

Surface free energy of ethylcellulose films and the influence of plasticizers

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Abstract

The surface free energy parameters of ethylcellulose (EC) films were determined using the Lifshitz–van der Waals/acid–base approach and the influence of plasticizers on their surface energetics was assessed. Films were prepared by dip-coating glass slides in organic solvents containing EC and the advancing angles of drops of pure liquids on the EC films were measured with a contact angle goniometer using the captive drop technique. EC has lower surface free energy than cellulose. The acid–base (AB) term made only a slight contribution to the total surface free energy and the surfaces exhibited predominantly monopolar electron–donicity. The addition of plasticizer (dibutyl sebacate or dibutyl phthalate) resulted in a small decrease in the total surface free energy. The effects of film forming variables, including solvent system, concentration and post-formation treatment (annealing), on the surface free energy parameters of EC films were also investigated. These data were then used to analyze how the surface energetics affect the interaction of the EC films with other surfaces based on interfacial tension, work of adhesion and spreading coefficient calculations. Lifshitz–van der Waals (LW) interactions provided the major contribution to the work of adhesion for EC with all of the solid substrates analyzed. However, the AB interactions contributed significantly to the work of adhesion for EC with ‘bipolar’ substrates and to the spreading coefficients of EC over substrates. The consideration of work of adhesion and spreading coefficient based on surface free energy parameters may have potential use in evaluating factors affecting film adhesion and, furthermore, in optimizing pharmaceutical film coating processes. © 1999 Published by Elsevier Science B.V. All rights reserved.

Keywords: Ethylcellulose; Contact angle; Surface free energy parameters; Lifshitz–van der Waals/acid–base approach; Film adhesion; Plasticizer

1. Introduction

A major pre-requisite for pharmaceutical film coatings applied for any purpose is good adhesion

to the solid substrate (Rowe, 1977, 1981). Adhesion between film and dosage form surfaces is a result of intermolecular bonding forces involving functional groups on the respective surfaces. The energetics of these surfaces are therefore important in determining adhesion between film and dosage form surfaces. Rowe (1988) proposed a

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theoretical approach to the adhesion of film coatings to tablet surfaces based on solubility parameters and derived equations to predict both the interaction parameter and ideal butt adhesive strength. Johnson and Zografi (1986) showed that the measured adhesion extrapolated to zero film thickness was proportional to the thermodynamic work of adhesion at the film–substrate interface calculated from independent surface free energy determinations. Evaluation of the thermodynamic work of adhesion requires knowledge of the surface free energy of the film and substrate. However, very little data are available regarding the surface energetics of pharmaceutical film coatings (Doelker, 1993; Sakellariou and Rowe, 1995a).

A limited number of studies assessing coating adhesion in fundamental terms, such as the interfacial interaction and the work of adhesion, have been reported (Johnson and Zografi, 1986; Bianchini et al., 1989). In these investigations, the polar and dispersive (non-polar) terms of surface free energy were used to determine the work of adhesion of polymeric coatings with solid substrates using Wu's method (Wu, 1971). This method has been frequently adopted to determine the surface free energy of pharmaceutical solids (Zografi and Tam, 1976; Rowe, 1989; Sheridan et al., 1995). However, it has been debated whether the separation of surface free energy into polar and non-polar forces is adequate to model practical interfacial interactions (Fowkes et al., 1990; Rillosi and Buckton, 1995a).

There is no direct method for measurements of solid surface free energy components. However, an approach for determination of the surface free energy of solids has been developed based on the theory of apolar and acid–base (AB) interactions by van Oss and coworkers (van Oss et al., 1988a, b), who described the importance of AB interactions in surface phenomena. This approach is recognized to provide accurate and real description of solid surface free energy components (Holysz and Chibowski, 1992; Wu et al., 1995), and has been applied to a variety of interfacial systems in many areas of surface science (Chibowski et al., 1992; Janczuk et al., 1992; Tous-saint and Luner, 1993; Lloyd et al., 1995).

van Oss et al. (1988a) proposed that the total surface free energy of a solid or liquid, γ^{TOT} , can be divided into two components:

$$\gamma^{\text{TOT}} = \gamma^{\text{LW}} + \gamma^{\text{AB}} \quad (1)$$

where γ^{LW} is the apolar (or non-polar) component associated with Lifshitz–van der Waals (LW) interactions which encompass London dispersion forces, Debye-polarization and Keesom forces. The γ^{AB} component results from electron-donor and electron-acceptor intermolecular interactions referred to as Lewis acid-base interactions. The most common AB interaction results from hydrogen bonding. The term γ^{AB} is further divided into two parameters:

$$\gamma^{\text{AB}} = 2(\sqrt{\gamma^+ \gamma^-}) \quad (2)$$

where γ^+ and γ^- are the electron-acceptor and electron-donor parameters of the AB component of the surface free energy of the substance, respectively. It is seen from Eqs. (1) and (2) that if either the γ^+ or γ^- parameter is zero, there is no AB component contributions to the overall surface free energy ($\gamma^{\text{TOT}} = \gamma^{\text{LW}}$). Under the assumption of negligible film pressure of the liquid on low energy solids (Fowkes, 1964), the Young equation can be combined with the Dupre equation to yield the following:

$$\gamma_{\text{L}}(1 + \cos\theta) = \gamma_{\text{S}} + \gamma_{\text{L}} - \gamma_{\text{SL}} = -\Delta G_{\text{SL}} \quad (3)$$

where ΔG_{SL} is the interfacial free energy and the subscripts S and L refer to the solid and liquid phases, respectively. van Oss et al. (1988b) have shown that ΔG_{SL} is separated into its LW and AB components:

$$\Delta G_{\text{SL}} = \Delta G_{\text{SL}}^{\text{LW}} + \Delta G_{\text{SL}}^{\text{AB}} \quad (4)$$

and that the interfacial energy, γ_{SL} , is defined as:

$$\begin{aligned} \gamma_{\text{SL}} = & (\sqrt{\gamma_{\text{S}}^{\text{LW}}} - \sqrt{\gamma_{\text{L}}^{\text{LW}}})^2 \\ & + 2(\sqrt{\gamma_{\text{S}}^+ \gamma_{\text{S}}^-} + \sqrt{\gamma_{\text{L}}^+ \gamma_{\text{L}}^-} - \sqrt{\gamma_{\text{S}}^+ \gamma_{\text{L}}^-} - \sqrt{\gamma_{\text{S}}^- \gamma_{\text{L}}^+}) \\ & \times \end{aligned} \quad (5)$$

By combining Eqs. (1)–(5) with appropriate substitution, the following equation is obtained:

$$\gamma_{\text{L}}(1 + \cos\theta) = 2(\sqrt{\gamma_{\text{S}}^{\text{LW}} \gamma_{\text{L}}^{\text{LW}}} + \sqrt{\gamma_{\text{S}}^+ \gamma_{\text{L}}^-} + \sqrt{\gamma_{\text{S}}^- \gamma_{\text{L}}^+}) \quad (6)$$

With known values of $\gamma_{\text{L}}^{\text{LW}}$, γ_{L}^+ , γ_{L}^- for three liquids and their contact angles, θ , on the solid, a

set of three equations of the form of Eq. (6) can be solved simultaneously to obtain the surface free energy parameters, γ_S^{LW} , γ_S^+ , γ_S^- , for the solid. It is possible to first determine γ_S^{LW} using an apolar liquid (one with no γ_L^+ or γ_L^-) and simplify the set of equations to a pair in the unknowns γ_S^+ and γ_S^- (Good, 1992). This LW/AB approach, which has become a standard technique in the surface chemical characterization of polymers and polar materials, has been applied to many interfacial systems of pharmaceutical interest with good success. Buckton and coworkers have modeled interactions of adhesives and bottles, and mucoadhesion by the use of surface free energy terms obtained using the LW/AB approach, and have demonstrated that this approach is useful for understanding and predicting interactions among biological or pharmaceutical components (Buckton and Chandraia, 1993; Rillosi and Buckton, 1995b). Vera et al. (1996) employed the LW/AB approach for studies on colloidal stability of a pharmaceutical latex. Luner et al. (1996) also used the surface free energy parameters determined by this approach to predict the wettability of a hydrophobic drug by surfactant solutions.

If only molecular interactions that form secondary bonds across an ideal interface are considered, the work of adhesion depends only on the surface energies of the materials and the interfacial energy between them. The thermodynamic work of adhesion between materials 1 and 2, W_A , is:

$$W_A = \gamma_1 + \gamma_2 - \gamma_{12} \quad (7)$$

Eq. (7) is a form of Eq. (3) where $W_A = -\Delta G_{12}$. The interfacial tension, γ_{12} , can be calculated from the LW and AB surface free energy parameters of the two substrates as:

$$\begin{aligned} \gamma_{12} = & (\sqrt{\gamma_1^{LW}} - \sqrt{\gamma_2^{LW}})^2 \\ & + 2(\sqrt{\gamma_1^+ \gamma_1^-} + \sqrt{\gamma_2^+ \gamma_2^-} - \sqrt{\gamma_1^+ \gamma_2^-} \\ & - \sqrt{\gamma_1^- \gamma_2^+}) \end{aligned} \quad (8)$$

As shown by van Oss et al. (1988b), the work of adhesion can also be divided into the works of adhesion due to LW and AB interactions (Eq. (9)) which can each be expressed in terms of the surface free energy parameters of the two substrates as (Eqs. (10) and (11)):

$$W_A = W_A^{LW} + W_A^{AB} \quad (9)$$

$$W_A^{LW} = 2(\sqrt{\gamma_1^{LW} \gamma_2^{LW}}) \quad (10)$$

$$W_A^{AB} = 2(\sqrt{\gamma_1^+ \gamma_2^-} + \sqrt{\gamma_1^- \gamma_2^+}) \quad (11)$$

Thus, once the LW and AB surface free energy parameters are determined for two different materials, their interfacial tension and work of adhesion can be calculated. It is also possible to determine a spreading coefficient for a film over a surface by calculating the difference between the work of adhesion (W_A) and cohesion (W_C) for the pair. The work of cohesion for any material can be considered as twice the value of the total surface free energy. The spreading coefficient (S) of material 1 over material 2 is:

$$S = W_{A(12)} - W_{C(11)} = \gamma_2 - \gamma_1 - \gamma_{12} \quad (12)$$

Ethylcellulose (EC) is widely used as a hydrophobic coating material for modifying the release of drugs from oral dosage forms (Wade and Weller, 1994; Sakellariou and Rowe, 1995a). Although EC aqueous dispersions are more commonly used in coating processes, these formulations contain surfactants, plasticizers and stabilizers that become incorporated in the film upon drying. The presence of several additives can make the results difficult to interpret (Vera et al., 1996). By first studying pure EC films prepared from organic solutions and comparing these to films containing known amounts of individual additives, changes in the surface energetics can be attributed to the nature of the additives themselves. Understanding the surface energetics of EC is also important because of its potential use in microencapsulated delivery systems (Palomo et al., 1996; Cedrati et al., 1997; Zinutti et al., 1998) and the fact that surface energetics play a significant role in the interaction of materials with biosurfaces (van Oss, 1995, 1997a). Surface energetics are also important factor determining the cohesion of powder blends (Barra et al., 1998).

This work therefore focused on determining the surface free energy parameters of EC films using the LW/AB approach and evaluating how plasticizers affect the surface free energy parameters of the films. In addition, the effects of film forming variables, including solvent system, concentration

and post-formation treatment on the surface free energy parameters of EC films were investigated. The results of these studies were then used to analyze how the surface energetics affect the interaction of the EC films with other surfaces based on interfacial tension, work of adhesion and spreading coefficient calculations.

2. Materials and methods

2.1. Materials and preparation of ethylcellulose (EC) films

EC (Acros Organics, Springfield, NJ) with ethoxyl content of 46% (w/w) was used in these studies. Methylene chloride, either alone, or in a 50:50 or 70:30 (v/v) mixture with methanol, was used as a solvent system for the organic solvent-based films. The EC films were prepared on well cleaned glass microscope slides ($25 \times 25 \times 0.25$ mm) using a dip-coating method (Sakellariou and Rowe, 1995b). EC was first dissolved in the solvent at the desired concentration and the polymer solution was placed in a covered TLC chamber. Glass slides were mounted to a custom-made dipping device that consisted of a glass slide holder vertically attached to a precision worm gear. The gear was powered by an electric synchronous motor (Model FYQF-33600-40, Colman Motor Products, Darlington, WI) equipped with a motor controller (Tech II Railpower 1400, Model Rectifier, Edison, NJ). The glass slide was lowered slowly into the organic solvent–EC solution where it remained for 2 min. The immersed slide was then withdrawn from the solution at a speed of 1 cm/min and suspended in the vapor until all the solvent evaporated, leaving a thin, smooth film.

To prepare plasticized EC films, dibutyl sebacate (DBS, Sigma Chemical, St. Louis, MO) or dibutyl phthalate (DBP, Sigma) was mixed for 12 h with the EC solution at 5, 10, or 20% (w/w) of the polymer. Films were then cast as described for the pure EC films. Pure EC films were annealed by heating at 130°C (T_g of EC $\approx 135^\circ\text{C}$) for 1 h and then cooled to room temperature. EC films plasticized by DBS and DBP were also annealed

at 75 and 100°C , respectively. Some pure EC films were not annealed to examine the effect of the treatment. The EC films were examined using a Hitachi Scanning Electron Microscope (Model S-4000 SEM, Hitachi, Tokyo, Japan; 5.0 kV) to assess surface uniformity and smoothness. The magnification employed ranged from 1000 to $5000 \times$. The surfaces of the EC films were observed to be very smooth, featureless and had no pores that could be visualized by SEM.

2.2. Contact angle measurements

The advancing contact angles of probe liquids on the ‘air-side’ of EC films were measured using a Rame-Hart Contact Angle Goniometer (Model 100-00, Mountain Lakes, NJ) equipped with an Image Analysis Attachment (IAA, Rame-Hart) and temperature controlled environmental chamber (Model 100-07, Rame-Hart). The system was verified with a standard angle (45°) plate (Swiss Precision Instruments, Los Angeles, CA). The IAA used a digital video camera in combination with a personal computer to scan an image of the drop and automatically calculated both the left and right contact angles and drop dimension parameters from the digitalized image. The probe liquids used were double distilled water, diiodomethane (Sigma), formamide (Sigma) and ethylene glycol (Sigma). Diiodomethane was chosen as an apolar liquid, which must be used with water and another polar liquid for the calculation of the surface free energy components of the unknown solids using the AB approach (Good, 1992).

The captive drop technique (Good and van Oss, 1992; Drelich et al., 1996) was employed for contact angle measurements and was validated using poly(methyl methacrylate) (PMMA) and water. All measurements were made at 20°C . A liquid drop was deposited and held captive on the surface through an assembly consisting of a micrometer syringe (2.0 ml, Gilmont Instrument, Chicago, IL), a stainless steel flat-tipped needle (0.45 mm diameter, Popper and Sons, New Hyde Park, NY) and teflon tubing (25 cm length). The needle was attached to a micro-manipulator which provided for precise movement for the

needle in three-dimensions. This assembly was devised to isolate the needle from vibrations that can occur during liquid addition and aid in the reproducible positioning of drops relative to the edge of the surface. The outer surface of the needle was coated with paraffin and the needle tip was always kept on the top of the liquid drop. The three-phase contact line of the drop was made to advance by slowly adding a small volume of liquid. The advancing angles were read every 5 s on both sides of the drop for 5 min. Drop size was regulated by the flow and kept consistent to minimize drop size effects. Evaporation of the drop was prevented by saturating the chamber with the vapor of the liquid being studied. Measurements were made on a total of ten drops on several replicate film samples to obtain a grand average.

Initial contact angles were also determined on some EC films using sessile drops for comparison to the advancing angles. With this technique, a liquid drop was placed on the substrate and the needle was not in contact with the drop. The contact angles were then measured as a function of time.

2.3. Data analysis

The surface free energy parameters of EC films were calculated using the advancing contact angle data of the probe liquids with Eq. (6). The surface free energy parameters for the four probe liquids used in this work are shown in Table 1 (Good and van Oss, 1992). The equations were solved according to Good (1992) using a numerical analysis and equation handling software program (SolverQ 1.25, Scientific Logics, Cupertino, CA)

Table 1
Surface free energy parameters (mJ/m²) of the liquids at 20°C used for contact angle determinations

Liquid	γ^{LW}	γ^+	γ^-	γ^{TOT}
Water	21.8	25.5	25.5	72.8
Diiodomethane	50.8	0.0	0.0	50.8
Formamide	39.0	2.28	39.6	58.0
Ethylene glycol	29.0	1.92	47.0	48.0

with a personal computer. γ^{LW} was first obtained using the diiodomethane data. Subsequently, the two simultaneous equations, defined explicitly in terms of γ^+ and γ^- , were solved using Newton's method. The AB components calculated from formamide or ethylene glycol in conjunction with water and diiodomethane were examined for consistency and subsequently averaged. The LW and AB surface free energy components of EC films were then used to calculate both the interfacial tension and the work of adhesion of the EC films to various solid surfaces of known surface energetics using Eqs. (7)–(11).

3. Results and discussion

3.1. Contact angles on EC films

The Young equation is theoretically based on rigorous assumptions: a solid must be smooth, homogeneous and rigid, the solid must not be perturbed by chemical interaction or by adsorption due to a liquid phase, and there should, thus, be a single, unique contact angle. It is, however, well known that chemical heterogeneity and surface roughness of practical solid surfaces results in contact angle hysteresis. The advancing contact angle on a smooth but heterogeneous solid surface has been regarded as a reasonable estimate of the equilibrium contact angle that would be observed on an ideal surface composed of the low energy surface component (Good, 1992; Grundke et al., 1996).

Ten sets of advancing contact angle data collected on several individual films were averaged and the mean angles were plotted against time. The S.D. of the mean angles for the majority of films was 1–3°. Variation in the contact angle over time was examined to assess changes in the properties of the EC films as a result of solvation or hydration. For all probe liquids measured on the EC films a small time dependence was observed. This type of behavior has been observed on other polymers (Johnson et al., 1986; Tous-saint and Luner, 1993; Drelich et al., 1996). A slight oscillation of the contact angle ($< \pm 1$) with a period of 30 s was also observed over 300

Table 2

Advancing contact angles of liquids at 20°C on ethylcellulose (EC) films prepared from solutions at varying concentrations (w/v%) in methylene chloride, surface free energy parameters, and effect of annealing

Sample surface	Contact angles (°) for liquids				Surface free energy parameters (mJ/m ²)					Polarity (%) ^a
	Water	DIM	FO	EG	γ^{LW}	γ^+	γ^-	γ^{AB}	γ^{TOT}	
0.5% EC (ann ^b)	– ^c	57.7	79.3	71.1	29.90	– ^c	– ^c	– ^c	– ^c	– ^c
1.0% EC (ann)	84.5	57.3	74.7	67.5	30.13	0.08	9.32	1.73	31.86	5.4
2.0% EC (ann)	84.5	62.0	75.5	66.7	27.42	0.04	8.61	1.17	28.59	4.1
2.0% EC (unann ^b)	87.0	62.4	79.3	70.3	27.19	0.12	9.03	2.08	29.27	7.1
5.0% EC (ann)	84.7	62.4	75.3	66.5	27.19	0.04	9.18	1.21	28.40	4.3
5.0% EC (Unann)	86.6	63.0	77.8	66.6	26.85	0.10	8.22	1.81	28.66	6.3
Cellulose ^d	30	41	5	–	39.1	2.0	39.7	17.6	56.7	31.8
Cellulose acetate ^d	55	43	42	–	38.2	0.21	28.2	4.9	43.1	11.4

^a Polarity (%) = $(\gamma^{\text{AB}}/\gamma^{\text{Total}}) \times 100$.

^b The films were annealed (ann) by heating at 130°C (T_g of EC \approx 135°C) for 1 h and then cooling to room temperature. Selected 2.0 and 5.0% EC films were not annealed (unann).

^c The advancing contact angle of water could not be determined because the drop was unstable on the 0.5% EC films. The acid–base parameters could also not be determined without the value of contact angle for water.

^d Toussaint and Luner, 1993.

s for formamide and ethylene glycol. However, this variation was within the S.D. and a consistent average value over time was achieved in 30–60 s. There were no visible changes in the film surface during measurement. On the basis of these observations, no macroscopic changes in the film bulk as a result of swelling or solvation by the liquids were evident. Contact angles in the 40–50 s region were stable and reproducible for all liquids and films studied. This time frame was also sufficient for stabilization of the drop following movement of the three-phase contact line after advancement. Therefore, the mean value at 45 s was selected as representative of the advancing angle for each liquid.

3.2. Surface free energy parameters of EC films

3.2.1. Effects of EC Concentration and Annealing

Table 2 shows the contact angle data and the calculated surface free energy parameters for EC films. The films were prepared from EC–methylene chloride solutions and were then annealed by heating at 130°C. EC has a lower surface free energy than cellulose and has low polarity (< 6%). The AB term (γ^{AB}) makes only a slight contribution to the total surface free energy

(γ^{TOT}) because the surface exhibits predominantly monopolar electron-donicity ($\gamma^- \gg \gamma^+ \approx 0$). These results are reasonable based on both the structure and composition of the polymer. The predominant monopolar Lewis base behavior is likely due to the intra- and intermolecular interaction between electron donating and accepting sites (Lewis neutralization) as well as the low hydroxyl content of the polymer. Because the degree of substitution of the EC (ethoxyl content of 46%) employed is \approx 2.4 (\sim 80% hydroxyl groups substituted), the EC has a low hydroxyl content. The large number of γ^- sites (the Lewis base oxygen atoms of ether groups) neutralize the few γ^+ sites (the hydroxyl groups) by hydrogen bonding (van Oss, 1997b). Additionally, the hydroxyls of EC would be oriented below the surface because of the Lewis neutralization (Good and van Oss, 1992). Cellulose itself is bipolar and its polarity is relatively high (Table 2). The γ^{AB} and γ^- values for EC are lower than those for cellulose acetate and this may be related to the different extent of substitution of hydroxyl groups by different substituent groups; for cellulose acetate only 39.5% of hydroxyl groups are substituted by acetyl groups (Toussaint and Luner, 1993).

The surface free energy decreased as the concentration of EC in methylene chloride was increased from 1 to 2% (w/v), which resulted mainly from the decrease in γ^{LW} and partly from the slight decreases in γ^+ and γ^- (Table 2, Fig. 1). As the concentration of EC was increased from 2 to 5%, there was almost no change in the total surface free energy and all of the surface free energy parameters remained almost constant. The surface free energy decrease upon increasing EC concentration (1–2%) may be associated with an increase in the bulk thickness of the film. At concentrations < 1% the glass surface may have an influence on the polymer during film formation, thus influencing the surface properties. This was also evidenced by the observation that stable water drops could not be obtained on 0.5% EC films. No difference in surface morphology was observed among the EC films with different EC concentration by the SEM study.

The surface free energy parameters determined for EC in this work are not consistent with those determined by Vera et al. (1996) ($\gamma^{LW} = 24.6$, $\gamma^+ = 0$, $\gamma^- = 19.6$) their value for γ^- is higher

than ours, while their value for γ^{LW} is lower than ours. The value of γ^+ obtained for EC in the present study is low but is not zero. This discrepancy might be due to differences in the preparation of the EC surface and the method of contact angle measurement. Vera et al. (1996) used the contact angles of sessile drops of liquids measured at 25°C on pellets obtained by compressing dry samples of EC products for the calculation of surface free energy components. There may be intrinsic differences in the EC surface between the compact made from dry powdered EC and the EC films cast from organic solution employed in this study. Their use of the contact angles of sessile drops for liquids instead of advancing contact angles used in this study may also contribute to the differences in the surface free energy parameters.

Stable water drops could not be consistently obtained on the 1% unannealed EC films (Fig. 2). Very early spreading of the water drop was frequently observed over these surfaces. The surface free energy of 2 and 5% EC films decreased slightly after annealing (Table 2). This was consis-

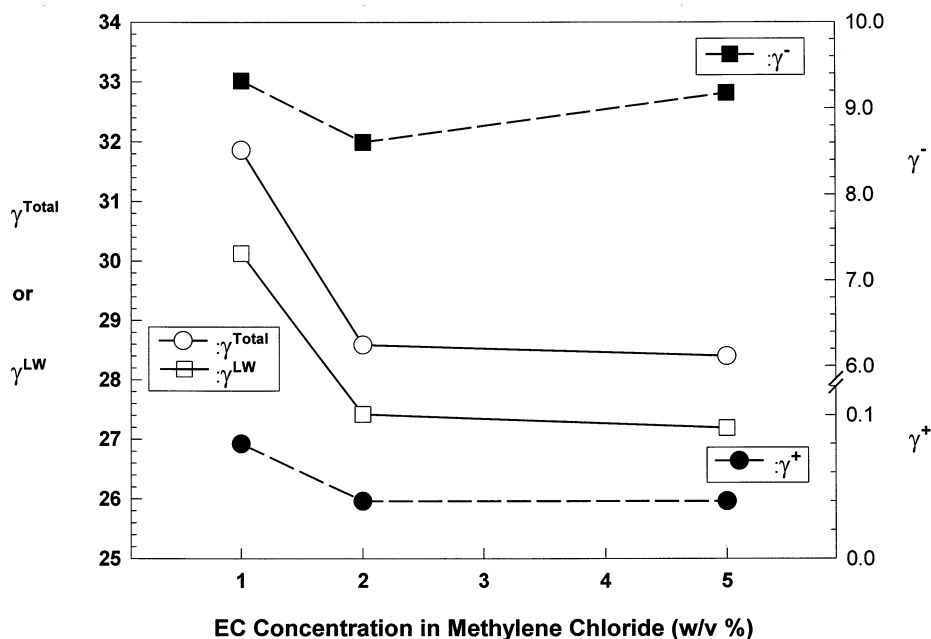
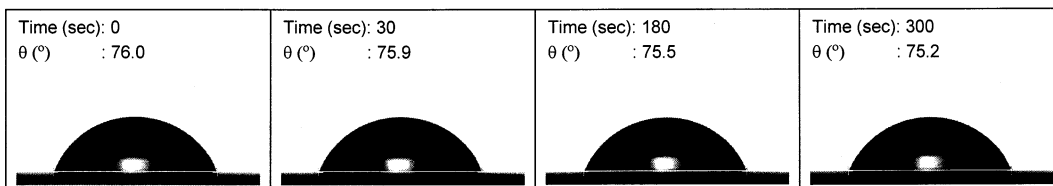
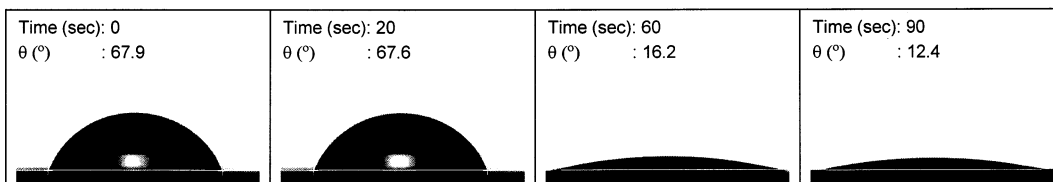


Fig. 1. Effect of ethylcellulose concentration on surface free energy parameters of EC films cast from methylene chloride solution.

A. Annealed Ethylcellulose Film Prepared from Methylene Chloride



B. Unannealed Ethylcellulose Film Prepared from Methylene Chloride



C. Unannealed Ethylcellulose Film Prepared from 7:3 Methanol-Methylene Chloride

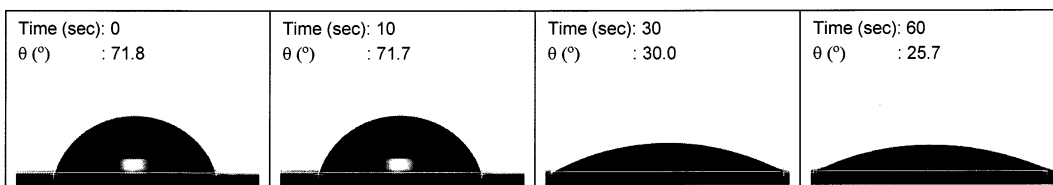


Fig. 2. Representative changes as a function of time in the initial contact angles of water sessile drops on EC films prepared from 1% solutions.

tent with the increase in the initial contact angle for water sessile drops on 1% films after annealing, increasing from 67.9 to 75.6°. These results suggest that annealing the EC films allowed reorientation of the polymer chains at the surface to achieve a lower energy state. It is possible that spreading of water drops on the unannealed EC films is a result of the presence of higher energy surface domains.

3.2.2. Effect of solvent

When EC is applied to dosage forms or tablets from organic solution, a binary solvent system is often used to optimize processing and final film coating formation. A common solvent system for controlled release oral drug delivery formulation consists of equal volumes of methylene chloride and methanol (Sakellariou and Rowe, 1995b). EC has been reported to swell slightly in alcohols, and alcohols have also been shown to reduce the

viscosity of EC solution in methylene chloride indicating coiling of the polymer chains. The two solvents generally show different capability of hydrogen bonding; methylene chloride forms weak hydrogen bonds while methanol is capable of strong hydrogen bonding (Kent and Rowe, 1978). Therefore, it was of interest to examine the effect of addition of methanol to the EC solution in methylene chloride on the surface energetics of EC. The surface free energy of EC decreased slightly as the amount of methanol added to the solvent mixture was increased (Table 3, Fig. 3). This change was mainly due to the decrease of γ^{LW} . Neither a significant change in γ^{AB} nor a consistent change in γ^+ was observed. The change in γ^{LW} may be associated with the difference in capability of hydrogen bonding of the two solvents as well as the slight swelling of EC in methanol. These factors could influence the orientation of polymer chains at the surface during film

formation. The presence of the methanol as an external Lewis base may disrupt some of the Lewis acid-base neutralization occurring on the EC chains leading to a different molecular surface configuration. This is consistent with the observation that γ^- and γ^+ increased slightly at 50:50 v/v methylene chloride–methanol, the ratio at which the solvent–solvent interaction is least (Sakellariou and Rowe, 1995a). Rosilio and coworkers (Rosilio et al., 1988, 1998) observed variation in water contact angle on EC films prepared from chloroform and ethanol. Additionally, factors such as the influence of the glass surface on the polymer, degree of interaction of the solvents with

the glass surface and the annealing process, may have contributed to attenuating the effect of solvent on surface free energy.

3.3. Surface free energy parameters of plasticized EC films

EC has a high glass transition temperature and does not form flexible films under normal coating conditions. Therefore, a plasticizer needs to be incorporated before application (Iyer et al., 1990). EC–plasticizer interactions have been studied by measuring the mechanical properties of EC films (Sakellariou et al., 1986; Guo et al., 1993; Bod-

Table 3

Advancing contact angles of liquids at 20°C and surface free energy parameters of ethylcellulose (EC) films made from 1% EC solutions in methylene chloride–methanol mixtures with varying concentrations of methanol (v/v%)

Solvent system % (v/v)	Contact angles (°) for liquids				Surface free energy parameters (mJ/m ²)					Polarity (%)
	Water	DIM	FO	EG	γ^{LW}	γ^+	γ^-	γ^{AB}	γ^{TOT}	
100 CH ₂ Cl ₂	84.5	57.3	74.7	67.5	30.13	0.08	9.32	1.73	31.86	5.4
50:50 MeOH–CH ₂ Cl ₂	83.5	59.6	76.3	68.5	28.81	0.12	11.14	2.31	31.12	7.4
70:30 MeOH–CH ₂ Cl ₂	86.2	59.8	75.7	64.9	28.69	0.08	7.59	1.56	30.25	5.2

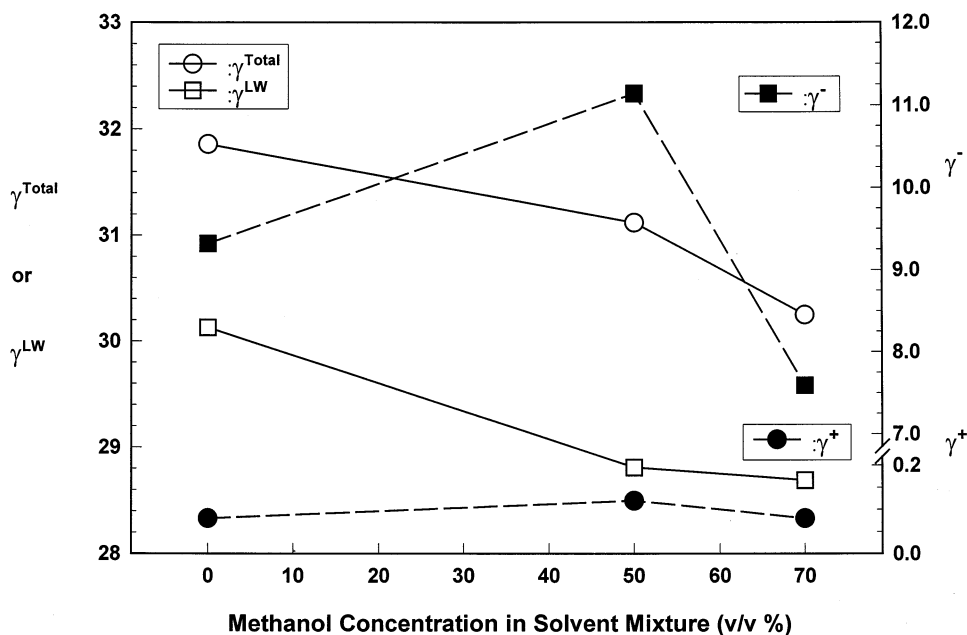


Fig. 3. Effect of solvent composition (methanol–methylene chloride) on the surface free energy parameters of EC films prepared from 1% solutions.

Table 4

Advancing contact angles of liquids at 20°C surface free energy parameters for 1% ethylcellulose (EC) films plasticized with dibutyl sebacate (DBS) and dibutyl phthalate (DBP)^a

Plasticizer used (w/w% of EC)	Contact angles (°) for liquids				Surface free energy parameters (mJ/m ²)					Polarity (%)
	Water	DIM	FO	EG	γ^{LW}	γ^+	γ^-	γ^{AB}	γ^{TOT}	
5% DBS	86.3	58.8	72.6	69.6	29.27	0.004	7.45	0.35	29.62	5.4
10% DBS	88.9	65.5	78.1	68.7	25.42	0.06	6.68	1.27	26.69	4.8
20% DBS	94.2	60.5	73.8	70.7	28.29	0.04	2.43	0.62	28.91	2.1
5% DBP	90.6	59.6	76.4	69.9	28.81	0.03	4.97	0.77	29.58	2.6
10% DBP	89.5	58.3	76.9	65.9	29.55	0.10	5.36	1.47	31.02	4.7
20% DBP	94.3	59.2	–	69.6	29.04	0.03	2.25	0.52	29.56	1.8

^a Methylene chloride was used as solvent.

meier and Paeratakul, 1994; Obara and McGinity, 1995; Hyppola et al., 1996). Recently, Lovrecich and Rubessa (1998) reported that the surface free energy of films made from blends of Eudragit RS were sensitive to the percentage of plasticizer. There has been no report on the effect of plasticizers on the surface free energy of EC films. The type and amount of the plasticizer used with EC is important with respect to plasticizing efficiency. Dibutyl sebacate (DBS) and dibutyl phthalate (DBP) have been evaluated as the most efficient plasticizers for EC films cast from organic solutions (Rowe et al., 1984; Hyppola et al., 1996). These two plasticizers were incorporated into EC films in concentrations varying from 5 to 20% by weight of EC. There were no observations that indicated leaching of the plasticizers from the polymer matrix by the probe liquids; e.g. no erratic changes or significant irreproducibility in contact angle.

The surface free energy parameters determined for 1% EC films plasticized with DBS and DBP (Table 4) were plotted versus the concentration of DBS and DBP (Figs. 4 and 5). The addition of DBS or DBP resulted in a small decrease of the total surface free energy and each of the parameters. In particular, the basic parameter decreased continually as the concentration of plasticizer (DBS or DBP) was increased. Both the structure and composition of the surface of the films may be influenced by the presence of the plasticizer. First, it is believed that these changes

in surface free energy are a consequence of the polymer–plasticizer interactions. Both DBS and DBP are capable of moderate hydrogen bonding based on their solubility parameters (Sakellariou and Rowe, 1995a). Interaction of the plasticizer with the polymer reduces polymer–polymer interactions and allows for greater polymer chain mobility that results in a slightly altered surface configuration. Second, it is also possible that some plasticizer molecules are present at the surface of polymer film. However, for DBP, the plasticizer is not dominating the surface properties because the surface free energy of the film is less than that of the plasticizer (33.2 mJ/m²) (Panzer, 1973).

DBS had a slightly greater influence on the surface free energy parameters than did DBP (Table 4). This observation may be attributed to the difference in plasticizer structure. DBS has a molecular structure more favorable for interacting with EC polymer chains than does DBP because of its linear structure while DBP is an aromatic ester. For the DBS–plasticized EC films, the total surface free energy and the apolar (LW) component initially decreased, but then increased at higher plasticizer concentrations (Fig. 4). This trend in the surface free energy of the films containing both plasticizers may be associated with addition of a critical amount of plasticizer, beyond which it begins to accumulate at the surface. Films plasticized with 10% DBS had the lowest surface free energy.

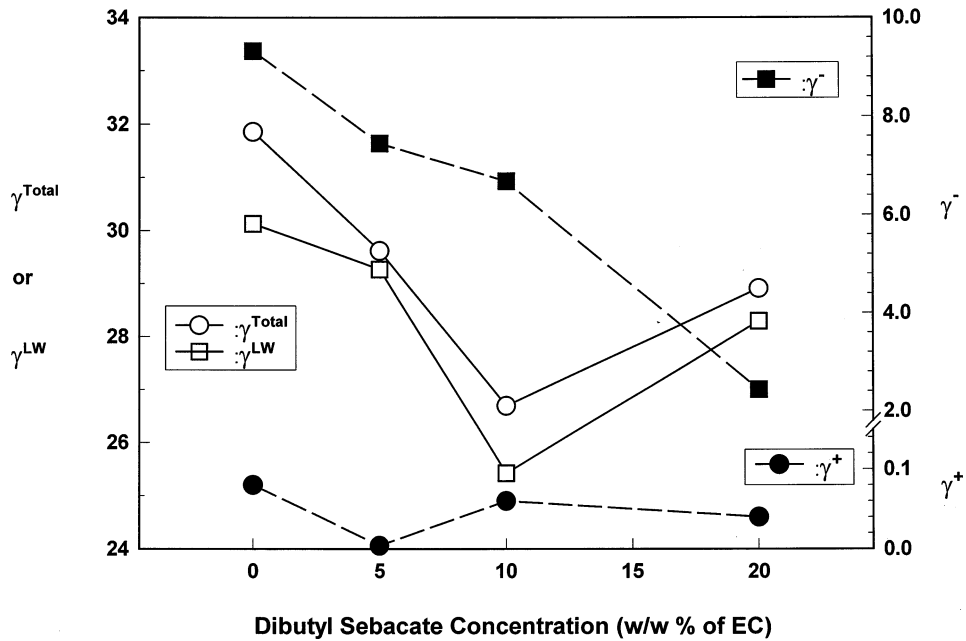


Fig. 4. Effect of dibutyl sebacate on surface free energy parameters of EC films prepared from 1% methylene chloride solution.

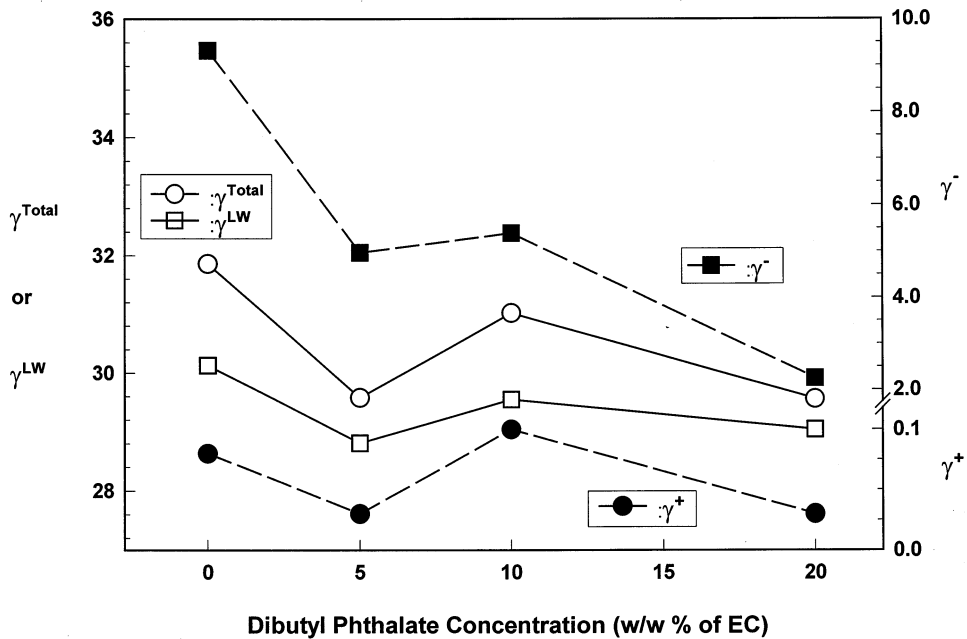


Fig. 5. Effect of dibutyl phthalate on surface free energy parameters of EC films prepared from 1% methylene chloride solution.

Table 5
Surface free energy parameters (mJ/m²) of substrates used for calculations in Tables 6 and 7

Substrate	γ^{LW}	γ^+	γ^-	γ^{AB}	γ^{TOT}
Cellulose ^a	39.10	2.00	39.70	17.60	57.70
Poly(methyl methacrylate) ^b	40.00	0.00	14.60	0.00	40.00
Polyethylene ^b	33.20	0.00	0.00	0.00	33.20
Nitrofurantoin ^c	43.80	0.38	23.20	5.94	49.74
CI-976 ^c	48.78	0.78	11.99	6.12	54.90

^a Toussaint and Luner, 1993.

^b van Oss, 1995.

^c Luner et al., 1996.

3.4. Work of adhesion between EC films and various substrates

The work of adhesion and interfacial energy between the EC films and several substrates approximating the surface free energy of solid dosage forms were calculated using the data obtained for EC films. The solid substrates analyzed with EC films were cellulose, poly(methyl methacrylate) (PMMA), polyethylene (PE), nitrofurantoin (NFT) and CI-976; their surface free energy parameters were obtained from the literature (Table 5). The three polymers and two drugs serve as models for the surfaces of tablets and granules. Cellulose is hydrophilic and higher in surface free energy relative to the other substrates. The PMMA and PE were selected as substrates having hydrophobic and low-energy surfaces. PMMA has a Lewis base 'monopolar' surface, while PE has a 'non-polar' surface. The two drugs have 'bipolar' surfaces.

Since polymer film adhesion to a substrate includes intrinsic bonding between the chemical groups of the polymer and substrate, work of adhesion is an indicator of adhesive bonding. Because EC has a hydrophobic, relatively low energy surface with dominant monopolar basic character, the LW interactions provided the major contribution to the work of adhesion for EC films with all of the solid substrates examined (Table 6). The contribution of the AB interactions to the work of adhesion was significant for the 'bipolar' substrates (cellulose and two drugs), but was not significant for a 'monopolar' substrate (PMMA) and absent for a 'non-polar' substrate (PE). Nevertheless, EC films had high values of work of

adhesion for all the substrates analyzed. The dominant monopolar basic character of EC, does not contribute to its total surface free energy or its work of cohesion, but improves its work of adhesion to substrates (Buckton and Chandraia, 1993). As shown in Eq. (7), W_A will be higher as the interfacial energy (γ_{12}) between each pair is lowered or as the surface energies (γ_1 and γ_2) of two materials are increased. The γ_{12} between EC-cellulose was ~ 3 times greater than that between EC and the drug compounds, because the AB surface free energy parameters of cellulose are higher than those of the drugs. However, the values of the W_A are comparable between EC-drug and between EC-cellulose, because the surface energies of the two drugs are lower than that of cellulose. The γ_{12} between EC and PMMA was very low, but the W_A was not high because PMMA has relatively a low surface free energy. The same argument is applicable to the results for PE.

The film forming variables and plasticizers considered in the present study had no significant influence on the work of adhesion for EC with all the substrates (Table 6). Their common effect on was a small decrease in total surface free energy. The changes in the surface free energy parameters of EC, discussed in the previous sections, were reflected in the work of adhesion for EC films. Particularly, the addition of 10% DBS to EC was observed to decrease both the total W_A and W_A^{AB} . There were small decreases in the contribution of the AB interactions to the W_A upon annealing because the annealing treatment affected the AB parameters. The use of the binary solvent system (MeOH:CH₂Cl₂) resulted in a slight decrease in the

W_A . This result is in good agreement with the effect of coating solvent on film adhesion observed by Nadkarni et al. (1975). They found that a solvent having a solubility parameter close to that of the polymer produced stronger film adhesion to tablet substrates than a solvent having a significantly different solubility parameter. The values of the solubility parameters for EC and methylene chloride are almost equivalent while methanol has a higher solubility parameter than EC (Kent and Rowe, 1978; Doelker, 1993).

In summary, the work of adhesion calculations using the LW/AB method give an indication of the extent that AB interactions contribute to the ideal work of adhesion. The practical implication of these results is that when adhesion of film coatings may be problematic because of substance properties, formulations can be adjusted with excipients designed to maximize adhesion by reinforcing AB interactions.

3.5. Spreading coefficients for EC Films over substrates

The extent of film adhesion to substrate is dependent upon the area of contact at the film-substrate interface as well as the intrinsic adhesive bonding (Aulton, 1995). Adequate spreading of the film material over the substrate is necessary for good film adhesion. The spreading coefficient for the film over the substrate, which can be calculated from the surface free energy parameters, can be another indicator of film adhesion. Rowe (1989) used both the spreading coefficient and the work of adhesion terms to study binder-substrate interactions in granulations. The interactions between adhesives and bottles have been modeled in these terms using surface free energy parameters by Buckton and Chandraia (1993). These authors pointed out that the magnitude of the work of adhesion is not the only critical factor in determining adhesive efficiency. A positive

Table 6

Works of adhesion (mJ/m^2) determined between EC films and various substrates (W_A), and the contribution of acid-base interactions to the work of adhesion (W_A^{AB})^a

EC Films		Cellulose	PMMA	PE	NFT	CI-976
1% EC	W_A	80.9	71.6	63.3	79.1	84.0
	W_A^{AB}	12.2	2.2	0.0	6.5	7.4
	% W_A^{AB}	15.1	3.0	0.0	8.2	8.7
2% EC	W_A	76.3	67.8	60.3	74.9	79.7
	W_A^{AB}	10.8	1.5	0.0	5.5	6.6
	% W_A^{AB}	14.2	2.3	0.0	7.4	8.2
2% Unannealed EC	W_A	78.1	68.6	60.1	76.1	80.5
	W_A^{AB}	12.9	2.7	0.0	7.0	7.7
	% W_A^{AB}	16.5	3.9	0.0	9.3	9.6
1% EC (in 70:30% MeOH-CH ₂ Cl ₂)	W_A	78.3	69.9	61.7	77.0	81.6
	W_A^{AB}	11.4	2.2	0.0	6.1	6.8
	% W_A^{AB}	14.5	3.1	0.0	7.9	8.4
1% EC+10% DBS	W_A	73.5	65.7	58.1	72.3	76.7
	W_A^{AB}	10.4	1.9	0.0	5.6	6.3
	% W_A^{AB}	14.2	2.9	0.0	7.7	8.2
1% EC+10% DBP	W_A	79.0	71.2	62.6	77.9	82.2
	W_A^{AB}	11.0	2.4	0.0	5.9	6.3
	% W_A^{AB}	13.9	3.4	0.0	7.6	7.7

^a Cast from methylene chloride unless otherwise specified.

^b % $W_A^{\text{AB}} = (W_A^{\text{AB}}/W_A) \times 100$.

Table 7
Interfacial tensions (γ_{12}), works of adhesion (W_A) and spreading coefficients (S) for EC films over substrates^a

1% EC (in 70:30% MeOH-Substrate or EC film)	γ_{12}	82.88 W_A	22.00 S
<i>A. 1% EC film-substrates</i>			
Cellulose	7.93	80.85	17.13
PMMA	0.26	71.59	7.89
PE	1.80	63.26	-0.45
NFT	2.45	79.14	15.42
CI-976	2.73	84.03	20.13
<i>B. EC films-cellulose</i>			
1% EC	7.93	80.85	17.13
2% EC	9.21	76.31	19.13
2% Unannealed EC	8.12	78.08	19.54
1% EC (in 70:30% MeOH-CH ₂ Cl ₂)	8.83	78.34	17.84
1% EC+10% DBS	10.16	73.45	20.07
1% EC+10% DBP	10.11	78.95	16.91
<i>C. EC films-CI-976</i>			
1% EC	2.73	84.03	20.31
2% EC	3.78	79.71	22.53
2% Unannealed EC	3.62	80.54	22.00
1% EC (in 70:30% MeOH-CH ₂ Cl ₂)	3.50	81.64	21.14
1% EC+10% DBS	4.89	76.69	23.31
1% EC+10% DBP	3.69	82.22	20.18

^a Cast from methylene chloride unless otherwise specified (all values in mJ/m²).

spreading coefficient indicates that spreading of the film over the substrate is energetically favorable and an adhering film is consequently formed around the substrate (Rowe, 1989; Buckton and Chandraia, 1993). Likewise, the higher spreading coefficient, the more energetically favorable spreading of the film on the substrate becomes and the stronger the film adheres. When the surface free energy parameters of polymer films and solid substrates are available, therefore, it is possible to consider the impact of both the spreading coefficient and the work of adhesion on theoretical film-substrate adhesion.

The interfacial tensions (γ_{12}), works of adhesion (W_A), and spreading coefficients (S) for 1% EC film-substrates are shown in Table 7A. The spreading coefficients of the EC film over all the substrates examined were positive except for PE.

The relative order in S values for the EC-substrate systems was the same as the order in W_A . Like the values in W_A , the values of S for EC over the substrates with higher surface free energy were found to be higher. It would be expected that EC films would have a very good adhesion to the 'bipolar', high surface free energy substrates (cellulose and two drugs). These substrates had significant AB interactions with EC and the values of the spreading coefficients for EC over the substrates were high. Since PMMA is a γ^- monopole, the S of EC was relatively low. For PE, the S value was negative, which was expected from the fact that PE has a 'non-polar', low energy surface. This result indicates that theoretically EC would not spread over PE surface and, consequently, there will be no adhering film on PE. Because there is intrinsic adhesive bonding between the EC-PE as determined by W_A , the initial wetting of a EC coating solution would have to be increased to enhance the spreading of EC over PE surface by using an appropriate surfactant or solvent. The change in surface free energy parameters due to the effects of film forming variables and plasticizers did not significantly influence the spreading of EC films over substrates (Table 7B and C). Upon addition of 10% DBS, however, a small increase in the spreading coefficient was observed.

4. Conclusions

We have determined the surface free energy parameters for EC, an important pharmaceutical material using the LW/AB method. These data are of theoretical and practical significance. The values obtained in this work were consistent with those of other cellulose polymers. EC is lower in total surface free energy than cellulose and the relative change in the surface free energy parameters can be rationalized in terms of the polymer chemical structure. Two commonly used plasticizers, DBS and DBP, did not greatly influence the surface free energy of the films because their surface free energy was already low, but they did lower the Lewis electron donor parameter. Analysis of work of adhesion and spreading coefficient

and the relative contribution of AB interactions to these terms shows that AB interactions can contribute significantly to the adhesion of EC to other substrates.

At this point, the question arises as to how surface free energy parameters and calculated adhesion terms are related to the adhesive strengths in practical coating systems. Although the magnitudes of the work of adhesion and the spreading coefficient cannot represent the film adhesion directly, the data obtained in this work can be used to predict or model the extent of adhesion of EC to specific substrates. The consideration of work of adhesion and spreading coefficient based on the LW and AB components of surface free energy may have potential use in evaluating factors affecting film adhesion and, furthermore, in optimizing pharmaceutical film coating processes. The influence of AB interaction on practical film adhesion to substrates has been documented in other polymer systems (Berg, 1993; Kaczinski and Dwight, 1993). Experiments focused on the measurement of adhesive strength of EC films to substrates are needed to relate the surface free energy parameters to practical adhesion measurements.

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References

- Aulton, M.E., 1995. Surface effects in film coating. In: Cole, G., Hogan, J., Aulton, M.E. (Eds.), *Pharmaceutical Coating Technology*. Taylor and Francis, Bristol, PA, pp. 118–151.
- Barra, J., Lescure, F., Falson-Rieg, F., Doelker, E., 1998. Can the organization of a binary mix be predicted from the surface energy, cohesion parameter and particle size of its components. *Pharm. Res.* 15, 1727–1736.
- Berg, J.C., 1993. The importance of acid–base interactions in wetting, coating, adhesion and related phenomena. *Nord. Pulp Pap. Res. J.* 8, 75–85.
- Bianchini, R., Resciniti, M., Vecchio, C., 1989. Aqueous-based enteric film coatings containing insoluble additives. *Congr. Int. Technol. Pharm.* 1, 416–425.
- Bodmeier, R., Paeratakul, O., 1994. Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms. *Pharm. Res.* 11, 882–888.
- Buckton, G., Chandraia, B., 1993. Consideration of adhesion to modified container walls, by use of surface energy and polarity data, and Lewis acid–Lewis base interactions. *Int. J. Pharm.* 94, 223–229.
- Cedrat, N., Bonneaux, F., Labrude, P., Maincent, P., 1997. Structure and stability of human hemoglobin microparticles prepared with a double emulsion technique. *Artif. Cells Blood Substit. Immobil. Biotechnol.* 25, 457–462.
- Chibowski, E., Bolivar, M., Gonzalez-Caballero, F., 1992. Studies on the surface free energy components of nitrofurantoin. *J. Colloid Interf. Sci.* 154, 400–410.
- Doelker, E., 1993. Cellulose derivatives. *Adv. Poly. Sci.* 107, 199–265.
- Drelich, J., Miller, J.D., Good, R.J., 1996. The effect of drop (bubble) size on advancing and receding contact angles for heterogeneous and rough solid surfaces as observed with sessile-drop and captive-bubble techniques. *J. Colloid Interf. Sci.* 179, 37–50.
- Fowkes, F.M., 1964. Attractive forces at interfaces. *Ind. Chem. Eng.* 56, 40–52.
- Fowkes, F.M., Riddle, F.L., Pastore, E.E., Weber, A.A., 1990. Interfacial interactions between self-associated polar liquids and squalene used to test equations for solid-liquid interfacial interactions. *Colloid Surf.* 43, 367–387.
- Good, R.J., 1992. Contact angle, wetting and adhesion: a critical review. *J. Adhes. Sci. Technol.* 6, 1269–1302.
- Good, R.J., van Oss, C.J., 1992. The modern theory of contact angles and the hydrogen bond components of surface energies. In: Schrader, M.E., Loeb, G.I. (Eds.), *Modern Approaches to Wettability*. Plenum, New York, pp. 1–27.
- Grundke, K., Bogumil, T., Werner, C., Janke, A., Doschel, K., Jacobasch, H.J., 1996. Liquid–fluid contact angle measurements on hydrophilic cellulosic materials. *Colloid Surf. A* 116, 79–91.
- Guo, J.H., Robertson, R.E., Amidon, G.L., 1993. An investigation into the mechanical and transport properties of aqueous latex films: a new hypothesis for the film-forming mechanism of aqueous dispersion system. *Pharm. Res.* 10, 405–410.
- Holysz, L., Chibowski, E., 1992. Surface free energy components and flotability of barite precovered with sodium dodecyl sulfate. *Langmuir* 8, 303–308.
- Hypola, R., Husson, I., Sundholm, F., 1996. Evaluation of physical properties of plasticized ethyl cellulose films cast from ethanol solution Part I. *Int. J. Pharm.* 133, 161–170.

- Iyer, U., Hong, W., Das, N., Ghebre-Sellassie, I., 1990. Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. *Pharm. Tech.* 14 (9), 68–86.
- Janczuk, B., Kerkeb, M.L., Bialopiotrowicz, T., Gonzalez-Caballero, F., 1992. Surface free energy of cholesterol and bile salts from contact angles. *J. Colloid Interf. Sci.* 151, 333–341.
- Johnson, B.A., Kreuter, J., Zografi, G., 1986. Effects of surfactants and polymers on advancing and receding contact angles. *Colloid Surf.* 17, 325–342.
- Johnson, B.A., Zografi, G., 1986. Adhesion of hydroxypropyl cellulose films to low energy solid substrates. *J. Pharm. Sci.* 75, 529–533.
- Kaczinski, M.B., Dwight, D.W., 1993. Enhancement of polymer film adhesion using acid–base interactions determined by contact angle measurements. In: Mittal, K.L. (Ed.), *Contact Angle, Wettability and Adhesion*. VSP, Utrecht, The Netherlands, pp. 739–751.
- Kent, D.J., Rowe, R.C., 1978. Solubility studies on ethyl cellulose used in film coating. *J. Pharm. Pharmacol.* 30, 808–810.
- Lloyd, T.B., Ferretti, K.E., Lagow, J., 1995. A new approach to chemical characterization of polymer surface. *J. Appl. Polym. Sci.* 58, 291–296.
- Lovrecich, M., Rubessa, F., 1998. Morphology and surface properties of blends of Eudragit RS with different poly(ethylene glycols). *Pharm. Dev. Technol.* 3, 123–129.
- Luner, P.E., Babu, S.R., Mehta, S.C., 1996. Wettability of a hydrophobic drug by surfactant solutions. *Int. J. Pharm.* 128, 29–44.
- Nadkarni, P.D., Kildsig, D.O., Kramer, P.A., Banker, G.S., 1975. Effect of surface roughness and coating solvent on film adhesion to tablets. *J. Pharm. Sci.* 64, 1554–1557.
- Obara, S., McGinity, J.W., 1995. Influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique. *Int. J. Pharm.* 126, 1–10.
- Palomo, M.E., Ballesteros, M.P., Frutos, P., 1996. Solvent and plasticizer influences on ethylcellulose-microcapsules. *J. Microencapsulation* 13, 307–318.
- Panzer, J., 1973. Components of solid surface free energy from wetting measurements. *J. Colloid Interf. Sci.* 44, 142–161.
- Rillosi, M., Buckton, G., 1995a. Modeling mucoadhesion by use of surface energy terms obtained from the Lewis acid–base approach. *Int. J. Pharm.* 117, 75–84.
- Rillosi, M., Buckton, G., 1995b. Modeling mucoadhesion by use of surface energy terms obtained from the Lewis acid–base approach. II. Studies on anionic, cationic, and unionisable polymers. *Pharm. Res.* 12, 669–675.
- Rosilio, V., Roblot-Treupel, L., Costa, M.L., Baszkin, A., 1988. Physico–chemical characterization of ethylcellulose drug-loaded cast films. *J. Control Release* 7, 171–180.
- Rosilio, V., Costa, M.L., Baszkin, A., 1998. Wettability of drug loaded polymer matrices. *J. Dispersion Sci. Technol.* 19, 821–841.
- Rowe, R.C., 1977. The adhesion of film coatings to tablet surfaces—the effect of some direct compression excipients and lubricants. *J. Pharm. Pharmacol.* 29, 723–726.
- Rowe, R.C., 1981. The adhesion of film coatings to tablet surfaces — a problem of stress distribution. *J. Pharm. Pharmacol.* 33, 610–612.
- Rowe, R.C., 1988. The adhesion of film coatings to tablet surfaces — a theoretical approach based on solubility parameters. *Int. J. Pharm.* 41, 219–222.
- Rowe, R.C., 1989. Binder–substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. *Int. J. Pharm.* 52, 149–154.
- Rowe, R.C., Kotaras, A.D., White, E.F.T., 1984. An evaluation of the plasticizing efficiency of the dialkyl phthalates in ethyl cellulose films using the torsional braid pendulum. *Int. J. Pharm.* 22, 57–62.
- Sakellariou, P., Rowe, R.C., 1995a. Interactions in cellulose derivative films for oral drug delivery. *Prog. Polym. Sci.* 20, 889–942.
- Sakellariou, P., Rowe, R.C., 1995b. The morphology of blends of ethylcellulose with hydroxypropyl methylcellulose as used in film coating. *Int. J. Pharm.* 125, 289–296.
- Sakellariou, P., Rowe, R.C., White, E.F.T., 1986. An evaluation of the interaction and plasticizing efficiency of the polyethylene glycols in ethyl cellulose and hydroxypropyl methylcellulose films using the torsional braid pendulum. *Int. J. Pharm.* 31, 55–64.
- Sheridan, P.L., Buckton, G., Strong, D.E., 1995. Development of a flow microcalorimetry method for the assessment of surface properties of powders. *Pharm. Res.* 12, 1025–1030.
- Toussaint, A.F., Luner, P., 1993. The wetting properties of grafted cellulose films. *J. Adhes. Sci. Technol.* 7, 635–648.
- van Oss, C.J., 1995. Hydrophobicity of biosurfaces — origin, quantitative determination and interaction energies. *Colloid Surf. B.* 5, 91–110.
- van Oss, C.J., 1997a. Hydrophobicity and hydrophilicity of biosurfaces. *Curr. Opin. Colloid Interf. Sci.* 2, 503–512.
- van Oss, C.J., 1997b. On the predominant electron-donicity of polar solid surfaces. *J. Adhesion* 5, 71–88.
- van Oss, C.J., Chaudhury, M.K., Good, R.J., 1988a. Interfacial Lifshitz–van der Waals and polar interactions in macroscopic systems. *Chem. Rev.* 88, 927–941.
- van Oss, C.J., Good, R.J., Chaudhury, M.K., 1988b. Additive and nonadditive surface tension components and the interpretation of contact angles. *Langmuir* 4, 884–891.
- Vera, P., Gallardo, V., Salcedo, C., Delgado, A.V., 1996. Colloidal stability of a pharmaceutical latex: experimental determinations and theoretical predictions. *J. Colloid Interf. Sci.* 177, 553–560.
- Wade, A., Weller, P.J., 1994. *Handbook of Pharmaceutical Excipients*, second ed. American Pharmaceutical Association, Washington, pp. 186–190.

- Wu, S., 1971. Calculation of interfacial tension in polymer systems. *J. Polymer Sci.: Part C* 34, 19–30.
- Wu, S., Giese, R.F., van Oss, C.J., 1995. Evaluation of the Lifshitz–van der Waals/acid–base approach to determine surface tension components. *Langmuir* 11, 379–382.
- Zinutti, C., Barberheyob, M., Hoffman, M., Maincent, P., 1998. In-vivo evaluation of sustained release of microspheres of 5-Fu in rabbits. *Int. J. Pharm.* 166, 231–234.
- Zografi, G., Tam, S.S., 1976. Wettability of pharmaceutical solids: estimates of solid surface polarity. *J. Pharm. Sci.* 65, 1145–1149.