Evaluation of solid-liquid equilibria for drug + water + cyclodextrin derivatives system using activity coefficient model

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Abstract

Drug candidates with strong pharmacological activity have increasingly been developed using combinatorial chemistry and high-throughput screening. As a result of these screening methods, the co-solvents are commonly used in the pharmaceutical industry in order to increase the solubility of relatively water insoluble drugs. The solid-liquid equilibria for systems containing drugs and co-solvents have been measured.

Some predictive method in order to predict the solubility of drugs using activity coefficient models have been proposed. Recently we have the interests to cyclodextrins as co-solvents.

This paper deals with evaluation of solubility for drug + water + solid co-solvent system using activity coefficient models. The drugs treated in this paper are etodolac, famotidine, naringin, and the co-solvents are cyclodextrin derivatives (α-CD, β-CD, 2-HP-β-CD, 2-HE-β-CD, M-β-CD, DM-β-CD, SBE-β-CD). The activity coefficient models used in this study is Wilson equation.

Keywords

Drug, solid-liquid equilibria, activity coefficient model

1. Introduction

Drug candidates with strong pharmacological activity have increasingly been developed using combinatorial chemistry and high-throughput screening. As a result of these screening methods, the number of drugs with decreased water solubilities has increased due to higher molecular weights and more complicated chemical structures. Therefore, the co-solvents are commonly used in the pharmaceutical industry in order to increase the solubility of relatively water insoluble drugs. The solid-liquid equilibria for systems containing drugs and co-solvents have been measured [1-5].

Some predictive method in order to predict the solubility of drugs using activity coefficient models have been proposed [6]. But the co-solvents are liquids. Recently we have the interests to cyclodextrins as co-solvents.

This paper deals with evaluation of solubility for drug + water + solid co-solvent system using activity coefficient models. The drugs treated in this paper are etodolac, famotidine, naringin, and the co-solvents are cyclodextrin derivatives (α-CD, β-CD, 2-HP-β-CD, 2-HE-β-CD, M-β-CD, DM-β-CD, SBE-β-CD). The activity coefficient models used in this study is Wilson equation.

2. Solubilities and activity coefficient

For drug, water, CD derivatives, the solubility of drug (1) in mixed solvents can be calculated using the following equation.

$$\ln x_1 = -\frac{\Delta H_{f,1}}{RT_{m,1}}\left(\frac{T_{m,1}}{T}-1\right)-\ln \gamma_1 \qquad (1)$$

Where x_1 and γ_1 are solubility and activity coefficient, $T_{m,1}$ and $\Delta H_{f,1}$ are melting pint and heat of fusion, respectively.

The systems discussed here are shown in Table 1.

Table 1 Systems discussed in this work

(1)	(2)	(3)	T[K]	Ref.
Etodolac	Water	α-CD	298.15	[3]
		β-CD	298.15	[3]
		2-HP-β-CD	298.15	[3]
		2-HE-β-CD	298.15	[3]
		M-β-CD	298.15	[3]
Famotidine	Water	β-CD	298.15	[2]
Naringin	Water	β-CD	298.15	[4]
		2-HP-β-CD	298.15	[4]
		DM-β-CD	298.15	[4]

2-hydroxypropyl-β-CD (2-HP-β-CD)
2-hydroxyethyl-β-CD (2-HE-β-CD)
methyl-β-CD (M-β-CD)
dimethyl-β-CD (DM-β-CD)

3. Melting point and heat of fusion for drugs and CD derivatives

The melting point and heat of fusion for drugs (etodolac, famotidine and naringin) used in this work are as follows.

Eodolac: T_m=426.89 K, ΔH_f= 26.175 kJ/mol

Famotidine: T_m=438.55 K, ΔH_f=48.6 kJ/mol

Naringin: T_m=436 K, ΔH_f=39.8 kJ/mol (Naringenin) [9]

In our model, we need the melting point and heat of fusion for CD derivatives. The melting points for CDs are literatured data. The literatured data of heats of fusion for α-CD and 2-HP-β-CD were 20.412 and 21.448 kJ/mol. The heats of fusion for another CDs were obtained from the following equation based of the both data.

$$\Delta H_{f,i}[J/mol] = 18{,}640 + 1.8217 M_i \qquad (2)$$

Where M_i is molecular weight.

Table 2 Melting point and heat of fusion of (a) drug and (b) CD derivatives

component	Molecular weight	Melting point[K]	Heat of fusion [J/mol]	Ref.
(drug)				
Etodolac		418.80	50,602	[7]
Famotidine		438.55	48,600	[2]
Naringin	580	436	39,800*	[8]
(CD derivatives)				
α-CD	972	551.2	20,412	[10]
β-CD	1135	533.2	20708**	
2-HP-β-CD	1400	599.51	21,448	[11]
2-HE-β-CD	1443	533.2	21269**	[12]
M-β-CD	1303	454.2	21014**	[12]
DM-ß-CD	1331	577.2	21065**	[13]

*: $\Delta H_{f,\ naringen} = \Delta H_{f,\ naringenin}$

**: calculated by Eq.(2)

4. Evaluation of solid-liquid equilibria using Wilson equation

4.1 Correlation equation

For the calculation of activity coefficient, the following Wilson equation was used by the reason that the prediction of phase equilibria for multi-

component system is possible.

$$\ln \gamma_i = -\ln\left(\sum_{j=1}^{N} x_j \Lambda_{ij}\right) + 1 - \sum_{k=1}^{N} \frac{x_k \Lambda_{ki}}{\sum_{j=1}^{N} x_j \Lambda_{kj}} \qquad (3)$$

Where γ_i is activity coefficient of component i, N and x_i are number of components and composition of component i. The Λij and Λji are interaction parameters. For Wilson equation for ternary system, there are six binary interaction parameters that consistent binary system have two parameters for Wilson equation.

4.2 Correlation of solid-liquid equilibria.

(a) drug (1) + water(2) system ($\Lambda_{12} = \Lambda_{21}$)

$$\ln \gamma_1 = -\Delta H_{f,1} / RT\left(1 - T / T_{m,1}\right) - \ln x_1 \qquad (4)$$

Using the solubility of drug in water, $\Lambda_{12} (= \Lambda_{21})$ was obtained.

(b) water (2) + CD (3) system ($\Lambda_{32} = \Lambda_{23}$)

$$\ln \gamma_3 = -\Delta H_{f,3} / RT\left(1 - T / T_{m,3}\right) - \ln x_3 \qquad (5)$$

Using the solubility of CD in water, $\Lambda_{32} (= \Lambda_{23})$ was obtained.

© drug (1) + water + CD (3) system (Λ_{13}, Λ_{31})

From the solubility of drug in water solution and Eq. (1), Λ_{13} and Λ_{31} were determined.

As an example, the Wilson parameters for 9 ternary systems are given in Table 3.

Table 3 Wilson parameters for drug(1) + water(2) + CD derivatives(3) system

(1)	(2)	(3)	$\Lambda_{12} = \Lambda_{21}$	$\Lambda_{32} = \Lambda_{23}$	Λ_{13}	Λ_{31}	Dev.(%)
Etodolac	water	α-CD	4.14e-04	1.01	7.12E-02	0.00	9.14
		β-CD	4.14e-04	3.00E-02	9.31E-02	0.00	7.70
		2-HP-β-CD	4.14E-04	1.01	9.69E-01	52.4	3.27

		2-HE-β-CD	4.14E-04	1.04	9.17E-01	3.07E+01	1.38
		M-β-CD	4.14E-04	2.54e-01	1.46	27.07	5.69
Famotidine	water	β-CD	8.00E-02	3.00E-02	0	26.22	9.34
Naringin	water	β-CD	1.00E-02	3.00E-02	139.37	3.00	5.98
		2-HP-β-CD	1.00E-02	1.01	11.14	1.43E+04	10.44
		DM-β-CD	1.00E-02	1.01	31.0	7.76E+04	15.32

An example of calculated results is shown in Figs. 1-5. Figs. 1 to 3 show the evaluated results for β-CD containing systems. Figs. 4 and 5 show the evaluated results for 2-HP-β-CD containing systems.

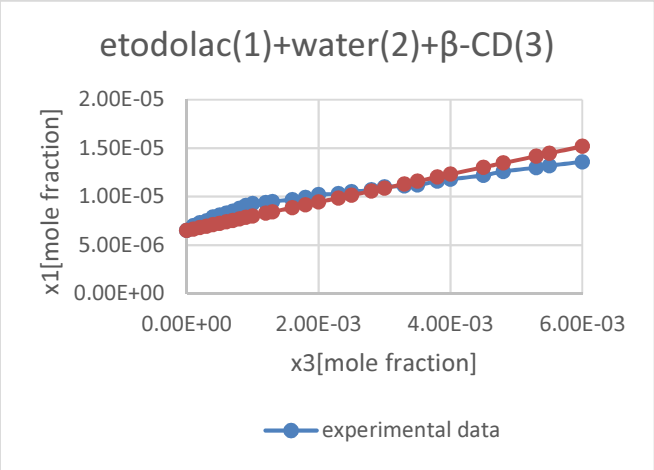

Fig. 1 Solid - liquid equilibria for etodolac (1) + water(2) + β-CD(3) system (298.15 K)

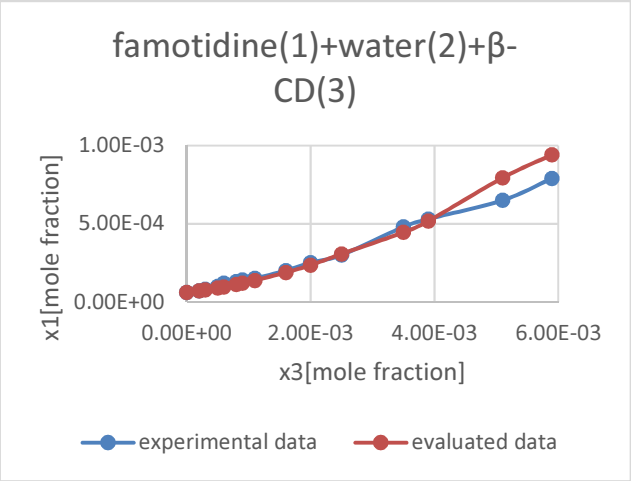

Fig. 2 Solid - liquid equilibria for famotidine (1) + water(2) + β-CD(3) system (298.15 K)

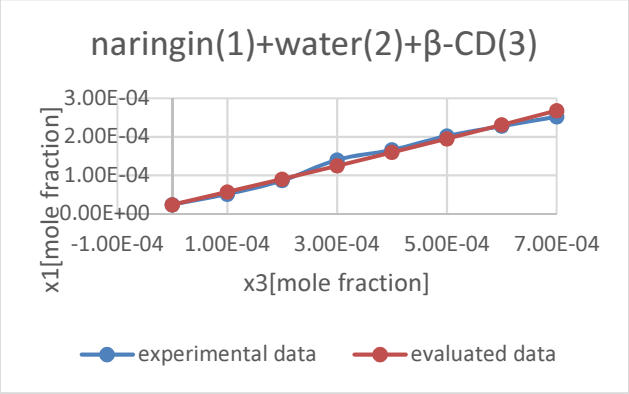

Fig. 3 Solid - liquid equilibria for naringin (1) + water(2) + 2-HP-β-CD(3) system (298.15 K)

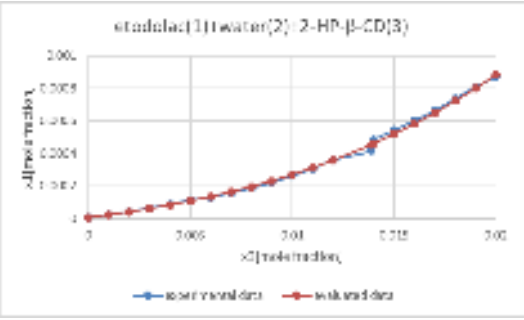

Fig. 4 Solid - liquid equilibria for etodolac (1) + water(2) + 2-HP-β-CD(3) system (298.15 K)

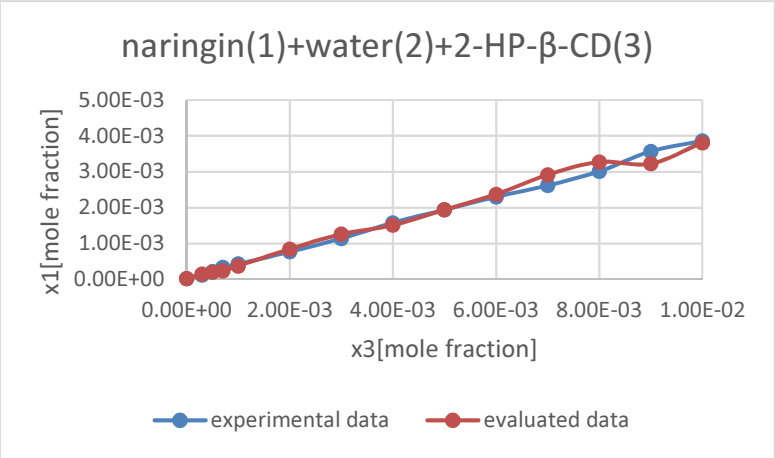

Fig. 5 Solid - liquid equilibria for naringin (1) + water(2) + 2-HP- β -CD(3) system (298.15 K)

Conclusions

The cyclodextrin derivatives are co-solvents that have been used for separation processes in drug industry. The solid-liquid equilibria for drug + water + CD derivatives system have been correlated using activity coefficient model.

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