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Methods for determining partial solubility parameters of potential film-coating polymers

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Summary

The partial solubility parameters of a film-coating polymer can be useful in formulating a good film-coating solution. Three experimental methods were used to determine the partial solubility parameters for a commercially available silicone polymer, Silastic Q7-4735. Prior to the initiation of the curing process, solutions of the polymer were examined by viscometry and turbidimetry. The cured polymer was evaluated by swelling measurements. Results of viscosity and swelling were found to agree. The solubility parameters δ_d and δ_p were determined to be 7.44–7.56 $(\text{cal/ml})^{1/2}$ and 0.23–1.69 $(\text{cal/ml})^{1/2}$, respectively. However, turbidity was shown to be a poor method for determining solubility parameters.

Introduction

The solvents used to apply film coatings have been reported to influence the properties of that coating. For example, the permeability of ethylcellulose films to oxygen and water vapor was found to be dependent on the casting solvent (Vemba et al., 1980). It was further shown that for acrylate films the change in permeability with different solvents was attributed to a different surface structure as well as different tortuosity within the film (Abdel-Aziz and Anderson, 1976). According to another report there was a difference in adhesion of hydroxypropyl cellulose coatings to tablet cores when different solvents were used (Fung and Parrott, 1980). More specifically, for poly(methyl vinyl ether/maleic anhydride) films the change in adhesion was correlated to the solubility parameter of the solvent (Nadkarni et al., 1975). Further, it has been reported that the best-performing plasticizers in the phthalate ester series for ethylcellulose were those with solubility parameters close to that of the polymer (Entwistle and Rowe, 1979). Thus it is clear from these reports that the degree of polymer–solvent interaction is an important formulation tool. These interactions can be quantitated by solubility parameters.

Solubility parameters were first described in the chemical literature (Hildebrand and Scott, 1964). Later an extended set of solubility parameters was described in the field of paints and industrial coatings (Hansen, 1967). More recently solubility

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parameters have been used to characterize drug molecules (Sunwoo and Eisen, 1971; Martin and Carstensen, 1981; Martin and Miralles, 1982; Martin et al., 1982; Phuoc et al., 1986). However, very few reports in the pharmaceutical literature have dealt with determination of solubility parameters of film-coating polymers (Kent and Rowe, 1978; Sakellariou et al., 1986). In their paper, Kent and Rowe pointed out that a data bank of information on the various polymers would be invaluable to formulators.

The solubility parameters of some of the more commonly used polymers can be looked up in tables (Burrell, 1975). However, those of new polymers or proprietary polymer composites are not readily available. Burrell lists experimental methods for direct estimation of solubility parameters: (a) solubility; (b) swelling values; (c) refractive index; (d) osmotic pressure or vapor pressure; (e) intrinsic viscosity; and (f) direct observation for cloudiness and gel particles. In addition gas chromatography can be used to estimate solubility parameters (Phuoc et al., 1986). Both the choice of experimental method and the method of data analysis affect the accuracy of solubility parameter estimates (Acree et al., 1981; Wu et al., 1982).

In this paper a proprietary silicone polymer being investigated as a potential film coating is used as an example in determining solubility parameters. Three experimental methods, namely intrinsic viscosity, swelling, and observed cloudiness are compared. A statistically sound data analysis previously used for other optimization problems (Schwartz et al., 1965) is used in determining solubility parameters.

Theory

Comparison of single with extended solubility parameters

The interaction, I, between solvent (subscript 1) and polymer (subscript 2) is a function of their respective solubility parameters, δ, as in Eqn. 1 according to theory (Hildebrand and Scott, 1964).

$$I = I_i - f\{(\delta_1 - \delta_2)^2\} \qquad (1)$$

where I_i is the interaction in an ideal solution and f indicates some function of the bracketed term. The exact form of the equation depends on the property of the polymer–solvent interaction being measured. In any case, it is clear from Eqn. 1 that the interaction reaches a maximum when $\delta_1 = \delta_2$.

In the Hansen approach, each component is characterized by a set of 3 solubility parameters: δ_d, characterizing the non-polar or dispersion forces, δ_p, characterizing the dipolar forces, and δ_h, for the hydrogen bonding and other strong permanent dipole forces. The two solubility parameter systems are mathematically related by Eqn. 2 (Hansen, 1967).

$$\delta = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \qquad (2)$$

Determination of solubility parameters – data analysis

As cited before, the method of data analysis can influence the solubility parameter estimate. The single solubility parameter of a polymer can be estimated both graphically and mathematically. Graphically, as in Fig. 1, a plot of a given property of the polymer in a series of solvents with known solubility parameters versus δ of the corresponding solvent is a curved line with a maximum. The value of δ at the maximum is the solubility parameter of the polymer. Alternatively, non-linear regression can be used to generate an equation that describes the curve. Generally, the root of the first derivative is the solubility parameter of the polymer.

When the solubility parameter is extended to two dimensions it is a vector, for example (δ_d, δ_p), describing both the non-polar and the polar nature of the compound. Graphically, as in Fig. 2, a plot of a given property of the polymer in a series of solvents of known solubility parameters versus (δ_d, δ_p) of the corresponding solvent is a 3-dimensional response surface. As before, the value of (δ_d, δ_p) at the maximum is the solubility parameter set or vector of the polymer. However, it is difficult to locate this maximum graphically. Mathematically, non-linear regression can be used to generate an equation that describes the surface.

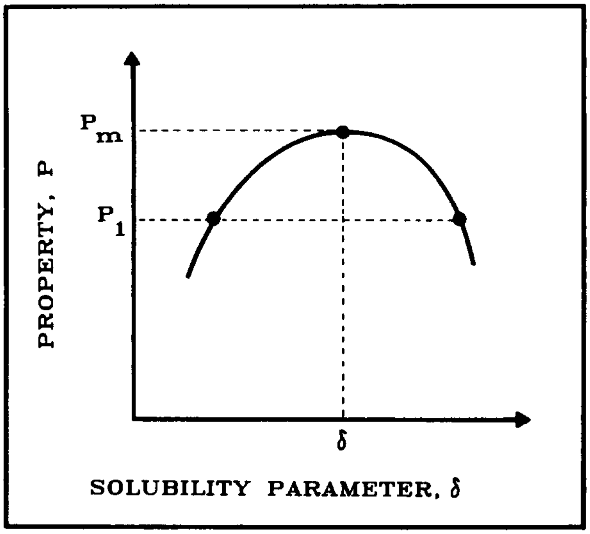

Fig. 1. Generalized plot of a solute property in various solvents versus the one-dimensional solubility parameter of that solvent. The maximum value of the property, P_m, corresponds to the solubility parameter of the polymer, δ. Any other value of the property, P_1, can be obtained using solvents characterized by either of two other values of δ.

The maximum can be located by any number of optimization algorithms.

When using non-linear regression to fit data points, both the form of the regression equation as well as the choice of experimental points will influence the predictive value of the equation. The form of the regression equation should be based on some knowledge of the system in order to obtain a good fit. Two properties – swelling and intrinsic viscosity – of a polymer in a solvent have been described by Eqn. 3 (Huglin and Pass, 1968).

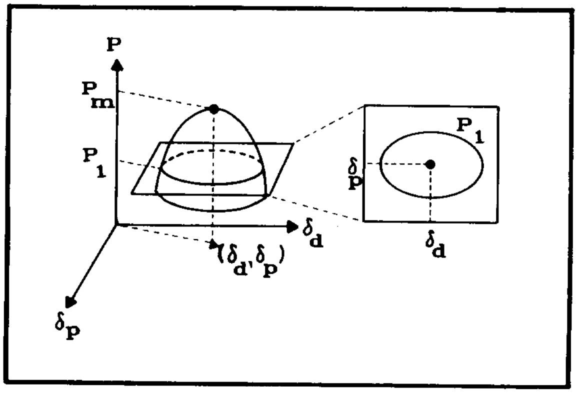

Fig. 2. Generalized plots of a solute property in various solvents versus the 2-dimensional solubility parameter set of that solvent. This figure shows the relationship between the response surface and contour plot. The maximum value of the property, P_m, corresponds to the set of solubility parameters of the polymer, (δ_d, δ_p). Any other value of the property, P_1, can be obtained using solvents characterized by any set (δ_d, δ_p) described by the ellipse in the contour plot.

$$P = P_{\max} \exp\left\{ -KV(\delta_1 - \delta_2)^2 \right\} \tag{3}$$

where P is the property (intrinsic viscosity or swelling), K is a constant and V is the molar volume of the solvent. Swelling of a polymer has also been described by a form of Eqn. 4 (Baney et al., 1977).

$$P^2 = k(\delta_1 - \delta_2)^2 \tag{4}$$

where P is the property (swelling) and k is a constant. Either of these equations provides a good starting point for predicting the solubility parameter of the polymer. However, the relationship between turbidity and solubility parameters has not been so well described (Suh and Clarke, 1967; Burrell, 1975). Either Eqn. 3 or Eqn. 4 or some general polynomial provides a good starting point for predicting the solubility parameter of the polymer.

In the past, most experiments done to determine solubility parameters of polymers and drugs have employed pure solvent systems only. This method leaves large regions of solubility parameters unexplored. A factorial experimental design can be approximated using binary solvent systems. There are 3 advantages to using a factorial design. First, the entire region of interest can be characterized. Second, there is a better opportunity to study systems near the maximum solubility parameter. Third, in the case of polymer composites where multiple maxima may exist, there is a better chance of identifying all the maxima. This can be seen in Fig. 3. The single and binary solvent systems are plotted on a map of 2-dimensional solubility parameters, respectively. It is clear from this figure that the area within the dashed lines would be largely unexplored if only pure solvents were used.

TABLE 1

Compositions of the solvent systems

Solvent system (% w/w)	Solubility parameters	
	δ_d	δ_p
25.5% methylene chloride/74.5% isopentane	7.0	0.42
32.8% methyl ethyl ketone/67.2% isopentane	7.0	0.68
100% *n*-heptane	7.5	0.00
38.5% cyclohexane/61.5% ether	7.5	0.89
71.9% ether/28.1% 1,2-dichloroethane	7.5	1.80
39.9% ether/60.1% methyl ethyl ketone	7.5	3.11
60.8% chloroform/39.2% *n*-heptane	8.0	0.63
72.9% chloroform/27.1% ether	8.0	1.46
45.0% ether/55.0% 1,2-dichloroethane	8.0	2.30
19.3% 1,2-dichloroethane/80.7% methyl ethyl ketone	8.0	4.29
62.3% cyclohexane/37.7% 1,2-dichloroethane	8.5	0.98
30.4% *n*-heptane/69.6% 1,2-dichloroethane	8.5	2.00
86.8% methylene chloride/13.2% ether	8.5	2.72
57.7% 1,2-dichloroethane/42.3% methyl ethyl ketone	8.5	4.03
22.0% cyclohexane/78.0% 1,4-dioxane	9.0	0.65
83.1% 1,4-dioxane/16.3% methyl ethyl ketone	9.0	1.60
54.2% chloroform/45.8% 1,2-dichloroethane	9.0	2.55
86.2% 1,2-dichloroethane/13.8% methyl ethyl ketone	9.0	3.76

When using binary solvents the parameter δ can be calculated from Eqn. 5:

$$\delta_i = \phi_a \delta_{i,a} + \phi_b \delta_{i,b} \tag{5}$$

where δ_i is a solubility parameter (δ, δ_d, δ_p, or δ_h), $\delta_{i,j}$ is the corresponding solubility parameter of the jth component and ϕ_j is the volume fraction of the jth component.

In summary, to determine the solubility parameter of a polymer, it is necessary to outline the approximate region within which the solubility parameter is expected to exist. Set up a factorial design within that region. Choose binary solvents that best fit the design. Collect data on the interaction of the polymer with each solvent system. Fit the data to an appropriate function. Use an algorithm to maximize the function. From this function, the solubility parameters are those which correspond to the maximum interaction.

Materials and Methods

Polymer

Silastic Q7-4735, a silicone polymer, was supplied by the manufacturer (Dow-Corning, Midland, MI) in two separate parts. When Part A and Part B are mixed together in a 1 : 1 ratio and heated, chemical crosslinks are formed which result in a highly tear-resistant material.

Solvent systems

Solvent selection was based on volatility due to potential use in film coating. Using this criterion the following solvents were selected: *n*-heptane, cyclohexane, ethyl ether, 1,2-dichloroethane, methyl ethyl ketone, chloroform, methylene chloride, dioxane, and isopentane (Fisher Scientific, Springfield, NJ). Binary solvents were selected by computer program* to approximate a half-factorial design. The resulting design is shown in Fig. 3. The specific compositions of the solvents are listed in Table 1.

Viscosity and turbidity measurement

The viscosity and turbidity behavior of the polymer in each of the 18 solvent systems were studied. For this purpose, 0.4% (w/v) mixtures of each of the polymer parts with solvent were stirred

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* Available from the authors upon request.

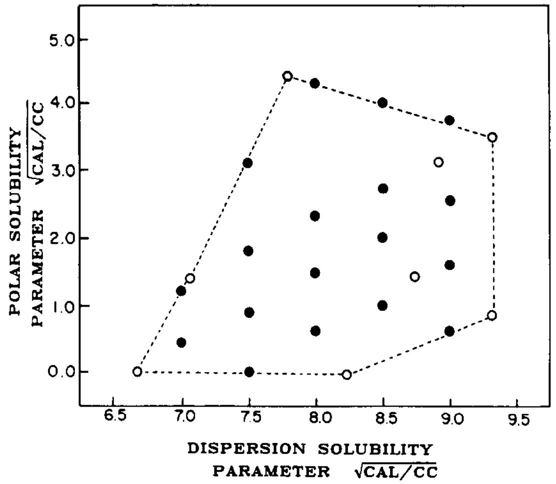

Fig. 3. Solubility parameter sets of (○) single solvents and (●) the binary solvent systems used in this study.

in sealed, jacketed beakers (Bellco Glass, Vineland, NJ) at 20 °C for 24 h. Lower concentrations 0.2% (w/v), 0.1% (w/v), and 0.05% (w/v) of polymer in solvent were obtained by serial dilution within the flask. The exact concentrations were determined by duplicate gravimetric analysis of 20 ml samples evaporated for 24 h at room temperature.

The reduced viscosity of each sample was determined at each concentration in triplicate at 20 °C using a jacketted U-tube viscometer (Schott Instruments, F.R.G.). The intrinsic viscosity of the polymer in the system was determined by extrapolating to zero from a plot of reduced viscosity vs concentration (Flory, 1953).

The turbidity of each sample was determined at each concentration in triplicate using a nephalometric turbidimeter (HF Industries, Fort Myers, FL). The index of turbidity of the polymer in the system is defined as the slope of a plot of average turbidity vs concentration.

Swelling and leaching experiments

Films were cast from a mixture of 10% (w/v) solutions of polymer parts A and B in chloroform. The films were evaporated to dryness and cured for 2 h at 90 °C. The resulting films weighed about 1.3 g each.

Each polymer film was weighed prior to swelling. The films were placed separately in 100 ml of each solvent system in 4 oz. jars which were kept at 20 °C in a water bath. Every 24 h the weight of the swelled polymer was determined by quickly removing it from the solvent, patting it dry with filter paper, and weighing it in a closed vessel to reduce evaporation of the swelling solvent. After 3 days the film was removed from the solvent, evaporated to dryness and reweighed. This method is based on a previously described method (Yerrick and Beck, 1964). The degree of leaching was calculated by:

$$\%\ \text{leached} = \left(\frac{\text{final dried wt.} - \text{initial wt.}}{\text{initial wt.}} \right) \times 100 \tag{6}$$

The degree of swelling was calculated by:

$$\%\ \text{swelled} = \left(\frac{\text{average change in volume}}{\text{dried volume}} \right) \times 100 \tag{7}$$

where

$$\text{dried volume} = \text{final dried wt.}/\text{density of polymer} \tag{8}$$

and

$$\text{change in volume} = \frac{(\text{swelled wt.} - \text{final dried wt.})}{\text{density of the solvent}} \tag{9}$$

The value for density of the polymer was 1.1 g/ml (Dow Corning, 1982). The density of each solvent system was determined by using a pycnometer. It was assumed in Eqn. 9 that the density of the solvent system within the polymer is equal to the density of the solvent system itself. The determination of swelling and leaching was done in triplicate for each solvent system.

Results and Discussion

Data treatment

Part A and Part B of the polymer were each studied by turbidimetry and viscometry in the solution state. The cured polymer (composed of 1 : 1 Part A : Part B) was studied by swelling measurements. The data from each method was fitted separately to equations using a non-linear regression program (XSTAT, Wiley, New York, NY). The data did not fit 3-dimensional extensions of either Eqn. 3 or Eqn. 4 ($r^2 < 0.25$). Nor did they adequately fit a second-order polynomial involving all 3 solubility parameters (δ_d, δ_p and δ_h). In this case the correlation coefficients were quite high ($r^2 > 0.9$). However, the standard errors of some of the coefficients were larger than the coefficients themselves. In addition, the solubility parameters obtained from these equations did not agree.

The data from intrinsic viscosity and swelling experiments fit second-order polynomials of the form:

$$P = A_1 + A_2\delta_d^2 + A_3\delta_p^2 + A_4\delta_d\delta_p + A_5\delta_d + A_6\delta_p \tag{10}$$

where $r^2 > 0.8$ and the standard error for each coefficient was much less than the coefficient itself. The residual errors are listed in Table 2. The lack of correlation of δ_h in describing polymer–solvent interaction properties implies that near the maximum any hydrogen bonding interactions are insignificant.

The deviation of experimental data from that predicted by the Eqn. 10 comes from 3 sources. (1) The equation is not exact. It is only an approximation fitted to the data. For our purposes this empirical expression needs only to fit the data best at the maximum. The various data sets fit the maximum rather well. The mean deviation of experimental from predicted near the point of maximum interaction is only 3.2–7.1% depending on the data set. (2) The theory assumes that there are no specific interactions between species. This assumption rarely holds. Specific interactions may scatter the data slightly. However, the use of binary mixtures of a variety of solvents and the use of solvent systems at approximately equal intervals over the δ_d vs δ_p map reduces this problem. (3) Also, of course, experimental error always causes some scatter in the data.

A typical plot of a property versus (δ_d, δ_p) is shown in Fig. 4. This is a response surface for swelling as a function of the solubility parameters. The response surface gives a good qualitative picture of the behavior of the function. In Fig. 5 the corresponding contour plot is shown. The contour plot gives a more quantitative picture of the results. The maximum value is more easily identified from the contour plot than from the response surface.

For comparison, the data was also fitted to the one-dimensional Hildebrand solubility parameter calculated from Eqn. 2. Fig. 6 shows the mathematical fit and actual data points from the swelling study.

Viscosity and swelling methods

Table 3 shows the solubility parameters determined by viscosity and swelling. There is good agreement among the 3 sets of values, especially for the value of δ_d. Furthermore, these values are very close to those obtained for pure poly(dimethylsiloxane) (Yerrick and Beck, 1964; Baney et al., 1977). It appears then that Silastic Q7-4735 is mostly composed of dimethylsiloxane units.

A possible explanation for the disparity in the polar solubility parameter component, δ_p, is as follows: a common crosslinking mechanism in synthetic polymers is shown in Fig. 7. It is an addition reaction involving a vinyl group from one chain to a hydrogen atom on a siloxane group from another chain. The vinyl group is more polar than the siloxane hydrogen. Perhaps Part A of the polymer contains vinyl groups on its silicone backbone while Part B contains bare siloxane groups in its silicone backbone. This would account for the difference in the polar solubility parameter component. The result of the addition reaction is an ethyl ($-CH_2-CH_2-$) linkage. This group has no significant polar character. Thus for the formed film in which all groups are cross-

TABLE 2

Intrinsic viscosity and % swelling for each polymer/solvent combination

Solubility parameters of solvent systems			Intrinsic viscosity of Part A			Intrinsic viscosity of Part B			% Swelling of film 1 : 1 (A : B)		
δ_d	δ_p	δ_h	expt.	pred.	|resid.|	expt.	pred.	|resid.|	expt.	pred.	|resid.|
7.0	0.42	0.41	1.29	1.40	0.11	1.27	1.41	0.14	253.4	251.7	1.7
7.0	1.20	0.68	1.52	1.45	0.07	1.31	1.30	0.01	239.0	228.8	10.2
7.5	0.00	0.00	1.33	1.38	0.05	1.63	1.49	0.14	284.7	295.4	10.7
7.5	0.89	1.59	1.81	1.62	0.19	1.56	1.51	0.05	279.9	288.3	8.4
7.5	1.80	2.41	1.48	1.60	0.12	1.46	1.37	0.09	249.5	259.1	9.6
7.5	3.11	2.50	1.28	1.10	0.18	1.08	0.90	0.18	190.5	178.2	12.3
8.0	0.63	1.17	1.49	1.39	0.10	1.34	1.35	0.01	294.4	284.7	9.7
8.0	1.46	2.67	1.44	1.52	0.08	1.10	1.34	0.24	264.4	274.4	10.0
8.0	2.30	2.30	0.96	1.43	0.47	0.73	1.20	0.47	224.1	245.2	21.1
8.0	4.29	2.43	0.37	0.30	0.07	0.44	0.34	0.10	100.4	100.9	0.5
8.5	0.98	0.55	1.25	0.99	0.26	1.19	0.92	0.27	260.3	225.7	34.6
8.5	2.00	1.11	1.12	1.09	0.03	1.15	0.91	0.24	226.5	212.7	13.8
8.5	2.72	2.89	1.27	0.96	0.31	0.95	0.79	0.16	205.1	186.8	18.3
8.5	4.03	2.27	0.00	0.29	0.29	0.00	0.31	0.31	83.1	104.2	21.1
9.0	0.65	2.62	0.00	0.05	0.05	0.00	0.13	0.13	125.5	109.9	15.6
9.0	1.60	3.38	0.00	0.33	0.33	0.00	0.26	0.26	42.2	118.2	76.0
9.0	2.55	2.40	0.48	0.32	0.16	0.48	0.23	0.25	133.0	102.3	30.7
9.0	3.76	2.10	0.00	−0.11	0.11	0.00	0.06	0.06	57.7	47.2	10.5

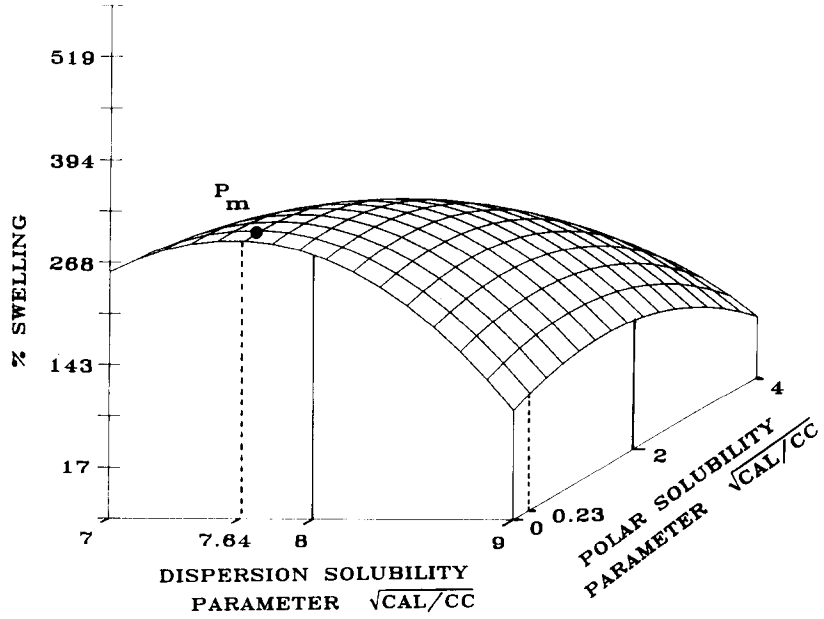

Fig. 4. Swelling response surface. The maximum swelling is indicated by point P_m.

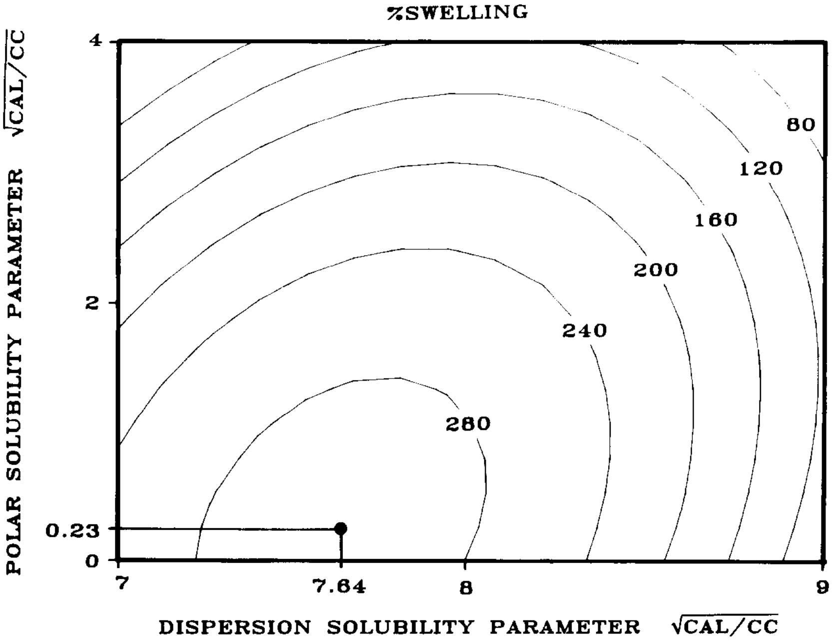

Fig. 5. Contour plot of swelling corresponding to Fig. 4.

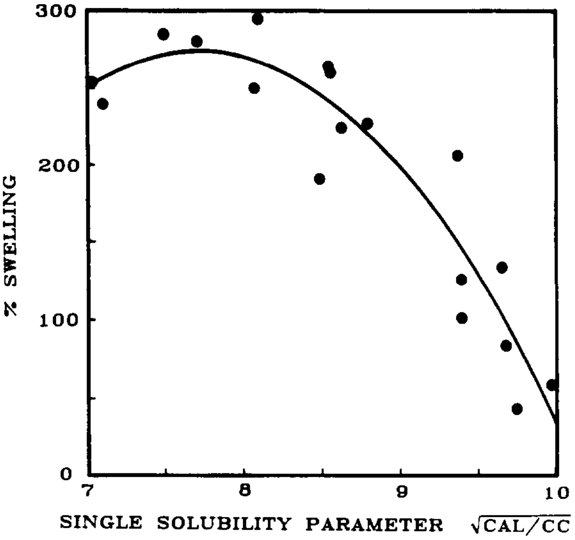

Fig. 6. Swelling as a function of the Hildebrand solubility parameter of each solvent.

linked, the polar solubility parameter component is very low.

Comparison of Hildebrand and Hansen solubility parameters

Table 3 lists 2-dimensional solubility parameters resulting from a multidimensional curve-fitting routine and the one-dimensional Hildebrand solubility parameter resulting from a simpler nonlinear curve fit. The agreement between the one- and 2-dimensional parameters through Eqn. 2 is quite good. However, it is clear that the 2-dimensional parameters yield more information about the polymer.

TABLE 3

Solubility parameters determined by viscosity and swelling methods

Material	Method	Parameters (cal/ml)$^{1/2}$		
		Two-dimensional		One-dimensional
		δ_d	δ_p	δ
Silastic Part A	Viscosity	7.56	1.30	7.65
Silastic Part B	Viscosity	7.44	0.51	7.46
Silastic Film	Swelling	7.64	0.23	7.73

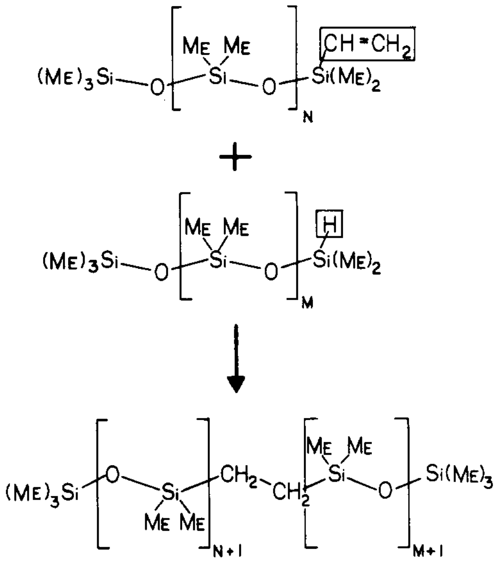

Fig. 7. Addition reaction for crosslinking silicone.

Turbidity methods

The response surface of the turbidity coefficient of Part A as a function of the solubility parameters of each solvent in Fig. 8 is planar. Thus, there is no "clearest solution". A set of solubility parameters cannot be obtained from this surface. However, the observation of solutions for cloudiness was cited earlier as a method for determining solubility parameters of polymers (Burrell, 1975). This implies that the clearest solution is characterized by a system in which solubility parameters of the polymer and solvent are equal. The implicit assumption in this method is that turbidity is caused by a separation in phases. Additionally, it is assumed that the discontinuous phase is opaque to light.

Actually, turbidity can be caused by either a separation in phases or Rayleigh scattering. In order for a two-phase system to be turbid the discontinuous phase must be opaque to light. However, if the refractive indices of the phases are equal, the light travels unaltered through the system. Hence, there is no turbidity. Rayleigh scattering is caused by interaction of light with scattering centers in a molecule. The interaction causes the incident beam to be scattered in all directions. The degree to which light is scattered depends on the difference in refractive indices of the solvent and

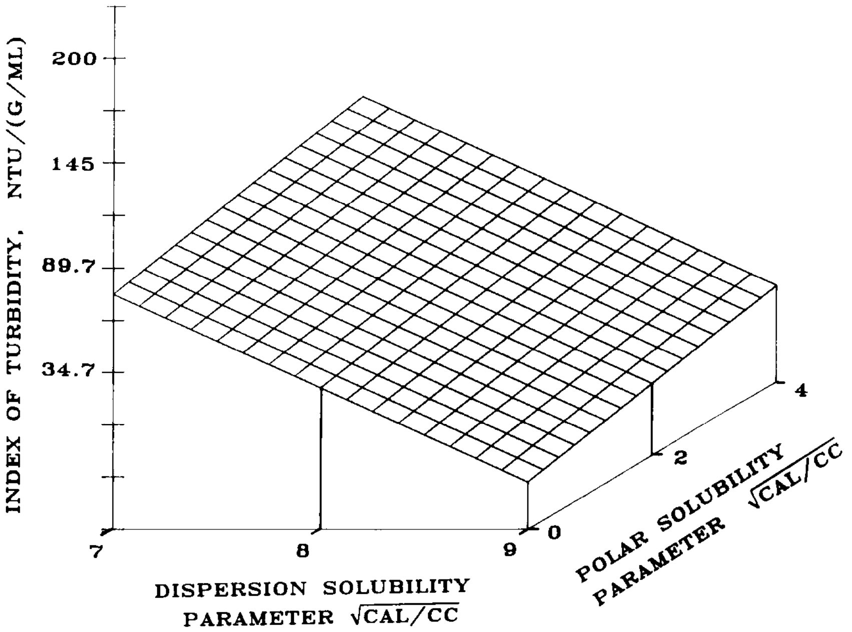

Fig. 8. Turbidity response surface.

polymer (Van Krevelen, 1976). Thus, in both cases turbidity is a function of the difference in refractive indices of the polymer and solvent.

The correlation of turbidity of this polymer with refractive indices of the solvents is shown in Fig. 9. A clear solution is predicted when the refractive index of the solvent is 1.426. The refractive index of silicone polymers is reported to be 1.43 (Burrell, 1975). Comparing these two values, clarity of solutions of this silicone polymer depends on the difference in refractive indices of polymer and solvent, not on the affinity of the solvent for the polymer. Thus, it appears that the method of detecting phase separation by turbidity may fail when complicated by optical phenomena related to differences in refractive indices.

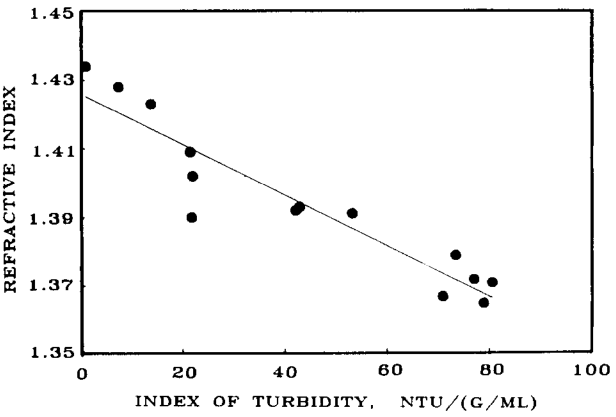

Fig. 9. Correlation between refractive index of the solvent and turbidity coefficient of the polymer–solvent mixture.

Leaching method

It was also noted that the amount of material leached from the polymer film varies. This incident has been reported by other investigators (Yerrick and Beck, 1964) as a nuisance in swelling studies. In the present study leaching was found to vary as a function of the solubility parameters (δ_d, δ_p). The maximum leaching occurs at (δ_d, δ_p) = (7.57,1.69). The large value for the polar component indicates that the material being leached is more polar in nature.

Conclusive remarks

The results of this work have led to the formulation of Silastic Q7-4735 as a film-coating using 55.3 : 44.7 (w/w) methylene chloride : isopentane as the solvent. The solubility parameters of this solvent system are $\delta_d = 7.5$ (cal/ml)$^{1/2}$ and $\delta_p =$

1.1 $(\text{cal/ml})^{1/2}$. It should be noted here that in some cases it is advisable to choose a solvent with solubility parameters far from the parameters of the polymer to obtain a lower viscosity solution that is easier to process. However, in this case it was necessary to choose a system with parameter values close to the solubility parameters of the polymer, because of the difficulty in eliminating gel particles from this long-chain polymer composite. This polymer has a low viscosity (less than 500 cps) up to a solids loading of 10% w/v.

Determining the solubility parameters was helpful not only in formulating the coating solution, but will also aid in the prediction of drug permeation through the film and prediction of adhesion of the film to different tablet cores.

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