International Journal of Pharmaceutics, 93 (1993) 221–231

IJP 03182

Surfactant mediated effects in pressurized metered dose inhalers formulated as suspensions. I. Drug/surfactant interactions in a model propellant system

Jeremy G. Clarke [a,1], Stephen R. Wicks [b] and Stephen J. Farr [a]

[a] *Welsh School of Pharmacy, University of Wales College of Cardiff, Cardiff CF1 3XF (UK) and* [b] *Pfizer Ltd, Central Research, Sandwich CT13 9NJ (UK)*

(Received 23 November 1992)
(Accepted 6 January 1993)

Key words: Surfactant; Adsorption isotherm; Electrophoretic mobility; Steric stabilization; Metered dose inhaler; Formulation; Aerosol

Summary

The surface interaction of surfactants (sorbitan trioleate and oleic acid) with various microparticulate systems dispersed in a model chlorofluorocarbon, trichlorotrifluoroethane (P113), has been examined. Oleic acid showed Langmuirian adsorption onto α-alumina, the extent of adsorption inversely proportional to the equilibrium moisture content of the adsorbent. ATR spectroscopy coupled to FTIR was employed to demonstrate that oleic acid adsorbed onto salbutamol via an acid-base reaction resulting in a breakdown of crystal structure at surfactant/drug weight ratios > 0.6. The same surfactant demonstrated relatively poor adsorption onto micronized particulate dispersions of the sulphate and bitartrate salts of isoprenaline. Sorbitan trioleate showed physisorption onto all drug particles; adsorption and multilayer formation were favoured at higher surfactant concentrations and with more hydrophilic surfaces (isoprenaline sulphate > isoprenaline bitartrate > salbutamol). The electrophoretic mobility of salbutamol in P113, determined by laser Doppler velocimetry, became more negative on increasing oleic acid concentration but remained largely unchanged in the presence of sorbitan trioleate. However, in all cases, calculated values for surface zeta potential were very low. The collective data are discussed in relation to the likely mechanism of stabilization of drug dispersions within metered dose inhalers formulated as suspensions.

Introduction

Metered dose inhalers (MDIs) are formulated predominantly as dispersions of a micronised drug in a liquified, chlorofluorocarbon (CFC) blend. Non-ionic surfactants of low HLB value are necessarily incorporated into these formulations to provide stability from inter-particulate aggregation, thus ensuring adequate homogeneity of the suspension and uniformity of emitted dose upon repeated actuation. Despite a long history of use, there is a paucity of published information investigating the mechanisms of surfactant stabilisation in CFC based systems. Empiricism has thus played a necessary if undesirable part of MDI formulation.

Correspondence to: S.J. Farr, Welsh School of Pharmacy, University of Wales College of Cardiff, PO Box 13, Cardiff CF1 3XF, U.K.

[1] Present address: Ciba Geigy Pharmaceuticals Ltd, Wimblehurst Rd, Horsham, West Sussex RH12 4AB, U.K.

For other non-aqueous systems, it is known that dispersion stability can result from steric repulsive forces arising when particles with adsorbed layers collide, and/or electrostatic repulsive forces originating from overlap of the electrical double layers of interacting particles (Pugh et al., 1983). Until recently, the assessment of electrophoretic mobility in non-aqueous media was beset with practical problems. Using a recently developed technique, phase analysis light scattering (PALS) based on laser Doppler electrophoresis, Wyatt and Vincent (1992) showed that some drugs possess inherent charge when dispersed in P113, and that this may be modified by the use of certain surface active agents. On the basis of these findings, they proposed that control of surface charge may be an aid to achieving good dispersion characteristics of drugs in MDI formulations. In contrast, Byron (1990) predicted that steric forces were the only variable which could be reasonably manipulated in MDI formulations. The force of steric repulsion will depend on the molecular characteristics of the adsorbate (i.e., surfactant), and the extent of its adsorption which, in turn, is related to its interaction with the solvent system. The number of pharmaceutically acceptable surfactants for inhalation is very small, thus knowledge of the mechanism and extent of adsorption of these surfactants onto drug particles in a CFC blend, and how this correlates with suspension stability, is an important consideration when attempting to optimise MDI formulations. The low solubility of currently used surfactants in HFA-134a (Dalby et al., 1990), a favoured candidate to replace CFCs in medicinal aerosol applications, gives further reason to elucidate surfactant stabilising mechanisms in MDI formulations, particularly in identifying chemical features required to promote good physical stability of the dispersed phase at the lowest surfactant concentration.

The aim of this work was to examine the interaction of oleic acid and sorbitan trioleate with various microfine particulates dispersed in trichlorotrifluoroethane (P113) as a model propellant system. In a first series of experiments, adsorption onto α-alumina was investigated; this adsorbent was considered, by virtue of having both basic and acidic groups on its surface (Lee and Rives, 1991), a good model for drug salts typically formulated in MDIs. Later experiments were conducted with a series of drug salts; salbutamol base, isoprenaline bitartrate and isoprenaline sulphate, chosen to cover a range of surface polarities. In addition, the nature of the surfactant-drug adsorption interaction was investigated using the technique of attenuated total reflection (ATR) spectroscopy coupled to an FTIR spectrometer. Measurement of the electrophoretic mobility of dispersions was also conducted to assess the possibility of a charge stabilisation mechanism operating in the apolar CFC environment.

Materials and Methods

Adsorbents

Submicron α-alumina (specific surface area 14.08 ± 0.20 m^2 g^{-1}; Metallurgical Services Laboratories, U.K.) was used as the model adsorbent. Micronised samples of salbutamol base and isoprenaline sulphate were generously donated by 3M Healthcare, U.K. Isoprenaline bitartrate (micronized) was kindly supplied by Pfizer (Central Research), U.K. For each batch of drug, particle morphology and size was investigated using scanning electron microscopy (Phillips) at 6400 $\times$ magnification. Samples were presented as a thin covering on double-sided adhesive tape. Volume mean diameter (VMD) and geometric standard deviation (GSD) were obtained by laser diffraction sizing (model 2600c, Malvern Instruments, U.K.) after uniformly dispersing each drug sample in P113 (Arklone 113; ICI, Mond Division, U.K.). The specific surface areas (m^2 g^{-1}) of the drug samples were determined after a 30 min degassing period using the Flowsorb II 2300 operating with a gas mixture of 30% N_2 and 70% He.

Adsorbates and their radiolabelled analogues

[1-^{14}C]Sorbitan trioleate (specific activity 0.424 MBq mg^{-1}; Amersham International, U.K.), was custom synthesised by ^{14}C-acylation of sorbitan monooleate. Sorbitan trioleate (Span 85) was purchased from Sigma Chemical Company, U.K.

Oleic acid (92%) and [1-^{14}C]oleic acid (specific activity 6.99 MBq mg^{-1}) were obtained respectively from BDH Chemicals U.K. and Amersham International, U.K. In order to demonstrate the appropriateness of the radiolabelled compounds as tracers for the unlabelled surfactants, TLC analysis was undertaken on silica gel plates (Merck Kieselgel 60; 0.2 mm layer thickness; 12 cm × 2.5 cm) eluted with a mobile phase of petroleum ether/ether/acetic acid (90:10:1) Specifically, oleic acid eluted to a single fraction ($R_f = 0.15$) in concordance with its radiolabelled analogue where over 98% of the radioactivity was within an R_f range of 0.1–0.2. Equivalent elution profiles were also achieved for the commercial source of sorbitan trioleate and the ^{14}C-labelled compound; indicating that the synthetic process conducted by Amersham International yielded a radiolabelled product of similar chemical composition to commercially available Span 85.

Adsorption of surfactants onto model and drug particles

Adsorption of oleic acid onto alumina from P113 was quantified by mixing alumina (2% w/v) with increasing concentrations of oleic acid spiked with aliquots of a stock solution containing 1.85 × 10^4 Bq ml^{-1} [^{14}C]oleic acid. The proportion of unlabelled to radiolabelled compound remained constant over the entire range of concentrations studied. After an equilibration period (18–24 h) in which the suspensions were tumble mixed, the alumina was allowed to sediment under gravity. Aliquots of clear supernatant (200 μl) were diluted with 3 ml scintillant (Cocktail T, BDH Chemicals, U.K.) in small polythene scintillation vials and counted on a liquid scintillation counter (RackBeta; LKB-Pharmacia, U.K.). A calibration curve of counting efficiency vs channels ratio was obtained by using standards of known activity quenched with increments of P113. Observed counts per minute (cpm) were thus corrected for chemical quenching by reference to the quench correction curve to yield the corresponding disintegrations per min (dpm). The amount of surfactant adsorbed was calculated from Eqns 1 and 2:

$$C_{eq} = C_i \times \mathrm{dpm}_f/\mathrm{dpm}_i \quad (1)$$

where C_{eq} is the equilibrium molar concentration, C_i denotes the initial molar concentration, dpm_f is the final counts in 200 μl aliquot and dpm_i represents the initial counts in 200 μl aliquot.

$$A = \left((C_i - C_{eq}) \times V \times \mathrm{MW}\right)/M \quad (2)$$

where A is the amount adsorbed (mg g^{-1}), V denotes the total suspension volume (ml), MW is the molecular weight of surfactant and M represents the mass of adsorbent powder (g).

Initial studies were conducted with alumina that had been stored over phosphorus pentoxide (0% relative humidity (RH)). To investigate the effect of surface moisture on the adsorption process, samples of alumina were conditioned over saturated salt solutions at constant temperature (20°C) yielding RHs of 23, 55, 75, 95 and 100%. The percentage moisture uptake was expressed as the equilibrium moisture content (EMC) as defined by Callahan et al. (1982).

Adsorption studies with drug salts were conducted in a similar manner. Salbutamol base, isoprenaline sulphate, and isoprenaline bitartrate (0.1% w/v), were mixed with P113 solutions of increasing surfactant concentration. The concentrations used were 0.005–0.1% w/v for oleic acid (corresponding to surfactant/drug weight ratios (S/D) = 0.05–1.0) and 0.025–0.16% w/v for sorbitan trioleate (S/D = 0.25–1.6) keeping the ratio of unlabelled to radiolabelled compound the same. After an 18–24 h equilibration period the adsorbent was allowed to cream, or sediment in the case of isoprenaline bitartrate. Aliquots of clear supernatant (200 μl) were analysed for radioactivity as before and the amount of adsorbed surfactant calculated from Eqns 1 and 2, using molecular weights for oleic acid and sorbitan trioleate of 282 and 958, respectively.

Surfactant-drug adsorption mechanism

Dispersions of salbutamol base (1% w/v) were prepared in P113 solutions of oleic acid (0.1–1.0% w/v) or sorbitan trioleate (0.25–10.0% w/v). Similar dispersions were also prepared with isoprenaline sulphate and oleic acid. After a 24 h

equilibration period the adsorbent drug powder was separated by vacuum filtration through a 0.2 μm pore size, 47 mm diameter cellulose nitrate membrane filter. The powders were carefully washed with small aliquots of P113 to remove any loosely held unadsorbed surfactant arising from the supernatant and then dried under a stream of N_2 gas. The powders were examined by carefully spreading them over the whole surface of a horizontally oriented zinc selenide ATR crystal coupled to a Nicolet (model no. 710) FTIR spectrometer. Typical sample spectra were obtained by collecting 1000 scans for the sample and background measurement and ratioing out the background. Reference spectra were also obtained for the drug powders and the liquid surfactants alone.

Electrophoretic mobility of drug dispersions

Triplicate dispersions (0.1% w/v) of salbutamol base were prepared in P113 solutions of surfactant of increasing concentration (oleic acid 0.005–0.1% w/v; sorbitan trioleate 0.025–0.1% w/v). The electrophoretic mobility of these dispersions at 15°C was examined by the technique of laser Doppler velocimetry using the Zetasizer III (Malvern Instruments, U.K.). An AZ26 cell with a narrow electrode gap (1 mm) was used with a field strength of 400 V cm^{-1}. Electrophoretic mobilities were converted to respective ζ potentials using a rearranged form of the Hückel equation (Goodwin et al., 1988):

$$\zeta = \frac{3U\eta \times 1000}{2\epsilon} \qquad (3)$$

where ζ is the zeta potential (mV), U represents the electrophoretic mobility ($\times 10^{-8}$ m^2 s^{-1} V^{-1}), ϵ is the dielectric constant (2.41 for P113), and η denotes the viscosity in centipoise (0.68 cp for P113).

Results and Discussion

The adsorption isotherm for oleic acid onto α-alumina (Fig. 1) had a steep initial slope, indicative of a high affinity of the adsorbate for the adsorbent surface. The initial slope steadily declined with progressive surface coverage until a saturation point (plateau) was reached. An excellent correlation coefficient was obtained when the results were plotted according to the linearised form of the Langmuir equation (Giles et al., 1974), suggesting that oleic acid adsorbs as a monolayer onto alumina. The equilibrium moisture content of alumina progressively increased upon storage in environments > 75% RH. For samples stored below this RH value, the adsorption of oleic acid from P113 was unaffected. An increase in equilibrium moisture content of the alumina resulted in a linear decrease in the plateau value (Table 1) although the steep initial slope to the isotherm was retained in all cases. This indicated that the surface affinity of oleic acid was not reduced by the presence of water, but that water molecules adsorb at similar sites to oleic acid on alumina with the net effect of the surfactant forming a 'monolayer' at a lower adsorbed amount. This purports to the importance of hydrogen bonding in the adsorption interaction, i.e., the interaction between the adsorbent and adsorbate is physical in nature.

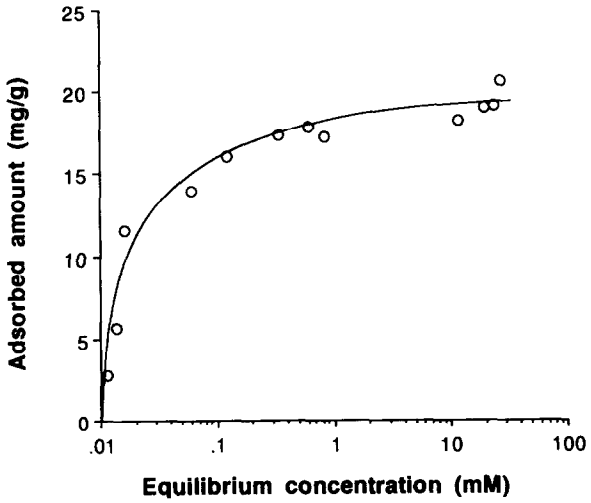

Fig. 1. Adsorption isotherm for oleic acid onto α-alumina. The molar equilibrium concentration was calculated from Eqn 1 and the amount adsorbed from Eqn 2. Each point represents the mean of three replicate determinations; coefficient of variation ± 5%.

In previous studies with mineral oxides it has been demonstrated that oleic acid adsorbs in a

trans configuration via both the carboxylic acid group and olefinic double bond (Sherwood and Rybicka, 1966; Ottewill and Tiffany, 1967; Marshall and Rochester, 1975). Whether this adsorptive mechanism is prevalent on interaction with alumina can be confirmed by comparing the experimentally derived surface coverage with a theoretical estimate. For an adsorbent of specific surface area, SA ($m^2\ g^{-1}$), the theoretical monolayer coverage, ML (mg g^{-1}) of a molecule of molecular weight, MW, with an adsorbing moiety of cross-sectional area, A (m^2) can be estimated from the following equation:

$$ML = \frac{SA \times MW \times 1000}{A \times N_a} \quad (4)$$

where N_a is Avogadro's number, 6.023×10^{23}.

Using a cross-sectional area for the adsorbing moieties of oleic acid of 5.0×10^{-19} m^2 (Doroszkowski and Lambourne, 1978), a value of 13 mg g^{-1} was calculated. Thus, the experimentally determined plateau value of 20 mg g^{-1} for alumina stored over phosphorus pentoxide represents a coverage of approx. 1.5 monolayers. Considering experimental error and the assumptions made this value supports the experimental findings and would suggest that oleic acid forms a monolayer on alumina, being adsorbed via hydrogen bonding involving the carboxylic acid group and the olefinic double bond.

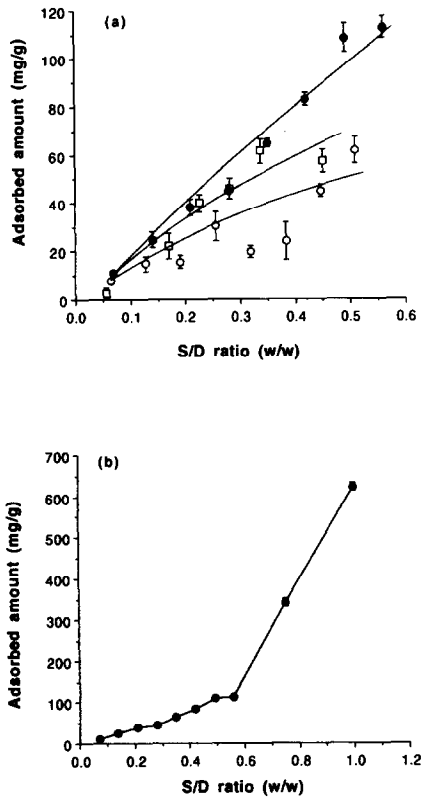

Fig. 2. Adsorption of oleic acid onto micronised drug particles as a function of surfactant/drug weight ratio: (a) (●) salbutamol, (□) isoprenaline bitartrate, (○) isoprenaline sulphate; (b) salbutamol at an extended range of S/D ratios. Each point is a mean of three replicates ± SD.

TABLE 1

The uptake of water by α-alumina at various storage humidities on the maximum (plateau) adsorbed amounts of oleic acid from P113

% relative humidity	EMC [a] (% dry basis)	Plateau value [b] (mg/g)
23	0.3	20.0
55	0.4	20.0
75	0.6	20.0
95	3.8	15.6
100	11.4	11.2

[a] EMC, equlibrium moisture content.

[b] Obtained from the gradients of linearised plots of the Langmiur equation; i.e., $C/(A/M)$ vs C, where C is the equilibrium adsorbate concentration, A is the amount adsorbed, and M is the mass of adsorbent. In each case, linear regression analysis showed a significant correlation ($p < 0.01$).

Adsorption of oleic acid onto the drug samples showed different extents of interaction. The wetting and dispersal of both isoprenaline salts were no better with oleic acid than with pure solvent, confirmed by the low and rather erratic adsorption of the surfactant onto these drug particle surfaces (Fig. 2a). In contrast salbutamol base showed significant adsorption of oleic acid, the amount adsorbed increasing with adsorbate concentration (expressed as S/D ratio). There was no evidence of a plateau for oleic acid adsorption onto salbutamol suggesting that saturation of binding sites was not reached over the concentration range studied. Prospectively, this may be explained by multilayer adsorption, a phe-

nomenon previously postulated for oleic acid onto titanium dioxide (Sherwood and Rybicka, 1966; Ottewill and Tiffany, 1967) and iron powders (Mikhailik et al., 1991). From the data obtained for an extended range of surfactant concentrations (Fig. 2b) it is evident that a pronounced increase in the amount of oleic acid adsorbed occurred at higher S/D ratios. These data strongly infer that breakdown in crystal structure occurs at an approximate S/D ratio of 0.6. This will occur on chemical reaction between adsorbent and adsorbate leading to fresh internal surface area, favouring a rapid increase in adsorption, which expands in proportion to the amount of oleic acid adsorbed. SEMs (Fig. 3) of micronised salbutamol crystals incubated in increasing oleic acid concentrations in P113 support this hypothesis by clearly showing a change in particle morphology from angular, well defined structures at a low (0.3) S/D ratios through to rounded, amorphous-like structures at a high (0.8) S/D ratio.

Hickey et al. (1988) showed that the association of lauric acid and capric acid with disodium fluorescein was far greater than predicted by simple adsorption, postulating from IR studies that the acids were chemically bound to the adsorbent. Lee and Rives (1991) suggested that linolenic acid was adsorbed onto alumina from toluene by an acid-base reaction that produced ion pairs, however IR spectroscopy studies did not provide any evidence for ionisation of linolenic acid on adsorption. In this study, the results of the ATR spectroscopy experiments coupled to FTIR were definitive in demonstrating chemical reaction between salbutamol and

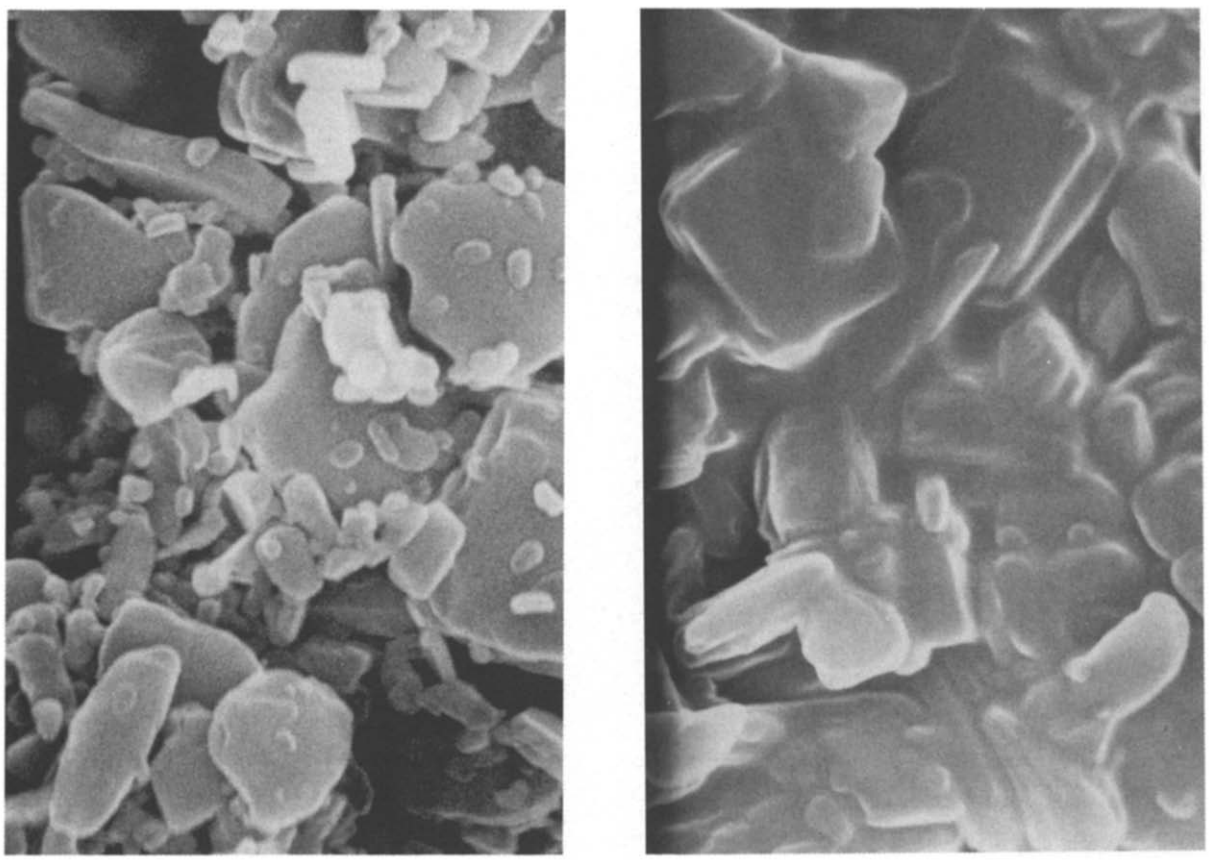

Fig. 3. Scanning electron micrographs of micronised salbutamol crystals incubated in P113 solutions of oleic acid equivalent to S/D ratios 0.3 (a) and 0.8 (b).

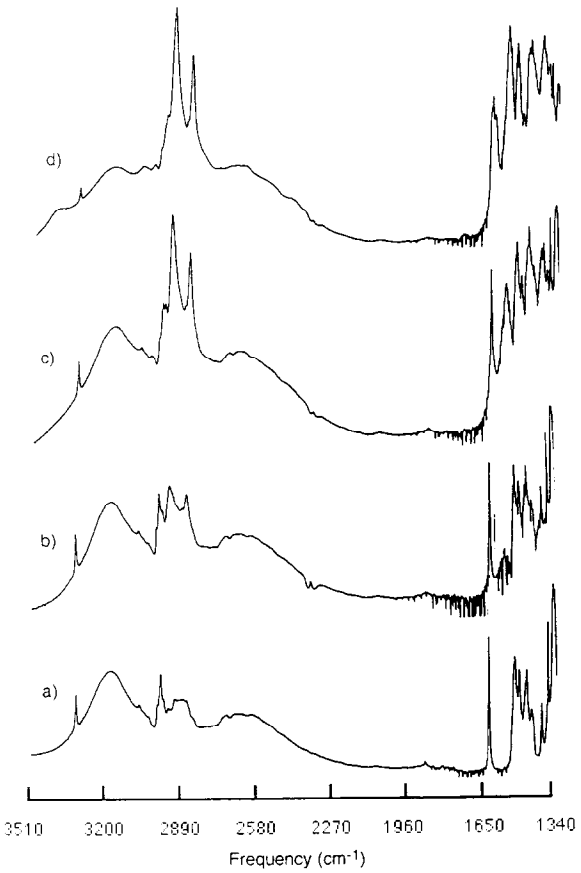

Fig. 4. Infrared spectra of salbutamol/oleic acid systems. Salbutamol alone (a), and salbutamol/oleic acid at original S/D ratios of 0.3 (b), 0.5 (c) and 0.8 (d). Note that in spectra (b)–(d) the alkyl ($C\text{-}H_{str}$) stretch (2922 and 2853 cm^{-1}) of the hydrocarbon chain and the asymmetric (ν_{as}) stretch of the ionised oleate group (1547 cm^{-1}) of oleic acid are superimposed onto the spectrum (a) of salbutamol base.

oleic acid in P113. Spectra from samples of micronised salbutamol previously incubated with increasing concentrations of oleic acid (Fig. 4) showed a proportionate increase in height of the $C\text{-}H_{str}$ of the hydrocarbon alkyl chain (2922 and 2853 cm^{-1}) as the spectrum for oleic acid was superimposed onto salbutamol base. No peak corresponding to the $C=O_{str}$ of free oleic acid (1707 cm^{-1}) was observed, only an increasingly predominant peak at 1547 cm^{-1}, which is assigned to the asymmetric stretch of the oleate ion. These data corroborate the findings of the adsorption studies with radiolabelled compounds, i.e., that the amount of oleic acid associated with salbutamol increases with surfactant concentration, but further demonstrate that the interaction involves donation of a proton from oleic acid to salbutamol with the formation of an ion-pair. The electrophoretic mobilities for salbutamol dispersions in oleic acid ranged from 2 to 0.2×10^{-10} $m^2\ s^{-1}\ V^{-1}$ at respective S/D ratios of 0.05 and 1.0. As charge generation is generally accepted to occur by proton transfer in non-aqueous media of low dielectric constant (Fowkes et al., 1982; Pugh and Fowkes, 1984), the increasing negative electrophoretic mobility at higher values of S/D ratio is probably due to the presence of oleate ions at the shearing plane, thus further suggesting chemical interaction between salbutamol and oleic acid. In contrast, the interaction of oleic acid with isoprenaline sulphate could not be demonstrated by FTIR, confirming that any association prior to the washing stage in the sample preparation was physical in nature. Although not investigated by FTIR, it is unlikely that ion-pair formation would have been demonstrated between oleic acid and isoprenaline bitartrate as, like the sulphate salt, the basic nitrogen is already protonated. Furthermore, the pK_a values of tartaric acid (2.93) and sulphuric acid (−3.00) (Gould, 1986) are such that displacement by oleic acid (pK_a approx. 4) is unlikely.

All drug samples formed good dispersions in P113 following the addition of sorbitan trioleate. When expressed according to the specific area of the drug particles (Fig. 5), a trend of increasing amounts of adsorbed surfactant occurred in the order isoprenaline sulphate > isoprenaline bitartrate > salbutamol. In all cases, adsorption appeared to follow the 'C' type adsorption isotherm, i.e., the number of binding sites for adsorption remained constant over the whole range of adsorbate concentrations studied. This type of isotherm is more usually observed with microporous adsorbents, where adsorbate penetration into the pores opens up more internal surface area for adsorption. However, no evidence of chemical reaction between sorbitan trioleate and any of the drug samples was revealed by FTIR, even at a S/D value (10) greatly in excess of those used in the adsorption studies with the radiolabelled analogue. Previous studies have demonstrated the

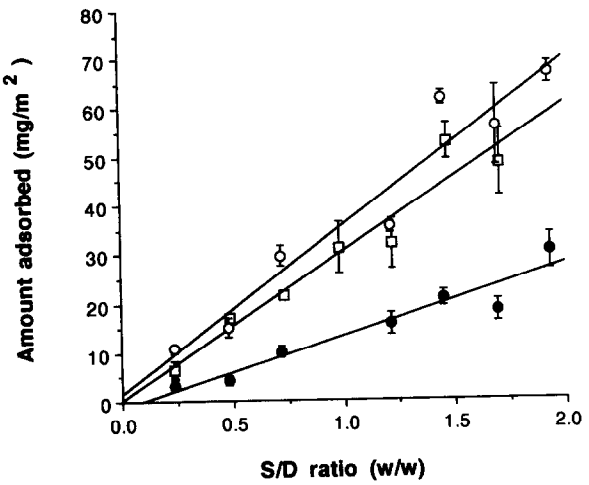

Fig. 5. Adsorption (per unit surface area) of sorbitan trioleate onto micronised drugs as a function of surfactant/drug weight ratio. Symbols refer to salbutamol (●), isoprenaline bitartrate (□) and isoprenaline sulphate (○). Each point represents the mean of three replicate determinations ± SD. The adsorbed amounts per unit surface area (mg/m^2) were obtained by dividing the adsorbed amounts per unit mass by the specific surface area of the drugs (Table 2).

importance of the sorbitan ring in aggregation phenomena of sorbitan esters in polar and apolar systems (Albers and Overbeek, 1960; Evans et al., 1988), therefore it is reasonable to assume involvement of this moiety in adsorption onto drug salts.

Given the probable importance of steric mechanisms to the stabilisation process, it is instructive to calculate the adsorbed film thicknesses as a function of drug particle surface character and surfactant concentration. These were expressed as the number of monolayer equivalents, a term used to correct for the fact that the number of molecules required to form a monolayer will increase as the adsorbent surface area increases on continuing adsorption. The number of molecules required to form a monolayer on 1 g of adsorbent, ml_M, was calculated from:

$$ml_M = SA/A \quad (5)$$

where SA is the specific surface area of the adsorbent (m^2 g^{-1}) and A is the cross-sectional area (m^2) of the adsorbing moiety (assumed as 8.2×10^{-19} m^2 for the sorbitan moiety, Ashurst, 1985). The amount adsorbed in mg g^{-1} (A_{ads}) was then converted into the amount adsorbed in molecules g^{-1} (M_{ads}) using the equation:

$$M_{ads} = (A_{ads} \times N_a)/(1000 \times MW) \quad (6)$$

where MW is the surfactant molecular weight. Assuming that the surfactant molecules can utilise the total area available to the gas molecules used for the surface area measurement, the theoretical number of monolayer equivalents adsorbed, N_{ml}, was finally calculated from:

$$N_{ml} = M_{ads}/ml_M \quad (7)$$

Using this treatment of the adsorption data for sorbitan trioleate, it can be demonstrated that the surfactant forms multiple layers on the surface of

TABLE 2

The adsorption of sorbitan trioleate onto micronised drug particles at 'low' and 'high' surfactant / drug weight ratios

	VMD [a] (μm)	GSD [a]	Surface area (m^2/g)	$S/D = 0.24$			$S/D = 1.90$		
				mg/g adsorbed	mg/m^2 adsorbed	Monolayer equivalents adsorbed	mg/g adsorbed	mg/m^2 adsorbed	Monolayer equivalents adsorbed
Salbutamol	1.59	1.7	8.2	27	3.3	1.7	200	24	13
Isoprenaline bitartrate	3.17	1.4	5.2	34	6.5	3.4	250	48	25
Isoprenaline sulphate	4.80	1.6	2.3	32	10.7	5.5	190	63	33

[a] Volume mean diameter (VMD) and geometric standard deviation (GSD) were calculated by graphical interpolation of data obtained by laser diffraction analysis.

all the drug particles investigated (Table 2). The extent of adsorption is greatest on drugs of greater hydrophilic character (as determined by moisture uptake studies; data not shown) and at higher surfactant concentrations. Together with the results of the FTIR experiments, these findings confirm that sorbitan trioleate adsorbs by a physical (i.e., hydrogen bonding) mechanism. Interestingly, Zhu and Gu (1989) proposed that multilayer adsorption occurs by the formation of hemimicelles. After an initial adsorption of a monlayer of surfactant molecules, each molecule may then act as a centre for aggregation. A maximum adsorption is reached when each molecule in the first adsorbed layer is involved in aggregate formation.

The studies with various bronchodilator drugs have conclusively demonstrated that two surfactants commonly employed in the formulation of MDI's show differences in adsorption phenomena, related to the surface chemistry of the dispersed drug and the surfactant itself. Provided there are no problems with respect to changes in particle morphology, resulting in reduced respirability of the emitted aerosol upon actuation, chemical reaction of adsorbent and adsorbate should promote a useful mechanism of imparting stability to a particulate in a CFC blend. By strongly anchoring the adsorbate onto the adsorbent surface, lateral movement away from the interaction zone may be prevented when adsorbed layers interact. When adsorption occurs by chemical reaction, increasing the actual surface area available, the number of monolayer equivalents adsorbed can only be estimated tentatively. Although the actual adsorbed film thickness for salbutamol and isoprenaline salts were calculated to be of similar dimension (< 5 at the lowest S/D ratio, assuming no change in surface area for salbutamol), the extremely poor physical stability of isoprenaline salts in P113 containing oleic acid may be postulated a consequence of the weak affinity between oleic acid and the surface of these drug particles, resulting in a tendency for desorption.

While a change in electrophoretic mobility was noted on adsorption of oleic acid onto salbutamol, it is questionable whether electrostatic stabilisation forms an important mechanism to the overall stabilisation process in MDIs. Wyatt and Vincent (1992) have also shown recently that the surface charge on drug particles dispersed in P113 is significantly modified by the addition of a suitable surfactant excipient (oleic acid, sorbitan trioleate, and lecithin) although measured electrophoretic mobilities were low, in the order of $< 10^{-9}$ m^2 s^{-1} V^{-1}. In the present studies, the electrophoretic mobility of salbutamol in P113 remained low and relatively unchanged by the addition of sorbitan trioleate ($1.2–2.5 \times 10^{-10}$ m^2 s^{-1} V^{-1}), but was decreased (i.e., became more negative) by the addition of increasing concentrations of oleic acid. Pugh et al. (1983) reported that electrostatic stabilisation was ineffective in non-aqueous dispersions of carbon black until ζ-potentials > 100 mV were achieved, far greater than were measured in salbutamol/oleic acid (approx. 0.9–9 mV) or salbutamol/sorbitan trioleate (approx. 5–10.5 mV) systems. Furthermore, using the theory of Kitahara (1974), it is possible to calculate that unless the suspended particles are large and possess substantial ζ potential, an electrostatic mechanism of stabilisation will be ineffective in media of low dielectric constant. This theory is based on the fact that the electrostatic repulsive force (V_R) is directly proportional to the dielectric constant and the square of the ζ-potential; therefore, for a signficant V_R, ϵ and ζ should be both of high value. It thus seems likely that for MDI formulations, where suspended solid concentrations are relatively dilute, a steric mechanism of stabilisation is likely to be of greater importance than electrostatic repulsion. As the magnitude of any steric interaction will depend, at least in part, on the adsorbed layer thickness (Kerkar and Feke, 1991), it would appear that sorbitan trioleate represents a good dispersant by demonstrating multi-layer formation on all drug surfaces investigated. The originators of the term 'steric stabilisation' (Heller and Pugh, 1960) predicted an increased stability when the volume of the adsorbed layer increased relative to the core particle volume. Ideally, the maximum adsorbed layer thickness should be achieved at the lowest surfactant concentration in order to avoid deleterious effects on propellant

evaporation. The results confirm that this is best achieved by use of a salt of greatest hydrophilic character.

The initial studies with alumina demonstrated the deleterious effect of water on the extent of surface association of surfactants that are hydrogen bonded to adsorbents. It may be postulated, therefore, that the presence of contaminant moisture in an MDI, introduced on manufacture and/or storage (Miller, 1990) may alter the physical stability of formulated suspensions containing drug/surfactant combinations which interact by hydrogen bonding. Sorbitan trioleate forms reverse micelles in apolar solvents (Evans et al., 1988), these may provide some protective capacity by providing an alternative location to the surface of the dispersed particles for water solubilisation in the formulation. Malbrel and Somasundaran (1989) provided a theoretical treatment of this phenomenon. The effect of water on the chemical reaction between oleic acid and salbutamol, however, may serve to increase the formation of ion-pairs thus radically altering particle morphology of the suspended drug. The range of techniques documented in this paper may be usefully employed to investigate these and other phenomena pertaining to MDI formulations.

Acknowledgements

This work was kindly supported by SERC and Pfizer Ltd (Central Research) by the provision of a CASE award for J.G.C. John Eilbeck (Department of Pharmaceutical Sciences, University of Sunderland) is greatly thanked for undertaking the specific surface area measurements.

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