Quantitative Relationship Between Solubility, Initial Dissolution Rate and Heat of Solution of Chiral Drugs

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Received June 18, 1999; accepted October 7, 1999

Purpose. The aim of this study was to clarify the quantitative relationship between solubility, initial dissolution rate and heat of solution of racemic compound and its enantiomers.

Methods. Propranolol, propranolol HCl, tyrosine, and tryptophan were used as typical chiral drugs. The heat of solution of chiral drug was measured by an isothermal microcalorimeter and the heat of fusion was measured by a DSC. The free energy difference for the dissolution of drug was calculated from the solubility and initial dissolution rate data.

Results. The free energy difference and enthalpy difference of the dissolution between the racemic compound and enantiomer of propranolol, propranolol hydrochloride, tyrosine, and tryptophan were obtained by the solubility, initial dissolution rate and heat of solution data. A good linearity was observed in the free energy difference and the enthalpy difference for the dissolution of them, except for propranolol HCl data. By considering the dissociation in solution, the data of propranolol HCl followed the regression line.

Conclusions. The free energy difference of the dissolution was linearly dependent on the enthalpy difference for the racemic compound and its enantiomers. The results fit the theoretical equation. It could be possible to estimate the solubility of chiral insoluble drug from the thermal data.

KEY WORDS: racemic compound; enantiomers; solubility; initial dissolution rate; dissociation constant; thermal analysis.

INTRODUCTION

The characterization of chiral drugs is receiving much increased attention from manufacturing and regulatory organizations due to their pharmacological effects (1,2). It is well known that the molecular arrangement in a crystal for enantiomers is different from that for racemic compound. If the difference in crystal structure results in a change in the melting point and heat of fusion, then the solubilities of the pure enantiomers may be different from that of the racemic compound.

Preferential crystallization of racemic mixtures or conglomerates has been one of the most frequently used methods for separating enantiomers. On the other hand, Tamura *et al.* have reported the first case of enantiometric resolution by simple recrystallization of a series of racemic compounds, although in principle this type of enatiometric resolution was believed to be infeasible (3–6). They have described that the physical information of solubility, polymorphic transformation and the melting point phase diagram of chiral drug are the important factors to elucidate the recrystallization behavior. Thermal analysis, e.g. differential scanning calorimetry and solution calorimetry, has been successfully employed to investigate differences in the melting point, heat of fusion and heat of solution of drugs and the polymorphic transformation (7–9). From these fundamental thermodynamic properties, the solubility may be predicted, and the knowledge of the solubility is essential practical information in developing pharmaceutical products, especially recrystallization process. However, it is very difficult to evaluate the solubility and dissolution rate of a new drug because of the insufficiency of a product.

This report illustrates the relationship between the free energy difference of the dissolution and the enthalpy difference for the racemic compound and its enantiomers and how to estimate the solubility and initial dissolution rate of chiral drugs using thermal analysis. The chiral drugs investigated are propranolol, propranolol hydrochloride, tyrosine, and tryptophan. Further, the dissociation of chiral salts in solution is discussed.

MATERIALS AND METHODS

Materials

R-(+)-, S-(−)- and (±)-propranolol hydrochloride (Sigma), L- and DL-tyrosine (Tokyo Kasei) and L-, D- and DL-tryptophan (Tokyo Kasei) were used as received. R- (+)- and (±)-propranolol were precipitated from alkaline solution then recrystallized from cyclohexane.

Differential Scanning Calorimetry (DSC)

DSC traces were measured by use of Perkin-Elmer DSC 7 under nitrogen gas flow at a heating rate of 5°C/min.

Isothermal Microcalorimetry

The samples (100 mg) were loaded into a glass ampoule. A 25 ml of distilled water was used as solvent for propranolol hydrochloride, 1 mol/L hydrochloric acid was used for tryptophan and tyrosine. The heat responses were measured by an isothermal microcalorimeter (MMC-5111, Tokyo Riko) at 25°C. The exact experimental method was as reported previously (10).

Dissolution Rate Measurement

Dissolution rate studies were performed according to a rotating disk method. The apparatus was similar to that described by S. Prakongpan *et al.* (11). The experiment was carried out at 25°C. 200 ml of distilled water or cyclohexane was used as the dissolution medium. A sample disk of 6 mm diameter compressed at 500 kg/cm^2 was attached at the end of the rotating spindle. The revolution speed of the disk was adjusted to 250 rpm. The dissolution medium was circulated at a constant rate of 600 ml/min. The concentrations of samples were determined spectrophotometrically. Tylosine disk was hardly prepared by compression because of the lamination of it, therefore the dissoluton rate of tyrosine was not determined.

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Solubility Measurement

The solubility of tylosine at 25°C was measured in distilled water. An excess amount of S-(−)-propranolol hydrochloride was added to 25 ml of distilled water containing various concentration of R-(+)-enantiomer and the mixtures were shaken at 25°C. After equilibration had been attained, the suspension was filtered. Then the filtrate was suitably diluted and analyzed spectrophotometrycally to measure the amount of dissolved S-(−)-enantiomer. A dissociation constant was calculated from the slope of the solubility diagram.

THEORETICAL SECTION

The Gibbs free energy of the dissolution of a racemic compound is given by Eq. (1),

$$\Delta G^{RC}_{Soln} = \Delta H^{RC}_{Soln} - T\Delta S^{RC}_{Soln} \quad (1)$$

where ΔH^{RC}_{Soln} and ΔS^{RC}_{Soln} are the enthalpy and entropy of dissolution of the racemic compound at temperature T, respectively. The free energy difference of the dissolution between the racemic compound and enatiomer is given by Eq. (2).

$$\begin{aligned}\Delta\Delta G^{RC-E}_{Soln} &= \Delta\Delta H^{RC-E}_{Soln} - T\Delta\Delta S^{RC-E}_{Soln} \\ &= \Delta\Delta H^{RC-E}_{Soln} - T\{-R(x^R\ ln\ x^R + x^S\ ln\ x^S)\} \\ &= \Delta\Delta H^{RC-E}_{Soln} - RT\ ln\ 2 \end{aligned} \quad (2)$$

where superscripts of ^{RC} and ^{E} show the racemic compound and enantiomer, and $\Delta\Delta H^{RC-E}_{Soln}$ and $\Delta\Delta S^{RC-E}_{Soln}$ are the enthalpy and entropy difference of the dissolution between the racemic compound and enantiomer, respectively. Racemic compound composed of the equimolecular mixture of its enantiomers has excess entropy compared to its enantiomer. The $\Delta\Delta S^{RC-E}_{Soln}$ would be the same as the excess entropy expressed by the entropy of mixing, $-R(x^R\ ln\ x^R + x^S\ ln\ x^S)$, where mole fractions of *R* and *S* enantiomer in racemic compound (x^R, x^S) are 0.5. The free energy difference of the dissolution between the racemic compound and enatiomer is also expressed by the following Eq. (3).

$$\Delta\Delta G^{RC-E}_{Soln} = \Delta G^{RC}_{Soln} - \Delta G^{E}_{Soln} = -RT\ ln\left(\frac{C^{RC}_S}{C^{E}_S}\right) \quad (3)$$

where ΔG^{RC}_{Soln} and ΔG^{E}_{Soln} are the free energy of the dissolution of the racemic compound and enantiomer, respectively. *R* is the gas constant, and C^{RC}_S and C^{E}_S are the solubility of the racemic compound and enantiomer, respectively. For the dissolution in the sink condition, we can use the Noyes-Whitney equation, which derives the initial dissolution rate of sample.

$$\textit{Initial dissolution rate of sample (IDR)} = dC/dt = kC_S$$

where dC/dt is the dissolution rate and *k* is the intrinsic dissolution rate constant. Nogami *et al.* reported the dissolution rate constants of sulfonamides (12). The variations of the observed k and the calculated diffusion coefficient were less than 10%, therefore, the(k^{RC}/k^{E}) could be approximated to 1, and it could be possible to replace (C^{RS}_S/C^{E}_S) with (IDR^{RC}/IDR^{E}) in Eq. (3). $\Delta\Delta G^{RC-E}_{Soln}$ could be also expressed by the following Eq. (4).

$$\Delta\Delta G^{RC-E}_{Soln} = -RT\ ln\left(\frac{IDR^{RC}}{IDR^{E}}\right) \quad (4)$$

Therefore, a plot of the free energy difference of the dissolution between the racemic compound and enatiomer obtained from their solubility data against the enthalpy difference between them assumed to give a straight line with a slope of 1.

$$\Delta\Delta G^{RC-E}_{Soln} = -RT\ ln\left(\frac{C^{RC}_S}{C^{E}_S}\right) = \Delta\Delta H^{RC-E}_{Soln} - RT\ ln\ 2 \quad (5)$$

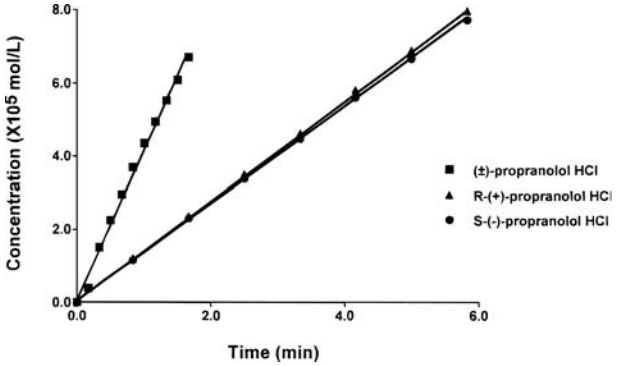

Fig. 1. Initial dissolution rates of propranolol HCl in distilled water.

RESULTS AND DISCUSSION

Relationship Between the Free Energy and Enthalpy Differences of Racemic Compound Dissolution

Figure 1 shows the dissolution profiles of propranolol hydrochloride in distilled water. The initial dissolution rate (IDR) of (±)-propranolol HCl was three times greater than that of enantiomers. A significant difference was hardly observed between the dissolution profiles of enantiomers. The ratio of racemic compound and enantiomer of IDR (IDR^{RC}/IDR^{E}) was 3.10, whereas the ratio of solubility (Cs^{RS}/Cs^{E}) was 3.70. The free energy difference between racemic compound and enatiomer obtained from IDR data ($\Delta\Delta G^{RC-E}_{soln}$) was calculated as −2.81, and this value was in fair agreement with that obtained from solubility data of −3.24. We have selected propranolol HCl, tyrosine, propranolol, and, tryptophan as typical racemic compound and calculated their $\Delta\Delta G^{RC-E}_{soln}$ and $\Delta\Delta H^{RC-E}_{soln}$ of dissolution from the dissolution rate and solubility data. Table 1 shows the free energy and enthalpy difference of the dissolution between the racemic compound and enantiomer. We have plotted these data as shown in Fig. 2. In accordance with Eq. (5),

Table 1. Free Energy and Enthalpy Difference of the Dissolution for Racemic Compound and Enantiomers

	$\Delta\Delta H^{RC-E}_{soln}$ (kJ/mol)	$\Delta\Delta G^{RC-E}_{soln}$ (kJ/mol)
Propranolol HCl	−0.10[a]	−3.24[c], −2.81[d]
Tyrosine	2.12[a]	0.85[c]
Propranolol	4.22[b]	3.07[d]
Tryptophan	5.94[a]	4.19[d]

[a] Heat of solution data.
[b] Heat of fusion data was used on account of the low solubility of propranolol in water (13).
[c] Calculated using Eq. (3).
[d] Calculated using Eq. (4).

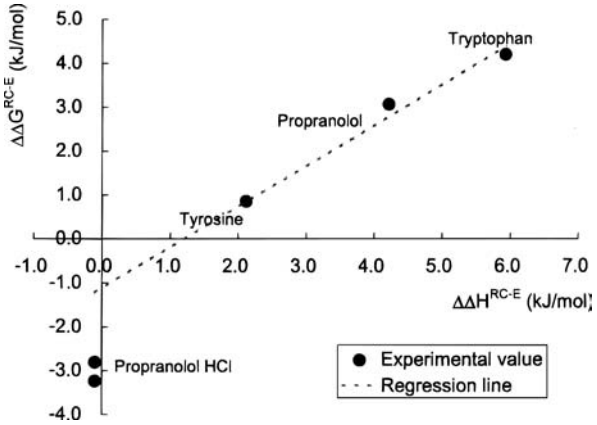

Fig. 2. Relationship between $\Delta\Delta G^{RC-E}$ and $\Delta\Delta H^{RC-E}$ of dissolution.

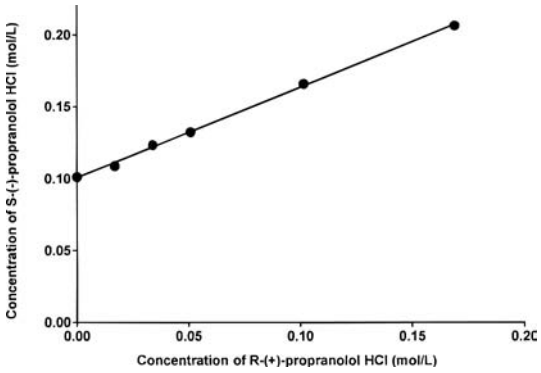

Fig. 4. Solubility of S-(−)-propranolol HCl in the presence of R-(+)-propranolol HCl.

a plot of $\Delta\Delta G^{RC-E}_{soln}$ against $\Delta\Delta H^{RC-E}_{soln}$ is found to be linear except propranolol HCl data.

Dissociation of (±)-Propranolol Hydrochloride in Solution

Figure 3 shows the dissolution profiles of propranolol HCl in cyclohexane. Interestingly, the IDR of racemic compound was smaller than that of enantiomers. This result suggested that the dissociation constant of racemic compound in water was different from that in cyclohexane, since the HCl salt of propranolol should be exsisted in molecular form in the non-polar organic solvent. The dissociation of HCl salt of racemic compound in solution is expressed by

$$[RHCl \cdot SHCl](Solid) \overset{Cs'}{\Leftrightarrow} [RH{\cdot}SH]^{2+} + 2Cl^- \overset{K}{\Leftrightarrow} RH^+ + SH^+ + 2Cl^-$$

where RH^+ and SH^+ are the ionic form of R and S enantimers respectively. Cl^- is the chloride ion. Cs′ is the solubility assuming the non-dissociation of racemic compound and K is the dissociation constant of racemic compound in solution. The Cs′ is given by

$$Cs' = Cs + 2K - (4K \cdot (Cs + K))^{1/2} \qquad (6)$$

where Cs is the solubility of racemic compound in solution. According to Eq. (6), the Cs′ value of (±)-propranolol HCl is calculated from the experimental data of Cs and K. Figure 4 shows the solubility of S-(−)-propranolol HCl in the presence of R-(+)-propranolol HCl. With the addition of R-enantiomer, the solubility of S-enantiomer rises linearly owing to racemic formation. From the slope of the solubility increase, we have successfully obtained the dissociation constant as 5.99×10^{-2} (mol/L) in this system. Since the enantiomer salts are completely dissociated in aqueous solution, the Cs′ of racemic propranolol HCl was obtained as 1.69×10^{-1} (mol/L) and $\Delta\Delta G^{RC-E}_{soln}$ of propranolol HCl was estimated as −1.30 (kJ/mol). In order to examine the relationship between $\Delta\Delta H^{RC-E}_{soln}$ and $\Delta\Delta G^{RC-E}_{soln}$ of dissolution, we have replotted the $\Delta\Delta G^{RC-E}_{soln}$ of racemic compounds against $\Delta\Delta H^{RC-E}_{soln}$ and calculated the regression line of this system (Fig. 5). The experimental data gave a straight line ($r^2 = 0.993$) and its slope was 0.930, indicating that the Eq. (5) express an existence of the relationship between the free energy difference of dissolution calculated from solubility or dissolution rate data and the enthalpy difference obtained by thermal analysis in this chiral system. The estimated y-intercept value of racemic compound (−1.13 kJ/mol) was found to be in fair agreement with the −RTln2 value (−1.72 kJ/mol). These data suggested the ratios of the solubility could be estimated from the enthalpy data obtained by thermal analysis.

CONCLUSIONS

From the above results, it was concluded that the free energy difference of the dissolution would be linearly related

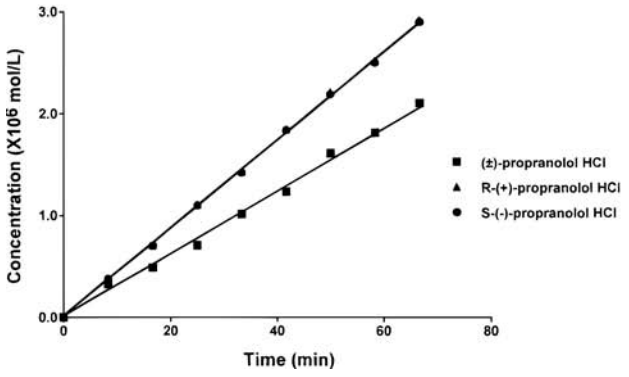

Fig. 3. Initial dissolution rates of propranolol HCl in cyclohexane.

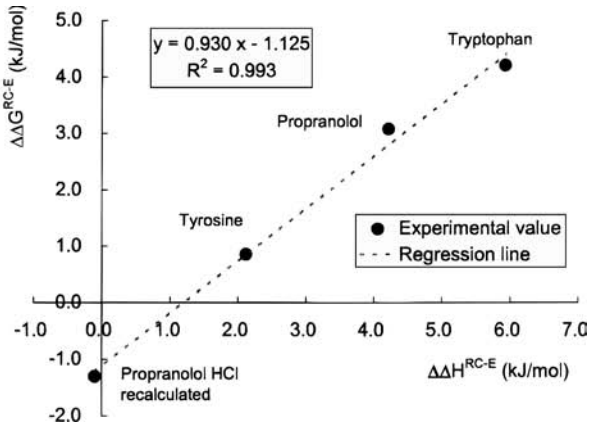

Fig. 5. Relationship between $\Delta\Delta G^{RC-E}$ and $\Delta\Delta H^{RC-E}$ of dissolution.

to the enthalpy difference for racemic compound and its enantiomer. By considering the dissociation of drug in solution, it could be possible to apply this relationship to the salt drug. According to this relationship, the solubility of chiral insoluble drug could be estimated from the thermal data.

ACKNOWLEDGMENTS

The authors are grateful to S. Gamou, N. Araki, and E. Takahashi for the assistance in the experimental work. E. Yonemochi thanks Uehara Memorial Foundation for supporting his research.

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