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Wettability of a hydrophobic drug by surfactant solutions

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Abstract

CI-976 (2,2-dimethyl-*N*-[2,4,6-trimethoxyphenyl] dodecanamide) was used as a model compound to study the interaction of surfactant solutions with a drug surface because of its high degree of hydrophobicity and low solubility. The advancing contact angles of sessile drops of commonly used surfactant solutions at various concentrations were measured on compressed disks of CI-976 using a contact angle goniometer. In addition, the surface tension of the solutions was measured at 25°C. At surface tensions near 40 mN/m, contact angles ranged from 16° to 65°. Adhesion tension plots for sodium lauryl sulfate and Triton X-100R initially showed near zero slopes at higher surface tensions, then became positive at about 40 mN/m. Tween 80 had a near zero slope over the whole concentration range tested. Calculations of surface energy parameters from contact angles of organic liquids using either two liquids or three liquids show that CI-976 is a low energy solid with surface characteristics similar to that of polymethylmethacrylate. Interaction energies calculated between surfactants and CI-976 correlate with the observed wetting data for the solutions. Dissolution testing of CI-976 powder in gelatin capsules in selected solutions showed large variation in amount dissolved versus time, independent of solubility and in good correlation with contact angle data. The results confirm the importance of wetting in selecting a surfactant for use in dissolution media and demonstrate the utility of contact angle measurements in analyzing wetting of drug substances.

Keywords: Contact angle; Surfactants; Solid surface energy; Dissolution media; Adhesion tension; Surface tension

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1. Introduction

Dissolution testing is an integral part of developing solid dosage forms. However, developing dissolution methods for poorly water soluble drugs can be problematic and surfactants are often required to improve solubility and dissolution rate. Although surfactants can influence drug dissolution in several ways (Schott et al., 1982), wetting is an important mechanism by which surfactants can mediate dissolution independent of solubility (Weintraub and Gibaldi, 1969; Efentakis and Fell, 1981; Bakatselou et al., 1991). Ideally, one desires a surfactant that provides the best combination of solubility, wetting, minimum assay interference and cost-effectiveness that can achieve a suitable and reproducible dissolution profile. A variety of surfactants are available for

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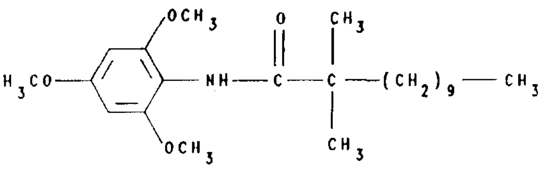

Fig. 1. Chemical structure of CI-976.

use as dissolution media (Shah et al., 1989) but wetting effects are often difficult and tedious to evaluate through dissolution testing because of the many variables associated with dissolution of solid dosage forms, such as drug particle size, surfactant concentration, excipient effects and surface area (Itai et al., 1985). An independent knowledge of the wetting properties of a surfactant for a drug may be useful in selecting surfactant based dissolution media.

Pyter et al. (1982) examined the wetting of different types of surfactants on several low energy polymer surfaces and observed considerable differences in wetting among surfactants at equivalent surface tensions. It is likely that different surfactants may display variation in wetting drug surfaces because the surface energies and polarities of drug surfaces are similar to that of semi-polar polymer surfaces (Zografi and Tam, 1976). In addition, surfactants used in pharmaceutical products and in dissolution testing have a wide range of chemical structures and physical properties that may influence their interaction with solids. It is also observed that for semi-polar surfaces, surfactant solutions can produce higher contact angles than those produced by pure liquids at the same surface tension (Burnett and Zisman, 1959). Thus, the objectives of this study were to evaluate the wettability of a hydrophobic drug by a variety of surfactants and gain an understanding of how commonly used surfactants interact with a drug surface.

CI-976 (see Fig. 1), an oral ACAT inhibitor indicated for hyperlipidemia, was used as a model drug in these studies based on its physical properties. CI-976 has less than 1 μg/ml solubility in water, an octanol/water Log P of 5.23, is non-hygroscopic, non-ionizable and is a waxy solid with a low melting point (60°C). Wetting of the surfactant solutions was evaluated by contact angle determination on compressed disks of CI-976. In addition, the contact angles of some organic liquids were also measured and these data were used to calculate surface energy parameters to gain insight into the nature of the drug surface. Finally, dissolution testing of CI-976 bulk drug capsules was performed in selected surfactant solutions to observe the extent to which differences in wetting of the drug surface are manifest in dissolution behavior.

2. Materials and methods

2.1. Chemicals

All surfactants were obtained from Sigma (St. Louis, MO) and used without further purification. The chemical names of the surfactants and their abbreviations are listed in Table 1. Triple distilled water or Purified Water USP was used and their surface tensions were 72.6 mN/m (at 22°C) and 71.8 mN/m (at 25°C), respectively, in agreement with literature values. Surfactant solutions were prepared by % w/v directly or by subsequent serial dilution. All organic liquids used were from Sigma and used without further purification. A single lot of CI-976 manufactured by Parke-Davis Pharmaceutical Research (Holland, MI) was used. The material was crystalline and had a particle size distribution (% mass retained) of 1% at 150 μm, 3% at 90 μm, 5% at 63 μm, 15% at 45 μm, and 19% at 32 μm, based on Alpine Sieve analysis.

2.2. Surface tension

The surface tensions of the surfactant solutions was measured at 25 ± 0.3°C using the Wilhelmy plate technique with a roughened platinum plate (Roller Smith Precision Balance, Laboratory Products, Boston, MA). The values represent the equilibrium surface tensions where surface tension was independent of time and are the average of at least four determinations. Standard deviations were generally well below 1.0 mN/m except in the

Table 1
Surfactant data, contact angle data for CI-976 and Parafilm® and other calculated parameters

Surfactant	Mol. weight	CMC[a] (g/ml)	Surfactant Concentration (g/ml)	γ(mN/m)	Surfactant solution pH	CI-976 solubility (mg/ml)	θ for CI-976	$\Delta\gamma_{SL}$ CI-976-water[b]	CI-976 adhesion tension[c]	θ for Parafilm®	$\Delta\gamma_{SL}$ Parafilm®-water[b]
AOT	444.5	1.11×10^{-3}	2.5×10^{-4}	41.3	6.1		60.1	−9.6	20.6	74.1	35.0
			1.0×10^{-2}	26.1	5.5	1.0	spreads	–	26.1	61.6	36.0
HTAB	364.5	2.92×10^{-4}	2.5×10^{-4}	41.5	5.7		24.7	7.6	37.8	77.6	32.6
			1.0×10^{-2}	35.4	6.0	4.8	spreads	–	35.4	61.6	40.5
Tween 20	1126	6.00×10^{-5}	3.0×10^{-5}	36.3	5.5		65.6	−15.2	15.0	93.0	21.7
			1.0×10^{-2}	33.5	6.0	nm[d]	41.9	−5.2	25.0	65.9	37.4
Brij 35	1200	7.20×10^{-5}	2.0×10^{-4}	42.1	5.1		54.2	−5.6	24.6	77.5	32.7
			1.0×10^{-2}	42.8	3.5	0.7	36.9	4.0	34.2	73.6	35.7
SLS	288.3	2.36×10^{-3}	5.8×10^{-3}	39.4	5.5		16.5	7.5	37.7	67.4	38.8
			2.0×10^{-2}	37.9	6.8	8.8	4.2	7.6	37.8	64.5	40.0
Tween 80	1309	1.30×10^{-5}	2.5×10^{-4}	38.3	6.3		53.4	−7.4	22.8	nm	–
			2.0×10^{-2}	33.9	6.4	2.0	45.5	−6.5	23.7	69.4	35.5
TXR[e]	624.9	1.50×10^{-4}	4.0×10^{-5}	39.6	6.7		59.4	−10.1	20.1	77.0	32.5
			5.0×10^{-3}	29.3	4.3	1.5	6.6	−1.1	29.1	nm	–
DCH	414.6	4.15×10^{-3}	2.0×10^{-2}	45.0	8.0	1.4	47.1	0.4	30.6	68.7	40.0
POE 10 LE	672	1.25×10^{-4}	4.0×10^{-6}	39.3	5.8		65.0	−13.6	16.6	97.8	18.3
			1.0×10^{-2}	30.9	4.4	1.4	17.4	−0.7	29.5	56.4	40.7
Water	18	–	–	72.0	6.3	< 0.1	65.2	0.0	30.2	109.2	–

AOT, dioctyl sulfosuccinate; HTAB, hexadecyltrimethyl ammonium bromide; Tween 20, polyoxyethylene 20 sorbitan mono-laurate; Brij 35, polyoxyethylene 23 lauryl ether; SLS, sodium lauryl sulfate; Tween 80, polyoxyethylene 20 sorbitan mono-oleate; TXR (Triton X-100R), polyoxyethylene 9 *p*-isooctyl phenyl ether; DCH, sodium deoxycholate; POE 10 LE, polyoxyethylene 10 lauryl ether. [a]Literature value. [b]From Eq. (1). [c]Adhesion tension equals $\gamma\cos\theta$. [d]Not measured. [e]The reduced form of Triton X-100 was used in the experiments; CMC and MW data are for the non-reduced form.

case of several dilute surfactant solutions where deviations reached a maximum value of 2.0 mN/m. Literature values were used for the surface tensions of the organic liquids.

2.3. Solid sample preparation

One-gram aliquots of CI-976 were compressed using a highly polished stainless steel punch and die (19 mm diameter) at 1815 kg force using a Carver Press (Model M, Menomonee Falls, WI) with a 1 min dwell time and subsequently carefully ejected from the die. The appearance of the surfaces under a low-power stereo microscope was smooth and reflective. Those samples that exhibited non-uniform surfaces or where sticking or picking occurred were not used. After compression the disks were stored in a 75% relative humidity chamber at ambient temperature for at least 48 h prior to use. Some additional contact angle measurements were made on Parafilm® M (American National Can Company, Greenwich, CT) as this material has been shown to behave similarly to paraffin (Zografi and Yalkowsky, 1974). Sections of Parafilm® were affixed to glass cover-slips with a small amount of pressure and the protective backing was removed prior to use.

2.4. Contact angle determination and surface energy calculations

The contact angles of sessile drops on CI-976 compressed disks or Parafilm® were determined using a Rame-Hart Contact Angle Goniometer (Model 100-00, Mountain Lakes, NJ) fitted with an environmental chamber (Model 100-07). The chamber atmosphere was kept saturated with water (or the organic liquid used) to prevent drop evaporation and maintained at 25°C with a circulating water bath. When hygroscopic organic liquids were used a desiccant was placed inside the chamber to prevent the liquids from absorbing water. Drops of 4 to 6 µl were placed on the surface using a micrometer syringe with a 22 gauge flat tip needle. The advancing angle on both sides of each drop was measured initially (within 15–45 s), at 5 min and at 10 min. For CI-976 samples contact angles were measured on at least two compressed disks using four to six drops. Standard deviations were generally 2–3°, although in several cases with some surfactants deviations were as high as 4–5°. Preliminary studies showed that contact angles on Parafilm® samples had standard deviations of less than 1°. Consequently, only 2 to 4 drops were measured on one sample of Parafilm®.

Surface energy calculations utilizing contact angle and surface tension data were performed using the methods outlined in Sections 3.4.2. and 3.4.3. The simultaneous equations were solved using the equation handling software program Solver-Q 1.2 (Scientific Logics Inc, Cupertino, CA) on a 80486 based PC computer.

2.5. Solubility and dissolution

Solubility measurements were conducted at 37°C with approximately 0.3 g of CI-976 placed in 10 ml of surfactant solution in glass vials. The samples were agitated for 2 h, filtered (0.45 µm glass microfiber filters), diluted and assayed by HPLC (described below). Preliminary studies showed no change in solubility from 2 to 24 h. Dissolution testing was performed using the USP method II (paddles) at 50 rev./min (Vankel 6000RC, Edison, NJ) in 900 ml of solution on hand filled gelatin capsules (no. 0) with CI-976 bulk drug which had first been passed through a 50 mesh sieve. Capsules were filled with a minimum of compaction and analyses were performed in triplicate. Aliquots (4–5 ml) were withdrawn at 15, 30, 45, and 60 min, filtered (0.45 µm glass microfiber filters) and assayed by HPLC. The HPLC method for CI-976 utilized an ODS Hypersil column (100 mm × 2.1 mm, 5 µm packing, Hewlett-Packard, Avondale, PA) and a mobile phase of 60:40 acetonitrile/water. Twenty microliter injections were made and the flow rate was 1 ml/min with a detection wavelength of 240 nm. For some surfactant solutions the mobile phase organic to aqueous ratio was changed to eliminate interference from the surfactants in the assay. A multi-point calibration curve was used for quantitation which was linear over the concentration range of approximately 5-280 µg/ml.

3. Results and discussion

3.1. Validity of contact angle measurements on CI-976 compressed surfaces

Contact angle determination on powder samples presents many theoretical and practical difficulties in sample preparation and measurement (Buckton, 1993). The experimental conditions were standardized as much as possible to minimize many of these variables. A single lot of material was used and no impurities were detected from the analysis of a sample with a stability indicating HPLC assay. Compressed disks were prepared with a fixed amount of material at a set compression force and dwell time, as these variables can have a significant effect on results (Buckton and Newton, 1986; Kiesvaara and Yliruusi, 1991). Prior to use the compressed disks were conditioned in an atmosphere similar to that during the measurement to ensure uniform treatment of the surfaces and eliminate transient effects related to water adsorption (Odidi et al., 1991). The drop size was also kept constant. No specific measures were taken to address issues related to surface roughness because the advancing angle on compressed disks is a reasonable estimate of the intrinsic equilibrium contact angle (Zografi and Johnson, 1984).

Contact angles were reproducible and standard deviations were in the same range as those for more ideal surfaces (Troster and Kreuter, 1988). Results for water on Parafilm® were comparable with those in the literature (Zografi and Tam, 1976) and results on compressed disks were reproducible between two operators. Buckton and Newton (1986) observed a decrease in contact angle as a function of compression force and attributed this variation to the formation of a higher energy layer at the surface due to plastic deformation. To evaluate whether CI-976 might undergo this type of change, X-ray diffractograms for CI-976 bulk powder and powder compressed at 2.5 times the working pressure were compared. The results indicated that there was no change in crystallinity or crystal form upon compaction. Also, the contact angle of water on CI-976 disks compressed at 1815 kg and 4540 kg force were not significantly different. Additionally, CI-976 did not exhibit any reduction in crystallinity upon milling. Therefore, it is unlikely that the compression at the working pressure significantly alters the surface characteristics of the CI-976 powder.

Contact angles were measured as a function of time over 10 min to avoid dissolution and sorption effects at longer times. The values at this time also had the smallest standard deviations. For all solutions tested on CI-976 compressed disks some time dependence was observed; however, the contact angle values showed an asymptotic approach to a constant value. Time dependent contact angles from surfactants have also been observed on polymer surfaces (Johnson et al., 1986). Consequently, the 10-min values for all liquids were used for consistency analysis. In addition, plotting of the data for several of the surfactants (Tween 80, SLS, TXR) revealed the same relative trends. In light of these results and precautions, the CI-976 compressed disk surface could be viewed as representative of the original powder.

3.2. Contact angles of surfactant solutions on CI-976 compressed disks

The surfactants used in these studies are listed in Table 1. The surfactants differ in molecular weight, critical micellar concentration (CMC), and charge. Table 1 shows contact angle, surface tension and other data for the surfactants at selected concentrations. The higher concentrations were selected for solubilizing capacity and minimization of surface tension and were later used for dissolution testing. The lower concentrations were selected to obtain a surface tension of approximately 40 mN/m so that the contact angles for each surfactant solution could be compared at the same surface tension. Except for SLS and HTAB, at surface tensions of about 40 mN/m all of the surfactant solutions had contact angles greater than 47°, despite the large reduction in surface tension relative to water. The high contact angles do not appear to be consistently related to

Table 2
Contact angle of liquids on CI-976 and liquid surface energy parameters (mJ/m^2)

Liquid			Wu's method[a]			van Oss' method[b]			
	θ(°)	cos θ	γ_2	γ_2^d	γ_2^p	γ_2^{LW}	γ_2^+	γ_2^-	γ_l
Water	65.2	0.4195	72.0	27.1	44.9	21.8	25.50	25.50	72.8
Glycerol	66.0	0.4067	63.7	31.2	32.5	34.0	3.92	57.40	64.0
Formamide	22.4	0.9245	58.3	32.5	25.8	39.0	2.28	39.60	58.0
1,3-Propanediol	31.3	0.8545	49.2	34.6	14.6				
Ethylene glycol	28.4	0.8796	48.9	33.0	15.9	29.0	1.92	47.00	48.0
1,3-Butanediol	24.3	0.9114	39.1	32.4	6.7				
1,2-Propanediol	33.1	0.8377	38.0	30.6	7.4				
Methylene iodide	16.3	0.9598	50.4	50.4	0.0	50.8	0.00	0.00	50.8

[a] Parameters based on Parafilm® as a reference from Pyter et al. (1982). [b] Parameters values for 20°C from Good (1992).

whether the surfactant concentration is below the CMC. At higher surfactant concentrations (0.01 and 0.02 g/ml), AOT and HTAB wet the solid completely (i.e. $\theta = 0$), SLS and TXR had near zero contact angles, but the remainder had relatively high angles. Comparison of the contact angles for the surfactants around 40 mN/m shows that a wide range of values are obtained at the same surface tension. Even at 1-2% concentrations some of the surfactant solutions cannot produce complete wetting at their surface tension minimums. There is a wide range of wetting behaviors by the surfactant solutions at 40 mN/m relative to a pure liquid such as 1,3-butanediol which has a surface tension of 39 mN/m and θ of 24.3° (see Table 2). Some of the surfactants had greater contact angles, whereas SLS and HTAB had contact angles of equal or lesser values at the same surface tension. These results suggest that specific interactions among the three phase interface may be occurring and that the contact angle is not solely a function of the surface tension of the solution. For some of the surfactants tested there is a strong dependence of contact angle on surfactant concentration. This effect is seen in the cases where the surface tension of the two solutions are similar but the contact angle is considerably less with the more concentrated solution and is not dependent on exceeding the CMC for the surfactant.

To quantify the effectiveness of wetting of the surfactants the difference in γ_{SL}, the solid-liquid interfacial tension, between the surfactant solution-solid and water-solid was calculated as outlined by Pyter et al. (1982) and the results are shown in Table 1. Assuming γ_{SV} , the solid-vapor interfacial tension, to be unaffected by surfactant, the change in the solid-liquid interfacial tension, $\Delta\gamma_{SL}$, upon addition of surfactant to water is given by the equation:

$$\Delta\gamma_{SL} \equiv \gamma_{SL(w)} - \gamma_{SL(c)} = \gamma_{L(c)}\cos\theta_{(c)} - \gamma_{L(w)}\cos\theta_{(w)} \tag{1}$$

where, (w) refers to water, (c) refers to the surfactant solution and γ_L is the corresponding solution surface tension. With the exception of SLS and HTAB, these calculations show that the presence of the surfactant results in an increase in solid-liquid interfacial tension. This is in contrast to the results for Parafilm® (Table 1) where the surfactant causes a large reduction in the interfacial tension. Calculation of $\Delta\gamma_{SL}$ for polymethylmethacrylate (PMMA), a semi-polar material, with contact angle data for some of the same surfactants (Johnson et al., 1986; Troster and Kreuter, 1988) shows a trend toward increasing values of $\Delta\gamma_{SL}$ with increasing surfactant concentration. However, for CI-976 at high surfactant concentrations the value of $\Delta\gamma_{SL}$ is still only modestly positive relative to that for Parafilm®. Even at very low surface tension, many of the solutions are unable to wet CI-976 completely. This is also observed with PMMA, where despite the surface tension of surfactant solutions being below 40 mN/m and the γ_C, the critical surface tension for PMMA, spontaneous wetting is not observed. For

CI-976, the surfactants produce only a small reduction in the interfacial tension relative to water and in most cases increase the interfacial tension. However, near complete or complete wetting is observed in some instances.

3.3. Adhesion tension analysis

Three of the surfactants (Tween 80, TXR and SLS) were studied in more detail over a wider concentration range. The data are presented in Fig. 2 as adhesion tension plots ($\gamma\cos\theta$ vs. γ). This approach, developed by Lucassen-Reynders (1963), provides a method for determining whether there is preferential adsorption at the solid-liquid or liquid-vapor interfaces (assuming γ_{SV} is equal to zero for low energy solids). The "wetting line", $\cos\theta = 1$ is also depicted in the graph where θ equals zero. For the adhesion tension plots a slope of -1 indicates equal adsorption at the solid-liquid and liquid-vapor interfaces; slopes tending toward zero indicate preferential adsorption to the liquid-vapor interface.

The adhesion tension plots for Tween 80, TXR and SLS are complex curves. The adhesion tension drops initially upon addition of surfactant, then begins to increase, approaching the wetting line above 40 mN/m, except in the case of Tween 80. The adhesion tension for Tween 80 is almost constant or slightly decreasing as a function of surface tension and complete wetting is not possi-

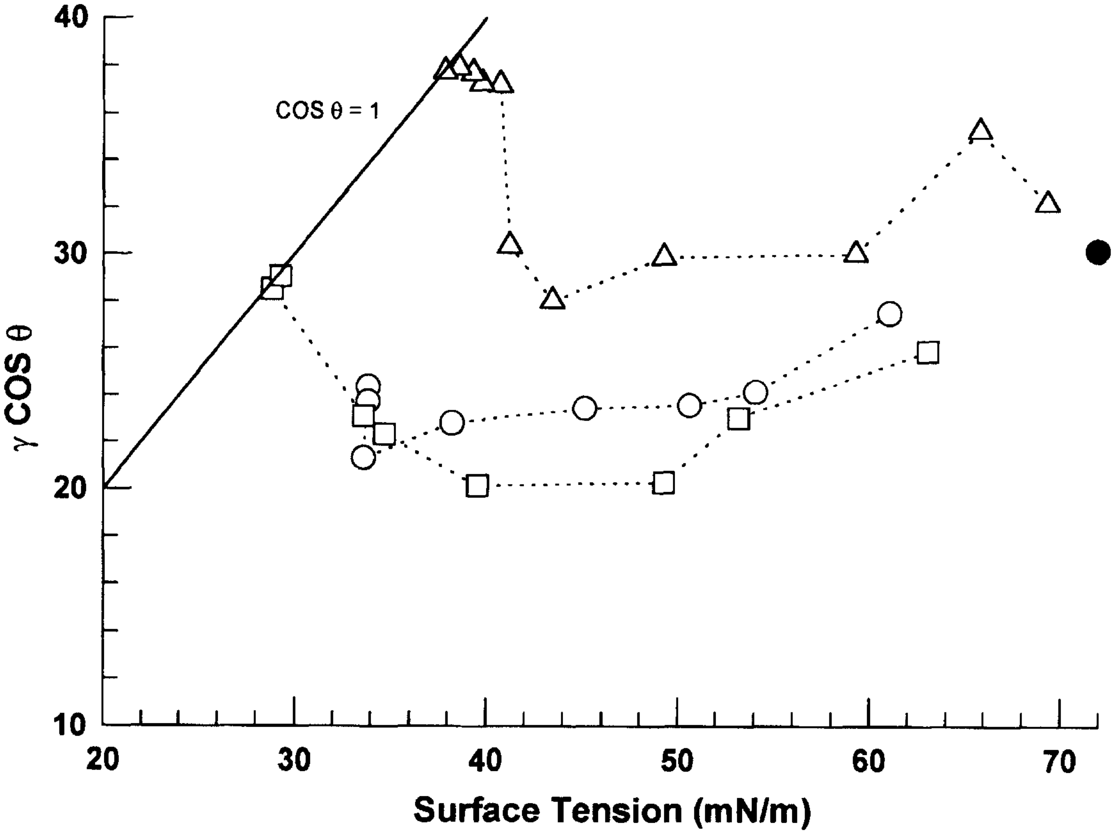

Fig. 2. Adhesion tension plot based on surfactant solution contact angle data on CI-976 compressed disks. Key: Tween 80 (○); Triton X-100R (□); SLS (△); Water (●).

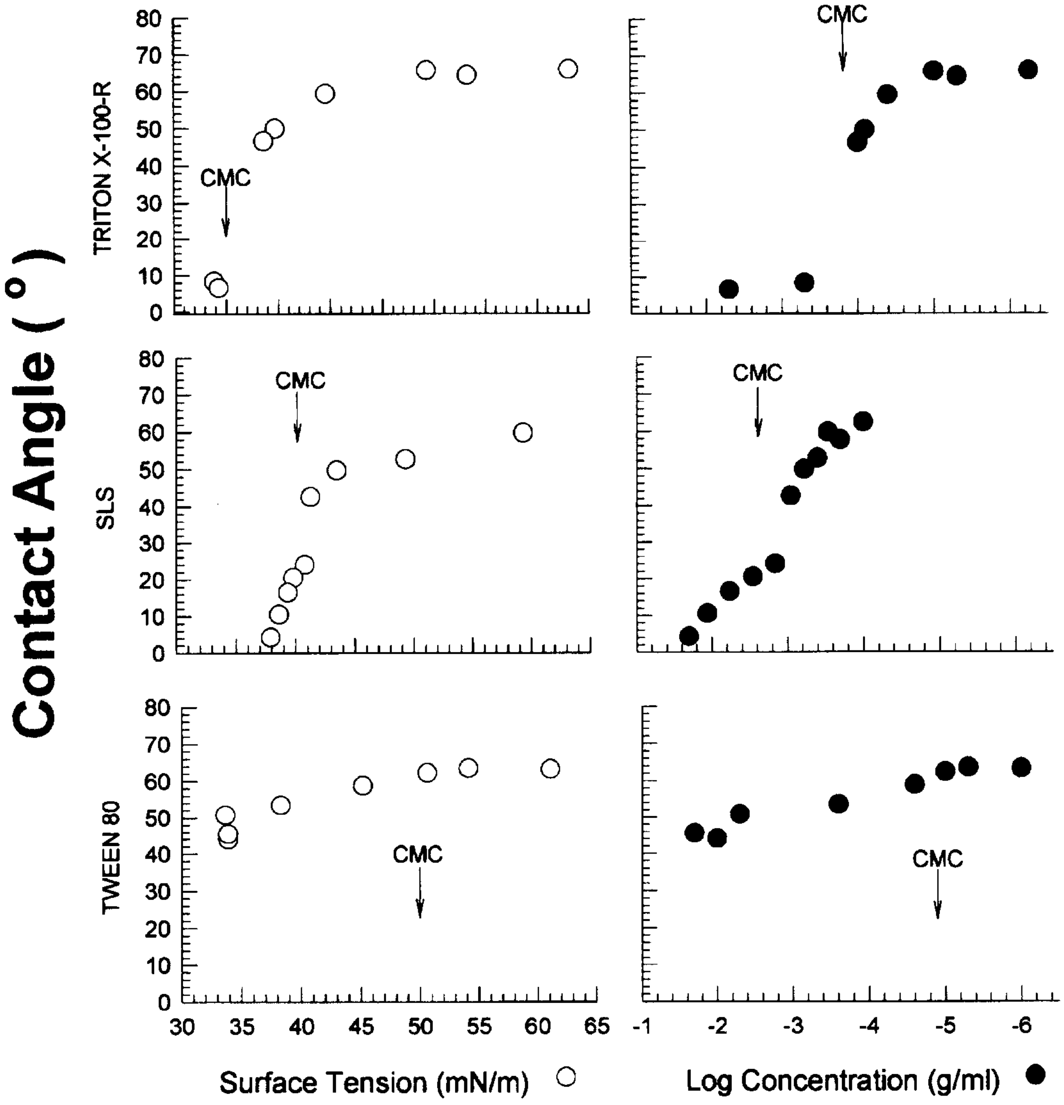

Fig. 3. Contact angle of surfactant solutions on CI-976 as a function of surface tension and concentration for Tween 80, SLS and Triton X-100R. The approximate CMCs from Table 1 are indicated on the plots.

ble even at 0.02 g/ml surfactant concentration. The zero to negative slope of the adhesion tension data for Tween 80 indicates preferential adsorption of the surfactant to the liquid-vapor interface over the solid-liquid interface. Gau and Zografi (1990) also observed preferential adsorption of polyoxyethylene surfactants to the liquid/air interface over the PMMA/liquid interface. For both SLS and TXR there is a sharp increase in the absolute value of the slope in the region of 40 mN/m and the wetting line is approached at lower surface tensions. Thus, at lower concentrations and higher surface tensions the surfactants are preferentially adsorbed to the liquid-vapor interface, but at lower surface tensions there is a shift toward more adsorption to the solid-liquid interface.

The shifts in slope in Fig. 2 for SLS and TXR at about 40 mN/m correspond to where the contact angles drop substantially and these changes occur near the CMC of the surfactants. This is highlighted in the plots of the contact angle data from the adhesion tension experiments shown in Fig. 3. The value of 40 mN/m is also the point where some critical changes in the wetting properties of PMMA by surfactant and polymer solutions occur. For non-ionic surfactants wetting PMMA, adhesion tension profiles could be well predicted from independent measurements of the surface excesses at the interfaces until about 40 mN/m, when measured contact angles were lower than predicted (Gau and Zografi, 1990). It has also been observed that on PMMA receding angles of non-ionic surfactant solutions become zero at surface tensions of about 40 mN/m (McNally et al., 1992). These results suggested that at about 40 mN/m there is a formation or reorganization of an adsorbed film which subsequently changes the wetting properties of the original surface (Johnson et al., 1986). Thus, for SLS and TXR wetting CI-976, it is possible that in the region of concentration where the surface tension is about 40 mN/m a similar phenomenon occurs.

The contact angles of Tween 80 solutions are independent of surface tension or concentration. This indicates that Tween 80 will not completely wet the CI-976 surface at any practical concentration. The surfactants in Fig. 2 also show similarly complex behavior on PMMA surfaces (Troster and Kreuter, 1988). Low concentrations of surfactants result in a reduction of adhesion tension on PMMA relative to water; however, this is not observed for surfactants on a non-polar surface such as Parafilm® (Zografi and Johnson, 1984). The adhesion tension profiles for CI-976 suggest that specific interactions occur between the surfactant and the solid, depending on the surfactant and its concentration or surface tension.

3.4. *Surface energy analysis*

3.4.1. *Contact angles of polar liquids*

To gain insight into the CI-976 surface, contact angles were measured for a series of polar liquids and methylene iodide (see Table 2). The lack of a linear trend in $\cos\theta$ for the polar liquids vs. surface tension is also indicative of specific interactions. Comparison of contact angles for 1,3-propanediol and 1,2 propanediol, which only differ by the position of an hydroxyl group, shows that despite a surface tension difference of over 10 mN/m, the contact angles are almost equivalent. A similar situation is observed with water and glycerol. In contrast, 1,3-butanediol and 1,2-propanediol have very similar surface tensions, yet significantly different contact angles. This type of behavior is not observed with these liquids on surfaces such as Parafilm®, polytetrafluoroethylene, and poly-ethylene and nylon (Zografi and Yalkowsky, 1974; Zografi and Tam, 1976) and the discrepant behavior of some of the liquids on CI-976 may be the result of molecular orientation effects due to specific interactions with the solid.

3.4.2. *Surface energy calculations*

The surface energy parameters for CI-976 were calculated using the contact angle data in Table 2 where the surface energy parameters of the liquids are also provided. Two methods were used to calculate the solid surface energy, γ_S. Wu's method (Wu, 1971) has been adopted frequently to determine the surface energy of drug compressed disks (Zografi and Tam, 1976; Rowe, 1989a,b). Wu's method employs the use of contact angle data from two liquids and the total surface energy is divided into non-polar, γ^d, and polar, γ^p, surface energy components. A detailed description of the method and its derivation are found elsewhere (Zografi and Tam, 1976).

A more recent method has been developed based on acid-base interactions by van Oss and coworkers (Good and van Oss, 1991) and has been applied to a variety of surfaces, including compressed disks of cholesterol and nitrofurantoin (Chibowski et al., 1992; Janczuk et al., 1992). Briefly, the total surface energy of a solid or liquid, γ^{TOT} can be divided into two components:

$$\gamma^{TOT} = \gamma^{LW} + \gamma^{AB} \tag{2}$$

where γ^{LW} is the apolar (or non-polar) component associated with Lifshitz-van der Waals interactions which encompass London dispersion forces,

Table 3
Surface energy terms for CI-976 and other materials using Wu's and van Oss' methods

Surface						% Polarity	Data source	Recalculated (C) or quoted (Q)	Liquids[a]
			van Oss' method						
	γ^{LW}	γ^{+}	γ^{-}	γ^{AB}	γ^{Total}	$(\gamma^{AB}/\gamma^{Total}) \times 100$			
Sodium deoxycholate	25.66	10.48	38.72	40.29	65.95	61.1	Janczuk et al., 1992	Q	MI-W-B
Cholesterol	34.62	0.96	1.16	2.11	36.73	5.7	Janczuk et al., 1992	Q	MI-W-B
Nitrofurantoin	43.80	0.38	23.20	5.94	49.74	11.9	Chibowski et al., 1992	Q	MI-W-Fo
PMMA	40.00	0.00	14.60	0.00	40.00	0.0	van Oss, 1994	Q	Not indicated
β-Sitosterol [b,c]	29.73	0.59	1.23	0.95	30.68	3.1	Zografi and Tam, 1976	C	MI-W/FO/EG/GL
Nylon 11[b,c]	39.61	0.10	9.03	1.60	41.21	3.9	Zografi and Tam, 1976	C	MI-W/FO/EG/GL
CI-976[c]	48.78	0.78	11.99	4.76	53.54	8.8		-	MI-W/FO/EG/GL
				Wu's method					
	γ^{d}			γ^{p}	γ_s	$(\gamma^{p}/\gamma_s) \times 100$			
Sodium deoxycholate[d]	26.40			44.52	70.93	62.8	Janczuk et al., 1992	C	MI-W
Cholesterol[d]	31.58			6.84	38.42	17.8	Janczuk et al., 1992	C	MI-W
Nitrofurantoin[d]	35.17			22.67	57.84	39.2	Chibowski et al., 1992	C	MI-W
PMMA	33.00			12.40	45.40	72.7	El-shimi and Goddard, 1974	Q	MI-W
β-Sitosterol	31.20			3.70	34.90	10.6	Zografi and Tam, 1976	Q	MI-W
Nylon 11	40.00			9.20	49.20	18.7	Zografi and Tam, 1976	Q	MI-W
CI-976	48.43			10.00	58.40	17.1		-	MI-W
CI-976	48.43			8.91	57.34	15.5		-	MI-W/MI-F0/MI-GL

[a] Liquids are methylene iodide (MI), water (W), formamide (FO), ethylene glycol (EG), glycerol (GL), and bromoform (B). [b] Calculations made using contact angle data obtained at 25°C and liquid parameters from Table 2. [c] Values are the average of parameters obtained from liquids paired with MI and W. [d] Liquid surface tension parameters from Ko et al. (1981) at 20°C.

Table 4
Surface energies and parameter values of surfactant substituent groups and calculated ΔG_{1W2}, the interaction energy for CI-976 or PMMA

Substituent	Surface energies (mJ/m^2)				ΔG_{1W2} (mJ/m^2)[a]	
	γ_s	γ^{LW}	γ^+	γ^-	CI-976[b]	PMMA[b]
SLS head[c]	34.6	34.6	0	46	−7.2	1.1
SLS tail[c]	23.8	23.8	0	0	−59.1	−64.1
C16 tail[c]	27.5	27.5	0	0	−60.8	−65.3
POE 6000[c]	43	43	0	64	−0.2	11.1
Surfactant γ+ head group[d]	35	35	50	0	−41.4	−50.2
	35	35	30	0	−46.5	−54.1
	35	35	15	0	−51.6	−58.0
DCH[e]	66	25.7	10.5	38.7	2.2	6.1

</TB4>[a]Calculated from Eq. (11).[b]Parameter values from Table 3. [c]van Oss and Constanzo (1992).[d]See Section 3.4.3. [e]Janczuk et al. (1992). [f]van Oss (1994)

Debye-polarization and Keesom forces. The γ^{AB} component results from electron-donor and electron-acceptor intermolecular interactions (i.e. Lewis acid-base interactions). The term γ^{AB} is further divided into two parameters:

$$\gamma^{AB} = 2(\sqrt{\gamma^+\gamma^-}) \quad (3)$$

where γ^+ and γ^- are the electron-acceptor and electron-donor contributions to the surface tension of the wetting liquid, respectively. It is seen from Eq. (2) and Eq. (3) that if either the γ^+ or γ^- parameters are zero, there is no acid-base component contribution to the overall surface energy. Under the assumption of negligible film pressure of the liquid on low energy solids (Folkes, 1964), the Young equation,

$$\gamma_S - \gamma_{SL} = \gamma_L \cos\theta \quad (4)$$

can be combined with the Dupre equation,

$$\Delta G_{SL} = \gamma_{SL} - \gamma_L - \gamma_S \quad (5)$$

to yield Eq. (6),

$$\gamma_L(1 + \cos\theta) = -\Delta G_{SL} \quad (6)$$

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., 1988 have shown that γG_{SL} can be separated into its Lifshitz-van der Waals and acid-base components (Eq. (7)) which are each defined in terms of their respective interfacial free energies (Eqs. (8) and (9)):

$$\Delta G_{SL} = \Delta G_{SL}^{LW} + \Delta G_{SL}^{AB} \quad (7)$$

$$\Delta G_{SL}^{LW} = -2(\sqrt{\gamma_S^{LW}\gamma_L^{LW}}) \quad (8)$$

$$\Delta G_{SL}^{AB} = -2(\sqrt{\gamma_S^+\gamma_L^-} + \sqrt{\gamma_S^-\gamma_L^+}) \quad (9)$$

By combining Eqs. (6)–(9), the following equation is obtained:

$$\gamma_L(1 + \cos\theta) = 2(\sqrt{\gamma_S^{LW}\gamma_L^{LW}} + \sqrt{\gamma_S^+\gamma_L^-} + \sqrt{\gamma_S^-\gamma_L^+}) \quad (10)$$

With known values of γ_L^{LW}, γ_L^+, γ_L^- for three liquids and their contact angles on the solid, a set of three equations of the form of Eq. (10) can be solved simultaneously. However, it is possible to first measure γ_s^{LW} using an apolar liquid (one with no γ_L^+, or γ_L^- parameters) and simplify the set of equations to a pair in the unknowns, γ_s^+ and γ_s^- (Good, 1992). This was the approach taken here.

Table 3 shows the calculated surface energy parameters for CI-976 compressed disks for several different combinations of liquids. For the acid-base method, only one liquid was varied because it is required that water and non-polar liquid be used (Good, 1992). For Wu's method, data are presented from calculations using methylene iodide paired with other liquids. For CI-976, calculations using methylene iodide and 1,3-butanediol or 1,2-propanediol resulted in unreasonable solutions and were omitted from the final results. It is possible that unreasonable values obtained with these liquids result from significant interaction at the surface (discussed above) and also that Wu's method does not include some types of interaction energies that are present.

The surface energy terms for CI-976 (Table 3) calculated using Wu's method are consistent with those of other poorly wetting drugs such as indomethacin, griseofulvin, and hydrocortisone (Zografi and Tam, 1976). The polar component originates from the methoxy and amide groups and the non-polar component arises mainly from the contribution of the $(CH_2)_9$ chain. PMMA also has surface energy components in the same range as CI-976 (Table 3). This similarity in surface energetics gives some rationale for why surfactants show similar wetting behavior on PMMA (see Section 3.2).

Surface energy parameters for CI-976 derived using van Oss' method are shown in Table 3 along with those for some other materials for which data are available. The surface energy parameters, γ_s^+ and γ_s^-, for CI-976 are consistent with its molecular structure. The methoxy groups and the benzene ring are electron donating and the N-substituted amide is electron donating as well, thus giving rise to the γ^- character. The γ^{LW} component is somewhat higher than other materials shown in Table 3, but is generally consistent with the hydrocarbon chain. PMMA has parameter values similar to CI-976 and is also γ^- in character. This is again consistent with the similarities in surfactant behavior on the two solids. The values of the surface energy components for CI-976 are in reasonable agreement with other crystalline organic compounds (Table 3) based on functionality and structure.

3.4.3. Calculation of interaction energies between solid and surfactant

The interaction energy between a solid surface and surfactant molecules in aqueous media, ΔG_{1W2}, can be calculated using the Lifshitz-van der Waals and acid-base parameters for the three components (substrate, water, surfactant) based on Eq. (11) below, as derived by van Oss et al., 1988:

$$\Delta G_{1W2} = (\sqrt{\gamma_1^{LW}} - \sqrt{\gamma_2^{LW}})^2 - (\sqrt{\gamma_1^{LW}} - \sqrt{\gamma_W^{LW}})^2 - (\sqrt{\gamma_2^{LW}} - \sqrt{\gamma_W^{LW}})^2 + 2[\sqrt{\gamma_W^+}(\sqrt{\gamma_1^-} + \sqrt{\gamma_2^-} - \sqrt{\gamma_W^-}) + \sqrt{\gamma_W^-}(\sqrt{\gamma_1^+} + \sqrt{\gamma_2^+} - \sqrt{\gamma_W^+}) - \sqrt{\gamma_1^+\gamma_2^-} - \sqrt{\gamma_1^-\gamma_2^+}] \quad (11)$$

Although there are only surface energy parameter data available for SLS and DCH, it is possible to use values for closely related compounds to obtain a relative estimate of whether interaction is energetically favorable. Table 4 shows the ΔG_{1W2} values for the interaction of CI-976 and various substrates in water. DCH has a positive ΔG_{1W2} and this indicates that it will not interact strongly with CI-976. The observed high contact angle for the DCH solutions on CI-976 supports this prediction. For SLS the ΔG_{1W2} values indicate that the hydrocarbon tail interacts strongly with CI-976, whereas the polar head interacts to a much lesser degree. However, overall the ΔG_{1W2} is negative and interaction is favorable and near complete wetting is observed based on the contact angle results. To put these ΔG_{1W2} values in perspective, the calculated interaction energy for two SLS tails in water is -102 mJ/m^2. Thus, the energy of interaction of the surfactants with the surface is likely to be secondary relative to other interactions in the liquid phase. The ΔG_{1W2} calculations also show that the interaction of a hydrocarbon surfactant with a monopolar, γ^+ head group will have a favorable interaction with CI-976, independent of the magnitude of γ^+. This may be the case for HTAB; however, surface energy parameters for the trimethylammonium head group are not available to confirm this hypothesis.

Assuming that the surface energy parameter values for POE 6000 (Table 4) can be taken as representative of the polyoxyethylene (POE) chain(s) of the polyoxyethylene surfactants (Tween 80, Tween 20, POE 10 LE and Brij 35, TXR), the calculations show only weak interaction for the POE moiety. For Tween 80, Tween 20 and Brij 35 the relative values of ΔG_{1W2} are consistent with the poor wetting of these surfactants on CI-976 as exemplified by the high contact angles at relatively low surface tensions. However, TXR and POE 10 LE show relatively good wetting. This may be due to the lower POE chain length (9–10 as POE 10 LE) compared with the Tweens and Brij 35, with POE residues of 20 and 23, respectively, which may allow the dominance of the interaction of hydro-

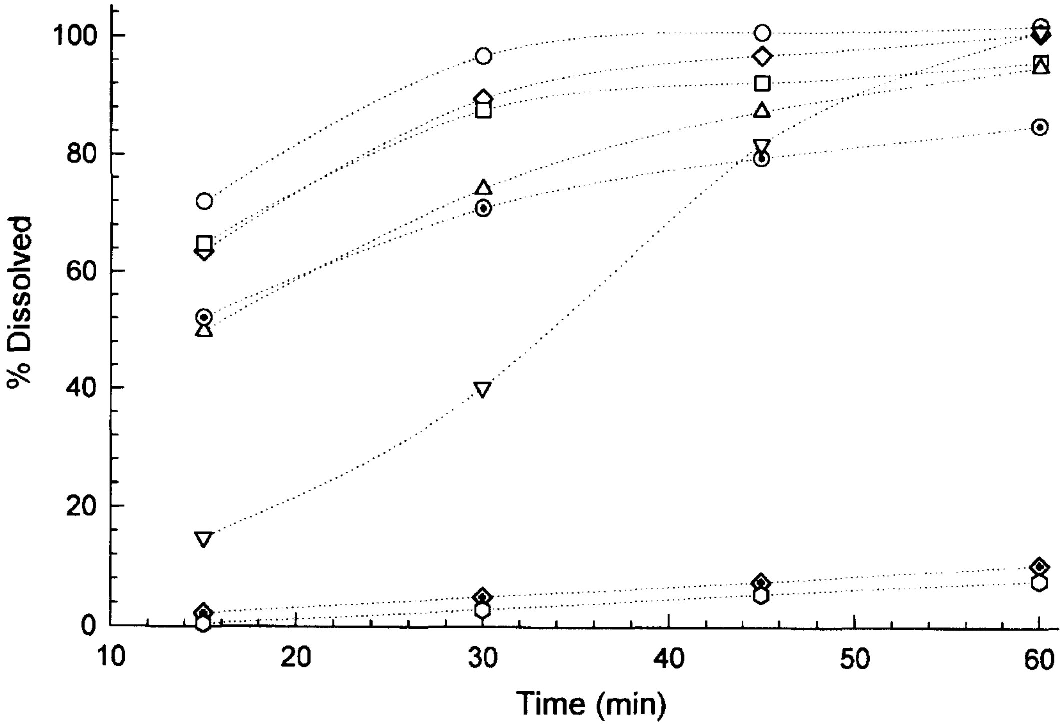

Fig. 4. Dissolution of CI-976 bulk drug capsules in surfactant solutions. Key: HTAB 1% (○); POE 10 LE 1% (◇); SLS 2% (□); AOT 1% (△); Triton X-100R 0.5% (⊙); Tween 80 2% (▽); DCH 2% (◇); Brij 35 1% (○).

carbon chain that results in more favorable interaction. Based on the ΔG_{1W2} values for the SLS chain, it is reasonable to assume that the hydrocarbon moieties for TXR, POE 10 LE and Brij 35 would result in negative ΔG_{1W2} values and that the interaction for these types of surfactants is driven by the hydrocarbon moiety. Note that when the number of POE residues is reduced in the case of Brij 35 and POE 10 LE, the surfactant with fewer POE residues (POE 10 LE) shows better wetting (Table 1). In addition, the POE chain distribution on the Tweens is structurally very different from that of the "linear" POE chains on Triton and Brij derivatives. Unfavorable energetics of interaction between the CI-976 surface and the sorbitan ring may also contribute to the lack of wetting by the Tween surfactants.

The relative ΔG_{1W2} values for PMMA are consistent with that of CI-976 and correlate with the wetting behavior for surfactants such as Brij 35, AOT, and Tweens on PMMA which show similar trends in contact angle values from 1% concentration solutions (Troster and Kreuter, 1988). Based on similarity in surface energy parameter values, it is likely that the same types of phenomena affecting surfactant interaction and preferential adsorption with PMMA is operative in the case of CI-976 (see Section 3.1). Although the effects of concentration, adsorption, or surface organization are not taken into account with the determination of ΔG_{1W2} values, these simple calculations provide insight at the molecular level that can assist in interpreting wetting data and demonstrate the utility of such an approach.

3.5. Dissolution of CI-976 bulk drug gelatin capsules

The effect of wetting and surface tension on dissolution of drugs has been studied for a number of surfactant/drug combinations (Banakar, 1992). The present dissolution studies were under-taken to determine whether differences in wetting of CI-976, as measured by contact angle on compressed disks, are perceivable under practical dissolution testing conditions. Fig. 4 shows rate of dissolution for 250 mg CI-976 gelatin capsules in surfactant solutions listed in Table 1. During dissolution testing all the capsule shells dissolved within 5 min so that the observed differences are due to media effects. Consideration of the solubility of CI-976 in the surfactant solutions (Table 1) shows that in each case there is solubilizing capacity of at least 2.5 times the dose present in the dissolution media.

For the Brij 35 and DCH solutions, with contact angles of 37° and 47°, respectively, dissolution was slow and incomplete. The powder from the capsules in these solutions formed plugs which probably was a result of the poor wetting of the solutions and gave rise to the zero order release rates. However, the Tween 80 solution had a CI-976 contact angle greater than that of Brij 35. Dissolution in the Tween 80 solutions was initially slow, then increased and 100% dissolution is ultimately observed, but a sigmoid profile was obtained. The powder in these capsules initially formed plugs which later dispersed into smaller aggregates that then dissolved. The faster dissolution rate for Tween 80 compared with Brij 35 despite the higher contact angle for Tween 80, is not due to solubility effects alone; otherwise the dissolution in DCH would have been expected to be faster than Brij 35. All three surfactants which resulted in delayed CI-976 dissolution had contact angles in the range of 40° and this may be related to the limit for effective capillary penetration. However, a distinct range for correlating contact angle with dissolution was not apparent. This is likely due to the fact that the contact angle is not a direct measure of some of the other complex processes involved in wetting of a powder bed (Heertjes and Witvoet, 1969/1970).

In all cases where the contact angle was below 17° dissolution was fairly rapid. It is interesting to note the range of dissolution profiles obtained for surfactant solutions in which the solubility of CI-976 is approximately identical. DCH, AOT, POE 10 LE, TXR and Tween 80 have solubilities of 1–2 mg/ml, but the percent dissolved varies significantly at each sampling time. The finding that such large variation in dissolution can occur virtually independent of solubility is significant because it demonstrates that a range of values are possible depending on the wetting of the drug by the surfactant. Wetting can also change substantially as a function of surfactant concentration as shown in Figs. 2 and 3. In cases where large variation in dissolution profiles are observed as a function of surfactant concentration (Shah et al., 1989), wetting effects may be partially responsible.

Variation in drug dissolution rate among surfactants would also be expected if the surface energy of the drug were altered due to milling or other processing. For tablets that are formed from granules in which the rate limiting step in dissolution is the penetration of the dissolution medium into the granule (Cruaud et al., 1980), surfactant wettability may have an influence the kinetics of drug release. These issues are of particular significance with respect to establishing dissolution media for product testing, process variable screening, bioequivalence testing or in-vitro/in-vivo correlations. The dissolution results support the concept that screening of surfactants based solely on solubilizing capacity is insufficient to assess the ability of a surfactant to improve dissolution and that wetting can be a critical factor affecting the dissolution of poorly water soluble drugs.

4. Conclusions

Based on contact angle data for surfactant solutions on CI-976 a wide range of wetting behavior is observed for surfactant solutions at equivalent surface tensions. Those surfactants that produced low contact angles on CI-976 did not provide a substantial lowering of the interfacial tension with respect to water. Adhesion tension analysis over a range of surface tensions for Tween 80, SLS and TXR shows a general tendency to preferentially adsorb to the liquid-vapor interface versus the solid-liquid interface up to about 40 mN/m. For SLS and TXR there was a marked decrease in contact angle at surface tensions below about 40 mN/m resulting in a shift in preferential adsorption to the solid-liquid interface. Surface energy calculations show that CI-976 is energetically similar to other poorly soluble drugs as well as to PMMA, which shows qualitatively similar surfactant wetting behavior. Calculation of surfactant-solid interaction energies qualitatively supports the trend in the contact angle data. More detailed study of surfactant wetting of semi-polar hydrophobic drug surfaces is needed to further elucidate the nature of these interactions and their influence in the wetting process. The differences observed in surfactant wetting CI-976 were borne out in dissolution testing of bulk drug capsules and illustrate how the choice of a surfactant can be critical in achieving dissolution of a poorly water soluble drug. These studies demonstrate that contact angle measurements obtained from compressed drug disks are a useful tool for analyzing qualitative differences in wetting of drug substances. In addition, the approaches outlined here have application in selecting surfactants as functional excipients for tablets, matrix formulations, solid dispersions and for surface adsorption to drugs for improving dissolution.

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