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Wetting characteristics of media emulating gastric fluids

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Abstract

A variety of dissolution media have been used to simulate the physiological environment of the gastric region. The objective of this study was to formulate and examine the wetting properties of dispersions composed of the dominant surface active species found in the stomach at physiologically relevant concentrations. Systems representing the fed and fasted states were studied and compared to other media that have been considered for use as simulated gastric fluids. Dilute bile salt/phospholipid solutions and bile salt-lipid emulsions were formulated on the basis of available physiologic data to represent the fasted and fed states, respectively. Wetting was evaluated through the determination of the surface tension and contact angle of the various solutions using poly(methyl methacrylate) (PMMA) as a model surface. Additional surfactant solutions and other biorelevant media were also tested. Data were evaluated in terms of contact angle, surface tension and the thermodynamic stages of wetting. The results indicate that solutions patterned after the composition of the GI tract have significantly different wetting properties relative to the fed and fasted states. The surfactant solutions tested were significantly better wetting agents for the surface than the physiologically representative formulations. The implications for the formulation of surfactant-based biorelevant media are discussed.

Keywords: Wetting; Dissolution; Bile salt-lipid solutions; Surface tension; Simulated gastric media; Contact angle; Surfactants

1. Introduction

Dissolution testing of oral solid dosage forms is often performed in aqueous solutions at low pH to simulate the environment of the gastric region (Cohen et al., 1990). Results of these tests are useful for quality control purposes and for in vitro-in vivo correlations. The recent development of the Biopharmaceutical Classification System (Amidon et al., 1995) has renewed interest in the formulation of physiologically relevant media for dissolution testing (Galia et al., 1998). In addition to pH, an important characteristic of gastric fluid is its lower surface tension relative to water. Finholt and Solvang (1968) determined that the surface tension of gastric fluid ranged from 35 to 45 mN/m and these data have been corroborated in more recent studies (Fimmel and Blum, 1983; Efentakis and Dressman, 1998). Various surfactants have been used to lower the surface tension of water to this range for use as dissolution media (Abdou, 1989). An aqueous solution of sodium

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dodecyl sulfate has been suggested as being physiologically representative of gastric fluid (Dressman et al., 1998). In a study comparing the dissolution of low solubility drug product in simulated gastric fluid (SGF) with and without 0.1% Triton X-100, it was suggested that because the surface tension was closer to that observed in vivo, the in vitro results obtained using the surfactant medium may be more meaningful with respect to in vivo dissolution (Galia et al., 1999). The FDA has recently promoted the use of surfactants in media for conducting dissolution studies of poorly soluble compounds (Shah et al., 1995; Noory et al., 1999).

Interfacial interactions between dissolution medium and the surfaces of drugs or excipients can have a significant bearing on the dissolution process (Ganderton, 1969; Samyn and Jung, 1970; Solvang and Finholt, 1970; Zografi and Tam, 1976; Lerk and Bolhuis, 1977; Murthy and Samyn, 1977; Hansford et al., 1980; de Lourdes Costa and Baszkin, 1985; Kerc et al., 1994; Luner et al., 1996). Surfactant type has been shown to influence the deaggregation of cohesive micronized powders (de Villiers et al., 1993; Liu and Stewart, 1998). Additionally, there is not always a positive correlation between the inclusion of surfactants in tablet formulations and increased dissolution (Lowenthal, 1972). Previous investigation of the wetting properties of surfactants on drug surfaces has shown that surfactants vary considerably in their ability to wet surfaces (Luner et al., 1996). For drugs or formulations where wetting is a critical factor affecting dissolution, surfactant-based dissolution media as representative of gastric fluid may under- or over-express the influence of wetting, depending on the specific surfactant and its interaction with the surface(s). A better understanding of the wetting properties of biorelevant media is necessary to rationally formulate dissolution media that accurately account for the critical factors involved in the dissolution process.

The objective of this study was to formulate and examine the wetting properties of dispersions composed of the dominant surface active species found in the stomach at physiologically relevant concentrations. Systems representing the fed and fasted states were studied and compare to other media that have been considered for use as simulated gastric fluids. Wetting was evaluated through the determination of the surface tension and contact angle of the various solutions using poly(methyl methacrylate) (PMMA) as a model surface. PMMA was used as a model substrate because its surface free energy is a reasonable estimate for hydrophobic compounds (Luner et al., 1996) which are known to have problematic wetting. It was also chosen because of the ease of performing reproducible contact angle measurements with it. Although the PMMA surface may not be representative of all drugs or formulation components, it serves as a useful model and starting point for objectively evaluating the wetting behavior of various solutions. Using these data it was possible to assess whether a solution possessed similar wetting characteristics with respect to the surface relative to media emulating the composition of gastric fluid in the fed and fasted states.

2. Materials and methods

2.1. Reagents

Taurodeoxycholic acid (TDC), dodecanoic acid (DDA), and dodecyl sulfate (SDS) were purchased from Sigma Chemical Company (St. Louis, MO) in the form of their sodium salts. With the exception of TDC, which had a minimum purity of 97%, the salts had purities higher than 99%. Triton X-100 was also purchased from Sigma. Lecithin (LT) derived from soybeans consisting of 90–96% phosphatidylcholine was purchased from ICN Biomedical (Aurora, OH) and lysolecithin (LY, purity $>99\%$) was purchased from Avanti Polar Lipids Inc. (Alabaster, AL). Sesame oil (Super Refined Grade) was obtained from Croda Inc. (Edison, NJ). Whole and skim cow's milk were obtained as fresh commercial samples from a food store and used as received. All other reagents were ACS grade or higher in purity.

2.2. Preparation of solutions

Simulated gastric fluid (SGF) was prepared without pepsin as described in USP 23 (US Pharmacopeia, XXIII, 1995). Components used for solutions were dissolved in SGF with the exception of the fed state gastric emulsion system (FSGES) and milk. FSGES was prepared by first preparing the aqueous phase at pH 5. The oil phase, when applicable, was then added and the mixture was shaken vigorously by hand for approximately 30 s. These dispersions were visually stable from separation within the period of usage.

The pH of the solutions were verified using a calibrated pH meter (Acumet 25, Fisher Scientific, Springfield, NJ) using a combination electrode. Solutions, other than the two milk samples, were used within two days and kept at room temperature when not in use. The milk samples were kept in the refrigerator and then equilibrated at room temperature before measurements were taken. Prior to measuring surface tensions or contact angles, all the solutions with the exceptions of the emulsion systems and milk samples were filtered through pre-rinsed 0.45 μm nylon syringe filter (Acrodisc 25 mm, Gelman Sciences, Ann Arbor, MI).

2.3. Determination of surface tension

Surface tension measurements were conducted using the du Noüy ring method (model 21 Fisher tensiometer). Calibration was performed prior to use of the instrument and then verified using deionized distilled water. The solutions were maintained at 25.0 ± 0.3°C using a heating circulator water bath (Isotemp 2150, Fisher Scientific). Five separate measurements were made on separate aliquots of each solution and the Zudiema–Waters correction factor was used to correct the apparent surface tension (Zuidema and Waters, 1941). The average value was reported and standard deviations were generally less than 0.3 mN/m.

2.4. Contact angle determination

Poly (methyl methacrylate) (PMMA) blocks (approximately 2.5×2.5 cm) were used as the substrate. Their preparation was previously described (Luner, 2000). The contact angles of the solutions determined using a Ramé–Hart Contact Angle Goniometer (model 100-00, Mountain Lakes, NJ) equipped with an image analysis attachment (IAA, Ramé–Hart) and temperature controlled environmental chamber (model 100-07, Ramé–Hart). A sessile drop technique was used in determining the contact angle. Details of the apparatus and procedure were previously reported (Luner, 2000). Contact angle measurement were obtained every 10 s for 5 min at 25.0 ± 0.3°C. A total of 10 drops were measured on at least two separate substrate samples. In addition, the drop dimensions (height and width) were also recorded by the image analysis software.

Some time dependent behavior in the first several minutes was noted for all solutions. This behavior was not attributable to evaporation because humidity in the chamber was $> 90\%$ RH, the drop size was relatively large, and the time scale was short. In the region 5 ± 0.5 min, the contact angle changed insignificantly ($< \pm 0.5$°) for solutions that did not wet out completely. Consequently, the values at 5 min for all solutions were used for comparison and a contact angle of 0° was assigned to those solutions that showed complete wetting. Contact angles reported are a grand average of the left and right values for all drops of a given solution at 5 min, for a total of 20 readings for most samples. Standard deviations generally ranged from 2 to 3° for most solutions. However, in specific instances the standard deviation was as high as 4° when wetting kinetics were rapid and there was a large difference between the initial contact angle and the 5 min value.

2.5. Data analysis

Data were analyzed using the solution surface tensions, contact angle, and the thermodynamic terms associated with wetting. The equilibria involved in the wetting process have been described and involve the separate stages: adhesion, immersion and spreading (Parfitt, 1973). An understanding of all three stages is necessary for complete evaluation of the wetting process (Heertjes and

Witvoet, 1969/1970). To evaluate the influence of solution type and composition on wetting, the following terms were calculated,

$$W_a = \gamma_{LA}(\cos\ \theta + 1)$$

$$AT = \gamma_{LA}\cos\ \theta$$

$$SC = \gamma_{LA}(\cos\ \theta - 1)$$

where $W_{a,}$ is the work of adhesion (adhesional wetting), AT is the adhesion tension (immersional wetting), SC is the spreading coefficient (spreading wetting), γ_{LV} is the solution surface tension and θ, is the contact angle of the solution on the solid. The terms W_a, AT, and SC represent the energy change associated with reversing the respective stage of wetting and can be viewed as the thermodynamic driving force for each type of wetting. Positive values of these terms indicate the spontaneity of the process for adhesion, immersion or spreading, respectively. Because of the complicated dynamic and equilibria processes involved with wetting and spreading of surfactant solutions on solids (Stoebe et al., 1997), the contact angles determined here do not represent true equilibrium angles and thus may not strictly satisfy the conditions of the Young equation (Myers, 1988). Consequently, the terms calculated utilizing these experimentally determined angles must be regarded as apparent and are used for comparative purposes only.

3. Results and discussion

3.1. Formulation of simulated gastric fluids

In the fasted state, concentrations of bile salts in the gastric fluid, presumably present due to reflux from the duodenum, are in the range of 0.01–0.08 mM (Spychal et al., 1990; Efentakis and Dressman, 1998). A value of 0.1 mM was chosen as a maximal upper estimate. Because phospholipids are present in intestinal fluid in the fasted state, it is reasonable to assume that they would also be present in reflux. The presence of lysolecithin and lecithin in gastric fluid has been previously hypothesized (Bates et al., 1967; Weintraub and Gibaldi, 1969; Efentakis and Dressman, 1998). Because the ratio of bile salts to phospholipids ranges from 2.5:1 to 5:1 in duodenal bile (fasted state) (Schersten, 1973), phospholipid concentrations in the stomach would not be expected to be higher than the bile concentration if solely due to reflux. Furthermore, lecithin can also be hydrolyzed in the duodenum to lysolecithin. Measured fasting gastric lysolecithin concentrations are in the range of 0.02 mM and other phospholipids may be present as well (Dewar et al., 1982; Slomiany et al., 1983). Because of these factors, we evaluated the effect of low concentrations (0.025–0.5 mM) of lysolecithin and lecithin at bile salt concentrations found in the stomach (0.1 mM). The value of 0.1 mM phospholipid was considered an estimated upper physiologic bound for the fasted state. The highest concentrations of phospholipid were used to examine the extent to which the lipid concentration was a critical factor. TDC was chosen as a representative bile salt because it remains soluble at low pH. TDC represents about 25% of the total tauro-conjugated bile salt pool and together with the other major dihydroxy tauroconjugate, taurochenodexycholate, comprises 20% of the total bile salt pool (Hofmann, 1976).

Recent studies have shown that in the fed state a significant amount of fat digestion occurs in the stomach and that the stomach contents are substantially emulsified in the fed state. Armand et al. (1994) found that over a 1–4 h interval after administration of a test meal, the diglyceride:free fatty acid ratio ranged from 0.8 to 1.1 and the phospholipid:triglyceride ratio ranged from 1:100 to 1:50 in the stomach. These ratios were significantly different than those determined for the input meal. Based on these findings it is logical to represent the fed gastric state by an emulsion based media composed of fatty acids, triglycerides, monoglycerides, diglycerides, cholesterol, phospholipids and enzymes. To somewhat simplify the composition of our media and focus on elements common to both the fed and fasted states (bile salts and phospholipids), we have omitted diglyceride because its dispersive proper-

ties are well approximated by triglycerides (Hofmann and Borgstrom, 1962; Hernell et al., 1990), monoglycerides, cholesterol and gastric enzymes. The composition of the fed state gastric fluid (FSGES) is outlined in Table 1. A bile salt concentration of 0.5 mM was used as an upper limit estimate for the fed state (gastric) (Fimmel and Blum, 1983). The other lipid concentrations were estimated from the composition of the stomach contents one hour after ingestion of a test meal (Armand et al., 1996). Under these conditions, the concentration of phospholipids in the stomach is approximately 3 mM due to their contribution from food (Armand et al., 1996).

The pH profile of the gastric region has been previously described (Dressman et al., 1990; Hörter and Dressman, 1997). In accordance with these findings, we have employed representative pH values of 1.5 and 5.0 for the fasted and fed states, respectively. In addition, several surfactant solutions advocated for use as dissolution media (Dressman et al., 1998; Galia et al., 1999) and milk, which has been proposed as reasonably physiologically representative of the fed state stomach (Dressman et al., 1998), were evaluated.

It is important to note that the media designed for this study have been formulated to examine the influence of the components in gastric fluids most likely to have an impact on wetting properties. Other factors relevant to dissolution, such as buffer capacity, solubilization, etc., have not been specifically addressed. Furthermore, these formulations represent a starting point for examining the role of various physiologic components of gastric fluids; as formulated they are not necessarily complete representations of gastric fluids.

Table 1
Composition of fed state gastric emulsion system (FSGES)

Component	Concentration (mM)
Taurodeoxycholate	0.5
Lauric acid	10
Sesame oil[a]	150
Lecithin	1.5
Lysolecithin	1.5
NaCl	8.6
KCl	32.2
PH	5

[a] Based on an weighted average MW derived from the major fatty acids in the oil.

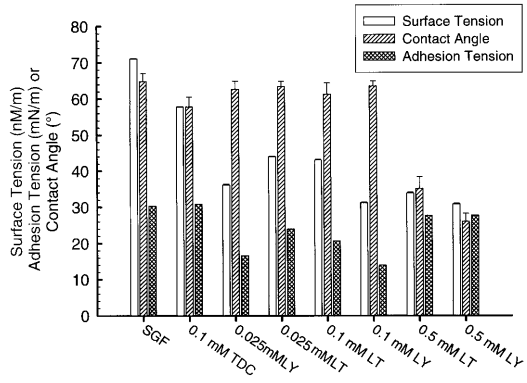

Fig. 1. Surface tensions of solutions simulating the amphiphile composition of the fasted state stomach and their contact angles and adhesion tensions on PMMA. All solutions at approximately pH 1.2. Error bars = S.D. All systems containing phospholipids (LY or LT) made in 0.1 mM TDC.

3.2. Wetting by simulated fasted state gastric fluids

As described above, mixtures of bile salt (TDC) and phospholipid were used to simulate the gastric fluid in the fasted state. At 0.1 mM TDC, a concentration representing the upper limit of bile salt concentration for the gastric region, the solution did not promote wetting as observed by the equivalent value of adhesion tension relative to SGF (Fig. 1). The surface tension of fasted state gastric juice ranges from 35 to 45 mN/m (Finholt and Solvang, 1968; Efentakis and Dressman, 1998). However, 0.1 mM TDC cannot reduce the surface tension to the values observed in gastric juice despite being one of the more surface active bile salts (Roda et al., 1983) (Fig. 1). Therefore, other components in the gastric fluid must be contributing to the surface tension lowering; but they have not yet been conclusively identified (Spychal et al., 1990; Efentakis and Dressman, 1998). LY has been shown to increase dissolution and particle deaggregation at micellar and premicellar concentrations (Lin et al., 1968; Weintraub and Gibaldi, 1969). Fell and Mohammad (1995) also observed that diluted gastric juice provided

better wetting than bile salt solutions on phenobarbitone.

Addition of 0.025 or 0.1 mM of either LT or LY reduces the surface tension to within the range observed in stomach aspirates (Fig. 1). Therefore, phospholipids may be a significant factor influencing the surface tension of gastric fluids. Note that despite the surface tension decrease relative to 0.1 mM TDC alone, there is not a commensurate reduction in the contact angle. However, an increase in the phospholipid concentration to 0.5 mM results in a significant reduction in contact angle and an overall improvement in wetting of the surface, as indicated by the higher adhesion tension. Comparison of the surface tension to the adhesion tension gives an indication of the completeness of wetting. However, the approach to complete wetting may not be directly proportional to surface tension reduction as has been shown for bile salts and surfactants wetting PMMA (Luner et al., 1996; Luner, 2000).

The surface tension was not reduced significantly when LY was increased to 0.5 mM compared to a 10 mN/m change for LT. The differences in wetting observed for LT and LY over this concentration range (0.025–0.5 mM) indicate that specific concentration dependent interactions between the substrate surface and lipid are a factor influencing wetting. At 0.1 mM TDC, the bile salt concentration is below the apparent CMC, however, LY alone is capable of micellization at low concentrations (Robinson and Saunders, 1958). LT is an insoluble swelling amphiphile and although it does not form micelles by itself, it is capable of forming other structures. It is not clear from the data available in this study to what extent aggregation behavior in solution and at the surface influence the wetting behavior.

3.3. Wetting by simulated fed state gastric fluids

To simulate the gastric contents in the fed state, a dispersion was prepared as shown in Table 1. The wetting behavior of this fed state gastric emulsion (FSGES) was significantly different from the 0.1 mM TDC/0.1 mM phospholipid solutions (Fig. 2). The surface tension of FSGES was slightly lower than the TDC-phospholipid solutions, but the contact angle was reduced markedly, resulting in an increase in the adhesion tension. A similarly composed solution without triglycerides showed a higher contact angle and slightly poorer wetting indicating that triglycerides may have an influence on the behavior of the lipids at the surface of the substrate. This is in contrast to similar experiments with and without an oil phase simulating intestinal fluids where no difference was observed (Luner and VanDer Kamp, 2000). On the basis of these solution compositions and using PMMA as a model surface, the wetting characteristics of the fasted versus the fed state in the gastric region appear to be different.

3.4. Comparison to surfactant and other media

An 8.68 mM (2.5×10^{-3} g/ml) SDS solution in a low pH buffer has been proposed as a test medium simulating fasted state gastric conditions (Dressman et al., 1998). The surface tension of this solution falls in the lower limit of observed surface tensions (fasted state) and is in between the TDC-phospholipid (0.1 mM) solutions (Fig. 1). For the 8.68 mM SDS solution, wetting was complete ($\theta = 0°$) well within the 5 min measurement interval. When this SDS solution was di-

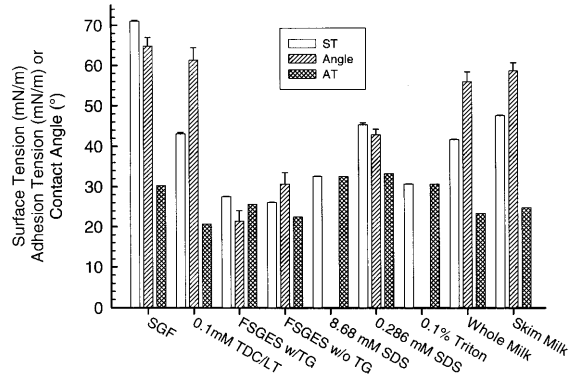

Fig. 2. Surface tensions of solutions simulating the amphiphile composition of the fed state stomach, surfactant solutions, and milk and their contact angles and adhesion tensions on PMMA. Where no bars are included for contact angle indicates complete wetting ($\theta = 0°$) was observed within the experimental time frame (5 min). SGF and 0.1 mM TDC/0.1 mM LT included for comparison. Error bars = S.D.

luted (0.286 mM) to achieve a surface tension that was at the upper limit of the physiologic range (35–45 mN/m), its wetting was still more effective than the TDC-phospholipid solutions based on the PMMA contact angles (Fig. 2).

Fig. 2 also shows the results for a 0.1% Triton X-100 solution which has been suggested as a medium representing in vivo conditions. The Triton X-100 solution wet the PMMA surface completely ($\theta = 0°$) within 140 s. This is in contrast to the bile salt-phospholipid solutions (Fig. 1) which demonstrated large and stable contact angles. Interestingly, the solutions of 8.68 mM SDS, 0.1% Triton X-100, and TDC/LT are all approximately equivalent in surface tension, but there was considerable variation in wetting of the surface. Clearly, the nature of the amphiphiles and their interactions at the liquid–vapor and solid-liquid interfaces are controlling the wetting rather than the surface tension itself (Pyter et al., 1982; Luner et al., 1996; Luner, 2000).

At bile salt and phospholipid levels representing the upper limit of physiological values in the fasted state in the stomach (i.e. 0.1 mM TDC/0.1 mM phospholipid), the SDS and Triton X-100 surfactant solutions (at their respective concentrations) do not exhibit similar wetting properties on the PMMA surface. Indeed, the surface and wetting behavior of these synthetic surfactant solutions are more comparable to FSGES. Overall, the wetting of the dispersions formulated in this study corresponding to the fasted and fed states were very different compared to the other surfactant solutions evaluated. These findings suggest that some synthetic surfactants, depending on both their surface tension and concentration, may have provide greater wetting for a given surface relative to bile salt-lipid solutions representative of physiologic conditions.

Both whole and skim milk were also evaluated (Fig. 2) because it has been suggested that these media (representative of the fed state) are useful for forecasting in vivo performance from in vitro dissolution (Nicolaides et al., 1999). Whole and skim milk had significantly higher surface tensions than the fed state emulsion systems by more than 15–20 mN/m and displayed much higher contact angles ($\approx 25–35°$). Whole milk is a good representation of the fat, protein and carbohydrate content of the fed gastric fluid. However, if surface tension is an important factor to simulate, then some adjustment of its surface tension may be considered.

Table 2
Work of adhesion (W_a), adhesion tension (AT) and spreading coefficient (SC) for solutions representing the fed and fasted state gastric fluid and surfactant solutions on PMMA[a]

Solution	W_a	AT	SC
SGF w/o pepsin	101.2	30.2	−40.8
0.1 mM TDC in SGF	88.6	30.8	−27.0
0.1 mM TDC/ 0.1 mM LY in SGF	45.1	13.9	−17.3
0.1 mM TDC/ 0.1 mM LT in SGF	63.8	20.7	−22.4
8.68 mM SDS in SGF	65.2	32.6	0.0
Triton X-100 @ 0.1% in SGF	61.4	31.7	0.0
Fed state emulsion w/ TG pH 5.0	53.1	25.6	−1.9
Whole milk	65.0	23.4	−18.2

[a] All values in mN/m.

3.5. Stages of wetting

It is useful to consider the thermodynamic stages involved in the wetting process (Parfitt, 1973) to compare the wetting properties of the various solutions in Figs. 1 and 2. The values for W_a, AT and SC are shown for selected solutions in Table 2. The addition of bile salts and phospholipids to the low pH buffer reduced the work of adhesion indicating that the phospholipids interfere with the interaction of water at the PMMA surface. They also lower the adhesion tension considerably, reducing the spontaneity of immersional wetting.

Comparison of the two surfactant solutions, which completely wet the surface, to the TDC/phospholipid solutions representing the fasted state gastric conditions (at 0.1 mM phospholipid), shows that TDC/phospholipid solutions have large (negative) values of SC. This indicates that spreading wetting does not occur spontaneously. This suggests that the spreading process for the TDC/phospholipid solutions would require more work than that for the surfactants. Comparison of

whole milk to the fed state emulsion systems shows that the spreading process is more spontaneous for the simulated gastric emulsion. Therefore, fat digestion by-products may be important components contributing to wetting in the fed state.

Solely relying on contact angle measurements as a basis for evaluating wetting does not provide a full description of wettability (Myers, 1988). Analysis of the stages of wetting provides a more descriptive means by which to compare wetting behavior. Although these results are somewhat specific to surfaces similar in energetics to PMMA, they demonstrate that various factors contribute to wetting and that emulation of surface tensions equivalent to that in the stomach cannot be expected to provide equivalent wetting for a surface. The magnitude of the spreading coefficient has been used as a reasonable predictor for the dispersibility of powders (Young and Buckton, 1990). The present findings show that the Triton X-100 and SDS solutions evaluated in this study are much more effective in wetting PMMA than the formulated solutions in this study emulating the fasted state gastric region. Thus, relative to surfaces like PMMA, the SDS and Triton X-100 solutions evaluated here may over-express the factor of wetting when used as dissolution media. Conversely, in vivo fluids, as modeled by the bile salt-lipid solutions used in this study, may not wet surfaces like PMMA as readily as some surfactant solutions. Consequently, slower dissolution of substrates with similar surface energetics may take place in vivo relative to dissolution in vitro with these surfactants.

3.6. Wetting kinetics

An additional characteristic difference in the wetting behavior of FSGES versus the TDC/phospholipid solutions simulating the fasted state was the kinetics of wetting and spreading. Wetting kinetics, as revealed by the changes in contact angle and drop width with respect to time, give additional insight into wetting process. FSGES showed a rapid decrease in the contact angle as a function of time, reaching a stable plateau after about 2 min with a total change of approximately 25° (Fig. 3). The 0.1 mM TDC/0.1 mM phospholipid solution had a total change in contact angle of about 13° but remained above 60°. Very little change in the spreading for the 0.1 mM TDC/0.1 mM phospholipid solution was observed (0.1 mm height, < 0.1 mm width). However, for FSGES, a significant change in height (> 0.2 mm) and width (> 0.5 mm) was noted. Increasing the LY concentration to 0.5 mM in the 0.1 mM TDC solution resulted in a significant alteration in the spreading kinetics relative to 0.1 mM LY. This is indicative of alteration of the dynamic equilibria at the three phase line (Stoebe et al., 1997). The kinetic behavior of all the other solutions was bounded by these two solutions. The dynamics of spreading of surfactant solutions is dependent on many factors including, adsorption kinetics at the three phase line, diffusional effects, surface tension gradients and viscoelastic effects (Damania and Bose, 1986; Stoebe et al., 1997; Langevin, 1998). However, it is likely that the phenomena governing the attainment of the quasi-equilibrium values seen in Fig. 3 are important in dynamic penetration processes (Hodgson and Berg, 1988).

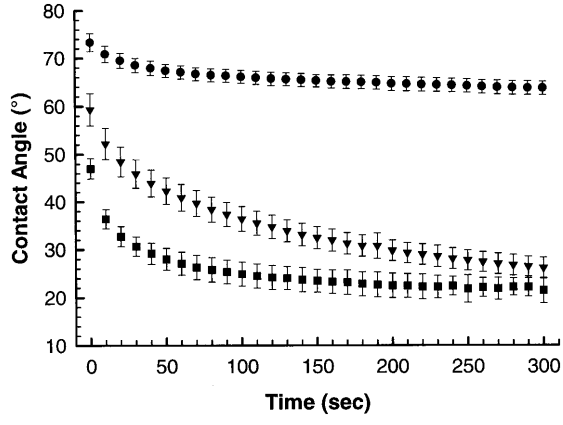

Fig. 3. Contact angle of solutions on PMMA as a function of time. (●): 0.1 mM TDC + 0.1 mM LY; (▼): 0.1 mM TDC + 0.5 mM LY; (■): Fed state gastric emulsion (FSGES). Error bars = S.D.

4. Conclusions

The results of these studies have shown that for a given surface, solutions representing the upper range of physiologic bile salt and lipid concentrations found in gastric fluids in the fed and fasted states can show distinctly different wetting characteristics as determined by quasi-static contact angle measurements. It is noted, however, that these studies have only evaluated the PMMA surface. These differences may be more or less pronounced for other surfaces. The extent to which the differences in wetting observed in these studies, as revealed by adhesion tension and spreading coefficient, are manifest in wetting processes for systems of capillary beds (tablets and capsules) needs to be determined. Nevertheless, the results of this study demonstrate that assessment of the interaction of physiologic components with pharmaceutical surfaces is needed and they serve as a starting point for evaluation of media on a range of surfaces.

It has been suggested that inclusion of surface active agents in dissolution media is important for poorly soluble compounds because lack of a surface tension lowering agent would result in poorer wetting and in vitro dissolution rates that are not representative of in vivo rates (Galia et al., 1999). The results of the present study suggests that a given surfactant utilized to produce wetting similar to in vivo systems may indeed show characteristically different behavior for a particular surface. Consequently, when selecting a surfactant to emulate the properties of gastric fluids for a particular surface, it may be useful to compare the wetting of a surfactant-based dissolution media to that of media simulating in vivo conditions to ensure that a reasonable correspondence in wetting properties is achieved.

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References

Abdou, H.M., 1989. Dissolution, Bioavailability and Bioequivalence. Mack, Easton, PA, pp. 37–52.

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailabilty. Pharm. Res. 12, 413–420.

Armand, M., Borel, P., Dubois, C., Senft, M., Peyrot, J., Salducci, J., Lafont, H., Lairon, D., 1994. Characterization of emulsions and lipolysis of dietary lipids in the human stomach. Am. J. Physiol. 266, G372–G381.

Armand, M., Borel, P., Pasquier, B., Dubois, C., Senft, M., Andre, M., Peyrot, J., Salducci, J., Lairon, D., 1996. Physicochemical characteristics of emulsions during fat digestion in human stomach and duodenum. Am. J. Physiol. -Gastroint. Liver Physiol. 271, G172–G183.

Bates, T.R., Lin, S.-L., Gibaldi, M., 1967. Solubilization and rate of dissolution of drugs in the presence of physiologic concentrations of lysolecithin. J. Pharm. Sci. 56, 1492–1495.

Cohen, J.L., Hubert, B.B., Leeson, L.J., Rhodes, C.T., Robinson, J.R., Roseman, T.J., Shefter, E., 1990. Development of USP dissolution and drug release standards. Pharm. Res. 7, 983–987.

Damania, B.S., Bose, A., 1986. Effects of surfactants in the spreading of liquids on solid surfaces. J. Colloid Interface Sci. 113, 321–335.

de Lourdes Costa, M., Baszkin, A., 1985. The effect of the surface free energy of pharmaceutical tablets on liquid penetration. J. Pharm. Pharmacol. 37, 455–460.

de Villiers, M.M., Lotter, A.P., van der Watt, J.G., 1993. Influence of surfactants and interactive mixing on the cohesive properties of a poorly wettable solid. Powder Technol. 75, 159–165.

Dewar, P., King, R., Johnston, D., 1982. Bile acid and lysolecithin concentrations in the stomach in patients with duodenal ulcer before operation and after treatment by highly selective vagotomy, partial gastrectomy, or truncal vagotomy and drainage. Gut 23, 569–577.

Dressman, J.B., Amidon, G.L., Reppas, C., Shah, V.P., 1998. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm. Res. 15, 11–22.

Dressman, J.B., Berardi, R.R., Dermentzoglou, L.C., Russell, T.L., Schmaltz, S.P., Barnett, J.L., Jarvenpaa, K.M., 1990. Upper gastrointestinal (GI) pH in young, healthy men and women. Pharm. Res. 7, 756–761.

Efentakis, M., Dressman, J.B., 1998. Gastric juice as a dissolution medium: Surface tension and pH. Eur. J. Drug Metab. Pharmacokin. 23, 97–102.

Fell, J.T., Mohammad, H.A.H., 1995. The wetting of powders by bile salt solutions and gastric juice. Int. J. Pharm. 125, 327–330.

Fimmel, C.J., Blum, A.L., 1983. Bile in the Stomach. In: Barbara, L., Dowling, R.H., Hofmann, A.F., Roda, E. (Eds.), Bile Acids in Gastroenterology. MTP Press, Boston, pp. 129–143.

Finholt, P., Solvang, S., 1968. Dissolution kinetics of drugs in human gastric juice-the role of surface tension. J. Pharm. Sci. 57, 1322–1326.

Galia, E., Hörton, J., Dressman, J.B., 1999. Albendazole generics — A comparative in vitro study. Pharm. Res. 16, 1871–1875.

Galia, E., Nicolaides, E., Hörter, D., Löbenberg, R., Reppas, C., Dressman, J.B., 1998. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm. Res. 15, 698–705.

Ganderton, D., 1969. Effect of distribution of magnesium stearate on the penetration of a tablet by water. J. Pharm. Pharmacol. 21, 9S–18S.

Hansford, D.T., Grant, D.J.W., Newton, J.M., 1980. The influence of processing variables on the wetting properties of a hydrophobic powder. Powder Technol. 26, 119–126.

Heertjes, P.M., Witvoet, W.C., 19690. Some aspects of the wetting of powders. Powder Technol. 3, 339–343.

Hernell, O., Staggers, J.E., Carey, M.C., 1990. Physical–chemical behavior of dietary and biliary lipids during intestinal digestion and absorption. 2. Phase analysis and aggregation states of luminal lipids during duodenal fat digestion in healthy adult human beings. Biochem. 29, 2041–2056.

Hodgson, K.T., Berg, J.C., 1988. The effect of surfactants on wicking flow in fiber networks. J. Colloid Interface Sci. 121, 22–31.

Hofmann, A.F., 1976. The enterohepatic circulation of bile acids in man. Adv. Intern. Med. 21, 501–534.

Hofmann, A.F., Borgstrom, B., 1962. Physicochemical state of lipids in intestinal content during their digestion and absorption. Fed. Proc. 21, 43–50.

Hörter, D., Dressman, J.B., 1997. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv. Drug Deliv. Rev. 25, 3–14.

Kerc, J., Srcic, S., Planinsek, O., Kofler, B., 1994. Contact angles and surface free energy parameters of some 1,4-dihydropyridine calcium antagonist powders. Farmacevtski Vestnik 45, 347–357.

Langevin, D., 1998. Dynamics of surfactant layers. Curr. Opin. in Colloid & Interface Sci. 3, 600–607.

Lerk, C.F., Bolhuis, G.K., 1977. Interaction of lubricants and colloidal silica during mixing with excipients. II. Its effect on wettability and dissolution velocity. Pharm. Acta Helv. 52, 39–44.

Lin, S.-L., Menig, J., Lachman, L., 1968. Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water-insoluble drugs. J. Pharm. Sci. 57, 2143–2148.

Liu, J., Stewart, P.J., 1998. Deaggregation during the dissolution of benzodiazepines in interactive mixtures. J. Pharm. Sci. 87, 1632–1638.

Lowenthal, W., 1972. Disintegration of tablets. J. Pharm. Sci. 61, 1695–1711.

Luner, P.E., 2000. Wetting properties of bile salt solutions and dissolution media. J. Pharm. Sci. 89, 382–395.

Luner, P.E., Babu, S.R., Mehta, S.C., 1996. Wettability of a hydrophobic drug by surfactant solutions. Int. J. Pharm. 128, 29–44.

Luner, P.E., VanDer Kamp, D., 2001. Wetting behavior of bile salt-lipid dispersions and dissolution media patterned after intestinal fluids, J. Pharm. Sci., 90, 348–359.

Murthy, K.S., Samyn, J.C., 1977. Effect of shear mixing on in vitro drug release of capsule formulations containing lubricants. J. Pharm. Sci. 66, 1215–1219.

Myers, D., 1988. Surfactant Science and Technology, VCH Publishers, Inc., New York, pp.349–379; 273–325.

Nicolaides, E., Galia, E., Efthymiopoulos, C., Dressman, J.B., Reppas, C., 1999. Forecasting the in vivo performance of four low solubility drugs from their in vitro dissolution data. Pharm. Res. 16, 1876–1882.

Noory, C., Tran, N., Ouderkirk, L., Brown, S., Perry, J., Lopez, J., Colon, M., Faberlle, M., Henry, K., Rorberg, J., Ali, S.N., Shah, V., 1999. Rethinking the use of water as a dissolution medium. Dissolution Technologies 6 (4), 6–7.

Parfitt, G.D., 1973. Fundamental aspects of dispersion. In: Parfitt, G.D. (Ed.), Dispersion of Powders in Liquids. John Wiley & Sons, New York, pp. 1–43.

Pyter, R.A., Zografi, G., Mukerjee, P., 1982. Wetting of solids by surface-active agents: The effects of unequal adsorption to vapor–liquid and solid–liquid interfaces. J. Colloid Interface Sci. 89, 144–153.

Robinson, N., Saunders, L., 1958. The physical properties of lysolecithin and its sols. J. Pharm. Pharmacol. 10, 384–391.

Roda, A., Hofmann, A.F., Mysels, K.J., 1983. The influence of bile salt structure on self-association in aqueous solutions. J. Biol. Chem. 258, 6362–6370.

Samyn, J.C., Jung, W.Y., 1970. In vitro dissolution from several experimental capsule formulations. J. Pharm. Sci. 59, 169–175.

Schersten, T., 1973. Formation of lithogenic bile in man. Digestion 9, 540–553.

Shah, V.P., Noory, A., Noory, C., McCullough, B., Clarke, S., Everett, R., Naviasky, H., Srinivasan, B.N., Fortman, D., Skelly, J.P., 1995. In vitro dissolution of sparingly water-soluble drug dosage forms. Int. J. Pharm. 125, 99–106.

Slomiany, A., Slomiany, B.L., Witas, H., Zdebska, E., Galicki, N.I., Newman, L.J., 1983. Lipids of gastric secretion in patients with cystic fibrosis. Biochim. Biophys. Acta 750, 253–260.

Solvang, S., Finholt, P., 1970. Effect of tablet processing and formulation factors on dissolution rate of the active ingredient in human gastric juice. J. Pharm. Sci. 59, 49–52.

Spychal, R.T., Savalgi, R.S., Marrero, J.M., Saverymuttu, S.H., Kirkham, J.S., Northfield, T.C., 1990. Thermodynamic effects of bile acids in the stomach. Gastroenterology 99, 305–310.

Stoebe, T., Hill, R.M., Ward, M.D., Davis, H.T., 1997. Enhanced spreading of aqueous films containing ionic surfactants on solid substrates. Langmuir 13, 7276–7281.

US Pharmacopeia XXIII, 1995. United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 2053.

Weintraub, H., Gibaldi, M., 1969. Physiological surface active agents and drug absorption: IV. Effect of pre-micellar concentrations of surfactants on dissolution rate. J. Pharm. Sci. 58, 1368–1372.

Young, S.A., Buckton, G., 1990. Particle growth in aqueous suspensions: The influence of surface energy and polarity. Int. J. Pharm. 60, 235–241.

Zografi, G., Tam, S.S., 1976. Wettability of pharmaceutical solids: Estimates of solid surface polarity. J. Pharm. Sci. 65, 1145–1149.

Zuidema, H.H., Waters, G.W., 1941. Ring method for the determination of interfacial tension. Ind. Eng. Chem. 13, 312–313.