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Surface treatment of the hydrophobic drug danazol to improve drug dissolution

S. Brown [a], G. Rowley [b,*], J.T. Pearson [b]

[a] *Sanofi Winthrop Pharmaceuticals Research Division, Alnwick, Northumberland, NE66 2JH, UK*
[b] *School of Health Sciences, Pasteur Building, University of Sunderland, Sunderland, SR2 7EE, UK*

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Abstract

The adsorption of the surfactant docusate sodium USP from aqueous solution onto the hydrophobic drug danazol USP has been investigated in relation to wetting and drug dissolution. An adsorption isotherm was constructed after equilibration of the drug in surfactant solutions with initial concentrations in the range 0.1 to 10^4 μM to determine docusate sodium uptake using the solution depletion technique. Danazol samples were treated with aqueous surfactant solutions at 30°C for 24 h, followed by filtration and drying of the treated drug. The treated and untreated samples were compared using particle dispersion, microelectrophoresis, contact angle and in vitro drug dissolution techniques and the results used to elucidate mechanisms for adsorption and consequent changes in drug dissolution. In all cases, the adsorbed docusate sodium improved the wetting and dissolution of the hydrophobic drug danazol. Reduction in contact angle from 91° for untreated danazol to 62° was achieved at typically low (0.02% w/w) surfactant uptake values, with a corresponding increase in drug dissolution rate.

Keywords: Drug dissolution; Hydrophobic solid; Particle wetting and dispersion; Solid surface treatment; Surfactant adsorption

1. Introduction

Hydrophobic drugs of low aqueous solubility frequently present a number of problems in the formulation and manufacture of oral solid dosage forms arising from poor wetting and dissolution characteristics. Improvement in drug dissolution may be achieved by altering the physical characteristics of the drug or use of solid dispersions to increase effective surface area (Sekiguchi and Obi, 1961; Hargreaves et al., 1979; Geneidi et al., 1981). The use of surfactants as formulation adjuvants to improve drug dissolution by enhanced wetting (Reddy et al., 1976), micellar solubiliza-

* Corresponding author.

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tion (Bakatselou et al., 1991) and deflocculation (Schott et al., 1982) has also been widely studied.

An alternative approach involves the physical adsorption of surfactant from solution onto the surface of hydrophobic drug particles and the subsequent recovery of the treated drug particles for encapsulation or tabletting (Rowley, 1979). Improved wetting, as indicated by contact angle (θ) measurements using aqueous media, was achieved for the hydrophobic drugs acetohexamide ($\theta = 124°$) and phenylbutazone ($\theta = 108°$) following treatment with aqueous solutions of the cationic surfactant hexadecyl trimethylammonium bromide (HTAB) at concentrations less than the critical micelle concentration (cmc) (Rowley et al., 1985a,b). Adsorption of HTAB by the drug crystals resulted in a reduction of contact angle to 52 and 47° for acetohexamide and phenylbutazone, respectively. In each case, the wetting and rate/extent of dissolution of treated drug samples was enhanced in comparison to the untreated samples. This technique provides an alternative to the empirical addition of relatively large quantities of surfactant to drug/excipient powder mixes. The work reported here relates to the adsorption of the anionic surfactant, docusate sodium USP onto danazol USP, a hydrophobic compound of low aqueous solubility.

2. Materials and methods

2.1. Materials

Danazol USP, micronized (Sanofi-Winthrop, UK), mean particle size 5.4 μm using laser diffraction (Malvern 2600C, Malvern Instruments, Malvern, UK) Docusate sodium USP (Complemix-100®, American Cyanamid Company).

2.2. Adsorption studies

Preliminary investigations ascertained that the equilibration time for the adsorption of docusate sodium onto danazol was achieved within 24 h at 30°C.

Known quantities of micronized danazol (~ 0.2 g) were added to solutions (15 ml) of docusate sodium ($0.1–10^4$ μM) saturated with danazol and equilibrated for 24 h at 30°C/300 rpm in a shaking waterbath (Aquatron, Infors, Bottmingen, Germany). Samples (2 ml) of suspension were removed using a pipette, centrifuged for 15 min at 13000 rpm using a microcentrifuge (Micro Centaur 1000, MSE, Loughborough, UK) and an aliquot (1.0 ml) of the supernatant assayed for surfactant. The analytical method depends on the formation of an ion associate with the dye cation ethyl violet, extraction of the ion associate into toluene and spectrophotometric assay at λ_{max} (611 nm). The method used was a modification of that described by Motomizu et al. (1982), using a shaking time of 25 min and a standing time of 5 min before measuring the absorbance of the toluene phase. The assay was reproducible, with a coefficient of variation (cv) $< 4\%$ and linear in the range 0.05–50 μM docusate sodium.

The amount of surfactant adsorbed per gram of danazol was calculated by the solution depletion method based on the difference between initial and final (equilibrium) concentrations and an adsorption isotherm was constructed.

Fig. 1 shows that a Langmuir type adsorption isotherm is obtained at low equilibrium surfactant concentrations up to ≈ 400 μM. Further adsorption occurs at higher concentrations (Fig. 2) up to a maximum in the region of the cmc (4150 μM), determined in a saturated solution of danazol.

Solutions of docusate sodium (250 ml) at initial concentrations of 40 μM (within the Langmuir region), 250 μM (near plateau of Langmuir region), 2000 μM (within the secondary adsorption phase) and 5000 μM (in the region of maximum surfactant adsorption) were added to glass stoppered flasks containing 4.0 g of danazol. These were sealed and equilibrated in a shaking waterbath (Aquatron, Infors) at 30°C/300 rpm for 24 h. Danazol was recovered by filtering the suspensions through a prefilter (1340047S, Sartorious, Gottingen, Germany) and then rinsing lightly by filtering Water for Injection EP (50 ml) through the filter cake of retained drug.

The recovered danazol crystals were dried at 50°C in a vacuum oven for 60 h. Any large aggregates were broken down by gently pressing with a spatula and the treated danazol was stored

in a sealed container at room temperature for use in wetting and dissolution studies.

2.3. Drug dispersion and particle micro-electrophoresis

Uniform suspensions of danazol (0.2 g) in 15 ml of docusate sodium solutions ($0.05–10^4$ μM) were obtained by sonicating samples in 20 ml screw capped glass containers for 10 min. Visual observation of particle sedimentation behaviour was recorded after standing at room temperature for 2, 24 and 168 h. Suspensions of danazol (50 mg) in Water for Injection EP (15 ml) adjusted to pH 1, 3, 5, 7 and 10 using hydrochloric acid 0.1M or sodium hydroxide 0.1M, were mixed in sealed test tubes in a shaking waterbath (Aquatron, Infors) at 300 rpm for 24 h at 37°C. Samples of each

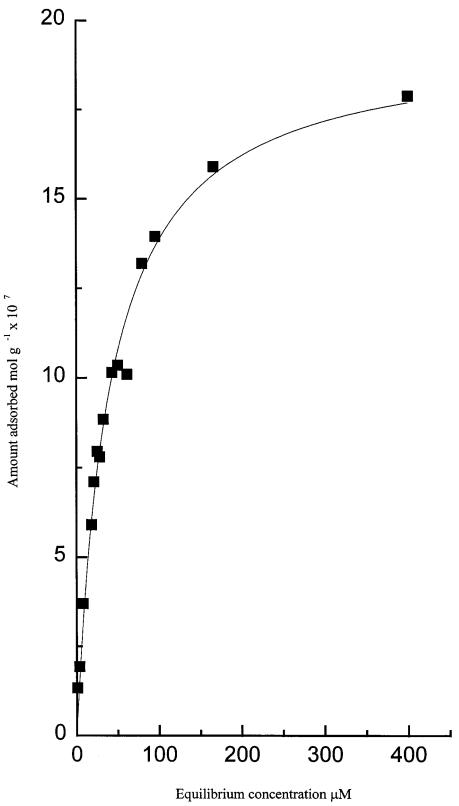


Fig. 1. Adsorption of docusate sodium from aqueous solution onto danazol at low equilibrium surfactant concentrations at 30°C.

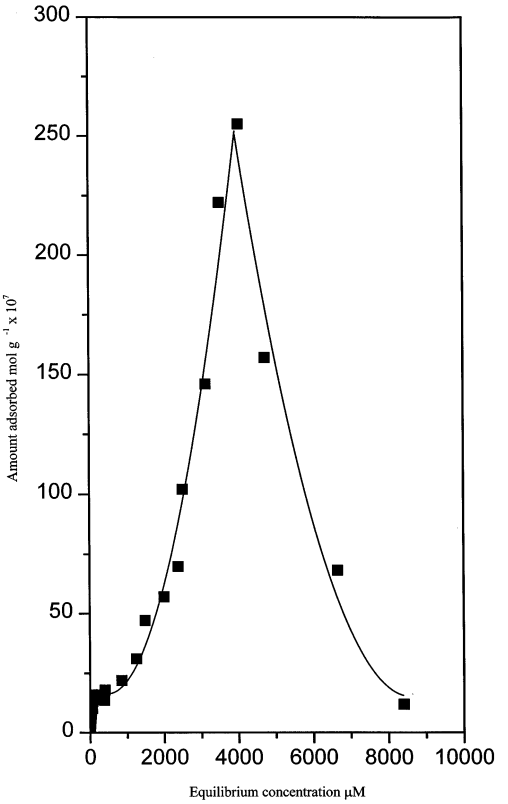


Fig. 2. Adsorption of docusate sodium from aqueous solutions onto danazol at high equilibrium concentrations at 30°C.

suspension were then diluted with Water for Injection EP and the pH was readjusted to 1, 3, 5, 7 and 10. The pH of these test suspensions was measured prior to, and during particle micro-electrophoresis using apparatus (Malvern Zetasizer 4, Malvern Instruments) fitted with a standard cylindrical electrophoresis cell (Malvern Zet 5104).

Measurements were carried out at 16°C in the stationary layer at a distance from the cell wall of 14.62% of the cell radius. The dielectric constant was set at 81.8 and the viscosity was automatically calculated by the software as that of water at 16°C. Measurements were conducted in the normal cross-beam mode, and the system alignment and set-up were checked using an electrophoresis standard (Malvern AZ55) when calibration values were found to lie within the accepted range of 55 ± 4 mV. All ζ potential values are reported as the mean of six determinations on a single sample.

Micro-electrophoresis measurements were also conducted on suspensions of danazol in docusate sodium solutions ($1–10^4$ μM) adjusted to pH 5.0 with hydrochloric acid 0.1M using conditions outlined above.

2.4. Contact angle determinations

Compacts of treated and untreated danazol were prepared at a pressure of 100 MPa on a physical testing machine (L6000R, J.J. Lloyd Instruments, Fareham, UK) fitted with flat faced cylindrical 19 mm diameter punches. The die walls were pre-lubricated with 4% magnesium stearate in methanol and compression and ejection speeds of 50 and 30 mm/minute, respectively, were employed. These compacts were used for contact angle determination according to the h-ε method proposed by Heertjes and Kossen (1967). A drop of liquid, saturated with respect to the solid phase was progressively formed on the compact, which itself had been previously saturated with liquid. The maximum height (h) of the drop on the drug surface was measured using a cathetometer and the porosity of the compact (ε) was calculated from compact dimensions, mass and density of danazol. From this data the contact angle was calculated using the equations given by Heertjes and Kossen (1967) and the results are the mean of values for four compacts of each powder sample.

2.5. Dissolution studies

Known quantities (50 ± 0.7 mg) of danazol powder, prepared by treatment with docusate sodium as described in Section 2.2, and a similar quantity of untreated danazol were hand filled into size 0 hard gelatin capsules (white, opaque Posilok® Elanco, Basingstoke, UK) and subjected to the USP XXII method 2 dissolution test. The medium consisted of 900 ml of propan-2-ol in 0.1 M hydrochloric acid (4 parts propan-2-ol to 6 parts acid) with a paddle speed of 80 rpm. Danazol solubility in this medium was 0.912 mg ml^{-1} at 37°C implying that sink conditions were applicable to the tests. An automated dissolution testing system (89026A, Hewlett Packard, Stockport, UK) attached to a UV spectrophotometer (8451A, Hewlett Packard) and a dissolution unit (DT6, Erweka, Heusenstamm, Germany) was used. The dissolution of danazol was monitored by the rate of appearance of drug in the dissolution medium as measured by UV spectrophotometry at 286 nm.

An attempt was made to develop a dissolution method which would: (a) provide sink conditions in water; and (b) model more closely the environment in vivo. Known quantities (50.0 ± 0.7 mg) of treated and untreated danazol were hand filled into hard gelatin capsules size 0 and subjected to dissolution testing using a modification of the USP XXII method 2. Dissolution was performed in 800 ml of Water for Injections EP layered with 100 ml of octanol using wing assisted paddles fitted 1 cm above the top of the main paddle rotating at 100 rpm. The octanol was included to provide sink conditions for dissolution of danazol which has an aqueous solubility of 0.4 μg ml^{-1} at 37°C, whereas the solubility in octanol is 21.8 mg $ml^{-1.}$ The dissolution of danazol was monitored by the rate of appearance of the drug in the octanol layer as measured by UV spectrophotometry at 286 nm using the equipment detailed above. Samples (15 ml) of the octanol layer were removed at selected time intervals and replaced with 15 ml of fresh octanol at each sample time.

2.6. Particle size analysis

Analysis was performed using a laser diffraction instrument (Mastersizer, Malvern Instruments) fitted with a 45 mm lens. The powder sample was dispersed in 1.5 mM docusate solution in water and sonicated for 5 min prior to analysis. The mean particle diameter derived from the volume distribution along with 10 and 90% undersize values were determined for danazol and treated danazol samples.

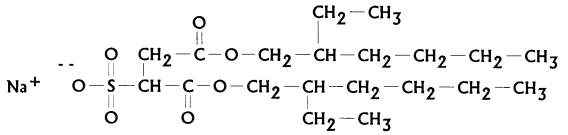
3. Results and discussion

3.1. Adsorption studies

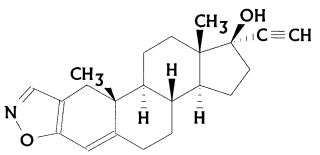
The adsorption isotherm for uptake of docusate sodium on danazol micronized powder is shown

in Figs. 1 and 2. Fig. 1 shows the adsorption at equilibration concentrations from 0.1 to 400 μM, whereas Fig. 2 shows the remaining data for all equilibration concentrations up to 8400 μM docusate sodium. Maximum surfactant adsorption occurs at an equilibrium concentration of $\approx$4000 μM docusate sodium, which is slightly below the cmc for this surfactant. A decrease in adsorption was recorded at equilibrium concentration values above the cmc and this may be due to a decrease in the activity of surfactant monomers in the presence of charged hydrophilic micelles. The micelles provide an energetically favourable location for surfactant molecules in the bulk phase, furthermore the system is of greater complexity due to drug solubilization. The decrease in adsorption cannot, however, be explained by loss of adsorbent surface due to danazol solubilization since the quantity dissolved at 10^4 μM docusate sodium with a danazol solubility of 12.8 μg ml^{-1} at 30°C accounts for only 0.076% w/w of the total quantity of danazol used in the adsorption experiment. An alternative explanation for the decrease in adsorption above the cmc is proposed whereby the repulsion of surfactant micelles from similarly charged surface layers leads to an anomalously high micellar bulk concentration and an underestimation of the true extent of adsorption.

The structure of docusate sodium, as shown in Fig. 3, indicates a hydrophilic negatively charged sulphonate group and a hydrophobic region corresponding to the two esterified octyl chains. Danazol is a heterocyclic steroid with an isoxazole group on the A ring of the parent compound ethisterone (Fig. 3). The molecule is very hydrophobic and has low aqueous solubility which is typical of this series of compounds. Although there are no ionisable groups in the danazol molecule, there is the possibility of a positive charge on the nitrogen atom of the isoxazole ring particularly at low pH and this is supported by ζ potential data in Table 1. During the initial Langmuirian adsorption phase (Fig. 1), adsorption may occur by electrostatic interaction between charged groups of the surfactant and the nitrogen atoms on the danazol surface. The surfactant



docusate sodium



danazol

Fig. 3. Structure of docusate sodium and danazol.

molecules may be adsorbed with the octyl groups oriented towards the aqueous bulk phase, but it is much more likely that they will occupy a flat orientation adjacent to the hydrophobic regions of the danazol surface. However, at the pH of the adsorption measurements (4–6), it is probable that interaction during the Langmuir phase is primarily due to the hydrophobic effect and that electrostatic interaction is absent or only minimally involved.

As the number of sites available for adsorption decreases, the extent of adsorption decreases and commences to level off at $\approx$400 μM. Beyond this equilibrium concentration, additional adsorption occurs through the mechanism of the hydrophobic effect, producing contact between the hydrophobic chains of the surfactant and hydrophobic regions of the danazol crystals or hydrophobic chains of previously adsorbed surfactant

Table 1
Effect of pH on ζ potential of danazol particles in water

pH	ζ Potential (mV)
1.0	5.5 ± 1.6
3.0	-2.4 ± 0.3
5.0	-22.0 ± 1.5
7.0	-36.7 ± 2.3
10.0	-35.7 ± 1.2

molecules. These conclusions are discussed more fully in conjunction with the results obtained from dispersion, micro-electrophoresis and contact angle studies.

3.2. Drug dispersion and particle micro-electrophoresis

Visual observation of the suspensions showed that immediately after mixing, unwetted drug was present at the surface of all samples containing surfactant concentrations up to 250 μM. After 2 h, the quantity of unwetted drug decreased with increasing surfactant concentration and was minimal at a concentration of 250 μM. At concentrations from 10 to 250 μM, the volume of sediment increased, indicating that the drug particles were becoming increasingly flocculated. In contrast, all samples with surfactant concentrations from 1000 to 10000 μM remained cloudy in appearance, i.e. deflocculated, and drug sedimentation was not apparent. After storage for 24 and 168 h, the flocculation zone extended up to 500 μM and suspensions at concentrations above this were deflocculated.

Particle micro-electrophoresis for suspensions of danazol in water adjusted to different pH values are presented in Table 1, whereas results for the drug suspended in docusate sodium solutions 1–10000 μM at pH = 5 are shown in Fig. 4 along with a summary of sedimentation behaviour in the pH range 4–6.

Docusate sodium (Fig. 3) is stable in acidic and neutral pH but hydrolyses slowly under basic conditions. It is assumed that the ionic character of the surfactant remains unchanged over the range of pH used in this work and any differences in adsorption with change in pH can be explained by changes in the adsorbent.

When considering the results for danazol contact angle (Table 2, discussed more fully in Section 3.3) and ζ potential (Table 1), it can be concluded that the danazol surface is predominantly hydrophobic ($\theta = 91°$) with sparsely located negatively charged sites. The increase in negative ζ potential values with increased docusate sodium concentration shown in Fig. 4 is evidence that the surfactant has adsorbed against a negative potential gradient. Furthermore, the contact angle decrease from 91° for untreated drug to 62° for danazol treated at a docusate sodium concentration of 40 μM, shows that a considerable improvement in drug wetting was achieved by treatment at this low surfactant concentration. This evidence suggests that interaction between the branched hydrophobic chains of the surfactant and hydrophobic surface sites on the danazol surface is the primary mechanism for adsorption up to 40 μM surfactant initial concentration.

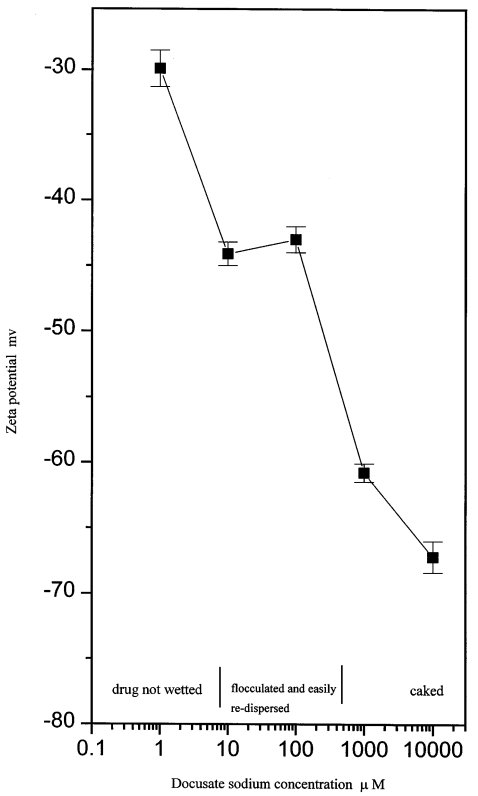


Fig. 4. Effect of docusate sodium concentration on ζ potential for danazol in aqueous media.

Fig. 1 shows a considerable increase in surfactant uptake in the concentration range 10–100 μM, which is not reflected in the values of potential at the plane of shear (Fig. 4). In this concentration range, the flocculated danazol particles

Table 2
Effect of surfactant treatment on surface coverage and contact angle of danazol

Initial docusate sodium concentration (μM)	0	40	250	2000	5000
Equilibrium docusate sodium concentration (μM)	0	25.4	166	1490	4030
% w/w Surfactant/drug	—	0.02	0.07	0.21	1.1
% Surface coverage (end-on orientation)	—	6.0	21	61	327
% Surface coverage (flat orientation)	—	10	36	107	573
Contact angle θ°	91	62	59	56	48

may be stabilized by the adsorbed surfactant molecules such that the ionic groups are oriented towards water pockets trapped within the flocs where they are able to produce only a very small change in potential at the plane of shear. Flocculation may arise due to a degree of interparticle bridging caused by hydrophobic adsorption and particles remain flocculated at surfactant concentrations of 100–2000 μM accompanied by considerable increases in both adsorption and ζ potential in this region. This would suggest that adsorption continues to occur through hydrophobic interactions on the outer envelope of the flocculated particles, with the ionic groups oriented away from the solid surface, thus giving an increase in the negative potential at the plane of shear.

The system becomes deflocculated at docusate sodium concentration >2000 μM and adsorption increases up to the cmc. The calculated values for surface coverage at high equilibrium concentrations given in Table 2 indicate multilayer adsorption. Furthermore, since the ζ potential continues to increase in this region, it may be inferred that more anionic groups of the surfactant become oriented towards the bulk aqueous phase. Deflocculation may therefore be attributed to electrostatic repulsion in addition to the steric effects produced by general multilayer adsorption.

It was postulated that the decrease in adsorption (Fig. 2) above the cmc was due to repulsion of micelles from the similarly charged surface layers at the drug surface and further increase in ζ potential in this concentration range would lend support to this explanation.

3.3. Contact angle determinations

The contact angle values for untreated danazol and four samples of danazol prepared by treatment with docusate sodium are reported in Table 2. The mean value for untreated danazol was 91°, whereas Bakatselou et al. (1991) also used a sessile drop technique but reported a value of 68° for the same drug in contact with water.

The experimental conditions used in the latter work were different from those described in Section 2.4, for example, the compact was not presaturated with measuring liquid, a constant volume, i.e. 2–3 μl of liquid was used to form the sessile drop and the contact angle was measured using a video camera technique. Although differences in θ values may be partly explained by use of different experimental procedures, it is important to consider the later work by Naylor et al. (1995), which reported values of 68 and 35° for danazol in contact with 0.1 and 8 mM sodium taurocholate, respectively, when using the same technique as Bakatselou et al. (1991). These results obtained with sodium taurocholate solutions $>$cmc provide evidence to suggest that a value of $\theta =$ 68°, for danazol with water, is low.

Treatment with a low concentration of docusate sodium (40 μM) produced considerable reduction of the contact angle to 62°. However, only small reductions to 59 and 56°, respectively were observed for danazol treated with 250 and 2000 μM docusate sodium. Thus, a further change in contact angle occurred for samples treated in the secondary adsorption phase and a more substantial decrease to 48° was obtained for the sample with maximum adsorbed surfactant shown in Fig. 2. The contact angles for each

surfactant treated danazol sample were significantly different from each other as demonstrated by the unpaired t-test ($p = 0.05$). These results show that the decrease in hydrophobicity of danazol is most pronounced during the primary adsorption (Langmuir) region of the isotherm but is substantiated during the secondary phase. The calculated % w/w docusate sodium adsorbed onto danazol in the mid-Langmuir phase is 0.02% and this gives an estimated 10% surface coverage using a value of 112 $Å^2$ for the cross sectional area of the docusate sodium molecule, assuming a flat orientation and specific surface area of 2.93 $m^2 g^{-1}$ for danazol. If an end-on orientation is assumed, then the estimated surface coverage would be 6%, using a value of 64 $Å^2$ for the cross sectional area of the docusate molecule. The surface areas occupied per docusate sodium molecule in flat or end-on orientation were determined using molecular modelling (Macro Model) software.

The results in Table 2 show that the hydrophobic nature of the surface can be reduced by use of small quantities of adsorbed surfactant, i.e. 0.02–0.07% w/w. However, the surface could be made more hydrophilic with further reduction in contact angle, provided that the surface coverage of hydrophobic sites could be increased.

It is also clear from the results that the equivalent of monolayer coverage (flat orientation) is achieved using an initial surfactant concentration of 2000 μM corresponding to an equilibrium concentration of 1490 μM. The amount of surfactant adsorbed at an equilibrium concentration of 4000 μM is equivalent to five times the surface area of the danazol, thus providing evidence for multiple layer adsorption. Particle size distribution of drug samples, after treatment with docusate sodium solutions was similar to that of the untreated drug. For example, the drug after treatment with 2000 μM surfactant solution had a mean diameter of7.5 μm and the 10 and 90% undersize diameters were 0.61 and 14 μm, respectively. The mean diameter of untreated danazol was 7.2 μm and the 10 and 90% values were 0.63 and 13.9 μm, respectively. Hence it was assumed that drug surface area did not change during treatment and it is valid to use this value in surface coverage calculations. The % surface coverage values aid the interpretation of the adsorption isotherm and support the formation of a monolayer at low equilibrium concentrations with multiple layer adsorption at high docusate sodium concentrations.

3.4. Dissolution studies

Dissolution results for capsules containing untreated and treated danazol in propan-2-ol/0.1 M HCl are shown in Fig. 5 as % danazol dissolved versus time using the mean values from six capsules. The results from tests in propan-2-ol/0.1 M HCl demonstrate a greater rate and extent of dissolution for all treated danazol capsules compared to untreated danazol capsules, and in addition, the variability in release rate was reduced for treated drug capsules. The rate and extent of drug

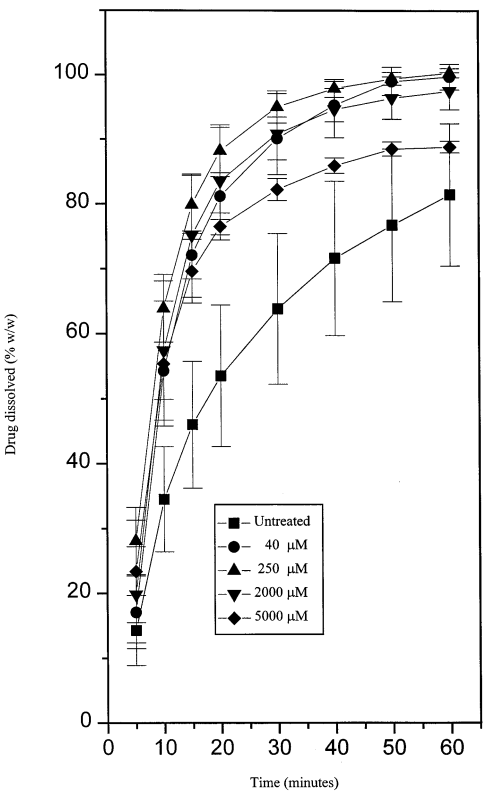


Fig. 5. Drug dissolution in propan-2-ol/0.1MHCl at 37°C from capsules containing surfactant treated and untreated danazol.

Table 3
Docusate sodium available for desorption from danazol during dissolution

Initial surfactant concentration (μmol l^{-1})	Amount of surfactant adsorbed (mol g^{-1})	Amount of surfactant available for desorption from 50 mg (mol)	Surfactant concentration in dissolution media assuming complete desorption (μM)
40	4.5×10^{-7}	2.2×10^{-8}	0.020
250	1.6×10^{-6}	7.9×10^{-8}	0.071
2000	4.7×10^{-6}	2.3×10^{-7}	0.21
5000	2.5×10^{-5}	1.3×10^{-6}	1.2

dissolution from capsules containing treated drug were similar and independent of surfactant concentration up to a treatment value of 2000 μM. Thus, dissolution enhancement at the lowest surface level (40 μM) was equivalent to that observed at the higher surfactant levels of 250 and 2000 μM. The rate and extent of danazol dissolution from capsules containing danazol treated with the highest surfactant level (5000 μM) was greater than that observed for the untreated danazol but was significantly less than for danazol treated at lower concentrations of docusate sodium. Comparison of the time to achieve 75% w/w dissolution (T_{75}) between samples, confirm these observations. The T_{75} for untreated danazol was 46 min, whereas T_{75} values for all treated danazol capsules were in the range of 14–19 min.

It may be postulated that docusate desorption from treated danazol may occur during the dissolution test. Micellization of the docusate may cause solubilization of the danazol, thus explaining the increased rate and extent of dissolution of treated drug. However, if complete desorption of the docusate from danazol is assumed, and the maximum surfactant concentration in the dissolution medium calculated, it is clear this mechanism cannot be supported. Surfactant concentrations in the dissolution medium obtained from these calculations are shown in Table 3 and found to be $\approx$4000–200000 times less than the cmc. However, it may be possible that in the immediate micro-environment of the drug crystal, the surfactant may be in high enough concentration for micellization to occur, hence increasing drug solubilization and dissolution.

Dissolution studies of danazol were undertaken in bile salt solutions (Bakatselou et al., 1991) and bile salts modified by the presence of lecithin (Naylor et al., 1995). This work showed that improvement in danazol dissolution rate was minimal when using either sodium taurocholate or sodium taurocholate/lecithin solutions less than the cmc.

Dissolution enhancement is almost certainly due to improved wetting of the danazol crystals in the presence of adsorbed docusate molecules, however, details of the mechanism of surface modification and its role in the improvement of drug dissolution cannot be provided from this investigation. Evidence for improved wetting and dissolution by surfactant molecules adsorbed at the solid surface rather than in solution was given by Rowley et al. (1985b). In order to achieve equivalent dissolution of untreated acetohexamide to that of treated drug, it was necessary to have a surfactant concentration in the dissolution medium which was 1000 times greater than that attainable by complete desorption of surfactant from the treated drug.

Using the water/octanol medium, the dissolution results (mean % dissolved from three capsules) for all samples, presented in Fig. 6, confirm those obtained in propan-2-ol/0.1 M HCl, with a greater rate and extent of dissolution for all treated danazol capsules compared to untreated danazol capsules. In addition, the variability in release rate was less for treated drug capsules and the rank order of % danazol dissolved from capsules was the same for the two dissolution test methods. The results from dissolution in water confirm that drug treatment by adsorbed surfactant can produce rapid and complete dissolution of a hydrophobic drug at very low concentrations of adsorbed hydrophilic material, e.g. 0.02–0.07% w/w docusate sodium.

The increase in dissolution observed for danazol treated at lower surfactant concentrations, i.e. up to 250 μM, corresponded to the initial adsorption phase on the isotherm and was achieved with up to 0.07 % w/w adsorbed surfactant and calculated surface coverage values of 21 and 36 % for end on and flat molecular orientation, respectively. This surfactant coverage reduced the contact angle of danazol from 90 to 59°. Thus, the considerable reduction in hydrophobicity of the danazol by adsorbed docusate molecules results in improved dissolution of the treated drug and complete dissolution after $\approx$60 min in propan-2-ol/0.1 M HCl and $\approx$120 min in water.

At higher surfactant treatment concentrations $>$250 μM, corresponding to the proposed secondary adsorption mechanism, further decreases in contact angle were obtained (Table 2), however a slight decrease in dissolution rate was observed at the highest treatment concentration, i.e. 5000 μM docusate, although drug release from this sample was still significantly higher than with the untreated sample.

The contact angle value of 48° for the sample treated with the highest concentration of docusate sodium indicates a more hydrophilic surface, however a corresponding increase in dissolution rate was not observed. This may indicate certain limitations of the contact angle technique in predicting dissolution behaviour or a more complex explanation for drug dissolution, including increased wetting and other factors possibly related to the hydrodynamics of the dissolution test, particularly in the case of octanol/water system where drug partitioning and dissolution need to be considered.

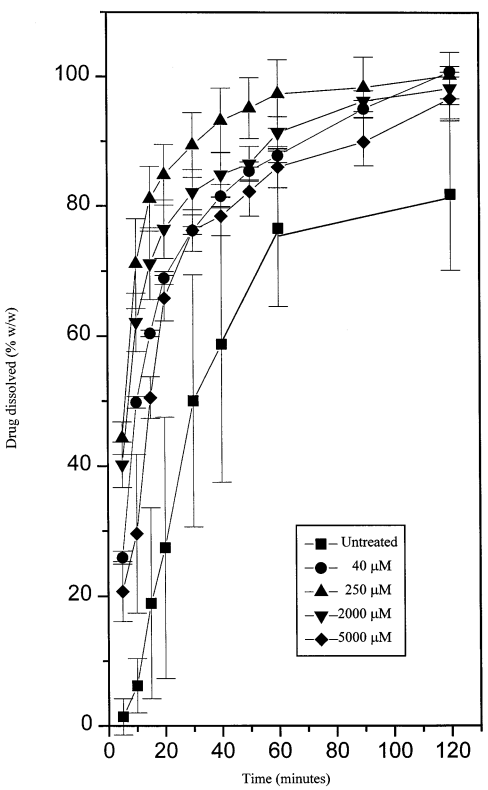


Fig. 6. Aqueous drug dissolution in water/octanol at 37°C from capsules containing surfactant treated and untreated danazol.

4. Conclusions

Evidence for the mechanism of drug surface modification by adsorption of surfactant from aqueous media has been provided from the results of dispersion, particle micro-electrophoresis, contact angle and in vitro dissolution studies. The contact angle of the hydrophobic drug can be reduced considerably with a corresponding change in dispersion and wetting behaviour in aqueous media. The dissolution results confirm improved wetting and dissolution properties for the treated drug samples with a surfactant content as low as 0.02% w/w. This finding provides evidence for the important role of the primary layer of adsorbed surfactant.

Detailed investigations of the crystal surface of danazol and docusate treated danazol are being undertaken in order to further elucidate the mechanism of drug surface modification by surfactant adsorption and its role in the improvement of drug release for treated samples.

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