 60°$$

$$\rightarrow (+)\text{-}EN\downarrow + Na^+ + Cl^- \quad 25°C$$

$$(+)\text{-}E^+ + (-)\text{-}E^+ + 2Cl^- + 2Na^+ + 2N^- \quad 60°C$$

$$\rightarrow (\pm)\text{-}EN\downarrow + 2Na^+ + 2Cl^- \quad 25°C$$

where E^+ represents the ephedrinium ion, N^- represents the 2-naphthalenensulfonate ion, and 1 mole of racemic compound (±)-EN is defined so as to consist of 1 mole of (+)-EN and 1 mole of (−)-EN.

Following cooling and crystal growth, the precipitate was filtered and dried over anhydrous calcium sulfate (Drierite, W.A. Hammond Drierite Company, Xenia, OH). The crystals of (±)-EN were further purified by two successive crystallizations from aqueous solution using HPLC-grade water (J.T. Baker, Phillipsburg, NJ). HPLC analysis described below indicated a 99.9% chemical purity of (±)-EN used as undoped crystals. All solvents including water were HPLC grade. Dibasic potassium phosphate and octanoic acid were obtained from Aldrich Chemical Company (Milwaukee, WI).

2.2. Methods

2.2.1. Doping crystals of (±)-EN

(±)-EN was crystallized from solutions containing a known amount of the dopant, either (+)-EN

or (−)-EN, ranging from 1 to 10 mole percent. The saturated solution at 60°C was allowed to cool to room temperature gradually. To the metastable supersaturated solution, seed crystals of (±)-EN (passing through 200 mesh, < 75 μm) were added. After 2 h, the precipitate was harvested by filtration and washing with the mother liquor. The crystals were spread on a glass Petri dish, air-dried overnight, and subsequently dried over anhydrous calcium sulfate for 48 h before use.

2.2.2. High performance liquid chromatography (HPLC) of ephedrine enantiomers

The HPLC system (Shimadzu, Kyoto, Japan) included a LC-6A pump, SCL-6A system controller, SIL-6A autoinjector, SPD-6A UV detector and C-R5A integrator. A chiral α_1-acid glycoprotein (AGP) bonded column (10 cm × 4.0 mm I.D. ChromTech AB, Högersten, Sweden) purchased from Regis Chemical Company (Morton Grove, IL) was used for direct separation of the enantiomers of ephedrine (Schill et al., 1986). The mobile phase consisted of 10 mM dibasic potassium monophosphate, 2 mM octanoic acid, pH 7, at a flow rate of 0.3 ml/min. The UV detector was set at 208 nm. The crystals were dissolved in HPLC-grade water and were then diluted with the mobile phase. The injection volume was 20 μl, containing 0.1 to 1 nmol of (±)-EN. Good baseline resolution of the two enantiomers, eluting at 16.25 and 20.4 min, respectively, was obtained and the amount of 2-naphthalenesulfonate ion, eluting at 5.9 min, was also determined (Fig. 2).

Because of the difficulty in discerning the small difference between two adjacent peaks of approximately equal area, the detection limit of the enantio-meric excess in the racemic compound was ±0.0025.

The mole fraction of excess enantiomer in a racemic compound, x, was calculated by the equation:

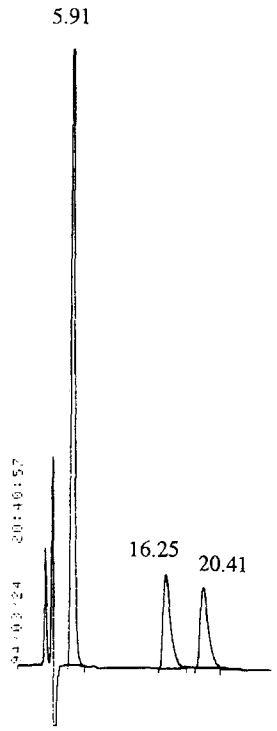

Fig. 2. A representative HPLC chromatogram illustrating the separation of 2-naphthalenesulfonate acid eluting at 5.91 min (+)-ephedrine at 16.25 min and (−)-ephedrine at 20.41 min.

where n_A is the number of moles of the enantiomer in larger quantity ($0.5 < n_A \leq 1$) and n_B is the number of moles of the enantiomer in lesser quantity ($0 \leq n_B < 0.5$). The number of moles of the racemic compound is equivalent to n_B, assuming that all opposite enantiomeric molecules are paired up to form the racemic compound.

2.2.3. Column dissolution — impurity distribution

The impurity distribution, reflecting the amount on the surface and inside the crystals, was measured by gradually washing and dissolving the crystals (Go and Grant, 1987). The doped crystals (25 mg) were placed at one end of a glass Econo-Column with a polymer bed support (pore size 20

$$x = \frac{\text{number of moles of excess enantiomer}}{(\text{number of moles of excess enantiomer} + \text{number of moles of racemic compound})} = \frac{n_A - n_B}{n_A} \quad (1)$$

when $n_A > n_B$

μm) and a flow adapter (Bio-Rad Laboratories, Hercules, CA). The crystals were dissolved with HPLC-grade water from a Waters 510 HPLC pump (Waters, Marlborough, MA) at a flow rate of 0.5 ml/min. During dissolution, the effluents were collected at 5-min intervals and after 40 min the crystals had completely dissolved. The mole fraction of excess enantiomer, x, in the effluent was analyzed by the HPLC method described above.

2.2.4. Differential scanning calorimetry (DSC)

Measurement of melting point and enthalpy of fusion of the doped crystals was performed using a Du Pont 910 differential scanning calorimeter equipped with a data station (Thermal Analyst 2000, TA instruments, New Castle, DE). The temperature axis and the cell constant were calibrated with indium (3 mg, 99.99%, peak maximum at 156.6°C and heat of fusion 28.4 J/g). Samples of 3 ± 0.1 mg in crimped aluminum pans were heated at a rate of 5°C/min, and the peak melting temperature was recorded. The melting point phase diagram was constructed from the measured melting point of physical mixtures consisting of various proportions of (+)-EN and (−)-EN crystals. There was no significant difference in melting points between the physical mixture and the melt that has been heated to the molten state and gradually cooled to room temperature.

2.2.5. Karl Fischer titrimetry (KFT)

The water content of the crystals was measured by Karl Fischer titration with a Moisture Meter Model CA-05 (Mitsubishi Chemical Industries Ltd., Tokyo, Japan).

2.2.6. Intrinsic dissolution rate (IDR)

The intrinsic dissolution rates (the dissolution rate per unit surface area) were determined using the compacted disk dissolution apparatus described by Doherty and York (1987), based on that of Collett et al. (1972). The compacts (1 cm in diameter) were prepared by compressing 100 mg of the powder into the sample holder under a hydraulic press (Carver Laboratory Press, Model C, Menomonie WI) at 125 MPa pressure for 60 s. A single face of the compact in the center of the cell base was exposed to 600 ml distilled water equilibrated at 25 ± 0.2°C. A 3-paddle stirrer was rotated at 50 rev./min directly above the compact. The concentration of ephedrinium 2-naphthalenesulfonate was measured by UV absorbance at $\lambda_{max} = 272$ nm. The cumulative amount of crystals dissolved in the solution was calculated and plotted against time. The intrinsic dissolution rates were determined by linear regression of the data during the first 15 min of the dissolution process.

3. Results and discussion

An equimolar mixture of ephedrinium 2-naphthalenesulfonate enantiomers forms a racemic compound with a distinct powder X-ray diffraction pattern different from that of the individual enantiomers (Fig. 3). A typical phase diagram of a racemic compound consists of two separate

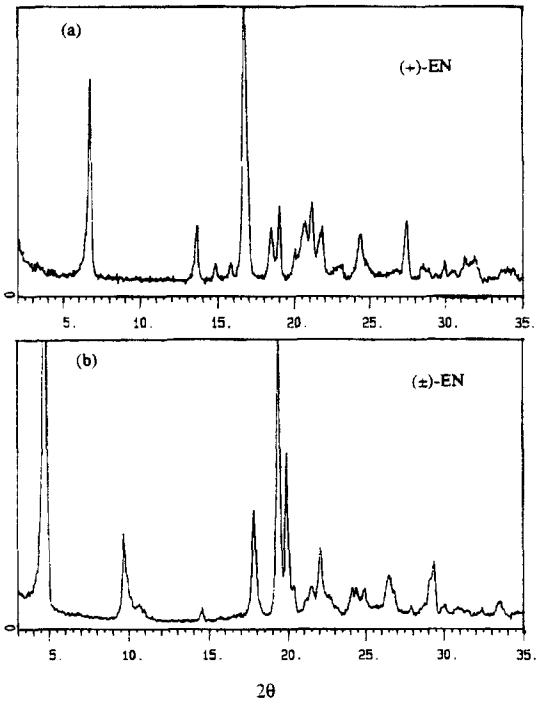

Fig. 3. The X-ray powder patterns of crystals of (a) homochiral, (+)-EN, and (b) the racemic compound, (±)-EN.

phase diagrams related by mirror symmetry (Fig. 1a), either half of which can be used to illustrate the binary system of (+)- or (−)-EN with (±)-EN. The melting point phase diagram of (±)-EN determined by DSC is shown in Fig. 1b, where T_E is the eutectic temperature and x_E is the eutectic composition. For the portion, $x_E \leq x \leq 1$, the liquidus line was predicted by the simplified Schröder-Van Laar equation (Schröder, 1893; Van Laar, 1903), and for the portion, $0 \leq x \leq x_E$, the liquidus line was calculated by the Prigogine and Defay (1950) equation, a modified form of the Schröder-Van Laar equation (see Appendix A). As shown, the experimental data agreed well with the calculated values. Although the melting point of (±)-EN, 172.6°C, is slightly higher than that of each enantiomer of EN, 171.9°C, the enthalpy of fusion of the racemic compound, ΔH_R^f, is 13.5% greater than that of the constituent enantiomers, $2\Delta H_A^f$, based on the molar basis of enantiomer. This result suggests that the crystals of (±)-EN have more efficient packing and greater lattice energy than the homochiral crystals.

The extent of solid solution formation in Fig. 4 was determined by slowly dissolving the doped crystals to determine the surface and bulk concentrations of impurity. A steady level of eluted impurity corresponds to the uniform distribution of impurity inside the crystals as a solid solution. A representative profile of the mole fraction of excess enantiomer in the effluents, y, as a function of time is shown in Fig. 4a, where the steady level of y represents the concentration of the dissolved solute (excess enantiomer) in the solid solvent (racemic compound). Low levels of doping gave an approximately steady level of the mole fractions of excess enantiomer throughout the dissolution process, whereas higher levels of doping (Fig. 4a) exhibited a rapid initial decrease of the concentration of excess enantiomer followed by a steady level after 10 min. The arithmetic mean value of y at the steady level, designated as $\bar{y}$, represents the mole fraction of excess enantiomer in the racemic crystals excluding the surface excess. Analogous to a liquid phase-solubility diagram (Higuchi and Connors, 1965), the steady level of the dissolved solute, of the doped crystals, $\bar{y}$, was plotted as a function of the total amount of excess enantiomer

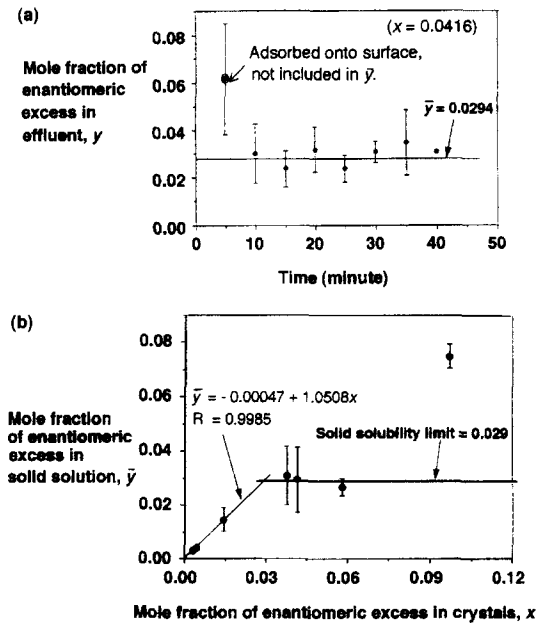

Fig. 4. Column dissolution profile of the doped crystals. (a) A plot of the distribution of excess enantiomer in the crystals of the racemic compound at high level of doping ($x = 0.0416$), showing an initial decrease corresponding to dissolution of the surface excess, and ((b) the solid phase-solubility diagram of the excess enantiomer in the racemic compound, (±)-EN. The vertical bars represent the standard error of the respective means ($n = 3$).

in the doped crystals, x, in Fig. 4b. The solid phase-solubility diagram revealed that the solid solubility first increased with a slope close to unity at $0 < x < 0.029$, then reached a plateau level, and the average concentration of the dissolved solute at the plateau level and the point of intersection of the two lines gave the limit of the solid solubility, $x = 0.029$ mole fraction. At the highest doping, $x \sim 0.10$, the mole fraction of surface excess was ~ 0.02 and the amount incorporated, $\bar{y}$ was ~ 0.08, which exceeds the solid solubility limit of 0.029 mole fraction. This discrepancy of ~ 0.05 mole fraction possibly corresponds to microcrystallites of an enantiomerically rich phase (α, in Fig. 1a) incorporated into the crystals of (±)-EN, perhaps on the surface of the mosaic blocks, a phenomenon termed interblock solubility by Kitaigorodsky (1973).

When (±)-EN was crystallized from a medium containing an enantiomeric excess, a small amount of the excess enantiomer (guest) became

incorporated into the racemic lattice (host). The rate of increase in the molar ratio of incorporated guest associated with the crystals with respect to the molar ratio in the liquid solution, known as the segregation coefficient, k, was found to be 0.078 (Fig. 5). The linear regression within the solid solution region ($0 < x \leq 0.029$) afforded approximately the same slope. Furthermore, the non-zero intercept ($x \sim 0.005$) in Fig. 5 arose from the presence of a small enantiomeric excess in the (apparently) undoped crystals. The fact that the observed segregation coefficient is smaller than 0.15 for doping of the homochiral crystals of EN (Duddu et al., 1994) indicates that the crystals of the racemic compound, (±)-EN, with higher symmetric packing, have a greater tendency to reject the enantiomeric impurity than the homochiral crystals. Nevertheless, a small amount of enantiomeric excess is found to be taken up by the crystals of (±)-EN.

The water contents in the undoped and doped crystals were about 0.75 ± 0.1% (w/w) and were independent of the concentration of enantiomeric excess ($0 < x < 0.05$) in the crystals. A higher proportion of water (1.0%, w/w) was found in the crystals at the highest level of doping ($x \approx 0.1$). Since no change prior to melting was observed in the DSC and TGA thermograms and the water contents appeared to increase with increasing aggregate size, the water molecules are probably adsorbed onto surfaces and are trapped between the particles in the aggregates.

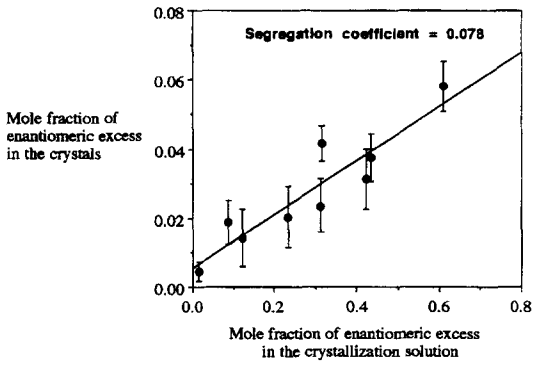

Fig. 5. Plot of the mole fraction of enantiomeric excess in crystals of the racemic compound, (±)-EN, against the mole fraction of enantiomeric excess in the crystallization medium. The value of the segregation coefficient, $k = 0.078$, is given by the slope of the linear regression ($r = 0.992$, $n = 4$).

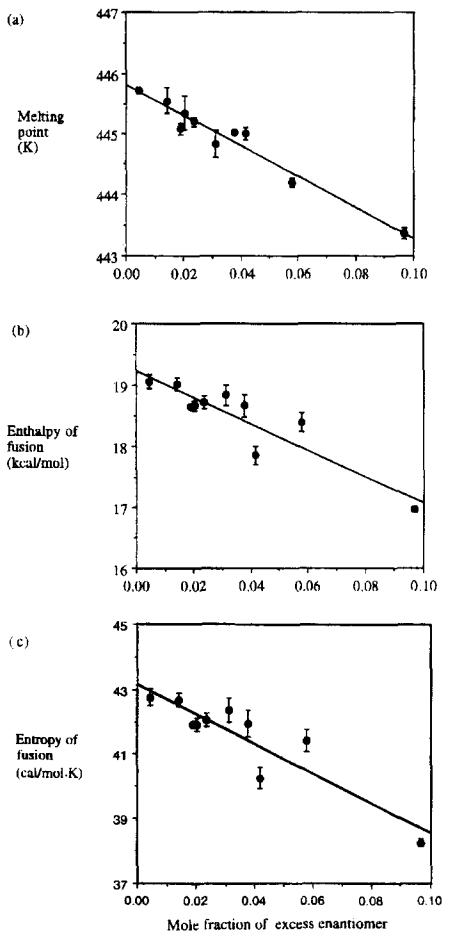

Fig. 6. Effects of excess enantiomer in the racemic crystals, (±)-EN, on (a) the melting point, (b) the enthalpy of fusion, and (c) the entropy of fusion. The vertical bars represent the standard error of the respective means ($n = 3$).

The melting point of (±)-EN (Fig. 6a) decreased approximately linearly with increasing mole fraction of enantiomeric excess in the crystals. Similarly, the enthalpy of fusion, ΔH^f, decreased monotonically with increasing mole fraction of excess enantiomer incorporated into the crystals (Fig. 6b), suggesting an increase in lattice strain. The entropy of fusion, ΔS^f, calculated as $\Delta H^f/T_m$, also decreased with increasing mole fraction of excess enantiomer in the crystals (Fig. 6c), suggesting increased lattice disorder in the host crystals. The total reductions in ΔH^f and

ΔS^f from $x = 0.005$ to 0.1 were about 10%, while the decrease over the solid solution region ($x \leq 0.029$) was approximately 3%, a value which was statistically significant although small. Unlike doping of homochiral crystals with the opposite enantiomer, for which the values of ΔH^f and ΔS^f declined initially and then increased at higher levels of doping (Duddu et al., 1994, 1995), the enthalpy and entropy of fusion of the doped racemic crystals continued to decrease with increasing mole fraction of the enantiomeric excess. This result indicates progressive increases of overall lattice strain and disorder of (±)-EN due to the formation of a solid solution and a separate phase. One noticeable difference between doping of homochiral and racemic crystals is the surface excess of chiral impurity, relatively large in the doped homochiral crystals (65–70%) and relatively small (< 20%) in the doped racemic compound, at high impurity concentrations. This excess chiral impurity on the surface may form a separate phase and may considerably influence the thermodynamic properties of the crystals depending on both the nature and location of the separate phase. Unfortunately, research in this area has been limited by the difficulty in detecting and determining subtle difference in the structure of organic solids as separate phases when present in relative small amounts in crystalline materials, particularly chiral systems.

To quantify the disruptive influence of an additive or impurity in solid solution, the disruption index was estimated (York and Grant, 1985). The disruption index, d.i., is a measure of the rate of change of the difference between the entropy of the solid and that of the liquid, with respect to the ideal entropy of mixing of the host with the guest. The negative slope of a plot of the entropy of fusion versus the ideal entropy of mixing (Fig. 7) gives the value of the disruption index (d.i. $= b - c$) according to the following equation:

$$\Delta S^f = \Delta S_0^f - (b - c)\Delta S_{mix}^{id} \quad (2)$$

At small mole fractions ($x < 0.03$) of the guest, the entropy of fusion decreased linearly with increasing ideal entropy of mixing of the guest with the host, corresponding to a disruption index value of 4.5 derived by linear regression. This d.i. value is much lower than 20 for the doping of (−)-EN with (+)-EN, but is comparable with that of doping of organic crystals with non-isomeric additives (Duddu and Grant, 1995). This observation suggests that reversed chirality can cause greater crystal disruption in homochiral crystals than enantiomeric excess in the crystals of a racemic compound. Apparently, disorder or disruption in the crystal lattice produced by a difference in the spatial arrangement of substituent groups of stereoisomers can be equal or greater than that induced by non-isomeric additives.

Two representative dissolution profiles of the undoped and doped crystals of (±)-EN are shown in Fig. 8a. With increasing mole fraction of excess enantiomer, x, the intrinsic dissolution rate increased rapidly, reached a maximum and then decreased to the original value (Fig. 8b). The maximum intrinsic dissolution rate, which occurred at $0.015 < x < 0.03$, was about 27% higher than the original value; this increase is statistically significant at the 95% confidence level. Fig. 8b shows large variations of IDR at an enantiomeric excess in the range from 0.02 to 0.03 near the solid solubility limit. A possible explanation is that crystal growth kinetics are extremely variable in the vicinity of the solid phase boundary which is created under conditions close to thermodynamic equilibrium. The relatively high supersaturation during crystallization may encourage the formation of microcrystallites as a separate phase even at impurity concentrations below the solubil-

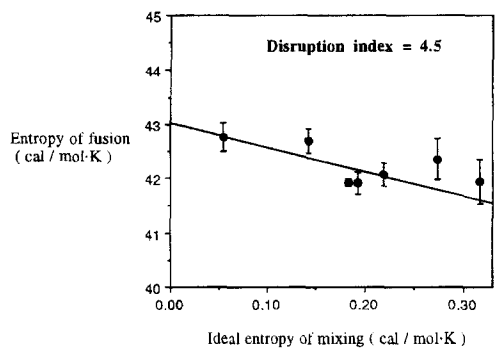

Fig. 7. Plot of the entropy of fusion vs. the ideal entropy of mixing of excess enantiomer in the racemic crystals, (±)-EN. The vertical bars represent the standard error of the respective means ($n = 3$).

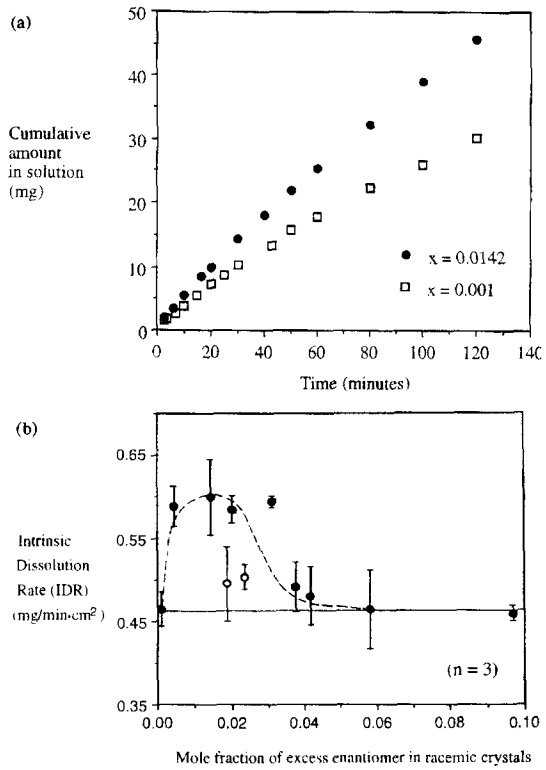

Fig. 8. (a) Representative disc dissolution profiles of the (apparently) undoped ($x = 0.003$) and doped ($x = 0.0142$) crystals of the racemic compound, (±)-EN. (b) Variations of the intrinsic dissolution rate of the doped racemic crystals, (±)-EN. The open circles represent the relative low IDR values of two doped crystals containing the excess enantiomer below the solid solubility limit. The dotted line indicates the trend of change of IDR values. The vertical bars represent the standard error of the respective means ($n = 3$).

ity limit, and may result in the low IDR values of the two samples shown by open circles in Fig. 8b.

The interesting features of the IDR plot for the doped crystals (Fig. 8b) are: (1) the IDR first increases sharply with increasing concentration of enantiomeric excess in solid solution ($x < 0.015$), (2) the IDR is variable in the vicinity of the solid phase boundary, and (3) the IDR decreases from the peak value when a separate phase is formed. The appreciable increase in IDR of the solid solution can be explained by an increase in the free energy of the doped crystals, because the impurity defects weaken and disorder the crystal lattice, but increase the lattice enthalpy more than the entropy term. As a result, the free energy of solution becomes more negative, thereby increasing the IDR. At higher levels of doping, however, the decrease in the IDR seems contradictory to the common conception that a higher impurity level in a solid usually leads to a greater dissolution rate. The observed lowering of the IDR with increasing enantiomeric excess (exceeding the solid solubility limit) suggests a decrease in the overall free energy of the solid, perhaps as a result of a more favorable entropy term that offsets the enthalpy term due to inclusion of microcrystallites into the solid. The phenomenon, reduction of the rate of dissolution by the presence of an impurity, has also been reported by Burt and Mitchell (1991) for several crystalline pharmaceutical materials and by Duddu et al. (1995) for (*SS*)-(+)-pseudoephedrinium salicylate doped with its opposite enantiomer, but the underlying mechanism is not yet known. Most significantly, an enantiomeric excess in (±)-EN crystals may give rise to appreciable and variable changes in dissolution behavior, which may also have implications for other pharmaceutical racemic compounds.

In summary, the results from this study demonstrate that a small excess of either enantiomer in crystals of the racemic compound significantly changes the thermodynamic properties and the intrinsic dissolution rate of (±)-EN. These observed changes in the properties of the racemic compound, (±)-EN, show various similarities and differences in comparison with those observed for the corresponding homochiral crystals doped with the opposite enantiomer. The contrast may reflect the subtle differences in the chiral impurity-induced solid-state interactions, such as crystal packing, lattice energy and disorder, despite the otherwise identical chemical composition of the racemic compound and the homochiral species.

To gain fundamental understanding about the nature of the solid solutions, the separate phase, and the intermolecular interactions between the enantiomers, structural data are needed. Unfortunately, (±)-EN crystallizes as fibrous needles, which are unsuitable for single crystal X-ray analysis. Although the crystal structure of (±)-EN has not yet solved, more efforts are being made to obtain suitable single crystals. Furthermore, additional qualitative and quantitative studies of the

solid-state interactions of stereoisomers are currently in progress using solid state NMR spectroscopy (Schmidt and Honigberg, 1991; Bugay, 1993) and molecular modeling.

4. Conclusions

During growth of racemic crystals of ephedrinium 2-naphthalenesulfonate, (±)-EN, from aqueous solutions, the segregation coefficient of the excess enantiomer was only 0.078, suggesting that crystal packing of high symmetry leads to substantial rejection of the homochiral EN. The solid solubility diagram reveals the formation of a rather limited range of solid solutions (at $0 < x \leq 0.029$) and suggests the formation of a separate phase beyond the solid solubility limit of the enantiomeric excess, on the surface (at $0.02 < x < 0.06$) and mixed in the crystals at $x \approx 0.1$. The melting point, enthalpy of fusion and entropy of fusion of the doped racemic crystals decreased approximately linearly with increasing enantiomeric excess ($0 < x \leq 0.1$) incorporated into the racemic crystals, indicating increases in lattice energy and disorder of the solid. The disruption index for the racemic crystals doped with excess enantiomer in the solid solution region was about 4.5, which is comparable with that produced by non-isomeric doping of organic crystals (York and Grant, 1985), indicating that the chiral impurity introduces comparable crystalline disorder. With increasing enantiomeric excess, the intrinsic dissolution rate increased to a maximum value and then decreased to the original value. The maximum IDR was about 27% higher than the original value and occurred at $x \approx 0.015$–0.03 in the vicinity of the solid phase boundary, suggesting that the dissolution rate of the solid is very sensitive to a change in the solid phase and/or to the distribution of impurity molecules. This suggestion may also explain the variable dissolution rates of some other pharmaceutical solids.

Appendix

For the mixtures of enantiomers of composition between a pure enantiomer and the eutectic composition (Fig. 1a), Schröder (1893) and Van Laar (1903) proposed the following equation (see Jacques et al., 1981) to calculate the liquidus curve of the binary phase diagram:

$$\ln x_{\Lambda} = \frac{\Delta H^{f}_{\Lambda}}{R}\left(\frac{1}{T^{f}_{\Lambda}} - \frac{1}{T^{f}}\right) \tag{A1}$$

where x^{Λ} represents the mole fraction of the enantiomer in larger quantity ($x_{ED} < x_{\Lambda} \leq 1$) in the mixture, ΔH^{f}_{Λ} and T^{f}_{Λ} are the enthalpy of fusion and the melting point, respectively, of the pure enantiomer, T^{f} is the melting point of the mixture and R is the gas constant.

The equation (see Jacques et al., 1981) of Prigogine and Defay (1950) for the liquidus curve between the racemic compound and the eutectic composition or between two eutectic compositions (Fig. 1a) is:

$$\ln 4x_{\Lambda}(1 - x_{\Lambda}) = \frac{\Delta H^{f}_{R}}{R}\left(\frac{1}{T^{f}_{R}} - \frac{1}{T^{f}}\right) \tag{A2}$$

where x_{Λ} represents the mole fraction of one of the enantiomers in the mixture ($x_{EL} \leq x_{\Lambda} \leq x_{ED}$), ΔH^{f}_{R} and T^{f}_{Λ} are the enthalpy of fusion and the melting point of the racemic compound containing 1 mole of each constituent, while T^{f} and R are defined above.

Both Eqs. (A1) and (A2) assume (a) immiscibility of the enantiomer in the solid sate, (b) ideality of the enantiomeric mixture in the liquid state and (c) negligible difference between the heat capacities of the liquid and solid states. For the system described here, these assumptions appear to represent fair approximations.

The relationship between mole fraction x_{Λ} in Fig. 1a and mole fraction x in Fig. 1b can be expressed as:

$$x = \frac{2x_{\Lambda} - 1}{x_{\Lambda}} \tag{A3}$$

where $0.5 < x_{\Lambda} < 1.0$.

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