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ETHYL CELLULOSE-SOLVENT PHASE RELATIONSHIPS RELEVANT TO COACERVATION MICROENCAPSULATION PROCESSES.

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ABSTRACT

Qualitative and quantitative solubility studies of ethyl cellulose, Type N-10, in 112 and 36 solvents respectively are reported. The relative contribution of dispersive, polar and hydrogen bonding intermolecular forces are depicted on two-dimensional and triangular solubility graphs. Phase separation phenomena may be explained in terms of the differences in both the solubility parameter (δ) and the polymer-solvent interaction parameter (χ_c) values between ethyl cellulose and each solvent. Coacervation occurs in very poor solvents with δ values just outside the solubility spectrum of ethyl cellulose.

A mean value for the solubility parameter and critical interaction parameter (χ_c) for ethyl cellulose obtained from turbidity titration measurements were 9.39 ± 0.17 $(cal/cm^3)^{\frac{1}{2}}$ and 0.38 ± 0.04 respectively. Gelation occurs with nonsolvents with δ

values significantly outside the solubility spectrum and with correspondingly larger χ_c values. Flocculation was observed only in polar solvents in which large χ_c values occur.

Theoretical values for the ethyl cellulose-solvent interaction parameters were calculated for 112 solvents. It is proposed these parameters can identify potentially useful solvents or solvent-nonsolvent systems for the preparation of microcapsules using coacervation.

INTRODUCTION

Coacervation is a liquid-liquid phase separation phenomenon which has been used for the preparation of pharmaceutical microcapsules. The coacervation of polyelectrolytes can be explained by the neutralization of charge and/or desolvation, and is well described by the general laws of thermodynamic equilibria[1]. However, the solution behavior and phase relationships of water-insoluble polymers in organic media used in the preparation of controlled-release microcapsules is limited.

Attempts to optimize microencapsulation procedures using coacervation usually evaluate experimental parameters such as concentration, temperature, pH, agitation rate, equilibration time, addition of surfactants, core-to-wall ratios and physical and chemical hardening. In general however, studies of macromolecular solutions relevant to microencapsulation of drugs are limited, especially in organic media. An understanding of polymer solution behavior should be helpful if coacervation phenomena and microencapsulation procedures are to be optimized.

The physical, chemical and mechanical properties explain the wide use of ethyl cellulose as an insoluble, pH-insensitive, controlled-release coating material for oral drug delivery systems including microcapsules. The aims of this research were to use the Flory-Huggins polymer solution theory and Hildebrand solubility parameter approach to characterize the solubility and phase separation behavior of ethyl cellulose in various solvents.

THEORETICAL

The following brief overview outlines the basic fundamentals of the Flory-Huggin's polymer solution theory and the solubility parameter concept as they have been applied to study the solubility and phase separation behavior of ethyl cellulose.

Flory-Huggins Polymer Solution Theory:

Solution theories are still unable to accurately describe phase separation from multicomponent polymer solutions. Using the two dimensional lattice model, Flory and Huggins[2,3] derived their basic equation for the reduction of the chemical potential of the solvent, μ_1^o , in the presence of solute, μ_1:

$$\Delta G_m = \mu_1 - \mu_1^o = R\,T\,[\ln(1 - \varphi_2) + (1 - 1/x)\,\varphi_2 + \chi\varphi_2^2] \quad \text{Eqn 1.}$$

where ΔG_m = change in free energy of mixing

μ_1 = chemical potential of the solvent

μ_1^o = chemical potential of the solution

R = gas constant

T = temperature in degrees absolute

φ_2 = volume fraction of solute

χ = Flory-Huggins interaction parameter

x = number of polymer segments occupying each lattice site

Despite limitations of the Flory-Huggins Theory[4], it remains the most widely used theory for the interpretation of polymer solution behavior. More recent theories such as the corresponding states models[5], equation-of-state model[6], cell models[7], and bridging models[8] are still imperfect and have relatively little experimental evaluation. Further, these theories sacrifice the relative simplicity of the Flory-Huggins Theory.

Solubility Parameter Concept:

Following the work of Hildebrand[9] and Scatchard[10], Hildebrand and Scott [11,12,13] proposed the square root of the cohesive energy density as a numerical value identifying solvency behavior and called this term the solubility parameter, δ. Hansen[14,15] introduced the three-dimensional solubility parameter to provide information about the nature and relative quantitative contributions of dispersive δ_d, polar δ_p, and hydrogen bonding δ_h interactions according to the equation:

$$\delta = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{\frac{1}{2}} \qquad \text{Eqn. 2}$$

Extensive tabulations of these solubility parameter for both solvents and polymers are available[16-22].

Phase Separation from Polymer-Solvent Systems:

The Flory-Huggins interaction parameter, χ, characterizes the energy difference of a solvent molecule immersed in pure solvent form one surrounded by molecules of its own kind. This theory predicts that polymer will dissolve in a solvent only if the interaction parameter is less than a critical value χ_c. At this critical value, phase separation begins to occur. For the polymer a very high molecular weight χ_c has a theoretical value of 0.5[23]. In practice most polymer-solvent combinations χ is positive (usually 0.2 to 0.6) and increases as solvent power decreases. Hence, a thermodynamically good solvent is characterized by a low interaction parameter. This is equivalent to the Hildebrand-Scatchard criterion that an ideal solvent is one which has a solubility parameter equal to the solubility parameter of the polymer.

Relationship of Interaction Parameter to Solubility Parameter:

The interaction parameter χ is characteristic for a given solvent-polymer combination. In particular, the interaction parameter can be related to the solubility parameter by the equation:

$$\chi = V_1 / RT \cdot (\delta_2 - \delta_1)^2 \qquad \text{Eqn. 3}$$

where V_1 = molar volume of the solvent

δ_1 = solubility parameter of the solute

Relationship Between the Interaction Parameter and Volume Fraction of Nonsolvent at the Cloud Point:

The relationship between the polymer-solvent interaction parameter and the volume fraction of nonsolvent added at the cloud-point during turbidity titrations has been described by Suh and Clarke[24]. By assuming that Scott's single liquid approximation[25], these authors derived the following relationship to calculate the solvent-polymer interaction parameter in mixed solvents at the critical point:

$$\chi_c = 0.34 + \left[\frac{\dfrac{V_1 V_3}{(\varphi_1 V_3 + \varphi_3 V_1)} (\delta_4 - \delta_2)^2}{RT} \right] \varphi_3^2 \qquad \text{Eqn. 4}$$

where subscripts 1, 2, 3 and 4 represent solvent, polymer, nonsolvent, and mixed solvent respectively, V = volume, φ_3 is the volume fraction of nonsolvent at the cloud point (sometimes referred to as φ_c), δ_4 is the solubility parameter of the solvent mixture at the critical point (sometimes referred to as δ_c), and 0.34 is the common value for the entropic contribution to the interaction parameter[26].

MATERIALS

Ethyl cellulose, Type N-10, batch was kindly donated by Hercules Inc., Delaware. All solvents were analytical grade and used without further purification.

METHODS

Determination of ethoxyl content of ethyl cellulose:

The ethoxyl content of ethyl cellulose was determined using a modified gas chromatographic procedure developed by Jacin and Slanski[27]. A series of 16 aqueous acetic acid calibration standards were prepared using propionic acid as the internal standard.

Qualitative Solubility of Ethyl Cellulose:

Approximately 100 mg of ethyl cellulose, Type N-10, was added to 10 ml of each of the 112 solvents. The sealed test-tubes were shaken at ambient room temperature overnight and solubilities recorded as soluble, partially soluble or insoluble. Solvents in which ethyl cellulose were poorly soluble were then heated in a water-bath at 40 ± 0.5°C and 70 ± 0.5°C, or until the solvent boiled, and any change in solubility behavior recorded. The type of phase separation occurring on cooling, if any, was classified as either a gel, coacervate or flocculate. Results were correlated with published solvent solubility parameters. Unlisted solvent solubility parameters were calculated either from solvent heats of vaporization values or, from Small's molar attraction constants at 25°C.

Quantitative Solubility of Ethyl Cellulose:

The quantitative solubility of ethyl cellulose, Type N-10, was determined in 36 solvents of varying polarity using a procedure similar to that described above. Ethyl cellulose was added to varying volumes of solvent and sealed in 100 ml glass containers at room temperature. If all the polymer dissolved within 24 hours, more ethyl cellulose was added until saturation was achieved. The solubility of ethyl cellulose was then determined by weighing at 10 ml of solution, and determining the amount of ethyl cellulose dissolved by gravimetric analysis after evaporating to constant weight.

Solubility Parameter Determinations using Turbidimetric Titrations:

Turbidimetric titrations were performed using a Brice-Phoenix light scattering photometer, Model 2000-D (Phoenix Precision Instrument Company, Pennsylvania) fitted with a green filter combination isolating monochromatic light at 546 nm. Scattering intensity (observed turbidity) was measured at 90° and recorded in arbitrary units (mm) on a Linseis recorder.

When a nonsolvent and solvent combination was miscible, dilute (0.5 %w/v) solutions of ethyl cellulose were titrated with two nonsolvents using the procedure developed by Suh and colleagues[24,25,28] for determining solubility parameters. The lower solubility limit was determined by adding a nonpolar solvent such as n-hexane or petroleum ether until the critical point was observed. Similarly, the upper solubility limit was determined using a polar solvent such as water. Critical δ_c values were calculated from equation 5, where φ is the volume fraction, and s and n refers to solvent and nonsolvent respectively:

$$\delta_c = \varphi_s \delta_s + \varphi_n \delta_n \qquad \text{Eqn. 5}$$

The solubility parameter for ethyl cellulose was calculated as the mid-point of the upper and lower critical solubility limits. The critical interaction parameter value for ethyl cellulose in each system, χ_c, was calculated from:

$$\chi_c = \frac{0.34 + V_1 (\delta_1 - \delta_n)^2}{R\,T} \qquad \text{Eqn. 6}$$

where V_1 is the molar volume of the solvent mixture calculated assuming that no volume change occurs on mixing.

Because ethyl cellulose is soluble in a wide range of polar and non polar solvents, the standard turbidity titration procedure developed by Suh and colleagues had to be modified since few nonsolvents are miscible with solvents for ethyl cellulose. A new procedure employing cosolvents was subsequently developed which enabled more accurate determinations of critical values of the cosolvent solubility parameter, δ_c, and the polymer-solvent interaction parameter, χ_c, using multiple titrations in ternary solvent systems and quadratic regression analysis. Experimental details of this procedure will be reported elsewhere. The solubility parameter of the ternary solvent mixture at the critical point was calculated from the equation:

$$\delta_c = \varphi_s \delta_s + \varphi_c \delta_c + \varphi_n \delta_n \qquad \text{Eqn. 7}$$

where subscripts s, c and n refer to solvent, cosolvent and nonsolvent respectively.

RESULTS AND DISCUSSION

The calibration curve for the determination of ethoxyl content of ethyl cellulose by gas chromatography was linear over the concentration range used and defined by the equation: $y = 0.32082x + 0.01919$, $R^2 = 0.999$, with a limit of detection of 1.3μg/ml. The mean ± standard deviation ethoxyl content for the ethyl cellulose was found to be 48.0 ± 1.6 % w/w, compared to stated content of 48.2 % w/w. This conforms to the requirements of Type N ethyl cellulose which specifies an ethoxyl content of between 47.5 to 49.0 % w/w corresponding to a degree of substitution of 2.43 to 2.53. Completely ethoxylated ethyl cellulose contains 3 ethoxyl groups per anhydroglucose monomer.

Qualitative solubility data for ethyl cellulose in 112 solvents is summarized if Figures 1 and 2. To illustrate the influence of dipole-dipole interactions on regions of solubility and insolubility of ethyl cellulose, a two dimensional solubility map, Figure 1, was constructed from the qualitative solubility data by plotting the fractional polarity of the solvent (p)[29] against the solubility parameter. This diagram illustrates that ethyl cellulose is soluble in solvents over a wide range of polarities ranging from 0 to 0.75; however, it is insoluble in strongly hydrogen bonding solvents.

A triangular solubility diagram was constructed to illustrate the effect of the relative fractional contributions of the

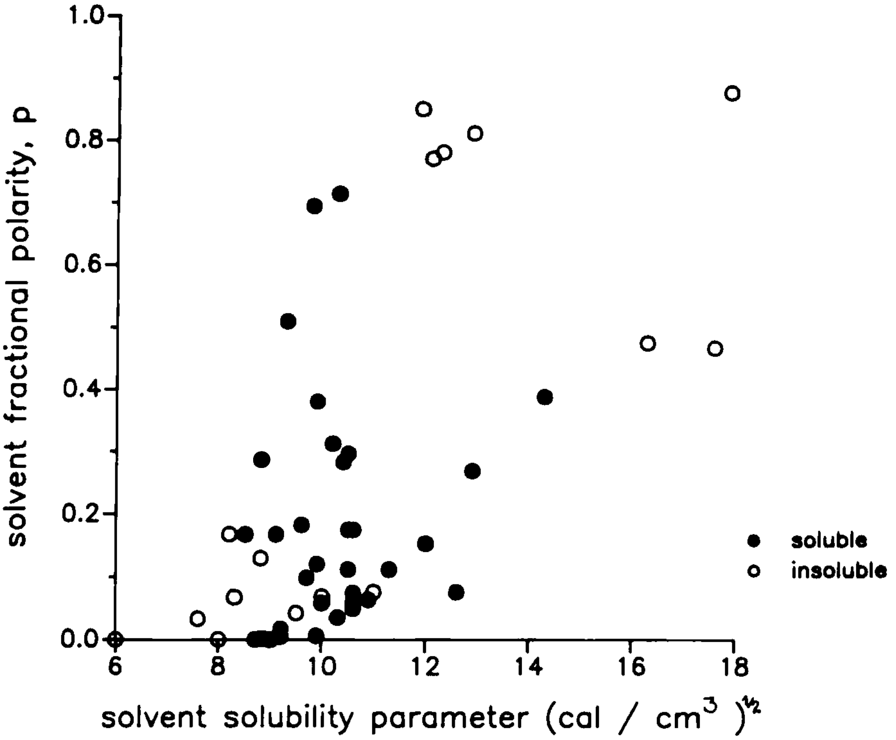
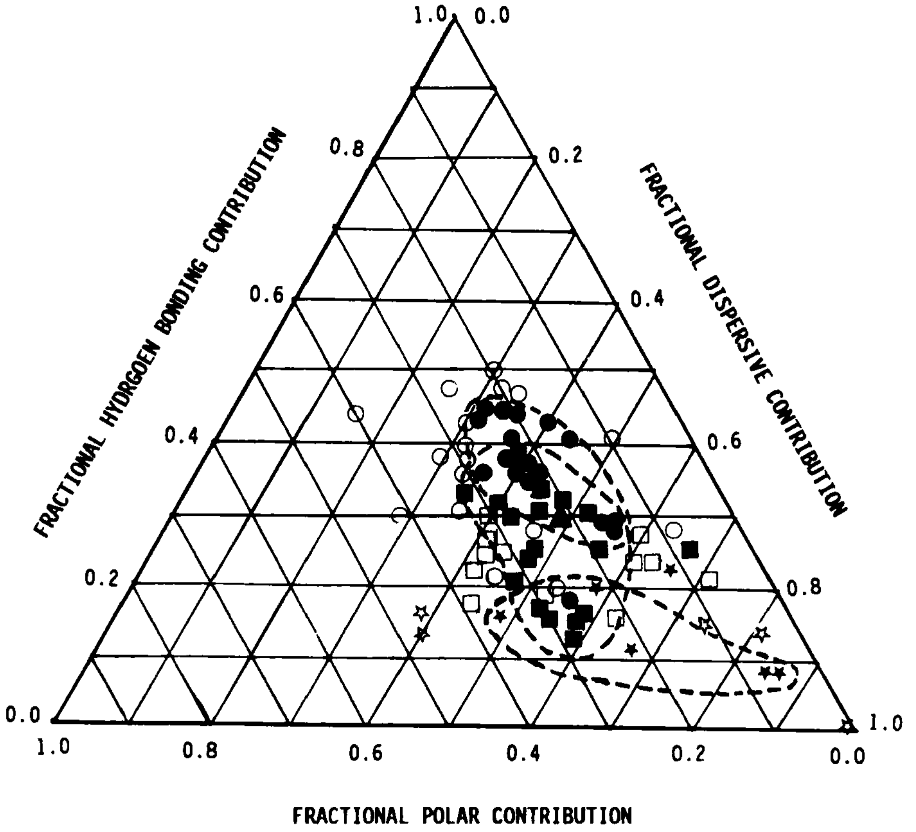


FIGURE 1
Two Dimensional Solubility Map of Ethyl Cellulose

dispersive, polar and hydrogen-bonding compontents of solvent solubility parameters to the solvent power of each class of solvents on the solubility of ethyl cellulose (Figure 2). Three areas of solubility overlap for each class of solvent and define a region characterizing the relative contributions of solvent intermolecular forces necessary to dissolve ethyl cellulose. Using the literature value for the ethyl cellulose solubility parameter of 10.3, and the calculated fractional dispersive ($f\delta_d$), polar ($f\delta_p$), and hydrogen-bonding contributions ($f\delta_h$) of 8.3, 3.5



▲ethyl cellulose solubility parameter

☆insoluble } weak hydrogen bonding solvents
★soluble

□insoluble } medium hydrogen bonding solvents
□soluble

○insoluble } strong hydrogen bonding solvents
●soluble

FIGURE 2
Triangular Solubility Diagram For Ethyl Cellulose

and 5.0 $(\mathrm{cal/cm^3})^{\frac{1}{2}}$ respectively[19]. Ethyl cellulose is seen to occupy a central position within the defined solubility regions. This triangular diagram provides ready identification of 'good' solvents in each class of solvent which should be useful in developing new microencapsulation systems, i.e. solvent and nonsolvents for ethyl cellulose.

Only aliphatic hydrocarbons and highly polar solvents have no solvent power for this polymer. The solubility spectrum and the mid point of the solubility spectrum (solubility parameter) for ethyl cellulose from both the qualitative and quantitative solubility data in the three classes of hydrogen bonding solvents are summarized in Table 1. Literature values[4,30], are also included in this table. The solubility spectrum of ethyl cellulose obtained from quantitative data was arbitarilly defined by those solvents in which the solubility of ethyl cellulose was greater than 10 % w/v produced a slightly larger solubility spectrum.

Solvents which dissolved ethyl cellulose only on heating generally exhibited phase separation on cooling as shown in Table 2. Coacervation was observed from liquids considered very 'poor' solvents for ethyl cellulose at room temperature with a solubility parameter near or just outside the solubility spectrum for ethyl cellulose. Gelation occurs with liquids which are usually considered nonsolvents for ethyl cellulose at room temperature; that is, their solubility parameter is significantly outside the solubility spectrum. Elevation of temperature allows for

TABLE I

Solubility Spectrum of Ethyl Cellulose in Poor, Medium and Strong Hydrogen Bonding Solvents

Solvent Class	Solubility Spectrum	Mid-point of Solubility Spectrum
(a) Qualitative Solubility Data		
(a) poor H-bonding	8.7 - 10.0	9.3
(b) medium H-bonding	8.5 - 10.4	9.4
(c) strong H-bonding	9.8 - 14.3	12.1
(a) Quantitative Solubility Data		
(a) poor H-bonding	8.8 - 10.2	9.5
(b) medium H-bonding	8.0 - 12.4	10.2
(c) strong H-bonding	8.6 - 15.4	12.0
(c) Literature Values[4,30]		
(a) poor H-bonding	8.1 - 11.1	9.6
(b) medium H-bonding	7.4 - 11.0	9.2
(c) strong H-bonding	9.5 - 14.5	12.0

solvation of the ethyl cellulose macromolecules which, on cooling, separates from solution as a viscous gel. Ethyl cellulose floccules were observed only from polar solvents, with solubility values well outside the solubility spectrum for ethyl cellulose. Both ethylene glycol and glycerol have similar fractional polarities indicating that both high polar and hydrogen bonding contribution to the solubility parameter are prerequisites for

TABLE II

Classification of Solvents Exhibiting Coacervation, Gelation or Flocculation Phase-separation Phenomena after Heating to 80°C

Solvent	Class	δ	δ_d	δ_p	δ_h
(a) Coacervation					
isopropyl myristate	m	8.1	-	-	-
glyceryl triacetate	m	9.9	7.3	5.7	5.5
(b) Gelation					
petroleum ether	w	7.1	7.1	0	0
hexane	w	7.2	7.2	0	0
cyclohexane	w	8.2	8.2	0	0
linseed oil	w	8.4	8.4	0	0
propylene glycol	s	14.8	8.2	4.6	11.4
(c) Flocculation					
ethylene glycol	s	16.3	8.3	5.4	12.7
glycerol	s	17.6	8.5	5.9	14.3

where: δ = solvent solubility parameter $(cal/cm^3)^{\frac{1}{2}}$
δ_d = dispersive contribution $(cal/cm^3)^{\frac{1}{2}}$
δ_p = polar contribution $(cal/cm^3)^{\frac{1}{2}}$
δ_h = hydrogen-bonding contribution $(cal/cm^3)^{\frac{1}{2}}$
\- = values not located in the literature
w = weak hydrogen-bonding solvent
m = medium hydrogen-bonding solvent
s = strong hydrogen-bonding solvent

flocculation. Solvents above this range such as water, are unable to solvate ethyl cellulose even when heated.

Quantitative solubility data for ethyl cellulose in a range of 36 solvents are shown in Figure 3. From this graph a value for the solubility parameter, but more particularly, the solubility

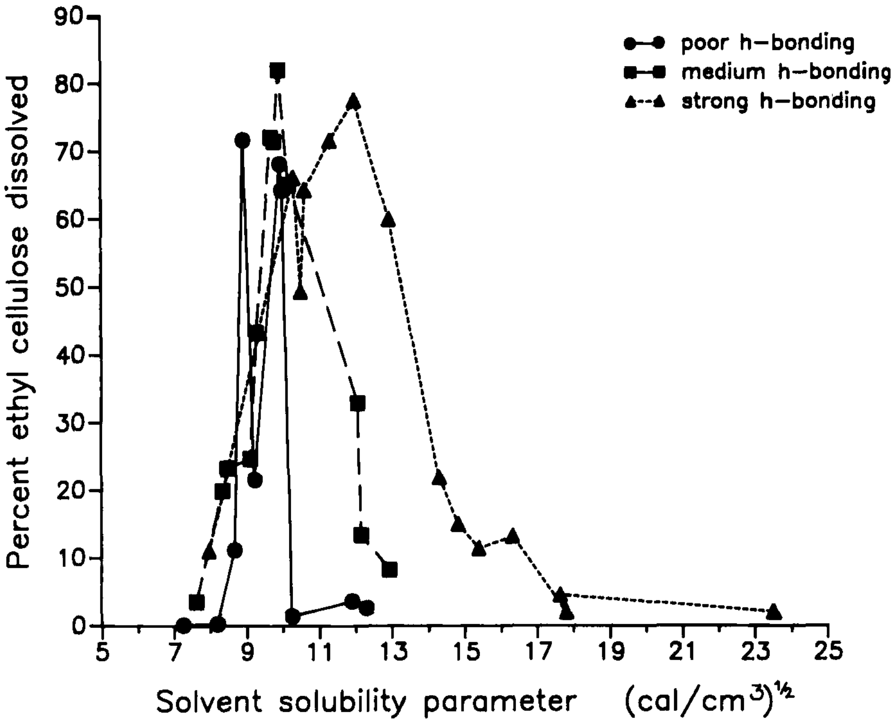


FIGURE 3
Quantitative Solubility of Ethyl Cellulose in Organic Solvents

spectrum of ethyl cellulose in each solvent class is defined. Experimental results from qualitative and quantitative solubility studies of ethyl cellulose can be explained by relating solvation and hydrogen-bonding effects to the structure of the macromolecule. Spurlin[31] states that there is no evidence for the solvation of alkoxyl groups in cellulose ethers, however, the high hydroxyl content of ethyl cellulose leaves ample opportunity for solvation and hydrogen bonding. Solvation, involving specific interactions between polar groups of solvent molecules and polymer chains, is believed to play and important part in the interaction of cellulose derivatives and solvents[31,32]. Cellulose derivatives are believed to be solvated in polar solvents by virtue of strong interaction between solvent molecules and substituted or unsubstituted hydroxyl groups[33]. Evidence from x-ray and infrared absorption studies indicates intermolecular hydrogen bonds between C_6 hydroxyl and bridge oxygens, and intramolecular hydrogen bonding between C_3 hydroxyl and adjacent ring oxygens[33]. Ethyl cellulose is insoluble in very nonpolar solvents where neither solvation of hydroxyl groups or hydrogen-bonding occurs. A wide range of nonpolar to polar solvents exist because of their ability to solvate or form hydrogen bonds with unsubstituted hydroxyl groups. In highly polar solvents, solvent-solvent interactions dominate because of the strong hydrogen bonding and dipole-dipole effects and subsequently the ethyl cellulose remains insoluble. Ethyl cellulose with lower degrees of substitution compared with Type N are soluble in polar solvents because of the increase in hydroxyl groups available for solvation.

Interaction parameters calculated from nineteen solvent-nonsolvent turbidity titrations are summarized in Table 3. The influence of concentration, temperature and molecular weight of ethyl cellulose on the cloud point and hence interaction parameters will be reported elsewhere. Excluding the two strongly hydrogen-bonding solvents, the mean value obtained at room temperature for Type N-10 ethyl cellulose in 17 solvents is 0.36 ± 0.03. Only Moore et. al.[32,33] previously published values ranging from 0.28 to 0.48 for χ_c values of ethyl cellulose obtained from osmotic pressure measurements.

TABLE III

Flory-Huggins Polymer-Solvent Interaction Parameters at Critical Points Calculated from Turbidity Titration Data at Room Temperature

Solvent	Nonsolvent	φ_c	δ_m	χ_c
toluene	hexane	0.29	8.42	0.38
toluene	petroleum ether	0.21	8.53	0.35
toluene	light liquid paraffin	0.24	0.40	0.35
toluene	medium liquid paraffin	0.17	8.56	0.34
toluene	maize oil	0.38	8.10	0.38
toluene	water[a]	0.06	10.32	0.34
ethyl acetate	hexane	0.41	8.32	0.38
ethyl acetate	petroleum ether	0.35	8.41	0.36
ethyl acetate	water[a]	0.10	10.53	0.34
acetic acid	hexane	0.66	8.32	0.40
acetic acid	petroleum ether	0.48	9.06	0.34
acetic acid	water	0.31	14.51	0.35
butyl acetate	light liquid paraffin	0.40	7.80	0.46
butyl acetate	water[a]	0.10	9.95	0.34
methyl ethyl ketone	water	0.20	12.02	0.36
acetone	water	0.17	12.09	0.36
ethanol	water	0.33	16.39	0.64
methanol	water	0.25	16.57	0.51
methylene dichloride	water[a]	0.01	10.06	0.34

mean ± standard deviation (N=17)[b] = 0.36 ± 0.03
mean ± standard deviation (N=19)[c] = 0.08

Key: a values obtained using a cosolvent and extrapolating to zero cosolvent concentration
b values calculated excluding the strongly hydrogen-bonding alcohols
c values for all 19 titrations
δ_m solubility parameter of solvent mixture at critical point
χ_c calculated from equation 1.53

The ethyl cellulose solubility parameter calculated from 8 turbidity titrations using the standard mid-point method of Suh and Clarke was 9.78 ± 1.12 which is consistent with results reported in Table 1. In comparison, the new method for the turbidimetric determination of polymer solubility parameters, in 36 ternary solvent systems containing a combination of a weak, medium and polar solvents, gave a mean ± s.d. of 9.39 ± 0.17 for the solubility parameter after the quadratic regression of the data. This is within the solubility parameter range for ethyl cellulose of 19.0 to 19.4 $MPa^{\frac{1}{2}}$, equivalent to 9.3 to 9.5 $(cal/cm^3)^{\frac{1}{2}}$, published by Kent and Rowe[34] from single-point viscosity measurements.

Using the solubility parameter value obtained from the turbidity titrations in ternary solvent systems of 9.39 $(cal/cm^3)^{\frac{1}{2}}$, theoretical solvent-ethyl cellulose interaction parameters were calculated for ethyl cellulose in 112 solvents using equation 6. The plot of the interaction parameter versus the solubility parameter of a range of medium polarity solvents is shown in figure 4. Almost identical profiles were obtained for non-polar and strongly-polar solvents. From this graph it is evident that a minimum interaction parameter occurs at the solubility parameter of ethyl cellulose. In solvents with significantly lower or higher solubility parameters the interaction parameter rapidly increases. For an infinitely large polymer molecules, phase separation occurs when $\chi_c > 0.5$. Therefore, an indication of which solvents may produce coacervation can be obtained from χ_c values. However the

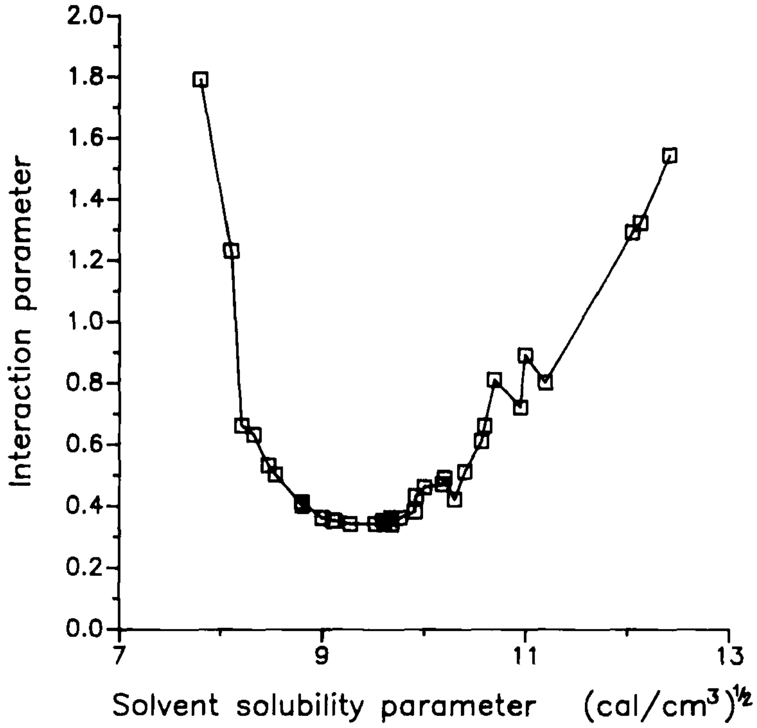


FIGURE 4
Ethyl Cellulose - Solvent Interaction Parameter in Medium Hydrogen Bonding Solvents

limitations of the Flory-Huggins theory to account quantitatively for polymer solution behavior in strongly hydrogen bonding media is also evident, since large χ_c values of 1.56 and 1.95 were calculated for ethanol and methanol respectively, even though these solvents are able to dissolve ethyl cellulose. With this limitation in mind however, the polymer-solvent interaction parameter approach should still be practically useful in selecting and/or optimizing microencapsulation procedures using coacervation.

CONCLUSIONS

1. Ethyl cellulose coacervates in a limited number of solvents because coacervation only occurs close to the critical point defined by χ_c.
2. Alternative solvent systems in which ethyl cellulose coacervates were identified.
3. The common factor that exists between systems in which coacervation occurs is that all single solvents or solvent mixtures have a solubility parameter near the limit of the ethyl cellulose solubility spectrum and a χ value near 0.38. If polar solvents are involved differences may be greater than 038.
4. Coacervation, gelation and flocculation phase separation phenomena can be differentiated and generally predicted, based on relative solubility parameters of the polymer
5. The Flory-Huggins solution theory together with the related extended solubility polymer concept, can serve as a quantitative basis to define and/or predict phase separation phenomena. Therefore, they serve as a basis for the rational selection of polymer-solvent-nonsolvent systems to optimize microencapsulation procedures.
6. If a polymer solubility parameter is known, the theoretical polymer-solvent interaction parameter can be calculated.

These values can then be used to identify solvents and solvent combinations from which phase separation will possibly occur. Thus, potentially useful solvents and solvent combinations can be selected as potential coacervation systems for the preparation of microcapsules.

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