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Effect of the opposite enantiomer on the physicochemical properties of (−)-ephedrinium 2-naphthalenesulfonate crystals

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Summary

During the growth of optically active crystals (host), trace quantities of the opposite enantiomer (guest) present in the solution may be taken up by the host. However, the enantiomeric guest, due to its opposite chirality, may distort the crystal lattice of the host. Thus, the incorporation of the guest may lead to changes in the pharmaceutically important properties of the host, such as dissolution rate and thermodynamic properties, perhaps through lattice disruption. This hypothesis was tested by growing crystals of a model compound, (−)-ephedrinium 2-naphthalenesulfonate, from aqueous crystallization media containing various trace quantities of its opposite enantiomer. A stereoselective HPLC method was developed to determine the trace amounts of the opposite enantiomer within and on the surface of the homochiral host crystals. Increasing concentrations of the guest in solution led to its increasing incorporation into the host crystals and to increasing intrinsic dissolution rate of the host. The enthalpy and entropy of fusion of the host decreased with increasing incorporation of the guest, suggesting the disruption of the crystal lattice of the host and an increase in its lattice strain. The water content and the melting point were not significantly affected. At higher levels of the incorporated guest, the enthalpy and entropy of fusion increased, suggesting a relaxation of the lattice strain, and subsequently reached a plateau value. A value of 20.6 was obtained for the 'disruption index', which is defined as 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 (York and Grant, *Int. J. Pharm.*, 25 (1985) 57–72). This relatively high disruption index indicates significant disruption of the crystal lattice of the host by the incorporated guest, suggesting changes in the nature and concentration of the crystal defects.

Introduction

Many drugs are chiral, that is, their molecules exist in right- and left-handed forms called enantiomers. Of the 1327 worldwide marketed synthetic drugs, 528 are chiral (Ariëns, 1990). Usually, only one enantiomer is therapeutically use-

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ful. The other enantiomer may be less active, inactive or even toxic. Increasing awareness of the implications of chirality in pharmacy and medicine has prompted regulatory agencies, such as the FDA, to issue specific guidelines for the manufacture of drug substances (De Camp, 1989). These guidelines consider even the opposite enantiomer to be an impurity in a chiral drug because the impurity may have significant pharmacological and toxicological effects. However, the effects of the opposite enantiomer on the physicochemical properties of a chiral drug have not yet been reported. Our previous study has demonstrated that raw materials from various suppliers and, indeed, different lots from the same supplier contain varying quantities of the enantiomeric impurity (Duddu et al., 1991). Since a large number of marketed drugs are chiral (Ariëns, 1990), and enantiomerically pure drugs are being increasingly formulated, the effect of the opposite enantiomer on the physical properties of a solid chiral drug are reported here.

Crystallization is still the main method for the resolution of racemates and the purification of enantiomers, and the opposite enantiomer is always present as an impurity in the crystallization medium. Although crystals preferentially incorporate molecules of the same kind, there is a large driving force for the incorporation of traces of the impurity into the growing crystals which results from a large negative value for the partial molar free energy of the impurity at low concentrations. Mechanistically, the impurity may be first adsorbed on to certain surface sites on specific faces of the crystals and may eventually become occluded within the crystal perhaps resulting in an anisotropic distribution of the impurity in the crystal (Addadi et al., 1986). Thus, the single crystal with incorporated impurity is actually composed of segments or mosaic blocks of different local symmetries coherently compounded together or intertwined (Weissbuch et al., 1991). The occlusion of the impurity corresponds to the formation of a solid solution and may result in a decrease in the overall symmetry of the crystals (Weissbuch et al., 1983). Symmetry reduction in a solid solution resulting from the incorporated impurity in organic crystals has been demonstrated by Weisinger-Lewin et al. (1989) using neutron diffraction.

Although the existence of continuous solid solutions in the crystals of chiral substances has been demonstrated (Jacques et al., 1981), the formation of terminal solid solutions in a eutectic system is not yet completely recognized or understood, probably because sensitive analytical methods for measuring low mole fractions of the enantiomeric impurity in the crystals of a chiral substance have only recently become available. Since the early 1980s, the determination of low mole fractions (< 0.01) of the enantiomeric impurity in a large excess of the desired enantiomer has been achieved by means of stereospecific HPLC methods (e.g., Perry et al., 1987).

When the impurity (guest) is the opposite enantiomer of a chiral molecule, it may distort the crystal lattice of the desired enantiomer (the host) because of its opposite chirality. We hypothesize that this distortion may lead to changes in the pharmaceutically relevant solid-state properties, such as the heat of fusion, melting point, dissolution rate and tableting behavior of the host, perhaps through lattice disruption. This paper reports the effect of trace quantities of the enantiomeric impurity on the intrinsic dissolution rate and thermodynamic properties of a model solid chiral drug, (−)-ephedrinium 2-naphthalenesulfonate [(−)-EN].

Materials and Methods

Materials

(*RS*)-(−)-Ephedrinium 2-naphthalenesulfonate [(−)-EN)] was prepared by mixing equimolar aqueous solutions of (−)-ephedrine hydrochloride and sodium 2-naphthalenesulfonate which were obtained in the solid state from Sigma Chemical Co. (St. Louis, MO) and Eastman Kodak Co. (Rochester, NY), respectively. The solid (−)-EN was recrystallized twice from HPLC grade water (J.T. Baker Inc., Phillipsburg, NJ), filtered, and dried over anhydrous calcium sulfate prior to the crystallization experiments. (*SR*)-(+)-Ephedrinium 2-naphthalenesulfonate [(+)-

EN] was prepared and purified by exactly analogous procedures. All solvents used were of HPLC grade.

Methods

Batch crystallization

Crystals of (−)-EN were obtained by cooling 150 ml of hot, supersaturated aqueous solutions (0.134 M) to which various concentrations (ranging from 0 to 6.7×10^{-3} M) of the opposite enantiomer, (+)-EN, had been added. The solution containing (−)-EN and the dissolved impurity at 60°C was cooled to 42°C at a rate of 0.2°C/min while being stirred at a rate of 200 rpm. The solution at this stage was clear and supersaturated with respect to (−)-EN. To the solution at 42°C, 2 mg of seed crystals (passing through 200 mesh, < 75 μm) of (−)-EN were added. The stirring was discontinued when the temperature reached 40°C, since continued stirring produced crystals which formed a hard cake on the filter paper and which were difficult to dry completely. The solution was cooled to 25°C at a rate of 0.2°C/min, and maintained at that temperature for 20 min. The slurry was quickly filtered through a 0.25 μm filter under vacuum. The crystals were washed with water, spread on a glass Petri dish and were air-dried at 40°C overnight, and then over anhydrous calcium phosphate at 22°C for 72 h.

Differential scanning calorimetry (DSC)

The heat of fusion, melting point and the entropy of fusion of the samples were determined using a DuPont 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 using indium (10 mg, 99.99%, peak maximum at 156.6°C and heat of fusion 28.4 J/g). Samples (3 ± 0.1 mg, 106–125 μm) in open aluminium pans were heated at a rate of 10°C /min.

Intrinsic dissolution rate (IDR)

The intrinsic dissolution rate (the dissolution rate per unit surface area) of the compacted disc was determined using the apparatus described by Doherty and York (1987), based on that of Collett et al. (1972). The sample holder containing the compact was screwed into the center of the cell base so that a single face of the compact was exposed to 600 ml of distilled water which had been outgassed and equilibrated at 25 ± 0.2°C. Directly above the compact, a three-paddle stirrer was rotated at 50 rpm by a synchronous motor (Slo Syn, Superior Electric Co., Bristol, CT). The samples were analyzed spectrophotometrically by measuring the absorbance at 272 nm.

Stereospecific analysis of the enantiomeric impurity

Enantiomeric purity can be determined by direct or indirect methods. In the direct method, the enantiomers are resolved on a chiral stationary phase (CSP). In the indirect method, the enantiomers are derivatized using a chiral derivatizing reagent (CDR) to form the respective diastereomers which are subsequently resolved on an achiral column. Each method has certain advantages and disadvantages (Duddu et al., 1991). In particular, the use of the indirect method for the determination of a trace quantity of the enantiomeric impurity is of questionable validity until the enantiomeric purity of the CDR and/or its lack of racemization during derivatization have been established.

Two technical requirements must be fulfilled for the accurate determination of low concentration of the enantiomeric impurity (approx. 0.001 mole fraction). (i) The enantiomeric impurity must elute before the main enantiomeric peak. (ii) The chromatographic resolution of the two enantiomers must be such that an accurate integration of the impurity peak is possible. With the availability of CSPs and CDRs of opposite chiralities, it may not be difficult to fulfil the first requirement, since the elution order of the enantiomers can be changed by changing the chirality of the CSP or the CDR. The resolution of the peaks then becomes an important factor in stereospecific analysis of the enantiomeric impurity.

Although direct methods for the separation of ephedrine enantiomers have been reported (Doyle et al., 1986; Armstrong et al., 1988; Schill et al., 1988; Yang et al., 1988), none of them affords a resolution which allows accurate quanti-

tation of the enantiomeric impurity. Hence, our reported indirect method (Duddu et al., 1991) was employed to quantitate the enantiomeric impurities in (−)-EN samples, since it offers a good resolution factor for the separation of ephedrine enantiomers. However, as mentioned above, the use of the indirect method for the quantitation of the enantiomeric impurity requires that the enantiomeric purity of the CDR and/or its racemization during derivatization be established. The following procedure was used to establish the enantiomeric purity of the CDR and/or its racemization during derivatization. A drug whose enantiomeric purity can be analyzed by both direct and indirect methods (in this case (−)-pseudoephedrine) was chosen as a reference sample. The enantiomeric impurity (x) in the reference sample was analyzed by a direct method (Doyle et al., 1986). The enantiomeric impurity (y) in the same (−)-pseudoephedrine sample was also analyzed by the indirect method (Duddu et al., 1991) using (*R*)-1-(−)-(1-naphthyl)ethyl isocyanate as the CDR. The difference ($y - x$) in the enantiomeric impurity concentrations of the reference substance [(−)-pseudoephedrine], measured using the direct and the indirect methods, was attributed to the enantiomeric impurity in the CDR and to its possible racemization during the derivatization reaction.

To determine the absolute enantiomeric impurity (a) in (−)-EN samples, they were first analyzed for the enantiomeric impurity (z) using the indirect method employing the same CDR used to analyze the reference sample. Subsequently, the value ($y - x$) for the enantiomeric impurity in the CDR and/or its possible racemization was subtracted from z to give the absolute enantiomeric impurity in the sample ($a = z - y - x$). The mean of the ($y - x$) values ($n = 6$), determined before, during and after the analysis of the (−)-EN samples by the indirect method, was used to determine the absolute enantiomeric impurity.

Measurement of the impurity incorporated into the crystals

The impurity may be present either on the surface of the crystals (adsorbed) or be taken up by the crystals (as a solid solution). In order to measure the concentration of the impurity taken up by the crystals, the crystals must first be washed free from the adsorbed impurity. To accomplish this, crystals of (−)-EN (25 mg), grown in the presence of the maximum concentration (6.7×10^{-3} M) of the opposite enantiomer, were placed on a 0.25 μm filter fitted to one end of a glass column. The crystals were then washed with isopropanol at a flow rate of 100 μl/min using an HPLC pump (510, Waters, Milford, MA). The enantiomeric impurity in the washings was analyzed by stereoselective HPLC every 5 min for a period of 40 min. At selected time points (0, 10, 15, 20, 30, 40 min) during the washing procedure, the crystals of (−)-EN were also analyzed for the enantiomeric impurity. 20 min washing was selected as the optimum time, since further washing resulted in no change in the concentration of the enantiomeric impurity.

Approx. 60% of the total enantiomeric impurity associated with the crystals grown in the presence of the opposite enantiomer (hereafter referred to as doped crystals) was found to be adsorbed onto the crystals. After the crystals had been washed for the optimum time period (20 min), the differences in the enantiomeric purity of the crystals and of the washings were found not to be statistically significant (two-tailed t-test, $p > 0.05$). These washing conditions were used for all batches of doped and undoped crystals. The enantiomeric impurity measured in the crystals by dissolution after washing is reported as the impurity incorporated into the crystals.

Statistical analysis

All data, unless specified, were analyzed by ANOVA ($\alpha = 0.05$). Individual means were compared by Bonferroni procedure ($\alpha = 0.05$) for multiple comparison in a completely randomized design.

Results and Discussion

A significant mole fraction (10^{-3}–10^{-2}) of the enantiomeric impurity (the guest) was progressively incorporated into the crystals of (−)-EN

(the host) with increasing concentration of the impurity in the crystallization medium (Fig. 1). This steady increase in the mole fraction of the incorporated enantiomeric impurity suggests the formation of a solid solution of the guest in the host crystals. Over the entire concentration range studied, saturation of the uptake of the enantiomeric guest was not observed suggesting that the solid solubility limit of the enantiomeric guest in the host had not been reached. The slope of the plot in Fig. 1 gives a measure of segregation coefficient, k, which was found to be 0.153 (95% confidence interval 0.139–0.166).

The non-zero intercept value (0.0003) in Fig. 1 suggests that even the undoped crystals contained a trace quantity of the opposite enantiomer. This further emphasizes the fact that enantiomerically pure crystals are the exception rather than the rule and that homochiral crystals usually contain trace quantities of the opposite enantiomer.

The mole fraction of water in the crystals was found to be 8×10^{-4} (0.08% w/w) using Karl Fischer titrimetry. This value was independent of the mole fraction of enantiomeric impurity in the crystals. Similarly, no correlation was observed between the impurity incorporated and the water

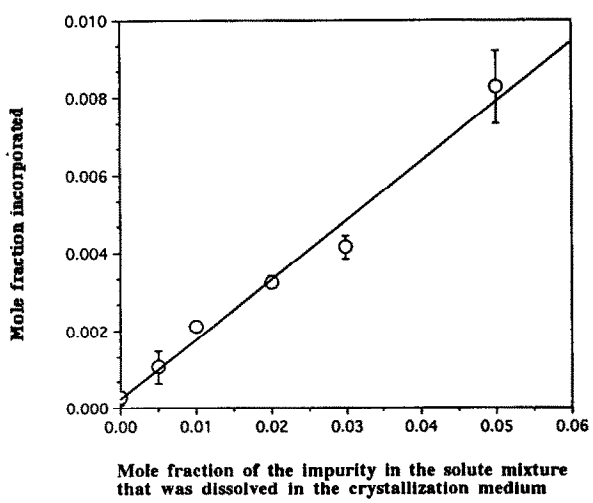

Fig. 1. Plot of the mole fraction of the opposite enantiomer incorporated into the crystals vs the mole fraction present in the solute mixture that was dissolved in the crystallization medium ($r = 0.979$). The vertical bars represent standard deviations ($n = 4$).

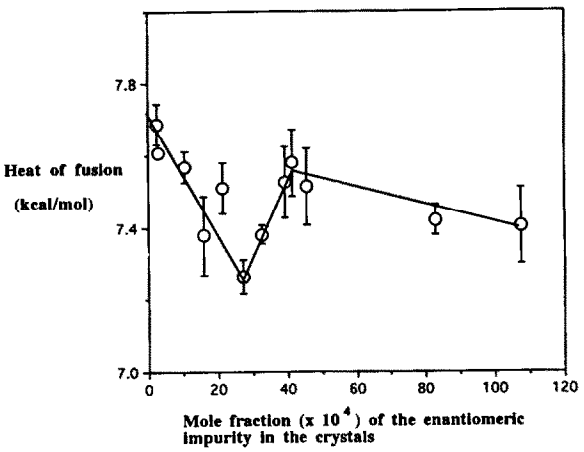

Fig. 2. Plot of the heat of fusion of (−)-ephedrinium 2-naphthalenesulfonate vs the mole fraction of the enantiomeric impurity in the crystals. The vertical bars represent standard deviations ($n = 3$).

content in the crystals of adipic acid crystallized from water containing an n-alkanoic acid or oleic acid as the additive (Chow, K.Y. et al., 1984, 1985). However, Chow A.H.-L. et al. (1985) found that a structurally related additive, p-acetoxyacetanilide, modulates the amount of the solvent of crystallization, water, taken up by acetaminophen crystals.

With increasing mole fraction of the enantiomeric guest in the crystals, the heat of fusion (ΔH^f) of the crystals of (−)-EN decreased to a minimum (Fig. 2) indicating disruption of the crystal lattice and an increase in the lattice strain. The linear decrease in ΔH^f was statistically significant ($p < 0.05$). At the minimum, corresponding to 0.0027 mole fraction of the enantiomeric impurity in the crystals, the ΔH^f was 5.4% lower than that of the undoped crystals. Table 1 shows that the melting point was not significantly affected by doping ($p > 0.05$). Thus, the resulting entropy of fusion ($\Delta S^f = \Delta H^f / T_m$) decreased to a minimum indicating an increase in crystal disorder to a maximum (Fig. 3). The linear decrease in ΔS^f was statistically significant ($p < 0.05$). At the minimum, corresponding to 0.0027 mole fraction of the enantiomeric impurity in the crystals, the ΔS^f was 5.2% lower than that of the undoped crystals. This increase in disorder with an increase in the concentration of the guest is proba-

TABLE 1

The melting point of (−)-ephedrinium 2-naphthalenesulfonate crystals containing various mole fractions of the enantiomeric impurity

Mole fraction ($\times 10^4$) of the enantiomeric impurity in the crystals	Melting point (mean ± SD) [a] (K)
2.65	447.4 ±1.3
3.00	444.1 ±0.7
10.60	448.2 ±0.5
16.00	444.7 ±1.2
21.20	448.3 ±1.0
27.15	445.75 ±1.1

[a] $n = 3$.

bly a result of an increase in lattice strain corresponding to an increase in the influence and concentration of crystal defects.

At higher concentrations of the guest in the crystals (> 0.0027), the enthalpy and entropy of fusion increased (Figs 2 and 3), suggesting a relaxation of lattice strain. Similar behavior was also observed when adipic acid was crystallized in the presence of trace quantities of fatty acid impurities for which an analogous explanation has been offered (Chow et al., 1984). At these higher concentrations of the additive, the defects may impede each other during heating in a DSC

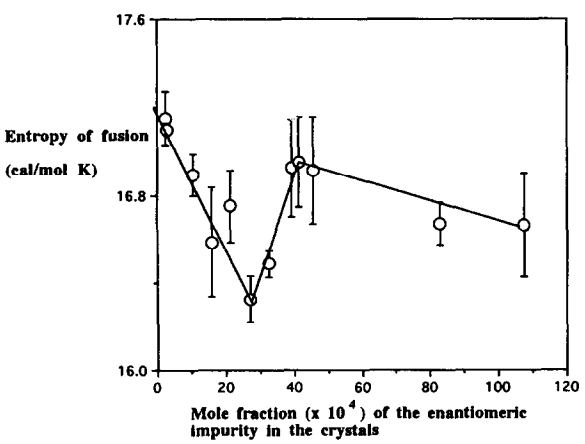

Fig. 3. Plot of the entropy of fusion of (−)-ephedrinium 2-naphthalenesulfonate vs the mole fraction of the enantiomeric impurity in the crystals. The vertical bars represent standard deviations ($n = 3$).

resulting in an overall increase in the entropy of fusion.

The fact that two independent systems, viz., adipic acid (Chow et al., 1984) and (−)-ephedrinium 2-naphthalenesulfonate, when doped with different structurally related impurities, undergo similar and systematic changes in their heat and entropy of fusion suggests a common underlying mechanism in the organic solid state. At present, the reason for observing a change in melting point when adipic acid is doped with octanoic acid but not when (−)-ephedrinium 2-naphthalenesulfonate is doped with opposite enantiomer, can only be a speculation until the actual changes in the nature and concentration of the of crystal defects are known. It is possible that significant changes in two- or three-dimensional defects may alter the cooperativity of melting of the crystal much more than changes in the zero- or one-dimensional defects. While one additive produces changes in certain types of defects, the other additive may produce changes in certain other types of defects.

At the mole fraction of the guest $\geqq 0.0042$, the enthalpy or entropy of fusion reached a plateau, suggesting a constancy of lattice strain, and showed no statistically significant change with an increase in the mole fraction of the incorporated guest. It is conceivable that at higher concentrations the impurity may become adsorbed on to the surfaces of the mosaic blocks of the crystals, rather than be incorporated into the bulk of the lattice. Adsorption onto the surfaces of the mosaic blocks (Weisinger-Lewin et al., 1989; Weissbuch et al., 1991) would not be expected to produce significant changes in the enthalpy and entropy of the crystals, and may explain the constancy of lattice strain at higher concentrations of the incorporated guest.

The changes in the thermodynamic properties of the host resulting from the incorporation of the guest can be quantified using the concept of disruption index (York and Grant, 1985). The negative slope of a plot of the entropy of fusion against the ideal entropy of mixing gives the disruption index (d.i.) which 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 (York and Grant, 1985). As shown in Fig. 4, for mole fractions of the guest $\leqq 0.0027$, the disruption index equals 20.6, suggesting that the increase in disorder of the crystal lattice of the host is approx. 20 times that expected for a random ideal solid solution of the guest in the host lattice. This substantial lattice disruption evidently arises from the opposite configurations of the guest and the host corresponding to differences in the spatial orientation of the atoms in the molecule. The d.i. value observed for the present system was close to the d.i. value of approx. 15 observed for pp-DDT doped with its structural isomer op-DDT. Interestingly, these two d.i. values are greater than the d.i. values for the other systems (York and Grant, 1985) in which the host is doped with a structurally related small molecular impurity that is not a stereoisomer. This comparison suggests that an impurity with differences in the spatial orientation of the atoms causes a greater disruption of the crystal lattice of the host than do other structurally related impurities.

However, at higher mole fractions of the impurity, corresponding to higher concentrations of crystal defects, motion of the defects may be mutually impeded during heating in a DSC by

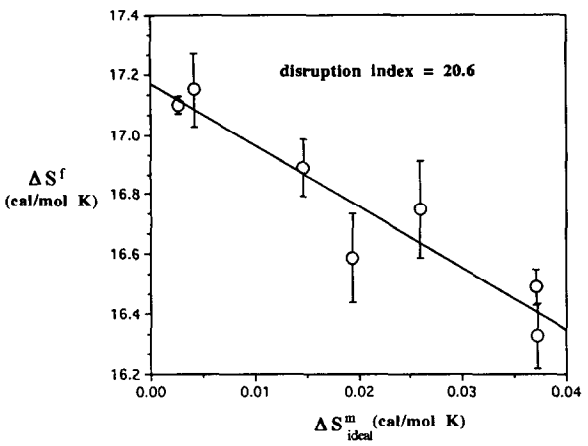

Fig. 4. Plot of the entropy of fusion of (−)-ephedrinium 2-naphthalenesulfonate vs the ideal entropy of mixing of (−)-ephedrinium 2-naphthalenesulfonate with the enantiomeric impurity ($r = 0.938$). The vertical bars represent standard deviations ($n = 3$).

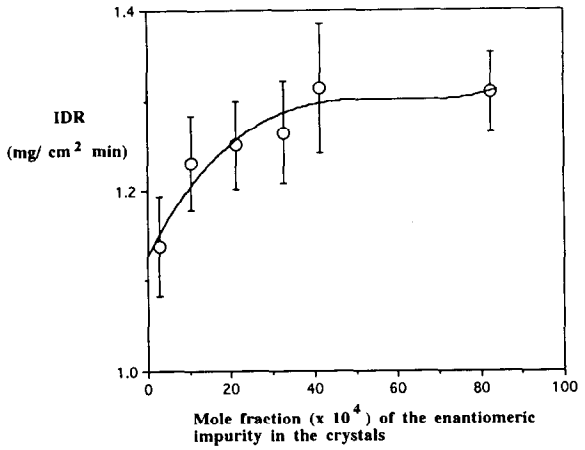

Fig. 5. Plot of the intrinsic dissolution rate (IDR) of (−)-ephedrinium 2-naphthalenesulfonate vs the mole fraction of the enantiomeric impurity in the crystals. The vertical bars represent standard deviations ($n = 3$).

processes which may occur during annealing, resulting in a reversal of the decreasing trend in the entropy of fusion. Thus, the entropy of fusion values at higher mole fractions of the guest (> 0.0027) will increase as a result of contributions from other thermal events and cannot be used to calculate the disruption index.

With increasing incorporation of the enantiomeric guest into the crystals of the host, the intrinsic dissolution rate of a disc compact of the host crystals (Fig. 5) was found to increase and then to plateau. The increase was statistically significant ($p < 0.05$) and the IDR reached a plateau when the mole fraction of the incorporated guest was $\geqq 0.0042$. At the plateau, the IDR was 14.5% higher than that for the undoped crystals. The increased intrinsic dissolution rate suggests a more negative free energy change for the dissolution process. This change in free energy may again arise from a change in the nature and concentration of defects in the crystal lattice of the host. An increase in the aqueous intrinsic dissolution rate of the host with an increase in the concentration of a structurally related additive was also observed when adipic acid was doped with 1-hexanoic acid or 1-octanoic acid (Chan and Grant, 1989).

A strong parallelism between the enthalpy of fusion and the intrinsic dissolution rate was, how-

ever, not observed suggesting a lack of enthalpy-entropy compensation (Vachon and Grant, 1987). This negative finding may be explained (a) by the large difference in temperature at which the heat of fusion was determined (174°C) and the temperature at which the intrinsic dissolution rate was determined (25°C) and (b) by the greater influence of surface defects (and consequent high energy surface sites) on the intrinsic dissolution rate in contrast to the greater influence of bulk defects (and consequent lattice strain) on the heat of fusion.

Conclusions

(1) During growth of crystals of (−)-EN from aqueous solutions containing the opposite enantiomer, the segregation coefficient, k, of the enantiomeric impurity was found to be 0.153.
(2) With increasing concentration of the opposite enantiomer in the crystallization medium, corresponding to mole fractions of enantiomeric impurity < 0.0027 in the crystals, the enthalpy and the entropy of fusion of (−)-EN decreased to minima, indicating increases in lattice energy and disorder, corresponding to increases in lattice strain. At the minimum, the enthalpy and entropy of fusion were 5.4 and 5.2% lower, respectively, than the corresponding values for undoped crystals.
(3) Crystallization in the presence of higher concentrations of the opposite enantiomer caused increases in the enthalpy and entropy of fusion of (−)-EN, suggesting decreases in lattice energy and disorder, corresponding to relaxation of the lattice strain. At mole fractions of the enantiomeric impurity $\geqq 0.042$ in the crystals, the enthalpy and entropy of the crystals reached a plateau suggesting a constancy of the lattice strain.
(4) With increasing mole fraction of enantiomeric impurity < 0.0027 in the crystals, the entropy of fusion decreased linearly with increasing ideal entropy of mixing, corresponding to a disruption index of 20.6.
(5) The intrinsic dissolution rate of (−)-EN increased with increasing concentration of the enantiomeric impurity in the crystals and reached a plateau value at mole fractions of enantiomeric impurity > 0.0042. The intrinsic dissolution rate of the plateau was 14.5% higher than that for the undoped crystals.

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References

Addadi, A., Berkovitch-Yellin, Z., Weissbuch, I., Lahav, M. and Leiserowitz, L., A link between macroscopic phenomena and molecular chirality: Crystals as probes for the direct assignment of absolute configuration of chiral molecules. In Eliel, E.L., Wilen, S.H. and Allinger, N.L. (Eds), *Topics in Stereochemistry*, Vol. 16, Wiley, New York, 1986, pp. 1–85.

Ariëns, E.J., Chiral drug analysis. *Chem. Eng. News*, March 19, 1990, p. 40.

Armstrong, D.W., Han Yoon, I. and Boon, M., Liquid chromatographic resolution of enantiomers containing single aromatic rings with cyclodextrin bonded phases. *Anal. Chim. Acta*, 208 (1988) 275–281.

Chan, H.-K., and Grant, D.J.W., Influence of compaction on the intrinsic dissolution of modified acetaminophen and adipic acid crystals. *Int. J. Pharm.*, 57 (1989) 117–124.

Chow, A.H.-L., Chow, P.K.K., Zhongshan, W. and Grant, D.J.W., Modification of acetaminophen crystals: Influence of growth in aqueous solutions containing *p*-acetoxyacetanilide on crystal properties. *Int. J. Pharm.*, 24 (1985) 239–258.

Chow, K.Y., Go, J., Mehdizadeh, M. and Grant D.J.W., Modification of adipic acid crystals: Influence of growth in the presence of fatty acid additives on crystal properties. *Int. J. Pharm.*, 20 (1984) 3–24.

Chow, K.Y., Go, J., Zhongshan, W., Mehdizadeh, M. and Grant, D.J.W., Modification of adipic acid crystals. II. Influence of growth in the presence of oleic acid on crystal properties. *Int. J. Pharm.*, 25 (1985) 41–55.

Collett, J.H., Rees, J.A.and Dickinson, N.A., Some parameters describing the dissolution rate of salicylic acid at controlled pH. *J. Pharm. Pharmacol.*, 24 (1972) 724–728.

De Camp, W.H., The FDA perspective on the development of stereoisomers. *Chirality*, 1 (1989) 2–6.

Doherty, C. and York, P., Mechanism of dissolution of frusemide/PVP solid dispersions. *Int. J. Pharm.*, 34 (1987) 197–205.

Doyle, D.T., Adams, M.W., Fry, S.F., Jr and Wainer, I.W., The application of HPLC chiral stationary phases to stereochemical problems of pharmaceutical interest: A general method for the resolution of enantiomeric amines as β-naphthyl carbamate derivatives. *J. Liq. Chromatogr.*, 9 (1986) 455–471.

Duddu, S.P., Mehvar, R. and Grant, D.J.W., Liquid chromatographic analysis of the enantiomeric impurities in various (+)-pseudoephedrine samples. *Pharm. Res.*, 8 (1991) 1430–1433.

Jacques, J., Collet, A. and Wilen, S.H., *Enantiomers, Racemates and Resolutions,* Wiley, New York, 1981, pp. 105–131.

Perry, J.A., Rateike, J.D. and Szczerba, T.J., Eluting trace components before major constituents: I. Sensitivity enhancement in analytical determination of optical purity. *J. Chromatogr.*, 389 (1987) 57–64.

Schill, G.S., Wainer, I.W. and Barkan, S.A., Chiral separation of cationic drugs on an α_1-acid glycoprotein bonded stationary phase. *J. Liq. Chromatogr.*, 9 (1986) 641–666.

Vachon, M.G. and Grant, D.J.W., Enthalpy-entropy compensation in pharmaceutical solids. *Int. J. Pharm.*, 40 (1987) 1–14.

Weisinger-Lewin, Y., Frolow, F., McMullan, R.K., Koetzle, T.F., Lahav, M. and Leiserowitz, L., Reduction in crystal symmetry of solid solutions: A neutron diffraction study at 15 K of the host/guest system aspargine/aspartic acid. *J. Am. Chem. Soc.*, 111 (1989) 1035–1040.

Weissbuch, I., Addadi, L., Berkovitch-Yellin, Z., Gati, E., Weinstein, S., Lahav, M. and Leiserowitz, L., Centrosymmetric crystals for the direct assignment of the absolute configuration of chiral molecules. Application to α-amino acids by their effect on glycine crystals. *J. Am. Chem. Soc.*, 105 (1983) 6615–6621.

Weissbuch, I., Addadi, L., Lahav, M. and Leiserowitz, L. Molecular recognition at crystal interfaces, *Science,* 253 (1991) 637–645.

Yang, Q., Sun, Z. and Ling, D., Resolution of enantiomeric drugs of some beta amino alcohols as their urea derivatives by high performance liquid chromatography on a chiral stationary phase. *J. Chromatogr.*, 447 (1988) 208–211.

York, P. and Grant, D.J.W., A disruption index for quantifying the solid state disorder induced by additives or impurities: I. Definition and evaluation from heat of fusion. *Int. J. Pharm.*, 25 (1985) 57–72.