Application of Solubility Parameters to the Formulation of Acrylate Methacrylate Film Coating Systems

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ABSTRACT: In order to optimize the formulation of the acrylate methacrylate (AMA) coating systems, the partial solubility parameters of AMA and those of various coating solvents and plasticizers have been computed using the group contribution method of Van Krevelan and Hoftyzer. The data were analyzed in accordance with the three-dimensional solubility parameters whereby δ_h (the hydrogen-bonding component) was plotted against the sum of δ_d (the dipole–dipole component) and δ_p (the polar component). The data were also analyzed according to a two-dimensional solubility parameters whereby δ_h was plotted vs δ_p to obtain the energy maps for the various compounds. With the three-dimensional analysis, the position of the reference polymer in the energy map was centrally located and was flanked by plasticizers and solvents that were shown experimentally to be compatible with the polymer. On the other hand, the two-dimensional analysis displaced the location of the reference polymer in the energy map leftward to the Y axis, and was not flanked by plasticizers and solvents that were compatible with it. The results show that the concept of the three-dimensional solubility parameters was more applicable to the theoretical selection of plasticizers and solvents for the polymer studied. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 87: 1339–1344, 2003

INTRODUCTION

The acrylate methacrylates (AMA) find use as barrier films in the controlled release of drugs.[1–6] The selection of suitable plasticizer and/or solvent for the formation of coating systems of these polymers have been largely empirical, involving a series of trial and error that is tedious and expensive. A rational selection of a plasticizer and solvent for a given polymer can be achieved theoretically by a consideration of the solubility parameters of these compounds.

The solubility parameter (δ) is defined as the square root of the cohesive energy density, i.e., the cohesive energy (E) per unit of the molar volume (V) and it is expressed mathematically thus[7]:

$$\delta = \sqrt{\frac{E}{V}} \tag{1}$$

Hildebrand and Scott[8] showed that molecules that have similar values of cohesive energy will mix readily since the cohesive exchange energy needed for the interaction will be minimal tending to zero. However, studies have showed that the Hildebrand and

Scott theory is applicable to nonpolar compounds only where the mechanism of intermolecular reaction is essentially dipole–dipole (i.e., van der Waal or London forces).[9,10] With polar compounds, polar interactions and hydrogen bonding are also important.[9–12] Hence these authors introduced the concept of three-dimensional partial solubility parameter to more clearly reflect the contribution of each components of these forces. The total solubility parameter δ_t of a compound is thus given by the equation below[13]:

$$\delta_t = \delta_d + \delta_p + \delta_h \tag{2}$$

where δ_d is the partial solubility parameter due to dispersion forces, δ_p is the partial solubility parameter due to polar interactions, and δ_h is the partial solubility parameter due to hydrogen-bonding interactions.

In order that the partial solubility parameters may be represented graphically as an energy map for the various compounds, Bagley combined two such partial solubility parameters to obtain what is known as the Bagley solubility parameter (δ_v); such that $\delta_v = \delta_p + \delta_d$. A plot of δ_h (i.e., the hydrogen-bonding component) vs δ_v (i.e., a three-dimensional analysis) is known as the Bagley diagram or the energy map showing the energy locations of the various compounds in relation to that of the reference polymer.[14] The distance between the point location of each of these compounds (e.g., plasticizer or solvent) and the point location of the reference polymer in the energy

R_1 =   H, CH_3

R_2 = CH_3, CH_2 CH_3
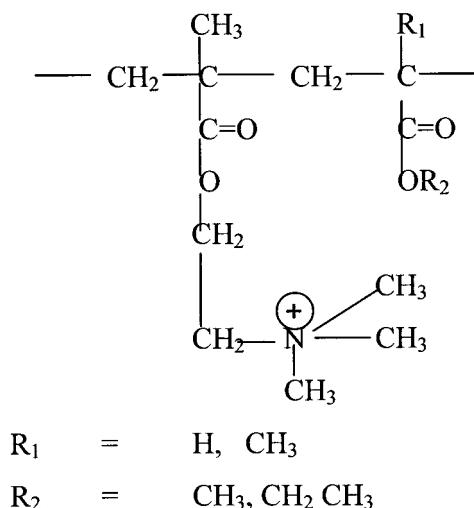
In Ethyl methacrylate R_1 = CH_3 and R_2 = C_2H_5

Figure 1 General structure of the acrylate methacrylate copolymer.

map is a measure of the exchange cohesive energy $((\Delta^2\delta)$, which is needed for the interaction to occur and it is given by the equation below:

$$\Delta^2\delta = \Delta^2\delta_h + \Delta^2\delta_v \qquad (3)$$

This three-dimensional approach has been used to predict the skin permeability of drugs using lecithin membrane as a skin model.[15]

In the two-dimensional analysis δ_h is plotted against δp instead of δv, which is a double component parameter. The corresponding expression for the exchange cohesive energy is

$$\Delta^2\delta = \Delta^2\delta_h + \Delta^2\delta_p \qquad (4)$$

This two-dimensional approach has been used to predict optimal solvent and plasticizer systems for certain polymers.[16] In the two-dimensional analysis it is assumed that the dipole–dipole interactions would be negligible. However, in the case of the acrylate methacrylate copolymers, the preponderance of hydrophobic alkyl groups in the polymer structure (Fig. 1) means that dipole–dipole intercations would contribute remarkably to the overall forces of cohesion. Besides, the polar (cation) groups per chain of this polymer are few—hence polar interactions are expected to be minimal.[4]

In the present study, therefore, the partial solubility parameters were analyzed according to the two- and three-dimensional solubility parameters to determine which of the two approaches would be more relevant to the rational selection of solvents and plasticizers for the polymer studied.

MATERIALS AND METHODS

Materials

An acrylate methacrylate copolymer (Fig. 1) obtained from Rohm Pharma, Darmstadt, Germany, was the test polymer.

This polymer contains a small proportion of quartenary ammonium groups, which confers some degree of hydrophilicity and hence it swells considerably in water. The structure also shows that polar, dipole–dipole, and hydrogen-bonding forces will be involved in the interaction of the polymer with other compounds. Solvents and plasticizers employed for miscibility or compatibility test were of reagent grade (BDH). The ranges covered are shown in Table II.

Computation of the solubility parameters

The group contribution method of Van Krevelan and Hoftyzer was employed.[17,18] In the computation, the partial solubility parameters of each structural group in the compounds were taken into account and the total for all the structural groups were summed up. For instance, the partial solubility parameter due to polar interaction (δ_p) is given by

$$\delta_p = \frac{\sum F_{pi}}{\sum V_i} \qquad (5)$$

where $\sum F_{pi}$ is the sum of the group solubility parameter due to polar forces in each structural group and $\sum V_i$ is the sum of the molar volume of each structural group within the molecule. The solubility parameters due to dispersion and hydrogen-bonding forces were similarly computed. To obtain the partial solubility parameter for the compounds, the value for each structural group[16,17] and the values of the molar volumes as published previously[17,18] were fed into the computer program SPWin version 2, which was de-
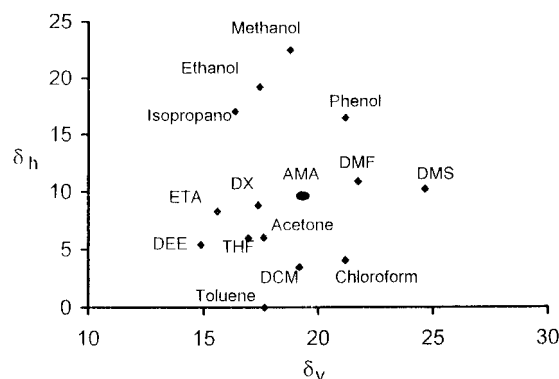

Figure 2 Energy map showing the point of the reference polymer AMA and those of various solvents: DMF = dimethylformamide, DMS = dimethylsulfoxide, DEE = diethylether, ETA = ethylacetate, DX = dioxan, THF = tetrahydrofuran, and DCM = dichloromethane.
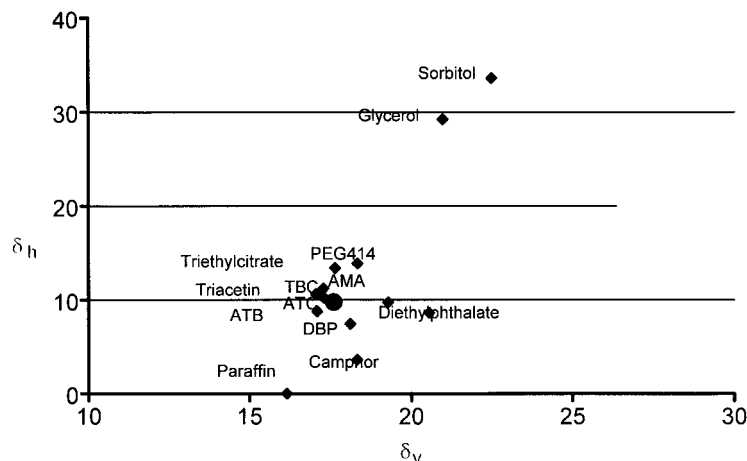
Figure 3 Energy map showing the point location of the reference polymer AMA and those of various plasticizers: ATB = acetyltributylcitrate, ATC = acetyriethylcitrate, DBP = dibutylphtalate, and TBC = trybutylcitrate.

veloped by the research group of Groning and Braun.[15] The program contains the various structural groups and the corresponding F and V values. For a given compound, the number of each type of structural group was typed into the computer program to obtain the total contribution by that group. The summation of the contributions of the various groups will give the partial solubility parameter, e.g., δ_p, δ_h, or δ_d of the compound. However, where two polar groups are in one plane of symmetry, the total polar contribution was reduced by half, or by 0.25, if they appear in two planes of symmetry in order to take into account the mutual repulsiveness of the polar groups.

Film casting technique and electron microscopy

Free films (about 11 μm thick) were prepared from 10% w/w solution of the test polymer in various solvents and containing different plasticizers as shown in Table II. In each case the content of plasticizer was 10% w/w based on polymer weight. Lower concentrations of plasticizer gave brittle films, while lower polymer concentrations gave films that were too thin for handling. Aliquots of 3 mL each were cast on glass plates. The films were allowed to dry for 24 h in a dust-free atmosphere. Free films were detached with a knife. Where the polymer was incompatible with the plasticizer, resulting films were brittle and difficult to detach.

Electron micrographs of film sample were produced to study film structure by the following technique. Free film samples were mounted on a specimen stub and vacuum- coated using Balzers Union Ltd., Model SCD 040. The coated specimens were examined at various magnifications using a scanning electron microscope (Model Stereoscan S4, TL 10701-OM-96118, Cambridge, England) for surface inhomogeneities.

RESULTS AND DISCUSSION

The computed partial solubility parameters for the polymer, solvents, and the plasticizers were plotted (i.e., δ_h vs δ_v) to obtain the energy maps in Figures 2 and 3 for the solvents and the plasticizers, respectively. Figures 4 and 5 are the energy maps based on the two-dimensional analysis (i.e., a plot of δ_h vs δ_p) for the solvents and the plasticizers, respectively. In the cases of the three-dimensional analysis (Figs. 2 and 3) it can be seen that the position of the reference polymer was centrally located and was flanged by the point locations of the various solvents and plasticizers.

The exchange cohesive energy ($\Delta^2\delta$) gives a measure of the energy barrier that must be overcome before interaction can take place between the polymer and plasticizer or between the polymer and solvent; the lower the energy barrier the more readily the interac-
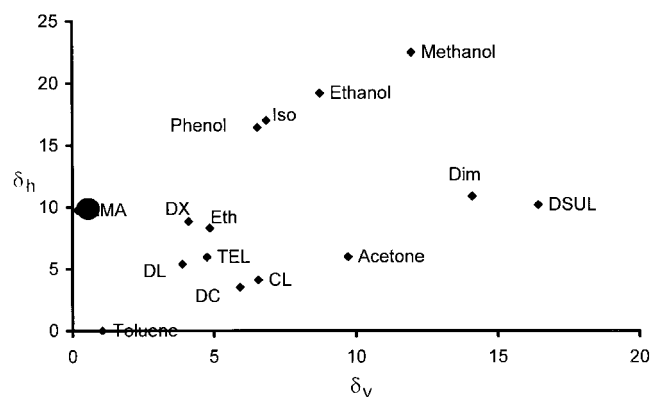

Figure 4 Energy map showing the point location of the reference polymer AMA and those of various solvents: ISO = isopropanol, DIM =dimethylformide, DSUL = dimethylsulfoxide, DX = dioxan, Eth = ethylacetate, TEL = tetrahydroforane, DL = diethylether, CL = chloroform, DC = dichloromethane.
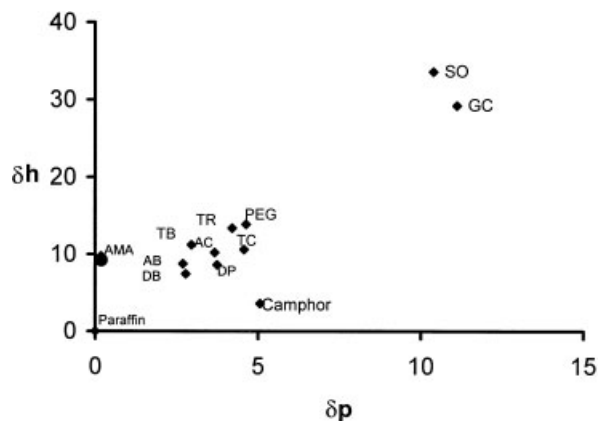
Figure 5 Energy map showing the point location of the reference polymer AMA and those of various platicizers: SO = sorbitol, GC = glycerol, PEG = PEG14, TR = triethylcitrate, TC = triacetin, TB = tributylcitrate, AC = acetyltriethylcitrate, AB = acetyltributylcitrate, DP = diethylphthalate, DB = dibutylphthalate.

tion take place. The $\Delta^2\delta$ values based on eq. (3) are presented in Table I in increasing order. Among the solvents, dioxane gave the lowest exchange cohesive energy (3.77 J · cm^{-3} · mol^{-1}) while methanol gave the highest value (162.41J · cm^{-3} · mol^{-1}). Experimentally solvents with $\Delta^2\delta$ values $\leq$ 38.69J · cm^{-3} · mol^{-1} gave homogenous films as revealed by scanning electron
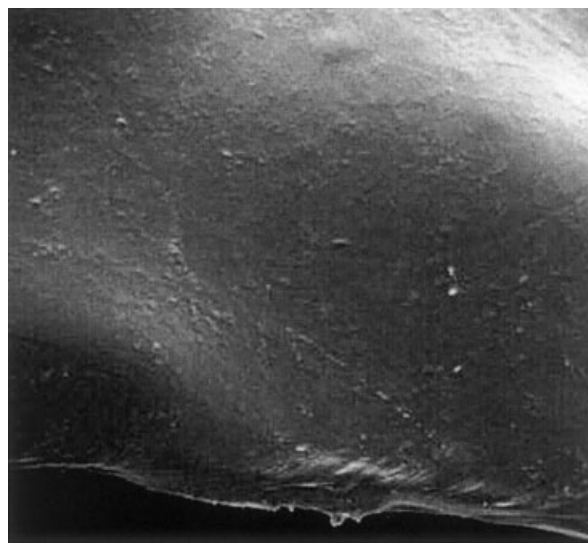

Figure 6 Electron micrograph (×900) of film cast from acetone showing a homogeneous surface due to polymer miscibility with the solvent.

micrography (SEM). An example of the SEM of a film cast from acetone is shown in Figure 6. Solvents with higher $\Delta^2\delta$ values gave inhomogenous films due to poor miscibility of the solvent with the polymer. An example of the SEM of an inhomogeneous film cast

TABLE I
Exchange Cohesive Energy (J · cm^{-3} · mol^{-1}) for the Interaction Between the
Polymer–Solvent and the Polymer–Plasticizer Based on
Three-Dimensional Consideration

|	$\Delta^2\delta_h$	$\Delta^2\delta_v$	$\Delta^2\delta$
Solvent			
Dioxane	0.81	2.96	3.77
Dimethylformamide	1.28	6.97	8.25
Ethylacetate	2.04	12.18	14.22
Acetone	14.06	2.19	16.25
Tetrahydrofuran	14.29	4.62	18.91
Dimethylsulfoxide	0.20	30.11	31.11
Chloroform	31.81	4.32	36.13
Diethylether	18.92	17.81	36.73
Dichloromethane	38.68	0.008	38.69
Phenol	44.76	4.33	49.09
Isopropanol	52.71	7.45	60.16
Ethanol	89.49	2.76	92.25
Toluene	95.06	2.04	97.10
Methanol	162.31	0.10	162.41
Plasticizers			
Diethylphthalate	1.23	0.19	1.42
Acetyltriethylcitrate	0.23	3.24	3.47
Triecetin	0.77	4.20	4.97
Acetyltributylcitrate	0.96	4.04	5.0
Tributylcitrate	2.16	3.31	5.47
Dibutylphthalate	5.29	0.98	6.25
Triethylcitrate	13.25	2.13	15.38
PEG414	17.22	0.59	17.81
Camphor	37.58	0.61	38.19
Glycerol	379.86	3.53	383.39
Sorbitol	569.30	11.56	580.86
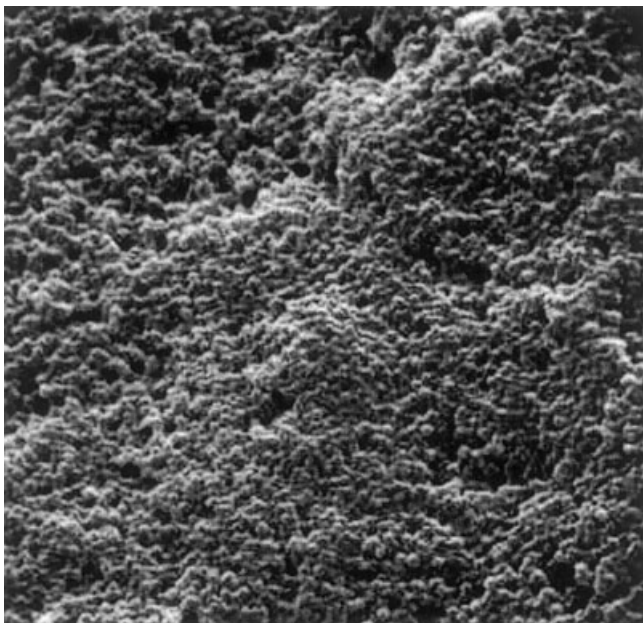
Figure 7 Electron micrograph ($\times 900$) of film cast from methanol showing inhomogeneities due to polymer immiscibility with the solvent.

from methanol is shown in Figure 7. Thus, the critical exchange cohesive energy for the polymer - solvent system studied, was 38.69 $J \cdot cm^{-3} \cdot mol^{-1}$. From this result, the solvents that are compatible with the test polymer are dioxane, dimethylformamide, dimethylsulfoxide, diethylether, ethylacetate, acetone, tetrahydrofuran, chloroform, and dichloromethane. However, the first five named solvents and ethylacetate, dichloromethane and tetrahydrofuran are too toxic to be used in pharmaceutical coating systems, leaving acetone and chloroform as the solvents of choice. The alcohols such as isopropanol, ethanol, and methanol were not compatible with the polymer because of their high polarity in contrast with the low polarity of the polymer.

Among the plasticizers, diethylphthalate displayed the lowest exchange cohesive energy of 1.42 $J \cdot cm^{-3} \cdot mol^{-1}$, while sorbitol displayed the highest exchange cohesive energy value of 580.86 $J \cdot cm^{-3} \cdot mol^{-1}$. Experimentally, plasticizers with $\Delta^2\delta$ values of ≤ 17.81 $J \cdot cm^{-3} \cdot mol^{-1}$ were compatible with the polymer and gave homogenous films similar to that shown in Figure 6. The amount of 17.81 $J \cdot cm^{-3} \cdot mol^{-1}$ is thus considered the critical exchange cohesive energy for the polymer–plasticizer interaction. Above this value the plasticizers were immiscible with the polymer and hence gave inhomogenous films similar to that in Figure 7. Examples of compounds that were incompatible with the polymer are paraffin, glycerol, and sorbitol. Paraffin is essentially a nonpolar compound, whereas

TABLE II
Exchange Cohesive Energy ($J \cdot cm^{-3} \cdot mol^{-1}$) for the Interaction Between the
Polymer–Solvent and the Polymer–Plasticizer Based on
the Two Dimensional Analysis

	$\Delta^2\delta_h$	$\Delta^2\delta_v$	$\Delta^2\delta$
Solvent			
Dioxan	0.81	15.37	16.18
Ethylacclate	2.04	21.81	23.85
Diethylether	18.92	13.69	32.61
Tefrahydrofurane	14.29	20.88	35.17
Dichloromethane	38.69	32.95	71.61
Chloromethane	31.81	40.70	72.51
Phenol	44.76	40.32	85.08
Toluence	95.06	0.76	95.82
Isopropanol	52.71	44.36	97.07
Acetone	14.06	91.01	105.07
Ethanol	89.49	72.93	162.42
Dimethylformamide	1.28	193.49	194.77
Dimethylsufoxide	0.20	263.41	263.61
Methanol	162.31	138.53	300.84
Plasticizers			
Acetyltributylcitrate	0.96	6.30	7.26
Tributylcitrate	2.16	7.67	9.92
Dibutylphthalate	5.29	6.76	12.05
Acetyletriethylcitrate	0.23	12.18	12.41
Diethylphthalate	1.23	12.67	13.90
Triacetin	0.77	19.27	20.04
Triethylcitrate	13.25	16.16	29.41
PEG414	17.22	19.80	37.02
Camphor	37.57	23.81	61.38
Paraffin	95.06	0.03	95.09
Glycerol	379.86	119.25	499.11
Sorbitol	569.30	104.04	673.34

sorbitol and glycerol are polar compounds. Hence miscibility with the polymer was not determined simply by the polarity or hydrophobicity of the compounds, but by the three component forces, i.e., hydrogen-bonding, dipole–dipole, and polar interactions taken together.

By the two-dimensional analysis (Figs. 4 and 5), the position of the reference polymer was displaced toward the Y axis of the δ_h vs δ_p plots, attributable to the low contribution of the polar component forces in the polymer. The values of the exchange cohesive energies obtained from eq. (4) are presented in ascending order in Table II. Among the solvents dioxane displayed the lowest $\Delta^2\delta$ energy (16.18 J $\cdot$ cm^{-3} $\cdot$ mol^{-1}) methanol displayed the highest $\Delta^2\delta$ (301 J $\cdot$ cm^{-3} mol^{-1}) as was the case with the three-dimensional analysis. However, these values are considerably higher than those obtained with the three-dimensional analysis. Also acetone, which is readily miscible with the polymer, experimentally gave a higher $\Delta^2\delta$ value of up to 105.07 J $\cdot$ cm^{-3} $\cdot$ mol^{-1} against the 38.69 J $\cdot$ cm^{-3} $\cdot$ mol^{-1}, which is the critical $\Delta^2\delta$ for the polymer–solvent interaction. This means that the two-dimensional analysis was not appropriate for the rational selection of solvents for the polymer.

Among the plasticizers acetyltributylcitrate gave the lowest $\Delta^2\delta$ (7.26 J $\cdot$ cm^{-3} $\cdot$ mol^{-1}) while sorbitol gave the highest $\Delta^2\delta$ (673.34 J $\cdot$ cm^{-3} $\cdot$ mol^{-1}). The values were generally higher than those obtained by the three-dimensional analysis. For instance, PEG, which was experimentally compatible with the polymer, displayed a higher cohesive energy of 37.2 J $\cdot$ cm^{-3} $\cdot$ mol^{-1} against the 17.8 J $\cdot$ cm^{-3} $\cdot$ mol^{-1}, which is the observed critical $\Delta^2\delta$ for the polymer–plasticizer interaction in the three dimensional analysis. This result together with the displacement of the position of the reference polymer from its central location (see Figs. 4 and 5) suggests that the two-dimensional analysis did not appropriately predict the optimal solvent and plasticizer for the polymer. This was so because such analysis omitted the dipole–dipole interactions, which are predominant in the structure of the polymer. The three-dimensional analysis, which took all three types of interactions into consideration, is therefore more appropriate for the selection of plasticizers and solvents for the polymer studied.

The conclusion therefore is that the three-dimensional solubility parameter can be used conveniently to predict the optimal solvent and plasticizer systems for the polymer studied.

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