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The effect of hydrate formation on the solubility of theophylline in binary aqueous cosolvent systems

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Summary

The solubility at 30 °C of theophylline in mixtures of water and the cosolvents ethanol, propylene glycol, dimethylformamide and PEG 400 has been measured. In all these systems the solid phase in equilibrium with the solution depended on the solvent composition; theophylline monohydrate was present for water-rich solutions and anhydrous theophylline for cosolvent-rich solutions. The volume fractions of water at which the transition between the solid phases occurred was $f' = 0.18$, 0.35, 0.35 and 0.25 for ethanol, propylene glycol, dimethylformamide and PEG 400, respectively. Maxima in the solubility vs composition profiles occurred for ethanol and propylene glycol, but not for dimethylformamide. The effects of hydrate formation on the solubility are analysed quantitatively in the case of ethanol/water mixtures. Hydrate formation depresses the solubility in water-rich solutions and distorts the shape of the solubility profile. In comparing experimental solubilities with the predictions of regular solution theory in the extended Hildebrand approach it is necessary to take account of the effect of hydrate formation.

Introduction

The solubility of drugs of varying polarity in aqueous cosolvent systems has received considerable attention in the literature (Martin et al., 1982; Paruta et al., 1965; Yalkowsky et al., 1972). However, only relatively recently has any semi-theoretical or theoretical treatment of drug solubility in aqueous cosolvent systems been reported (Yalkowsky et al., 1972; Gould et al., 1984), and a comprehensive assessment of the solubility relationships of polar, semi-polar and non-polar drugs in binary and tertiary cosolvent systems of varying polarity been attempted (Gould et al., 1984).

For hydrophobic drugs whose polarity is significantly lower than that of either of the solvents in the binary mixture, the solubility (S_m) usually follows the log-linear Yalkowsky equation (Yalkowsky, 1980):

$$\log_{10} S_m = \log_{10} S_w + f\theta \quad (1)$$

where S_w is the aqueous solubility of the drug, θ is a parameter representing the solubilization power of the cosolvent which is related to the ratio of the activity coefficients in the pure cosolvent to

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water, and f is the volume fraction of the cosolvent in the binary mixture.

Using Hildebrand solubility parameters (Hildebrand et al., 1978) or hydrophobicity measurements, Eqn. 1 usually gives a good fit for drugs in a number of aqueous cosolvent binary mixtures, particularly when the solubility parameter of the drug (δ_d), is more than 3 solubility parameter units lower or higher than that of the binary aqueous co-solvent mixture (δ_1). Under these conditions the drug–solvent interactions dominate the solubility relationship.

If the cosolvent does not strongly solvate the drug (Martin et al., 1982), and the solubility parameter of the drug lies between pure water and the pure cosolvent, Eqn. 1 breaks down and the solubility relationship becomes significantly curved with a maximum where the solvent composition has a solubility parameter equal to that of the drug. With polar solvents extended Hildebrand approaches using various polynomial functions are considered (Martin et al., 1980; Adjei et al., 1980) and also many empirical assessments based on a dielectric requirement for the drug deduced using a dioxane-water solvent system have been reported (Paruta et al., 1965, 1969).

However, in the experimental assessment of these semi-theoretical approaches to drug solubility in binary cosolvent systems only minimal attention has been paid to the maintenance of the same crystalline phase in equilibrium with the solvent mixture. In particular, the role of hydrate formation on cosolvent solubility profiles has largely been ignored. Bogardus (1982; 1983) has pointed out that many of the solutes evaluated using the extended Hildebrand solubility approach undergo crystalline anhydrous–hydrous phase transformation as the water content of the solvent mixture is changed, which has the potential to fundamentally change the nature of the solubility–solvent composition profile.

To investigate the role of the crystalline phase on the nature of the cosolvent solubility profile we have conducted a study on the solubility of theophylline; a semi-polar drug ($\delta = 14.0$) which exists in the solid state at 30 °C as anhydrous and monohydrate forms. The hydrate is the favoured form in equilibrium with aqueous solution at temperatures < 337 K (Fokkens et al., 1983). Solubility studies were conducted in binary aqueous cosolvent systems of propylene glycol, polyethylene glycol 400, ethanol and dimethylformamide.

Materials and Methods

Materials

The solvents employed were of normal pharmaceutical grade and used as received. The ethanol employed has a residual moisture content of 0.2% by gas chromatography. The theophylline (anhydrate) was a gift of Alfa Chemicals (Wokingham, U.K.).

Methods

Preparation of theophylline hydrate. Theophylline monohydrate was prepared by slow crystallisation at 4 °C from a saturated solution of anhydrous theophylline prepared at 23 °C. The harvested crystals were filtered from the supernatant, air dried and characterised by gas chromatography and differential scanning calorimetry (Perkin Elmer, Model DSC 2; heating rate 20 °C/min under nitrogen) or thermal gravimetric analysis (Perkin-Elmer Model TGS2, using a nitrogen atmosphere).

No evidence could be found, despite extensive differential scanning calorimetry studies, for (pseudo-) polymorphs of theophylline anhydrate, as reported by Fokkens et al. (1983).

Solubility determinations. The solubility of theophylline anhydrate and monohydrate was measured at 30 ±1 °C at varying cosolvent compositions in the systems outlined earlier. All solvent compositions were determined on a volume/volume basis with no correction being made for volume contraction. The theophylline concentrations at equilibrium were determined spectrophotometrically at 270.9 nm. All solubility determinations were performed in duplicate.

The solubility experiments were so designed that 200–300 mg of theophylline remained at solution saturation. This excess was removed by filtration, washed with diethyl ether to remove residual cosolvent, then air-dried and submitted to water content analysis using gas chromatographic

and/or thermogravimetric analysis. On occasions DSC was also used to characterise the filtrate. The diethyl ether washing/drying procedure was previously validated with anhydrous and hydrated theophylline samples.

Gas chromatography assay of water in samples. The water content in the theophylline samples was determined by comparison of the gas chromatography peak areas for the samples (100 mg) prepared in dried dimethyl sulphoxide/pyridine (1 : 1 v/v) to 5% w/v water standard solutions. Samples were assayed using a Perkin-Elmer Sigma 3B GC employing a 90 cm × 0.78 cm glass column packed with 80–100 mesh Porapak Q (Water Associates) at 100 °C using an injection port temperature of 180 °C (injection volume 2 μl) and thermal conductivity detection at 200 °C. The carrier gas employed was helium at 30 ml/min.

Results and Discussion

Aqueous solubilities of theophylline anhydrate and theophylline hydrate were experimentally indistinguishable at all cosolvent compositions for the various cosolvent systems studied (Table 1). This implies that in all systems a common solid phase was in equilibrium with the solutions. The results of the solid state analyses from the systems are given in Table 2, and the water volume fractions (f') at the solid state transitions given in Table 3.

The mean log molar solubilities are plotted against % cosolvent in Fig. 1. As would be expected from the similarity of the solubility parameters of the cosolvents to that of theophylline, the Yalkowsky equation breaks down and ethanol (E) and propylene glycol (PG) show maxima in their solubility profiles at approximately 60% and 75% cosolvent fraction. Dimethylformamide (DMF) shows a plateau in its profile at similar fractional solvent compositions to these cosolvents (66%). However, it is clear from Table 2 that the equilibrium crystalline phases with these various cosolvents differ throughout the solubility profiles.

Transformation of the binary solvent compositions to solubility parameters and molar solubilities to mole fraction solubilities (X_2) yields Fig. 2. The ideal solubility of anhydrous theophylline at 30 °C, calculated from the data of Fokkens et al. (1983) is $X_2 = 17.8 \times 10^{-3}$. The mol fraction solubility of theophylline in propylene glycol/water exhibits a maximum solubility of $X_2 = 5.9 \times 10^{-3}$ at a solvent solubility parameter (δ_1) of ~ 14.2. The occurrence of a maximum in the solubility profile at the point where the solubility parameter of the solvent is equal to that of the solute theophylline ($\delta_2 = 14.0$) is in agreement with

TABLE 1

Measured solubilities (g/liter) of theophylline in various binary aqueous cosolvent systems at 30 °C

% Cosolvent	Propylene glycol		Ethanol		PEG 400		DMF	
	S_{Th}	S_{Th}^{H}	S_{Th}	S_{Th}^{H}	S_{Th}	S_{Th}^{H}	S_{Th}	S_{Th}^{H}
0	8.557	8.705						
10			10.35	10.43				
20	11.17	11.42	12.78	12.76			18.76	18.39
30			17.11	16.96				
40	16.22	16.19	22.35	21.72			24.78	22.54
50			26.42	27.00				
60	22.19	21.79	29.42	28.45	13.00	13.70	30.64	32.92
70	26.15	25.70	26.59	26.95	17.24	18.12	35.40	33.94
75							38.45	39.83
80	22.89	23.82	24.82	23.72	16.22	16.42	40.37	41.82
85							44.40	45.55
90	18.95	19.19	13.47	14.34			45.53	41.52
100	12.60	12.92					54.26	54.57

S_{Th}^{H} relates to the solubility measured using theophylline hydrate and S_{Th} to that of the anhydrate.

TABLE 2

% Water in solid phase at equilibrium

Solvent		Percentage of solvent								
		40	50	60	70	80	85	90	95	97.5
Ethanol	(A)		9.7	9.8	9.4	9.9	0.9	< 0.1	< 0.1	< 0.1
	(H)		8.3	9.9	9.4	9.7	0.8	< 0.1		
Propylene	(A)	8.7		7.4	0.2	0.1	0.1			
glycol	(H)	9.7		7.6	3.0	0.2	0			
PEG 400	(A)			9.1	8.6	1.2	1.4	1.1		
	(H)			8.9	8.6	1.8	1.4	0.8		
DMF	(A)			8.8	< 0.5	< 0.5	< 0.5	< 0.5		
	(H)			8.7	< 0.5	< 0.5	< 0.5	< 0.5		

(A), initial solid phase as anhydrous; (H), initial solid phase as hydrate.

regular solution theory (Hildebrand and Scott, 1962). However, the maximum solubility is significantly less than the predicted value for a regular solution, which is equal to the ideal solubility, and the shape of the solubility profile differs from that predicted for a regular solution.

Such differences have been considered by Martin et al. (1980), who suggest an empirical extended Hildebrand solubility approach in which the regular solution expression is modified by the replacement of $\delta_1\delta_2$ by a term W representing the drug–solvent interaction. δ_1 and δ_2 are the solubility parameters of the solvent and solution, respectively, and in this instance for a solvent of the composition corresponding to the solubility maximum, W is less than $\delta_1\delta_2$. The solubility of theophylline in dioxane-water mixtures also reaches a maximum at a value of δ_1 of about 14 (Martin et al., 1980; Moes, 1981).

However, inspection of Table 2 shows that below ~ 35% water (f') in the PG solvent mixture (i.e. $\delta_1 \leq 16.4$), the solid phase at equilibrium is anhydrous theophylline, whilst at higher water levels the favoured solid species is the hydrate. In the case of PG the solubility maximum occurs at least two solubility parameter units away from the change of equilibrium solid phase.

DMF, because it is strongly solvating, does not exhibit similar behaviour (Martin et al., 1982,

TABLE 3

Volume fraction of water (f') at which solid theophylline anhydrate and hydrate are in equilibrium

Solvent	f'
Ethanol	0.175
PG	0.35
PEG 400	0.25
DMF	0.35
Dioxane	0.05 *

* From Bogardus (1983).

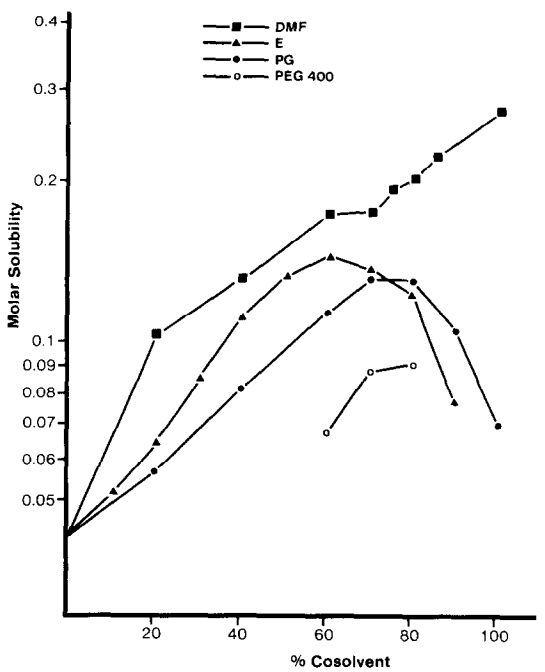

Fig. 1. Molar solubility of theophylline in binary aqueous cosolvent systems at 30 °C. Data are presented as mean of data for hydrate and anhydrate given in Table 1.

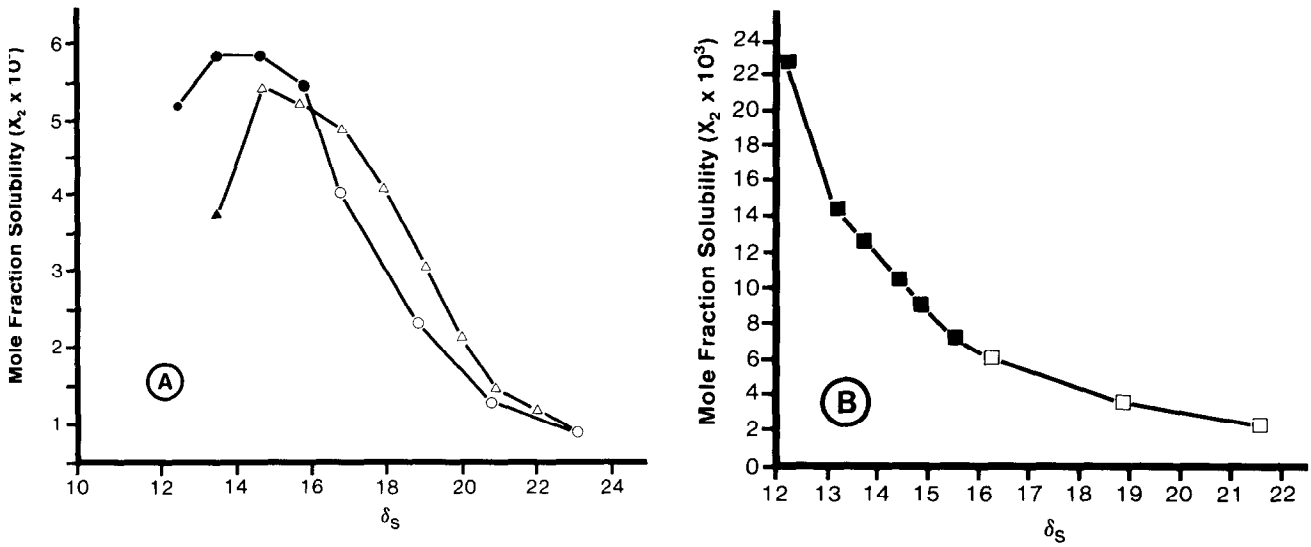

Fig. 2. Mole fraction solubility of theophylline vs solvent solubility parameter. Open and closed legends relate to solid phase at equilibrium being the hydrate and anhydrate respectively. A: ethanol and PG. B: DMF.

1985) and shows no solubility maximum despite its having a solubility parameter (12.1) less than that of the drug. The mole fraction solubility increases rapidly as the solubility parameter of the binary system falls, and produces an absolute value of X_2 in pure DMF ($\delta_1 = 12.1$) that exceeds that of any of the cosolvent studies. Interestingly, the solubility profile of the DMF system in Figs. 2 and 3 show a slight plateau at $\delta_1 \sim 13.5$, i.e. similar to that of the drug, but remote from the solid phase transition occurring at $\delta_1 = 16$.

The data for ethanol again show a maximum solubility at $\delta_1 \sim 14.8$, an appropriate value for theophylline. However, the solubility maximum occurs at a composition close to that at which the change in the solid phase in equilibrium with the solution occurs, and this influences the shape of the solubility curve near the maximum.

Thus, the solubility curves in Figs. 1 and 2 are complicated by the fact that they are composite curves, partly representing the solubility of anhydrous theophylline and partly that of theophylline monohydrate. If we consider mixtures of water and one particular cosolvent, then for any particular solvent composition either anhydrous theophylline (Th) or theophylline monohydrate ($Th \cdot H_2O$) may be in equilibrium with the solution.

$$Th(s) \rightleftharpoons Th(solution) \quad (2)$$

$$TH \cdot H_2O(s) \rightleftharpoons Th(solution) + H_2O(Solution) \quad (3)$$

In a solution containing a high proportion of water the activity of theophylline in solution is reduced by equilibrium (3) to a value below that required for equilibrium with the anhydrous solid (2) and consequently the solid in equilibrium with the solution is the monohydrate. The effect of hydrate formation is to depress the solubility of theophylline. In solutions containing a lower proportion of water the activity of theophylline rises until it is limited by equilibrium (2) and the solid in equilibrium with the solution is anhydrous theophylline. There is one particular solvent composition for which both Th (s) and $Th \cdot H_2O$ (s) are in equilibrium with the solution. The activity of water in this solution, i.e. at the phase transition, is a'_{H_2O}.

This critical activity of water at which both Th (s) and Th · H_2O (s) are in equilibrium with the solution should be the same for each of the cosolvents, and the composition of these solutions in which water has the activity a'_{H_2O} can be deduced from the solid phase analysis (Table 2). Thus, the volume fractions of water (f') for which $a_{H_2O} = a'_{H_2O}$ are shown in Table 3. It is likely that as the volume fraction of water falls below f' for each solvent system the activity of water falls steeply. This is supported by the value of f' for PEG 400 (~ 0.75) being almost in exact agreement with that inferred from the progesterone solubility studies of Fulford and others (1986) where the free water in solution was found to be zero at a PEG 400 volume fraction of 0.73. By considering the equilibria [2] and [3] it can be easily shown that

$$\frac{a^{H}_{Th}}{a^{A}_{Th}} = \frac{a'_{H_2O}}{a_{H_2O}} \tag{4}$$

where a^{H}_{Th} and a^{A}_{Th} are the (hypothetical) activities of theophylline in equilibrium with theophylline monohydrate and with anhydrous theophylline in a solvent of a particular composition in which the activity of water is a_{H_2O}.

Thus if data on the activity of water in particular solution is available, it is possible to calculate a hypothetical solubility of anhydrous theophylline from the measured solubility of theophylline monohydrate. For dilute solutions of the same solvent composition we may assume that

$$\frac{x^{H}_{Th}}{x^{A}_{Th}} \approx \frac{a^{H}_{Th}}{a^{A}_{Th}} = \frac{a'_{H_2O}}{a_{H_2O}} \tag{5}$$

where x^{H}_{Th} and x^{A}_{Th} are the mole fraction solubilities of theophylline hydrate and anhydrous theophylline, respectively.

Calculation of the solubility profile of anhydrous theophylline from measured solubilities of theophylline hydrate can be used to eliminate the competing effects of hydrate formation by revealing the variation in solubility of a single species over the whole range of solvent composi-

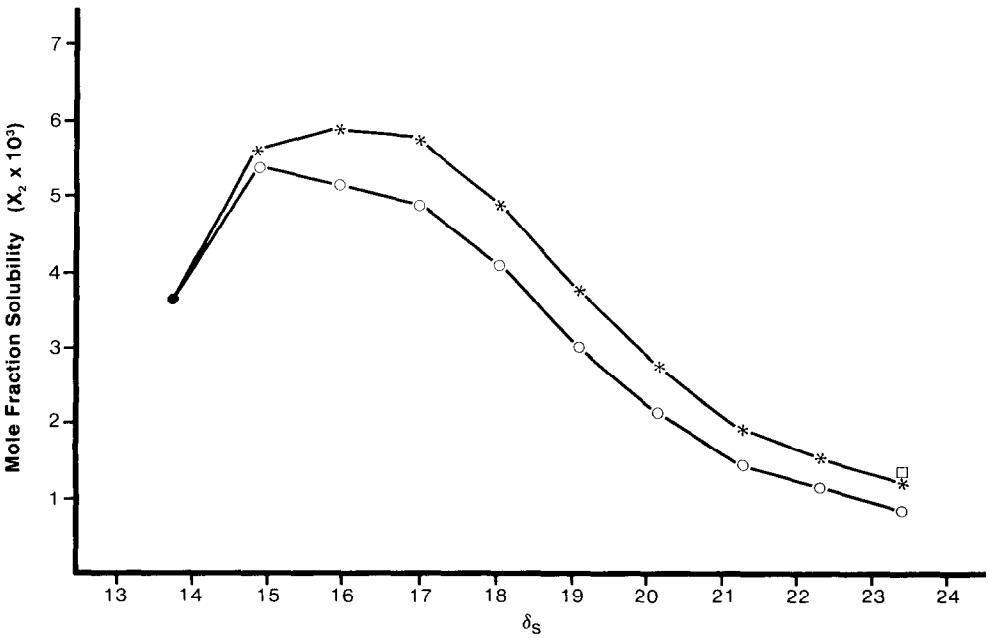

Fig. 3. Mole fraction solubility of theophylline hydrate and anhydrate (calculated) vs solvent solubility parameter in ethanol–water binary cosolvent system. (●), Experimental solubility of anhydrous theophylline; (*), solubility of anhydrous theophylline calculated from equation 5; (□), solubility of anhydrous theophylline calculated from equation 7, (○), experimental solubility of theophylline monohydrate.

tion. This calculation has been carried out for theophylline in mixtures of ethanol and water. Approximate values of the activity of water in ethanol/water mixtures were estimated from data in Butler (1951). These showed a rapid fall in a_{H_2O} below a volume fraction of water of ~ 0.2, consistent with the value of $f' = 0.18$ for the anhydrous/hydrate transition. For the solution of this particular composition at which both solid phases are in equilibrium $a_{H_2O} \sim 0.69$. This value and the activities of water a_{H_2O} were used to estimate x^A_{Th}/x^H_{Th} from Eqn. 5 for all the solutions studied experimentally, and x^A_{Th} was then calculated from the experimental solubility of theophylline monohydrate. The results are shown in Fig. 3. It is interesting to note that the maximum calculated solubility of anhydrous theophylline ($X_2 = 5.9 \times 10^{-3}$) is almost exactly equal to the maximum measured solubility of anhydrous theophylline in propylene glycol/water mixtures (Fig. 2).

A value of the solubility of anhydrous theophylline in water at 303 K can also be calculated in an alternative way. If the transition temperature

$$Th \cdot H_2O(s) \dashrightarrow Th(s) + H_2O(solution) \qquad (6)$$

for the conversion of theophylline monohydrate into anhydrous theophylline is T_{tr}, and the enthalpy of transition, process (6), is ΔH_{tr}, then at a temperature T

$$\ln\frac{(x^A)}{(x^H)} \sim \ln\frac{(a^A)}{(a^H)} = \frac{\Delta H_{tr}}{R} \cdot \left(\frac{1}{T} - \frac{1}{T_{tr}}\right) \qquad (7)$$

where ΔH_{tr} has been assumed independent of temperature. The value of x^A at 303 K calculated from the experimental x^H, $T_{tr} = 337$ K and $\Delta H_{tr} = 11.2$ kJ mol^{-1} (Fokkens et al., 1983) is shown in Fig. 3 and is in reasonable agreement with the value calculated from Eqn. 5.

It is evident from Fig. 3 that hydrate formation causes considerable distortion in the solubility profile of theophylline and in this particular case causes a shift in the position of maximum solubility. The maximum in the hypothetical solubility curve of anhydrous theophylline occurs at a value of δ_1 of 15–17. In comparing experimental solubilities with the prediction of regular solution theory using the δ value of anhydrous theophylline it is clearly important to recognise and, if possible, to allow for the effect of hydrate formation where present. In cases where the experimentally measured solubility is that of the hydrate, for example for mixtures of dioxane and water containing more than $\sim 5\%$ water (Bogardus, 1983), the hypothetical solubility of anhydrous theophylline is greater than the measured solubility and the value of W required to reconcile experimental and predicted results is greater than that calculated directly from the measured solubility (Martin et al., 1980).

Conclusion

The solid phase of theophylline in equilibrium with mixtures of water and the co-solvents ethanol, propylene glycol, PEG 400 and dimethylformamide is the anhydrous compound in co-solvent-rich solutions and the monohydrate in water-rich solutions. Hydrate formation depresses the solubility of theophylline in water-rich solutions and distorts the shape of the solubility curve; in the case of ethanol this shifts the composition of the solution for which the mole fraction solubility is a maximum. In comparing the experimental solubility of theophylline or similar drugs with the predictions of regular solution theory in the extended Hildebrand approach it is necessary to take account of the effect of hydrate formation.

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