

# **MERIT OF ESTIMATIONS FROM DSC MEASUREMENTS FOR THE EFFICIENCY OF OPTICAL RESOLUTIONS**

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## **Abstract**

Chiral drugs are generally resolved through formation of diastereoisomeric salts of different solubility. When the diastereoisomer salts form a eutectic in the solid phase, a good estimate can be made for the efficiency of the resolution ( $S$ ), through a calculation based on the eutectic composition ( $x_{eu}$ ). The eutectic composition can be computed from thermal data of a differential scanning calorimetric (DSC) measurement of the diastereoisomeric salts [1].

In this work we investigated the influence of uncertainties of thermal data on the estimation of the efficiency of resolution ( $S$ ), spreading throughout the calculations involved. Performance of our error-estimating method is demonstrated on 6 diastereoisomer salt pairs. The obtained deviations are close to the deviations of resolution experiments. Thus, it can be concluded that the DSC measurements are useful means in predicting the efficiency of resolutions.

**Keywords:** DSC, efficiency of optical resolution, error estimation, eutectic phase diagram

## **Introduction**

Resolution via diastereoisomeric salt formation is the most common way of separation of optical isomers. It is based on the formation of diastereoisomeric salt mixture from the racemate with the aid of a resolving agent; then fractional crystallisation can be used to separate the salts. This method is of growing importance in the pharmaceutical industry. Recently we have pointed out [1] that

\* Deceased

in the case of crystal conglomerate-forming diastereoisomeric salt pairs the efficiency of optical resolution\*

$$S = \frac{1 - 2x_{eu}}{1 - x_{eu}} \quad (1)$$

where  $S$  is the efficiency of optical resolutions,  $x_{eu}$  is the eutectic composition (the molar fraction of the higher melting salt).

Assuming that the melting phase diagram can be described by a pair of equations of Schröder-van Laar, it is known that the  $x_{eu}$  eutectic composition can be computed from the melting point and heat of fusion of the two pure diastereoisomeric salts, which are parameters of the equations. We have suggested another method to calculate  $x_{eu}$ , using the thermal data of 1:1 mixture of diastereoisomeric salts obtained by differential scanning calorimetry (DSC) [1]. This method is very useful, for at the beginning of the work one has only the salt mixture of 1:1 molar ratio, but not the pure salts themselves, which are the targets of the resolution. Screening the 1:1 mixtures of various salt pairs by DSC, a good resolving agent can be selected and the efficiency of the resolution predicted.

In this paper, we present a detailed error-estimation study of both predictions mentioned above. In the calculations, providing eutectic composition and the corresponding theoretical resolution, the uncertainties of thermal data are considered as the only source of the errors, while the Schröder-van Laar's equations are supposed to be valid. This way the three-step calculations were analysed by the law of error propagation, and with the error terms of the fix point iteration-method.

## Equations and calculation methods

Our considerations are based on the observations that in a eutectic two-phase component the melting diagram ( $T-x_2$ ) can be approximated by a pair of equations of Schröder-van Laar [3]:

$$\ln(1 - x_2) = \frac{\Delta H_1}{R} \left( \frac{1}{T_1} - \frac{1}{T} \right) \quad (2)$$

\* The efficiency ( $0 < S < 1$ ) of an optical resolutions has been defined as product of the optical purity ( $0 < OP < 1$ ) and the yield of precipitation ( $0 < Y < 1$ ):  $S = OP \cdot Y$

$$\ln x_2 = \frac{\Delta H_2}{R} \left( \frac{1}{T_2} - \frac{1}{T} \right) \quad (3)$$

where  $x_2$  is the molar fraction of higher melting salt in the crystal mixture;  $T$  is the final melting points of a crystal mixture with composition of  $x_2$ ;  $T_1$ ,  $T_2$  are the melting point of the pure diastereoisomeric salts,  $\Delta H_1$ ,  $\Delta H_2$  are the molar heats of fusion of the pure salts,  $R$  is the universal gas constant (8.314 J/K/mol).

Equation (2) is valid from  $x_2 = 0$  up to  $x_2 = x_{eu}$ , while the Eq. (3) is from the  $x_2 = x_{eu}$  up to  $x_2 = 1$ . At the eutectic composition ( $x_2 = x_{eu}$ ) the eutectic temperature ( $T = T_{eu}$ ) satisfies both equations.

In the two cases, when either the thermal data of the pure salts, or the thermal parameters of an 1:1 diastereoisomeric salt mixture are known, the eutectic composition and temperature ( $x_{eu}$  and  $T_{eu}$ ) cannot be calculated explicitly. This can be carried out only by numerical equation-solving methods. One of the simplest numerical methods is fix point iteration, which was chosen from the suitable methods.

### Fix point iteration

Fix point iteration is designed to solve implicit equations of type  $x = g(x)$ , with the aid of a series  $x_n = g(x_{n-1})$ . If  $g(x)$  is a continuous function and this series is a converging one, then  $\lim_{n \rightarrow \infty} x_n = \xi$  is a solution (a fix point) of  $x = g(x)$ . In the following the uniqueness of the root of equation, the error terms, and the stop conditions of the iteration are summarised shortly [4].

Uniqueness of the solution:

The following conditions should be fulfilled together

- 1.)  $g$  is a continuous function and differentiable on the  $[a, b]$  interval;
- 2.) there is a number  $q < 1$ , that  $|g'(x)| \leq q < 1$  for  $\forall x \in [a, b]$ ;
- 3.)  $g(x) \in [a, b]$  for  $\forall x \in [a, b]$ ;

then

- a.)  $g$  has a fix point on the  $[a, b]$  interval;
- b.) it has only one fix point ( $\xi$ );
- c.) and the  $x_n = g(x_{n-1})$  series is converging to this fix point, irrespectively of choice of initial guess  $x_0$ .

Errors can be estimated with the following expressions:

$$\text{I.) } |\xi - x_n| \leq q^n |a - b|;$$

$$\text{II.) } |\xi - x_n| \leq \frac{q}{1-q} |x_n - x_{n-1}|; \text{ e.g., if } q < 0.5 \text{ then } |\xi - x_n| \leq |x_n - x_{n-1}|.$$

Stop conditions for the iteration:

$$\alpha) n \geq n_{\max}, \text{ e.g., } n_{\max} = 1000;$$

$$\beta) \text{ or } |x_n - x_{n-1}| \leq \varepsilon, \text{ e.g., } \varepsilon = 0.0001;$$

The concrete forms of equations are selected more or less fulfil these requirements.

### Calculation of $x_{\text{eu}}$ from the thermal data of the pure diastereoisomeric salts

The values of  $T_1$ ,  $\Delta H_1$ , and  $T_2$ ,  $\Delta H_2$  are obtained from the individual DSC measurements of the pure salts ( $T_1 < T_2$ ). The following equation can be obtained from Eqs (2, 3) at the common eutectic point ( $x_{\text{eu}}$  and  $T_{\text{eu}}$ ).

$$\ln x_{\text{eu}} = \frac{\Delta H_2}{\Delta H_1} \ln(1 - x_{\text{eu}}) + \frac{\Delta H_2}{R} \left( \frac{1}{T_2} - \frac{1}{T_1} \right) = E \ln(1 - x_{\text{eu}}) + D \quad (4)$$

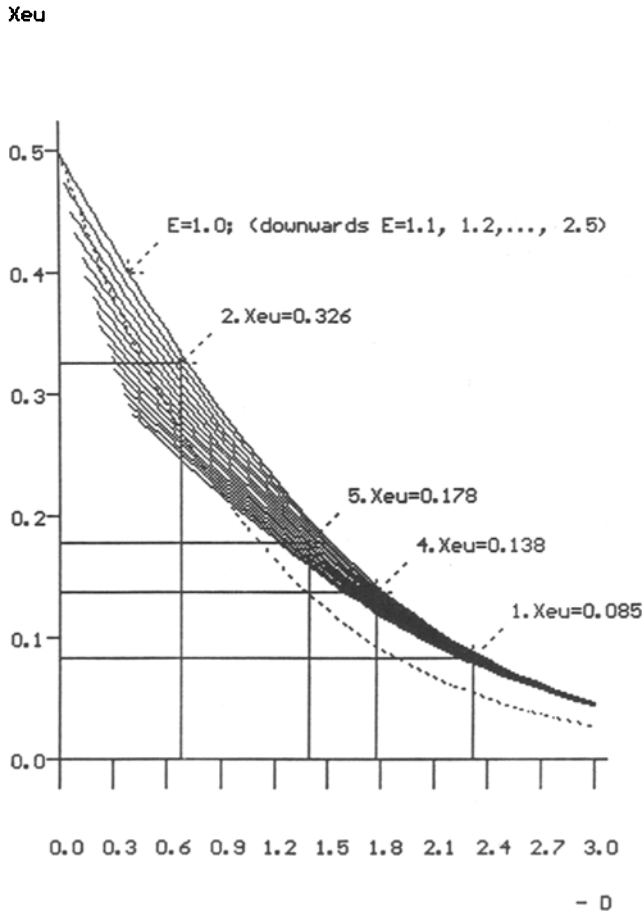
where  $D = \frac{\Delta H_2}{R} \left( \frac{1}{T_2} - \frac{1}{T_1} \right) < 0$  is a negative and  $E = \frac{\Delta H_2}{\Delta H_1} > 0$  is a positive parameter.

The appropriate iterative formula is:

$$x_n = \exp [E \ln(1 - x_{n-1}) + D] = e^D (1 - x_{n-1})^E. \quad (5)$$

The eutectic composition is considered to be valid on the  $[0, 1]$  interval. The  $g(x) = e^D(1-x)^E$  function is continuous and  $0 < g(x) = e^D(1-x)^E < 1$  is true on the same interval. They only question is whether  $|g'(x)| = e^D E(1-x)^{E-1} \leq q < 1$  is fulfilled for  $0 < x < 1$  or not. The answer depends on values of  $D$  and  $E$ . It can be shown that this inequality is true, when  $D < -\ln E$ . According to the theorem of uniqueness, in this case the original equation has only one solution, in the other cases convergence depends on the  $[a, b]$  interval of iteration and the  $x_0$  initial guess chosen.

We carried out fix point iterations for a large set of  $D$  and  $E$  parameter pairs chosen systematically in the experimentally observed range of  $D$  and  $E$  values ( $-3.0 < D < -0.01$  and  $1.0 < E < 2.5$ ). An iteration was finished, when the



**Fig. 1** Eutectic composition  $x_{eu}$  calculated from the melting parameters ( $-D$  and  $E$ ) of the pure diastereoisomeric salts by fix point iteration. The curves belong to  $E = 1.0, 1.1, 1.2, \dots, 2.5$  values from the top to the bottom, in order. Convergence problems of the fix point iteration may appear under the dotted line

change of  $x$  had become less than 0.0001 ( $|x_n - x_{n-1}| \leq 0.0001$ ) or the 1000<sup>th</sup> iteration step reached ( $n \geq 1000$ ). The obtained eutectic compositions  $x_{eu}$  are plotted against ( $-D$ ). Points belonging to the same  $E$  value are bound together with a solid line on Fig. 1. Curves from the top to the bottom belong to  $E = 1.0, 1.1, 1.2, \dots, 2.5$  values, in order.

The dotted line corresponds to  $-D = \ln E$  equality, under this line convergence is restricted to a narrower interval of  $x$ , or divergence occurs. It means, that the  $x_0$  initial guess has to be chosen close to the fix point, or an appropriate  $x_0$  cannot be found at all. Calculating this part of the curve, each fix point was

used as an initial guess of iteration at the neighbouring point. Some curves were not further drawn, because no fix point could be obtained even this way.

### Calculation of $x_{eu}$ from thermal data of the 1:1 mixture of diastereoisomeric salts

The considerations resulting in Eq. (6) can be found in [1]. The  $T_{eu}$ ,  $T_{50}$  and  $Q_2$  parameters are obtained from the DSC run of 1:1 molar mixture, Fig. 2, ( $T_{eu} < T_{50}$ ).

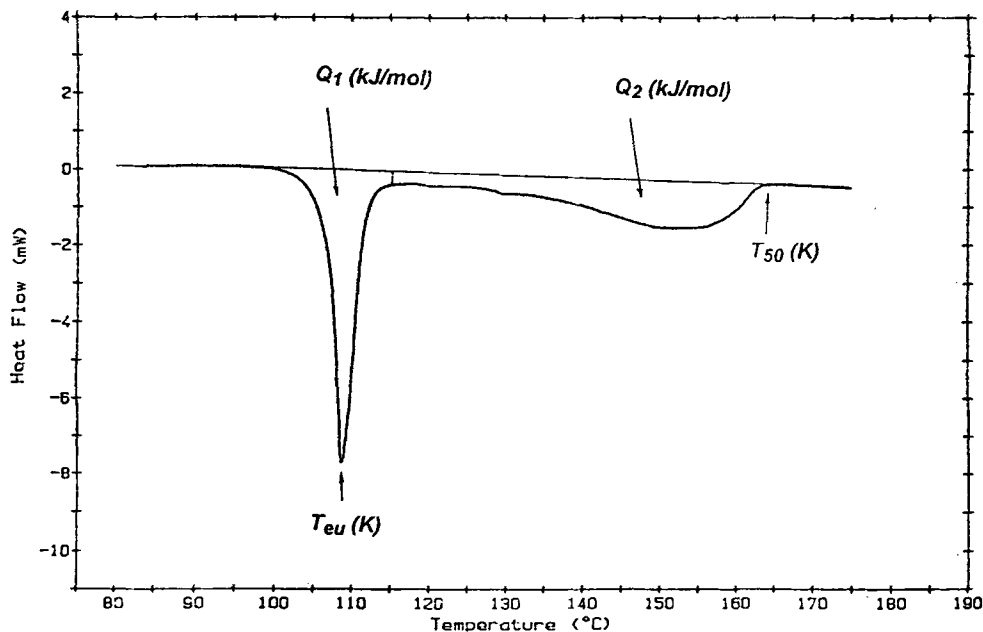


Fig. 2 DSC (heat flow vs. temperature) plot of a 1:1 mixture of diastereoisomeric salts. The sharp peak corresponds to eutectic melting ( $T_{eu}$  is the eutectic temperature,  $Q_1$  is the appropriate molar heat effect). The elongated peak belongs to the gradual melting process of the excess component, ( $T_{50}$  is the final temperature of melting,  $Q_2$  is the cumulated molar heat effect of it). (Endothermic effects downwards)

$$\ln(2x_{eu}) = \frac{2 - 2x_{eu}}{1 - 2x_{eu}} \frac{Q_2}{R} \left( \frac{1}{T_{50}} - \frac{1}{T_{eu}} \right) = C \frac{2 - 2x_{eu}}{1 - 2x_{eu}} \quad (6)$$

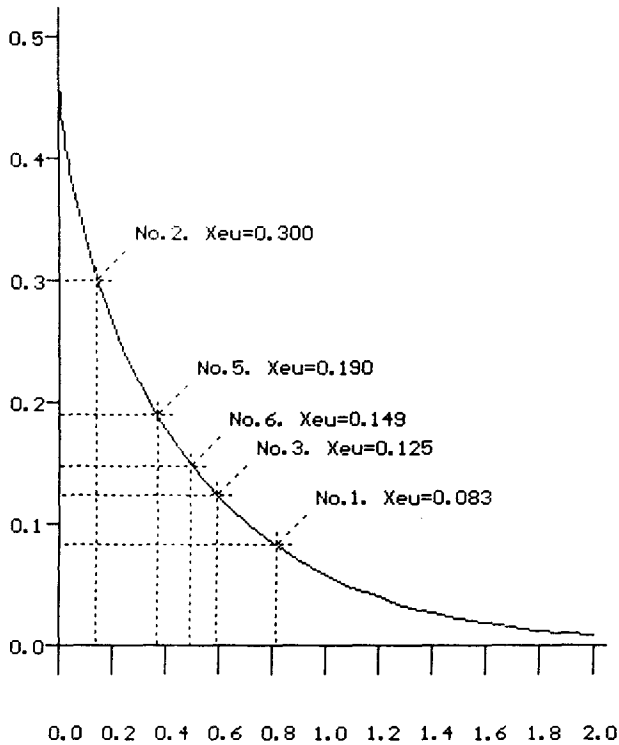
where  $C = \frac{Q_2}{R} \left( \frac{1}{T_{50}} - \frac{1}{T_{eu}} \right) < 0$  negative parameter,

and the iterative formula is:

$$x_n = \frac{1}{2} \exp \left[ C \frac{2 - 2x_{n-1}}{1 - 2x_{n-1}} \right] = \frac{1}{2} \exp \left[ C \left( 1 + \frac{1}{1 - 2x_{n-1}} \right) \right] \quad (7)$$

Eutectic composition is considered to be valid on the  $[0, 0.5]$  interval. The  $g(x) = \frac{1}{2} \exp \left[ C \left( 1 + \frac{1}{1 - 2x} \right) \right]$  function is continuous on the  $[0, 0.5]$  interval, and  $0 < g(x) = \frac{1}{2} \exp \left[ C \left( 1 + \frac{1}{1 - 2x} \right) \right] < 0.5$  is true on the same interval. The third requirement is not discussed, because no convergence problem has occurred during the computations.

$x_{eu}$



- C

**Fig. 3** Eutectic composition  $x_{eu}$  calculated from the melting parameter ( $-C$ ) of the 1:1 mixture of diastereoisomeric salts by fix point iteration

A systematic calculation of the eutectic compositions was also carried out for the experimentally observed range of  $C$  ( $-2 < C < -0.0005$ ). The results are plotted as a curve against  $-C$ , in the Fig. 3. Stop conditions were the same as above ( $|x_n - x_{n-1}| \leq 0.0001$  or  $n \geq 1000$ ).

If we consider  $D$ ,  $E$  and  $C$  parameters as precise ones, the fix point iteration provides a precise numerical solution of the Eqs (4, 6). The difference of eutectic composition from the real fix point is less than 0.001 (as molar fraction) using the above stop conditions. Actually the parameters  $C$ ,  $D$  and  $E$  are calculated from thermal data, thus their uncertainty arises from the thermal measurements. To take into account these uncertainties we used the law of error propagation.

### Law of error propagation

Let  $F$  be a function of  $x_1, x_2, \dots, x_n$  independent variables:

$$F = F(x_1, x_2, \dots, x_n).$$

The error propagation law provides an estimate of the variance of  $F$ :

$$\text{Var } F = \sum_{i=1}^n \left( \frac{\partial F}{\partial x_i} \right)^2 \text{Var } x_i;$$

$$(\Delta F)^2 \cong \sum_{i=1}^n \left( \frac{\partial F}{\partial x_i} \right)^2 (\Delta x_i)^2,$$

where  $\Delta x_i$  is a measurement error of  $x_i$ .

The applications of this law for the  $D$ ,  $E$  and  $C$  parameters are detailed in the following. The estimated experimental error of  $Q_2$  is chosen greater than usual because of the difficulties appeared in resolution of two overlapping peaks (Fig. 2).

**Law of error propagation for  $D = \frac{\Delta H_2}{R} \left( \frac{1}{T_2} - \frac{1}{T_1} \right)$ :**

$$\text{Var } D = \left( \frac{\partial D}{\partial (\Delta H_2)} \right)^2 \text{Var } \Delta H_2 + \left( \frac{\partial D}{\partial T_2} \right)^2 \text{Var } T_2 + \left( \frac{\partial D}{\partial T_1} \right)^2 \text{Var } T_1$$



$$\begin{aligned}
 (\Delta D)^2 &\cong \left[ \frac{1}{R} \left( \frac{1}{T_2} - \frac{1}{T_1} \right) \right]^2 (\Delta(\Delta H_2))^2 + \left[ -\frac{\Delta H_2}{R} \frac{1}{T_2^2} \right]^2 (\Delta T_2)^2 + \left[ \frac{\Delta H_2}{R} \frac{1}{T_1^2} \right]^2 (\Delta T_1)^2 \\
 \left( \frac{\Delta D}{D} \right)^2 &\cong \left( \frac{\Delta(\Delta H_2)}{\Delta H_2} \right)^2 + \left[ \frac{\frac{1}{T_2}}{\frac{1}{T_2} - \frac{1}{T_1}} \right]^2 \left( \frac{\Delta T_2}{T_2} \right)^2 + \left[ \frac{\frac{1}{T_1}}{\frac{1}{T_2} - \frac{1}{T_1}} \right]^2 \left( \frac{\Delta T_1}{T_1} \right)^2
 \end{aligned} \quad (8)$$

Temperature ranges:

$$350 \text{ K} < T_{\text{cu}} < T_{50} < 500 \text{ K} \text{ and } 10 \text{ K} < T_{50} - T_{\text{cu}} < 40 \text{ K}$$

$$\frac{1}{T} \approx 2 - 3 \times 10^{-3}; \quad \left| \frac{1}{T_{50}} - \frac{1}{T_{\text{cu}}} \right| \approx 1 - 3 \times 10^{-4};$$

Estimated deviations:

$$\left| \frac{\frac{1}{T_2}}{\frac{1}{T_2} - \frac{1}{T_1}} \right| \approx 10; \quad \left| \frac{\Delta T}{T} \right| \approx 0.005; \quad \left| \frac{\Delta(\Delta H_2)}{\Delta H_2} \right| \approx 0.05.$$

Relative deviation of  $D$ :

$$\left| \frac{\Delta D}{D} \right|^2 \approx 0.05^2 + 0.005^2 \cdot 10^2 + 0.005^2 \cdot 10^2 = 0.0075$$

$$\left| \frac{\Delta D}{D} \right| \approx 0.087$$

Law of error propagation for  $E = \frac{\Delta H_2}{\Delta H_1}$ :

$$\text{Var } E = \left( \frac{\partial E}{\partial(\Delta H_2)} \right)^2 \text{Var } \Delta H_2 + \left( \frac{\partial E}{\partial(\Delta H_1)} \right)^2 \text{Var } \Delta H_1;$$

$$(\Delta E)^2 \cong \left( \frac{E}{\Delta H_2} \right)^2 [\Delta(\Delta H_2)]^2 + \left( \frac{-E}{\Delta H_1} \right)^2 [\Delta(\Delta H_1)]^2;$$

$$\left( \frac{\Delta E}{E} \right)^2 \cong \left( \frac{\Delta(\Delta H_2)}{\Delta H_2} \right)^2 + \left( \frac{\Delta(\Delta H_1)}{\Delta H_1} \right)^2; \quad (9)$$

Estimated deviation of enthalpy measurement:  $\left| \frac{\Delta(\Delta H)}{\Delta H} \right| \approx 0.05$ .  
 Relative deviation of  $E$ :

$$\left( \frac{\Delta E}{E} \right)^2 \approx 0.05^2 + 0.05^2 = 0.005$$

$$\left| \frac{\Delta E}{E} \right| \approx 0.071.$$

**Law of error propagation for  $C = \frac{Q_2}{R} \left( \frac{1}{T_{50}} - \frac{1}{T_{eu}} \right)$ ;**

$$\text{Var } C = \left( \frac{\partial C}{\partial Q_2} \right)^2 \text{Var } Q_2 + \left( \frac{\partial C}{\partial T_{50}} \right)^2 \text{Var } T_{50} + \left( \frac{\partial C}{\partial T_{eu}} \right)^2 \text{Var } T_{eu}$$

$$(\Delta C)^2 \cong \left[ \frac{1}{R} \left( \frac{1}{T_{50}} - \frac{1}{T_{eu}} \right) \right]^2 (\Delta Q_2)^2 + \left[ -\frac{Q_2}{R} \frac{1}{T_{50}^2} \right]^2 (\Delta T_{50})^2 + \left[ \frac{Q_2}{R} \frac{1}{T_{eu}^2} \right]^2 (\Delta T_{eu})^2$$

$$\left( \frac{\Delta C}{C} \right)^2 \cong \left( \frac{\Delta Q_2}{Q_2} \right)^2 + \left[ \frac{\frac{1}{T_{50}}}{\frac{1}{T_{50}} - \frac{1}{T_{eu}}} \right]^2 \left( \frac{\Delta T_{50}}{T_{50}} \right)^2 + \left[ \frac{\frac{1}{T_{eu}}}{\frac{1}{T_{50}} - \frac{1}{T_{eu}}} \right]^2 \left( \frac{\Delta T_{eu}}{T_{eu}} \right)^2 \quad (10)$$

Temperature ranges:

$$350 \text{ K} < T_{eu} < T_{50} < 500 \text{ K} \quad \text{and} \quad 10 \text{ K} < T_{50} - T_{eu} < 40 \text{ K}$$

$$\frac{1}{T} \approx 2 - 3 \times 10^{-3}; \quad \left| \frac{1}{T_{50}} - \frac{1}{T_{eu}} \right| \approx 1 - 3 \times 10^{-4};$$

Estimated deviations:

$$\left| \frac{\frac{1}{T_{50}}}{\frac{1}{T_{50}} - \frac{1}{T_{eu}}} \right| \approx 10; \quad \left| \frac{\Delta T}{T} \right| \approx 0.005; \quad \left| \frac{\Delta Q_2}{Q_2} \right| \approx 0.1.$$

Relative deviations of  $C$ :

$$\left| \frac{\Delta C}{C} \right|^2 \approx 0.1^2 + 0.005^2 \cdot 10^2 + 0.005^2 \cdot 10^2 = 0.015$$

$$\left| \frac{\Delta C}{C} \right| \approx 0.122.$$

In a similar way the error of efficiency of resolution, inherited from the error of eutectic molar fraction, can also be estimated by the law of error propagation.

### Law of error propagation for efficiency of resolution $S$

$$S = \frac{1 - 2x_{eu}}{1 - x_{eu}} = 2 + \frac{1}{x_{eu} - 1}$$

$$\text{Var } S = \left( \frac{dS}{dx_{eu}} \right)^2 \text{Var } x_{eu};$$

$$(\Delta S)^2 \cong \left[ \frac{-1}{(x_{eu} - 1)^2} \right]^2 (\Delta x_{eu})^2;$$

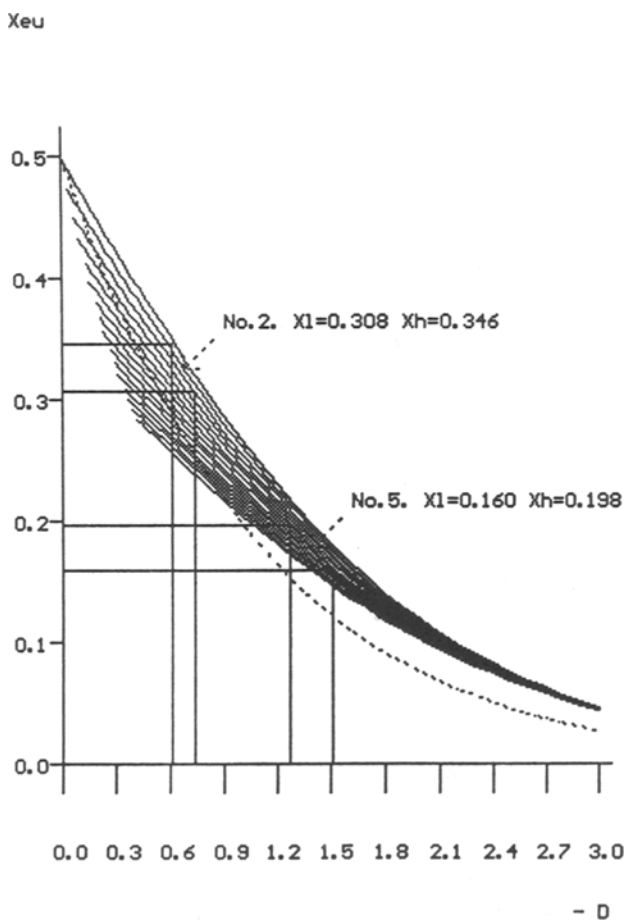
$$|\Delta S| \cong \frac{1}{(1 - x_{eu})^2} |\Delta x_{eu}|. \quad (11)$$

### General procedure for estimating error of the efficiency of resolution

The procedure consists of three stages according to the three steps of calculations. First the appropriate  $D$ ,  $E$  or  $C$  parameters and their errors are calculated using Eqs (8, 9 or 10) respectively. Considering the extent of deviations obtained for these parameters, the error of fix point iteration itself can be neglected, so the curves of Figs 1 and 3 allow to take into account exactly the alterations of  $x_{eu}$  eutectic composition, arising from the uncertainty of the above parameters. Using simple projections on these graphs, a band of  $x_{eu}$  can be obtained, showing the indirect effects of the experimental uncertainties, Figs 4 and 5. Then uncertainty of the efficiency of resolution can be estimated by calculation of the appropriate range from lower and upper limit of the band obtained for  $x_{eu}$ , or graphically, by similar projections as above on the Figs 6 and 7 (which are showing the relationship between  $S$  vs.  $x_{eu}$ ), or by using the generalised Eq. (11).

### Results and conclusions

We present here the error calculations for six diastereoisomeric salt systems. The compositions of these systems are listed in Table 1. The differential scanning calorimetric (DSC) measurements have been carried out earlier by a



**Fig. 4** Error ranges of eutectic composition ( $x_1$  and  $x_h$ ) for systems of No.2 and 5, calculated from relative uncertainties of the melting parameters  $-D$  and  $E$  (8.7% and 7.1%) of the pure diastereoisomeric salts

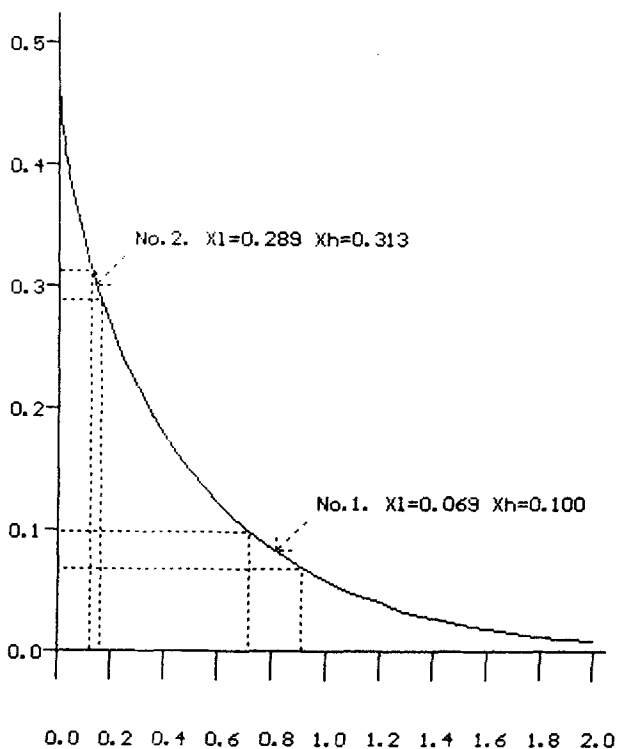
**Table 1** Chemical compositions of the diastereoisomeric salt systems

System	Racemate	Resolving agent	Ref.
No. 1	mandelic acid	<i>R</i> - $\alpha$ -phenyl-ethyl-amine	[5]
No. 2	mandelic acid	<i>S</i> -2-aminobutanol	[6]
No. 3	mandelic acid	<i>R</i> -2- <i>tert</i> -butyl-3-methylimidazolidin-4-one	[7]
No. 4	methamphetamine	<i>R,R</i> -tartaric acid	[8]
No. 5	<i>p-F</i> -methamphetamine	<i>R,R</i> -tartaric acid	[9]
No. 6	naproxene	<i>N</i> -methyl- <i>D</i> -glucamine	[10]

**Table 2** Thermal data of the pure diastereoisomeric salts

System	$T_1 / \text{K}$	$\Delta H_1 / \text{kJ}\cdot\text{mol}^{-1}$	$T_2 / \text{K}$	$\Delta H_2 / \text{kJ}\cdot\text{mol}^{-1}$
No. 1	382	30.3	450	48.9
No. 2	357	28.8	381	32.1
No. 3	352	30.6	391	51.5
No. 4	387	35.9	437	50.0
No. 5	393	35.0	426	58.9
No. 6	398	30.4	431	61.6

Xeu



- C

**Fig. 5** Error ranges of eutectic composition ( $x_1$  and  $x_h$ ) for systems of No.1 and 2, calculated from relative uncertainties of the melting parameters -C (12.2%) of the 1:1 mixture of the diastereoisomeric salts

Du Pont 1090B Thermal Analysis System. In each salt system both the pure diastereoisomeric salts and their 1:1 mixture were measured. Melting points and heats of fusion of the pure diastereoisomeric salts obtained experimentally are listed in Table 2. Thermal features of the 1:1 mixtures are summarised in Table 3. The uncertainty of temperature measurement was considered to be 1–2 degree, and the relative error of enthalpy determinations was assumed to be 5% for the pure salts, whilst 10% for the second peak enthalpy  $Q_2$  of the 1:1 mixtures, because the two peaks were generally overlapping, Fig. 2.

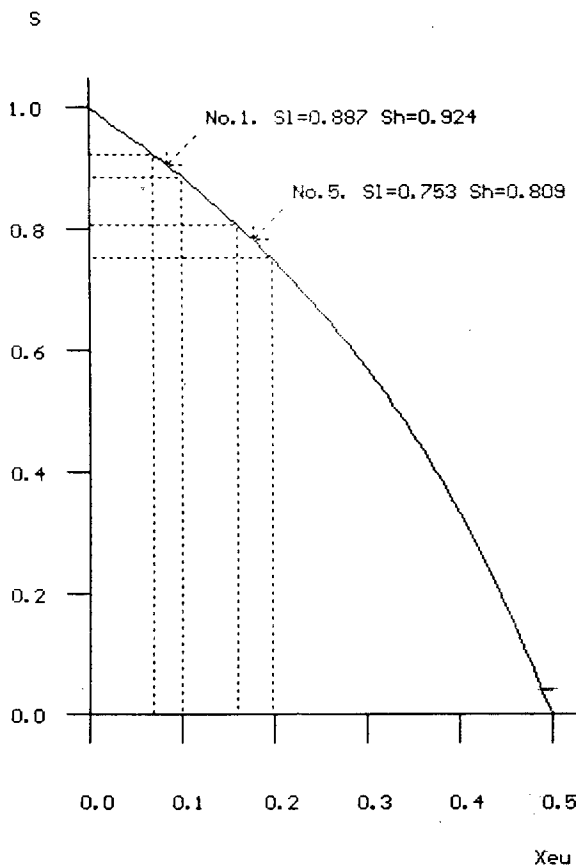


Fig. 6 Error ranges of efficiency of resolution ( $S_1$  and  $S_h$ ) from measurement of the pure diastereoisomeric salts for systems No.1 and 5

Considering the measured thermal data to be precise, we carried out the calculations of the eutectic composition and resolution-efficiency by both methods (graphical presentation for some systems can be found on Figs 1 and 3). These

results, obtained by fix point iterations and presented in Table 4, were satisfactorily close to each other and to the experimentally achieved resolutions. To demonstrate the reliability of our method (that is calculation from data of the 1:1 mixture) we also present melting points and heats of fusion of the pure salts, calculated using eutectic compositions gained from data of the 1:1 mixtures [1], Table 5. They are comparable with the experimental ones, Table 2.

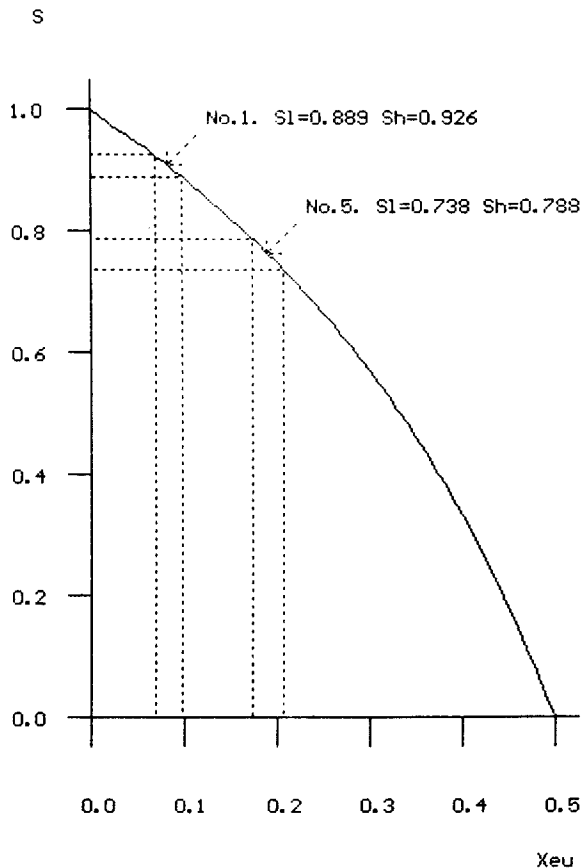


Fig. 7 Error ranges of efficiency of resolution ( $S_1$  and  $S_h$ ) from measurement of the 1:1 mixture of diastereoisomeric salts for systems No.1 and 5

Then we calculated the relative error of parameters  $D$ ,  $E$  and  $C$ , according to the law of error propagation. As detailed above,  $\Delta D = 8.7\%$ ,  $\Delta E = 7.1\%$ ,  $\Delta C = 12.2\%$  were obtained. The uncertainties of eutectic molar fractions caused by these deviations are demonstrated for two systems on Figs 4 and 5. Both methods provide almost the same deviation of  $x_{eu}$ , within a range of

0.03–0.04. The upper and lower limits obtained for each system in a similar way, are summarised in Tables 6 and 7 for the two methods, together with the corresponding range of  $S_{eu}$  resolution values. The resulting error ranges of the efficiency of resolution for two systems are also demonstrated in Figs 6 and 7.

**Table 3** Thermal data of the 1:1 mixture of the diastereoisomeric salt pairs

System	$T_{eu}$ / K	$Q_1$ / kJ·mol <sup>-1</sup>	$T_{50}$ / K	$Q_2$ / kJ·mol <sup>-1</sup>
No. 1	382	18.2	428	24.1
No. 2	341	23.0	356	9.8
No. 3	348	16.8	375	23.9
No. 4	381	23.4	417	19.6
No. 5	387	33.3	409	22.1
No. 6	395	37.2	418	29.8

**Table 4** The calculated eutectic composition and efficiency of resolutions by both methods and the experimentally achieved resolutions

System	$x_{eu}$ from pure diastereoisomeric salts	$x_{eu}$ from 1:1 mixture of the salts	$S_{eu}$ from pure diastereoisomeric salts	$S_{eu}$ from 1:1 mixture of the salts	$S$ experimentally observed [Ref.]
No. 1	0.085	0.083	0.908	0.909	0.86* [5]
No. 2	0.326	0.300	0.516	0.571	0.46 [6]
No. 3	0.135	0.125	0.844	0.857	0.82 [7]
No. 4	0.138	0.140	0.841	0.838	0.87 [8]
No. 5	0.178	0.190	0.784	0.765	0.81 [9]
No. 6	0.166	0.149	0.800	0.825	0.79 [10]

\* - result of a reverse resolution

**Table 5** Thermal data of pure diastereoisomeric salts calculated from data of their 1:1 mixture

System	$T_1$ / K	$\Delta H_1$ / kJ·mol <sup>-1</sup>	$T_2$ / K	$\Delta H_2$ / kJ·mol <sup>-1</sup>
No. 1	385.4	31.6	448.9	53.0
No. 2	352.4	31.3	378.6	34.3
No. 3	353.3	25.6	390.1	55.7
No. 4	385.7	39.2	439.6	46.8
No. 5	292.0	53.0	426.4	57.8
No. 6	398.4	61.7	432.4	72.2



**Table 6** The upper and lower limits obtained for the eutectic compositions and the efficiency of resolutions from the measurements of the pure diastereoisomeric salts

System	D	E	$x_{eu}$ lower	$x_{eu}$ higher	$S_{eu}$ lower	$S_{eu}$ higher
No. 1	-2.327	1.614	0.070	0.102	0.887	0.924
No. 2	-0.681	1.115	0.308	0.346	0.471	0.556
No. 3	-1.755	1.683	0.118	0.155	0.817	0.866
No. 4	-1.778	1.393	0.120	0.158	0.812	0.864
No. 5	-1.396	1.683	0.160	0.198	0.753	0.809
No. 6	-1.425	2.026	0.149	0.185	0.773	0.824

**Table 7** The upper and lower limits obtained for the eutectic compositions and the efficiency of resolutions from the measurements of the 1:1 mixture of the diastereoisomeric salts

System	C	$x_{eu}$ lower	$x_{eu}$ higher	$S_{eu}$ lower	$S_{eu}$ higher
No. 1	-0.816	0.069	0.100	0.889	0.926
No. 2	-0.146	0.289	0.313	0.545	0.594
No. 3	-0.595	0.109	0.143	0.833	0.877
No. 4	-0.534	0.124	0.158	0.813	0.859
No. 5	-0.370	0.175	0.208	0.738	0.788
No. 6	-0.499	0.133	0.167	0.800	0.846

The deviation ranges of  $S_{eu}$  are about 0.05–0.08 wide. The experimentally achieved resolutions are close to these ranges.

Considering that the measured resolution values also have similar deviations, it can be concluded, that our calculation methods give satisfactorily good predictions for the efficiency of resolution, and their uncertainty is almost the same as that of the resolution experiments.

\* \* \*

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**Zusammenfassung** — Ganz allgemein erfolgt die Trennung chiraler Arzneimittel über die Bildung diastereomerer Salze unterschiedlicher Löslichkeit. Bilden die diastereomeren Salzformen in der Feststoffphase ein Eutektikum, kann über eine auf der eutektischen Zusammensetzung ( $x_{eu}$ ) basierende Berechnung eine gute Schätzung der Effizienz der Trennung ( $S$ ) vorgenommen werden. Die eutektische Zusammensetzung kann anhand der thermischen Angaben aus DSC-Messungen an den diastereoisomeren Salzen berechnet werden [1].

Vorliegend untersuchten wir den Einfluß der Ungenauigkeiten der thermischen Angaben auf die Schätzung der Effizienz der Trennung ( $S$ ) bei den angewandten Berechnungen. Die Durchführung dieser Fehlerschätzungsmethode wird am Beispiel von 6 diastereoisomeren Salzpaaren dargestellt. Die erhaltenen Deviationen liegen den Deviationen der Trennungsexperimente sehr nahe. Somit scheinen DSC-Messungen nützliche Hilfsmittel bei der Voraussage der Effizienz des Trennungsvorganges zu sein.