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Characterisation of surface modified salbutamol sulphate-alkylpolyglycoside microparticles prepared by spray drying

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Abstract

There were three aims of this work: (1) to study the suitability of spray drying to prepare surface modified microparticles coated with alkylpolyglycoside surfactants (for potential use in metered dose inhalation systems, although their use is not reported here); (2) to assess the utility of inverse phase gas chromatography (IGC) as a means of assessing the surface properties of modified microparticles; and (3) to attempt to relate dynamic surface tension measurements with the ability for a molecule to diffuse to a surface during spray drying. Microparticles of salbutamol sulphate—alkylpolyglycosides were prepared by spray drying from solution and then characterised using scanning electron microscopy, particle size analysis (laser diffraction) and inverse gas chromatography. Further to this, the critical micelle concentration (CMC) and the dynamic surface tension of alkylpolyglycosides were measured. Spray drying a solution of salbutamol sulphate with alkylpolyglycosides produced spherical amorphous microparticles with a diameter of less than 10 μm. The analysis of the surface energies of spray dried salbutamol sulphate showed that the addition of alkylpolyglycosides, at concentrations below and above their CMC, decreases substantially the basic component of the surface energy. This demonstrates that it is possible to sequentially modify the surface energy of the particles. Dynamic surface tension measurements of the alkylpolyglycosides above their CMC showed that the surfactant that has the least effect on the surface energy of the particles, presents the slowest diffusion in water. This may indicate that the diffusion of this particular molecule in water may be too slow to allow the surfactant to migrate to the surface of the microparticle during the drying process. IGC can be useful to analyse the surface energy of the particles after spray drying in order to assess the presence of the surfactant on the surface of the microparticles.

Keywords: Surface modified microparticles; Spray drying; Salbutamol sulphate; Alkylpolyglycosides; Inverse gas chromatography; Dynamic surface tension

1. Introduction

The ability to prepare surface modified particles is useful in order to have the potential to optimise material behaviour in a variety of dosage forms. One possible application of modified particles is the pressurised metered-dose inhaler (pMDI), a dosage form that currently has a need of novel methods of surface adaptation due to problems encountered as a consequence of the move away from CFC propellants (Montreal Protocol, 1989).

Spray drying is a well-established drying process traditionally used for thermolabile materials (Masters,

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1991). It has been used successfully by the pharmaceutical industry to produce products of defined physical and chemical properties. In this study we have investigated spray drying as a potential method for the production of particles of a model drug (salbutamol sulphate) with a range of surface energetics. It is especially difficult to change the surface nature of water soluble drugs (such as salbutamol) by surfactant adsorption from solution. This is because they dissolve when equilibrated with aqueous solutions of surfactants and the use of organic solvents is not desirable, and often not practical, due to solubility limits of the surfactants as well as the changes in orientation, self-association and tendency to adsorb as a consequence of using an organic solvent.

A specific class of non-ionic biodegradable surfactants, alkylpolyglycosides, was selected for this study. They are characterised by an alkyl chain (the hydrophobic part of the molecule) attached to a glucose ring (the hydrophilic part of the molecule) through a glycosidic linkage. Alkylpolyglycosides (APGs) with different amount of glucose (indicated as average degree of polymerisation, DP) and different alkyl chain lengths were selected to be spray dried with salbutamol sulphate at concentrations below and above their critical micelle concentration (CMC) to obtain microparticles of drug-surfactant. The morphology and the particle size of the microparticles were studied to establish whether they were suitable for pulmonary delivery. The surface energy of the particles was then investigated using inverse gas chromatography, to assess the presence of the surfactant on the surface of the spray-dried drug. Dynamic surface tension measurements of the APG surfactants in water were undertaken to see if there was a correlation between the diffusion rate of the surfactants tested and their capacity to migrate to the surface of the microparticle during the rapid drying of the droplet in the last phase of the spray drying process.

2. Materials and methods

2.1. Materials

Crystalline salbutamol sulphate was supplied by Avocado.

The nomenclature for the APGs is C_nG_m for "pure surfactants", where n is defined as the number of carbons in the alkyl chain and m the number of glucose units attached as the head group. The term "pure" is a relative one, as the pure surfactants are not pure in surface chemistry terms, but are more homogeneous than the technical grade surfactants. The technical materials are described by a range of alkyl chain lengths ($C_{a–b}$) as they are derived from natural alcohols, which have a range of alkyl chains, and an average number of glucose groups per molecule which is expressed as a degree of polymerisation (DP), thus $C_{10–12}$ DP 1.4 has a range of alkyl chains from decyl to dodecyl and an average of 1.4 glucose units per alkyl chain in the sample.

The "pure" APG *n*-dodecyl-β-D-maltoside (C_{12} G_2) was obtained from Sigma (purity >98%). The technical APG C_{10} DP 2.7 was supplied by Akzo-Nobel while $C_{10–12}$ DP 1.4 and $C_{12–14}$ DP 1.4 (Glucopon 600) were from Henkel. Two of the materials (C_{10} DP 2.7 and $C_{12–14}$ DP 1.4) were supplied as a dispersion in water and consequently these were freeze–dried prior to use, to allow the subsequent preparation of solutions of exact known concentrations.

2.2. Surface tension measurements of APGs

Surface tension of APGs in water at 25 °C was measured using the Wilhelmy plate technique (Cahn DCA 312). The CMC of the alkylpolyglycosides was determined by plotting the surface tension values versus concentration.

2.3. Spray drying

Microparticles of salbutamol sulphate and salbutamol sulphate-alkylpolyglycosides were prepared by spray drying from solution in water using a Büchi 190 mini spray drier fitted with a 7 mm pneumatic nozzle. A 10% w/v salbutamol sulphate solution in water, or in a solution of alkylpolyglycosides was spray dried. Two concentrations of APGs were selected, one above and one below their CMC. The conditions and spray drying parameters were selected based on the work of Chawla et al. (1994): pump speed, 5 ml/min; air flow rate, 800 l/h; aspirator level, 5; inlet temperature, 150 °C (±5 °C) and outlet temperature 80 °C (±5 °C). The material was desiccated immediately after drying.

2.4. Assessment of the degree of crystallinity via powder X-ray diffraction

Powder X-ray diffraction was used to assess the degree of crystallinity of spray dried salbutamol sulphate and salbutamol sulphate-APG microparticles, at ambient temperature using a Siemens D5000. Approximately 10 mg of material was placed into a sample holder (made from a single crystal of silicon). The following conditions were used: Cu Kα ($\lambda = 1.542$ Å) radiation, 2–30° 2θ, step size: 0.02°, time per step: 2 s.

2.5. Particle morphology

The morphology and shape of spray dried salbutamol sulphate and salbutamol sulphate-APG microparticles were examined using a Philips XL 20 scanning electron microscope (Philips, Cambridge, UK).

2.6. Particle size distribution

The mass median particle size and size distribution of spray dried salbutamol sulphate and salbutamol sulphate-APGs microparticles were measured using laser diffraction (Malvern Mastersizer, Malvern Instruments). The particles were suspended in cyclohexane by sonication for 30 s before measurements (Chawla et al., 1994). Three suspensions were prepared for each sample tested, each suspension was analysed five times (results mean of $n = 15$).

2.7. Inverse gas chromatography

Inverse gas chromatography at infinite dilution was carried out using a Perkin–Elmer F33 gas chromatograph fitted with a flame ionisation detector and an integrator (Shimadzu CR5A). A silanised U-shaped column (3 mm i.d., 30-cm length) was packed with approximately 500 mg of the test powder (spray dried salbutamol sulphate or salbutamol sulphate-APGs) and dried under nitrogen at 50 °C for 24 h. The powder bed was then allowed to settle for 24 h at 35 °C (temperature used during the experiments) under nitrogen. The test probes used were hexane, heptane, octane (Sigma) as non-polar probes; chloroform, CCl_4 and benzene (Aldrich) as acidic probes; tetrahydrofuran and ethyl acetate (Aldrich) as basic probes; acetone and diethyl ether (Aldrich) as amphoteric probes. Methane was used as a reference probe to calculate the minimum retention time, as it does not interact with the test powder. One microliter of air containing a minute concentration of gaseous probe was injected into the column using a Hamilton syringe and the retention time measured. Each probe was injected five times and each set of experiments was repeated at least three times for each solid tested. The flow rate of the carrier gas was measured with a bubble meter.

2.8. Dynamic surface tension measurements of APGs

The dynamic surface tension of aqueous solutions of APGs above their CMC was measured by the maximum bubble pressure method (Sensadyne PC9000) at bubble rates in the range 0.1–10 s per bubble. The temperature of the solution was controlled using a water circulator (25 ± 0.2 °C). The instrument was calibrated after each change in bubble rate using water and methanol–water 50:50 as markers for high and low surface tension, respectively.

3. Results and discussion

3.1. CMC values of the surfactants

In Table 1, the values of CMC in water at 25 °C for the alkylpolyglycosides are given. The CMC value for C_{10} DP 2.7 was taken from Johansson et al. (1996).

3.2. Properties of the microparticles

The percentage yield data for various batches of salbutamol sulphate and salbutamol-APGs are given in Table 2. The presence of the surfactant (especially, $C_{10–12}$ DP 1.4 and $C_{12–14}$ DP 1.4) led to an increase

Table 1
CMC values of APGs in water at 25 °C

Alkylpolyglycoside	CMC (g/l)
C_{12} G_2	0.145
C_{10} DP 2.7	1.300[a]
$C_{10–12}$ DP 1.4	0.343
$C_{12–14}$ DP 1.4	0.130

[a] From Johansson et al. (1996).

Table 2
Percentage yield data for salbutamol sulphate spray dried on its own or in the presence of APGs at concentration below and above CMC

Material	Yield (%)
Salbutamol sulphate batch 1	19
Salbutamol sulphate batch 2	17
Salbutamol sulphate batch 3	22
Salbutamol + C_{12} G_2 (0.08 g/l)	29
Salbutamol + C_{12} G_2 (0.8 g/l)	32
Salbutamol + C_{10} DP 2.7 (0.3 g/l)	29
Salbutamol + C_{10} DP 2.7 (1.6 g/l)	33
Salbutamol + $C_{10–12}$ DP 1.4 (0.15 g/l)	44
Salbutamol + $C_{10–12}$ DP 1.4 (0.8 g/l)	25
Salbutamol + $C_{12–14}$ DP 1.4 (0.06 g/l)	37
Salbutamol + $C_{12–14}$ DP 1.4 (0.3 g/l)	38

in product yield. The scanning electron micrograph of spray dried salbutamol sulphate (Fig. 1) showed spherical particles with a diameter generally less than 5 μm. The presence of the surfactant (e.g., $C_{10–12}$ DP 1.4 at concentrations below and above the CMC. Figs. 2 and 3) does not affect the morphology of the particles. The APG-salbutamol samples appear homogeneous, with no evidence of two different populations of particles, so either surfactant particles are of identical appearance to those of the drug, or the APGs are present as solid dispersions within the structure of the drug and/or on the surface of the material. It is inconceivable that a spray dried solution could yield two distinct populations of identical spheres, so it is logical to believe that the particles contain an amorphous mixture of the drug and surfactant molecules. The amorphous nature of the spray-dried samples was proved by X-ray diffraction, which revealed no evidence of crystalline structure (see Fig. 4).

The particle size distribution of spray dried salbutamol sulphate and salbutamol-APGs appear very similar with the mass median diameter of the drug on its own slightly smaller than in the presence of the surfactants. It seems that APGs have only a small influence on the diameter and size distribution of the spray dried particles. The dimensions of the spray-dried material are compatible with pulmonary delivery (50% of the particle have a diameter within 5 μm, considered optimal for pulmonary delivery, and the size distribution is tight, see Table 3).

Inverse gas chromatography (IGC) was used to analyse the surface energy of the spray dried materials. This technique relies upon the retention properties of different adsorbates when injected into a glass column packed with the solid of interest. From the retention time of any probe vapour it is possible to calculate V_N:

$$V_N = JF(t_r - t_0) \quad (1)$$

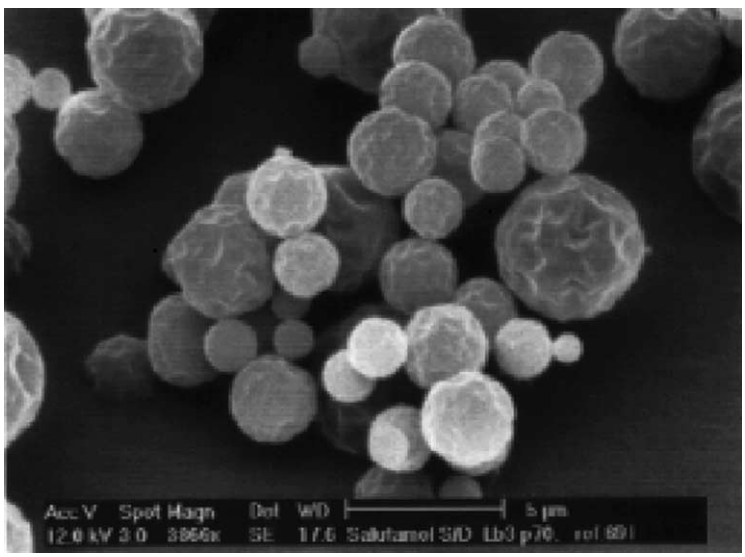

Fig. 1. Electron micrograph of spray dried salbutamol sulphate.

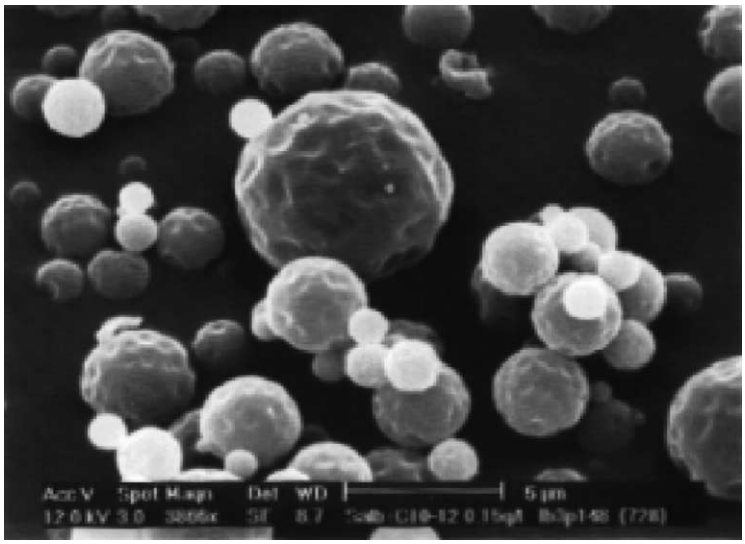

Fig. 2. Electron micrograph of spray dried salbutamol sulphate + $C_{10–12}$ DP 1.4 at 0.15 g/l.

where F is the carrier gas flow rate (ml/min), J is a correction factor due to pressure difference across the column, t_r is the retention time of the probe and t_0 is the retention time of a non-interacting standard (methane). As the probes are injected at infinite dilution, they will only interact with the most energetic sites of the solid.

From V_N it is possible to calculate the dispersive (non-polar) component of the solid surface energy (γ_S^D):

$$RT \ln V_N = 2N(\gamma_S^D)^{1/2} a(\gamma_L^D)^{1/2} + K \quad (2)$$

where a is the area of one adsorbate molecule, N is the Avogadro's number, γ_S^D is the dispersive component

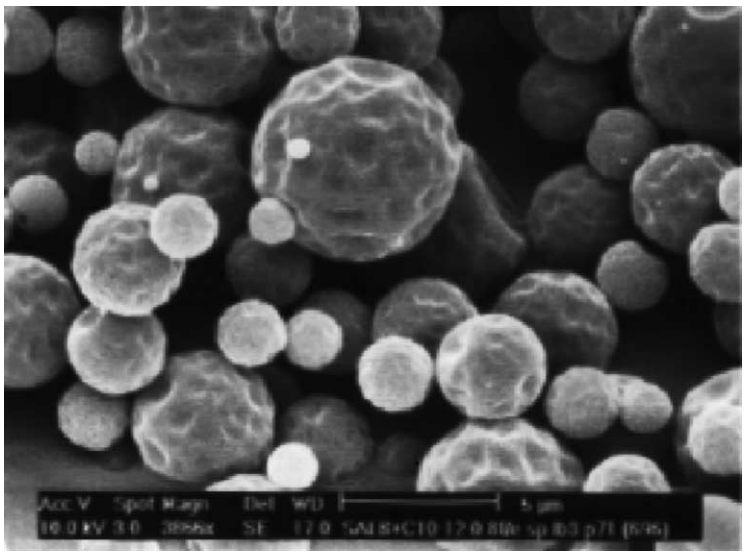

Fig. 3. Electron micrograph of spray dried salbutamol sulphate + $C_{10–12}$ DP 1.4 at 0.8 g/l.

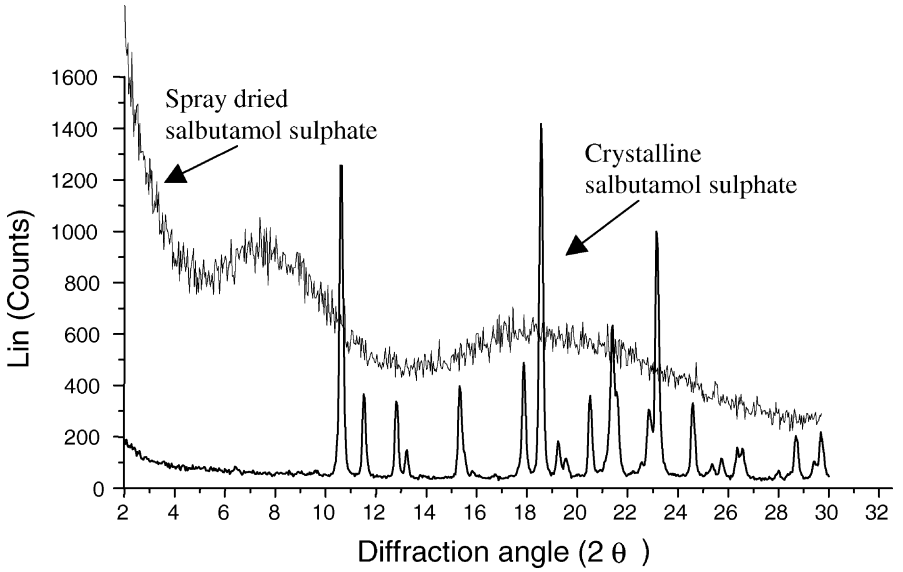

Fig. 4. Powder X-ray diffractograms of crystalline salbutamol sulphate (Avocado) and spray dried salbutamol sulphate.

of the solid surface energy, γ_L^D is the dispersive component of the liquid (adsorbate) surface energy and K is a constant (Schultz et al., 1987). A plot of $RT\ln V_N$ as a function of $a(\gamma_L^D)^{1/2}$ for the alkane probes yields a straight line, the gradient of which is $2N(\gamma_S^D)^{1/2}$. This can be used to calculate the dispersive component of the surface free energy of the adsorbent.

The retention of polar probes in the column is a consequence of both dispersive and polar interactions. The cause of the retention over and above that due to dispersive forces is described as their specific interaction. This specific interaction, $-\Delta G_a^{SP}$, can be obtained from a $RT\ln V_N$ versus $a(\gamma_L^D)^{1/2}$ plot, where $-\Delta G_a^{SP}$ is the displacement of the probe above the alkaline line. $-\Delta G_a^{SP}$ can be used to calculate acidic and basic characteristic of the surface of the solid according to:

$$\frac{-\Delta G_a^{SP}}{AN^*} = K_a \frac{DN}{AN^*} + K_d \tag{3}$$

where DN and AN* are the probe's electron donating (base) and electron accepting (acid) properties according to the theory developed first by Gutmann (1993) and developed by Riddle and Fowkes (1990). A plot of

Table 3
Particle size distribution of spray dried salbutamol sulphate and salbutamol-APGs as mass median diameter (D, 50 vol.%) and coefficient of spread (SPAN, 90% undersize divided by 50% undersize)

Material	D (50 vol.%; μm; $n = 15$)	SPAN ($n = 15$)
Salbutamol sulphate batch 1	2.9 (0.074)	1.4 (0.051)
Salbutamol sulphate batch 2	3.5 (0.11)	1.6 (0.12)
Salbutamol + C_{12} G_2 (0.08 g/l)	4.3 (0.35)	2.0 (0.21)
Salbutamol + C_{12} G_2 (0.8 g/l)	4.4 (0.50)	2.1 (0.32)
Salbutamol + C_{10} DP 2.7 (0.3 g/l)	4.9 (0.60)	1.8 (0.10)
Salbutamol + C_{10} DP 2.7 (1.6 g/l)	4.4 (0.25)	1.7 (0.086)
Salbutamol + $C_{10–12}$ DP 1.4 (0.15 g/l)	4.3 (0.35)	1.7 (0.14)
Salbutamol + $C_{10–12}$ DP 1.4 (0.8 g/l)	3.9 (0.19)	1.7 (0.034)
Salbutamol + $C_{12–14}$ DP 1.4 (0.06 g/l)	4.2 (0.21)	1.8 (0.92)
Salbutamol + $C_{12–14}$ DP 1.4 (0.3 g/l)	3.1 (0.10)	1.8 (0.16)

Table 4
Surface energy from IGC data of different batches of spray dried salbutamol sulphate

Material	γ_S^D (mJ/m^2; $n = 3$)	K_d	K_a	K_d/K_a
Salbutamol sulphate batch 1	32.6 (0.90)	0.13	0.023	5.95
Salbutamol sulphate batch 2	35.4 (0.54)	0.20	0.021	9.57
Salbutamol sulphate batch 3	34.4 (1.05)	0.16	0.020	8.10

$-\Delta G_a^{SP}/AN^*$ as a function of DN/AN^* allows determination of values for the acidic (K_a) and basic (K_d) parameters of the test powder.

The surface energy of spray dried salbutamol sulphate (see Table 4) shows a relatively low dispersive component and a relatively high K_d/K_a ratio. This indicates that the drug presents a predominantly basic polar surface. There is some variability when spray drying different solutions (Table 4). The addition of APGs at concentrations below and above their CMC in the spray dried salbutamol sulphate solution (see Table 5) does not result in major changes to the dispersive component but decreases the K_d/K_a ratio substantially, this is not a surprise as the droplet will obviously go through rapid changes in concentration during drying, and hence all samples will end up in concentrations above the CMC. The change in the K_d/K_a ratio is mainly due to a change in K_d as K_a stays almost constant for all microparticles tested. This effect is proportional to the amount of surfactant present in the feed solution. For example, Fig. 5 shows the relationship between surfactant concentration and K_d when C_{10} DP 2.7 was spray dried at three different concentrations with the drug. The IGC data indicate that the amount of surfactant present on the surface of the spray-dried particles is related to the concentration in the original solution and at higher concentrations of surfactant the basic sites of the surface of salbutamol sulphate are covered, perhaps by interaction with the marginally acidic glucose head groups of the APGs, resulting in a decreased K_d/K_a ratio. The reason why there is no significant change in the dispersive component of the surface energy, following addition of the APGs, is not clear. This may simply be due to the fact that the dispersive nature of the two materials could well be very similar, especially when the measurements are at infinite dilution and thus preferentially assess the high energy parts of the surface.

Of all the surfactants tested, $C_{12–14}$ DP 1.4 is the one that had the least effect on the surface energy of salbutamol sulphate. This could be due to the fact that this is the most hydrophobic molecule employed or that there is less surfactant present on the surface of the particle. It is interesting to understand why different surfactants are present at the surface of the particles to different extents.

3.3. Dynamic surface tension

Dynamic surface tension measurements are useful to understand the diffusion rate of surfactants toward surfaces. Spray drying is characterised by quick drying of an atomised solution, which will result in rapid

Table 5
Surface energies from IGC data of spray dried salbutamol sulphate + APG particles

Material	γ_S^D (mJ/m^2; $n = 3$)	K_d	K_a	K_d/K_a
Salbutamol + C_{12} G_2 (0.08 g/l)	35.3 (2.02)	0.090	0.021	4.33
Salbutamol + C_{12} G_2 (0.8 g/l)	34.6 (3.42)	−0.026	0.021	−0.83
Salbutamol + C_{10} DP 2.7 (0.3 g/l)	35.2 (0.95)	0.045	0.020	2.23
Salbutamol + C_{10} DP 2.7 (1.1 g/l)	33.3 (0.48)	0.015	0.019	0.82
Salbutamol + C_{10} DP 2.7 (1.6 g/l)	31.9 (1.11)	−0.023	0.017	−1.35
Salbutamol + $C_{10–12}$ DP 1.4 (0.15 g/l)	35.7 (2.51)	0.035	0.020	1.72
Salbutamol + $C_{10–12}$ DP 1.4 (0.8 g/l)	32.6 (0.88)	0.011	0.023	0.46
Salbutamol + $C_{12–14}$ DP 1.4 (0.06 g/l)	35.17 (0.99)	0.075	0.023	3.24
Salbutamol + $C_{12–14}$ DP 1.4 (0.3 g/l)	35.9 (2.66)	0.046	0.015	3.00

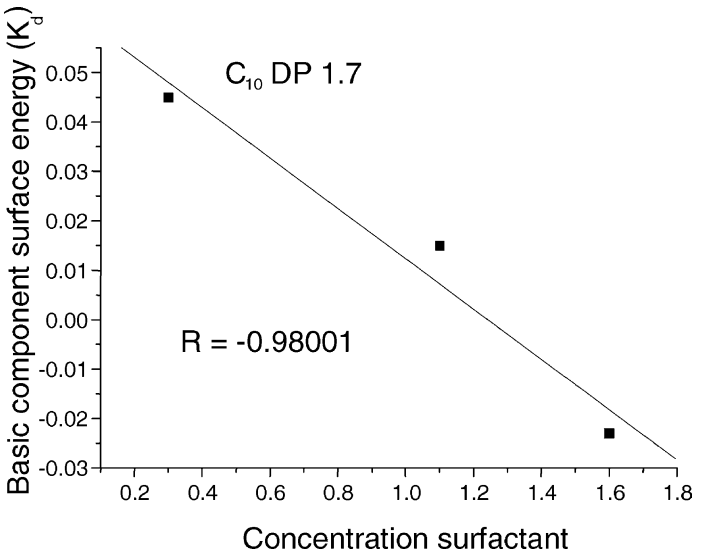

Fig. 5. The basic component of surface energy as a function of the quantity of C_{10} DP 2.7 used to make the particles (g/l).

changes of concentration with time. Consequently it is not possible to model the exact diffusion behaviour of the surfactants during drying, but an indication of their relative ability to diffuse with a drying water-front can be obtained. Fig. 6 shows the results obtained from dynamic surface tension measurements of the surfactants above their CMC. The surface tension of C_{10} DP 2.7, $C_{10–12}$ DP 1.4 and C_{12} G_2 appear to have similar dependence on surface age. However, $C_{12–14}$ DP 1.4 has a slower diffusion rate to the surface. In Figs. 7 and 8, the surface tension/surface age curves are shown for $C_{10–12}$ DP 1.4 and $C_{12–14}$ DP 1.4, these have been fitted with a second order exponential decay. The first part of the curve (shortest surface age) is the most

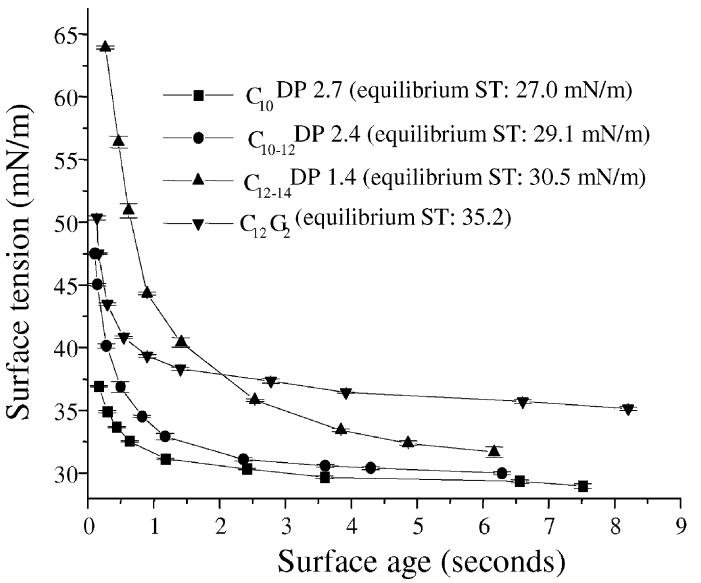

Fig. 6. Surface tension of different APGs at concentration above their CMC at different bubble rate ($n = 4$).

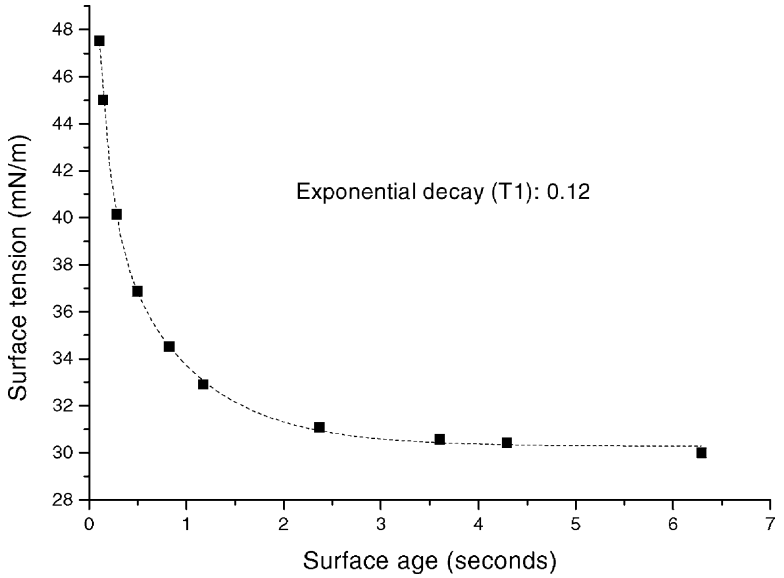

Fig. 7. Surface tension–surface age curve for $C_{10–12}$ DP 1.4 fitted with second order exponential decay.

significant in this study, as the drying phase in spray drying is very rapid. The decay constant T1 is four times bigger for $C_{10–12}$ DP 1.4 compared to $C_{12–14}$ DP 1.4 (from 0.12 to 0.46) indicating a faster diffusion at rapid bubble rate. This behaviour may explain why the surface energy of the salbutamol—$C_{12–14}$ DP 1.4 particles is the least affected by the presence of the surfactant (Table 5). $C_{12–14}$ DP 1.4 is probably too slow to migrate to the surface of salbutamol during the drying process with the consequence that it has less of

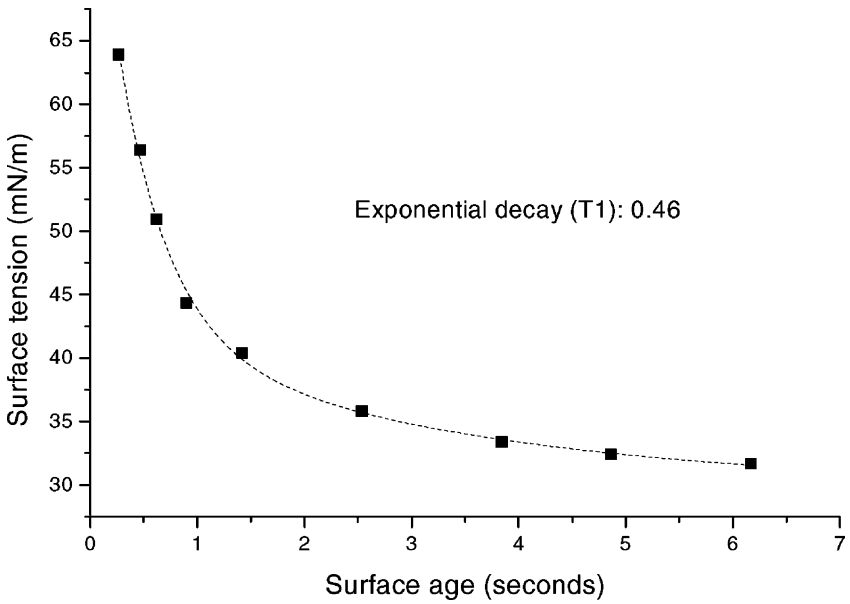

Fig. 8. Surface tension–surface age curve for $C_{12–14}$ DP 1.4 fitted with second order exponential decay.

an effect on surface energy compared with the faster diffusing surfactants.

4. Conclusion

It has been shown that it is possible to prepare microparticles with included surfactants using the spray drying technique and that the size range that is produced is suitable to allow pulmonary delivery. The presence of the surfactant improves the yield of the spray-dried material. Inverse gas chromatography is a useful tool to analyse the surface energy of the particles after spray drying, in order to assess the presence of the surfactant on the surface of the microparticles. It may be possible to correlate the diffusion rate of the surfactant tested with the capacity to migrate to the surface of the solid during rapid drying.

This limited dynamic surface tension study is encouraging as it gives an indication of circumstances where material does/does not reach the surface of a rapidly drying drop. This could be of great significance in other work, for example where there is a desire to exclude proteins from the surface of particles in order to protect them from degradation. Further work is required in this area.

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References

Chawla, A., Taylor, K.M.G., Newton, J.M., Johnson, M.C.R., 1994. Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation. Int. J. Pharm. 108, 233–240.

Gutmann, V., 1993. The Donor–Acceptor Approach to Molecular Interaction. Plenum Press, New York (Chapter 2).

Johansson, I., Strandberg, C., Karlsson, B., Gustavsson, B., 1996. Structure–property relationship for some alkyl glucosides. In: Proceedings of the Fourth World Surfactant Congress, Barcelona, vol. 2.

Masters, K., 1991. Spray Drying Handbook, 5th ed. Longmans, New York.

Montreal Protocol of Substances that Deplete the Ozone Layer, 1989. Liaison Office of the United Nations Environmental Program, New York.

Riddle, F.L., Fowkes, F.M., 1990. Spectral shifts in acid-base chemistry. 1. Van der Waals contribution to acceptor numbers. J. Am. Chem. Soc. 112, 3259–3264.

Schultz, J., Lavielle, L., Martin, C., 1987. The role of the interface in carbon fibre-epoxy composites. J. Adhesion 23, 45–60.