The Effect of Alkylpolyglycoside Surfactants on the Crystallization of Spray-Dried Salbutamol Sulphate: a Gravimetric Near-Infrared Spectroscopy Study

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Angela Columbano¹, Graham Buckton¹ and Philip Wikeley²

¹Department of Pharmaceutics, School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK

²AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH, UK

ABSTRACT This study monitored the effect of a series of structurally related surfactants on the crystallization of amorphous salbutamol sulphate. Amorphous salbutamol sulphate was prepared by spray drying from a solution in water and in the presence of various alkylpolyglycosides (APGs) at different concentrations. The particles were then analyzed using isothermal microcalorimetry and water vapor sorption (Dynamic Vapour Sorption, DVS) analysis combined with near-infrared spectroscopy (DVS-NIR). Both isothermal microcalorimetry and DVS-NIR were able to detect the transition from the amorphous to the crystalline state. The presence of APG surfactants modified the shape of the crystallization peak obtained using isothermal microcalorimetry. The gravimetric study combined with NIR revealed that while the crystallization was similar for the particles with or without surfactant, there was a great difference in the release of water from the newly formed crystal. In the presence of some of the surfactants tested, salbutamol sulphate released the water much faster than in the absence of surfactant. These results helped to explain the differences found in the isothermal microcalorimeter data. Differences were observed in the shapes of the NIR water peaks related to water due to the presence of the surfactant. In conclusion, the use of DVS combined with NIR has helped to analyze and understand the effect of APGs on the crystallization of amorphous salbutamol sulphate.

KEYWORDS: Salbutamol Sulphate, Alkylpolyglycosides (APGs), Amorphous, Crystallization, Water Sorption, Near-Infrared Spectroscopy (NIR).

INTRODUCTION Alkylpolyglycosides (APGs) are nonionic, biodegradable surfactants consisting of an alkyl chain (the hydrophobic part of the molecule) attached to a glucose ring (the hydrophilic part of the molecule) through a glycosidic linkage. Commercial

APGs are complex mixtures: in the same sample it is possible to have molecules with different glucose contents (indicated as the average degree of polymerization of the APG, which is the average number of glucose units per molecule of surfactant) and different types of alkyl chains. In addition, each glucose ring can exist in the α or β form (the α anomer being generally dominant with a level of 65%), which, along with the different possibilities for linkage of the glucose ring, rapidly increases the number of isomers. The nomenclature used to describe the APGs is C_nDP_m , where n describes the number of carbon atoms in the alkyl chain and m describes the average number of glycoside units in the polar head group (the degree of polymerization).

Technical APGs are used widely in personal care products and as detergents especially because they are of relatively low toxicity and are available from renewable sources.¹ Chemically pure APGs are mainly used to reconstitute biologically active proteins as they have nondenaturing properties.²

APGs with different amounts of glucose and different alkyl chain lengths were selected to be spray dried at concentrations below and above their critical micelle concentrations (CMCs) to obtain drug-surfactant microparticles with salbutamol sulphate. The aim of this study was to investigate the effect of the presence of APGs on the crystallization of amorphous salbutamol sulphate obtained by spray drying. The crystallization event was monitored by use of isothermal microcalorimetry and a gravimetric method (Dynamic Vapor Sorption [DVS]) combined with near-infrared spectroscopy (DVS-NIR).

Vapor sorption analysis is a powerful method with which to study the amorphous content of powders, as the uptake and release of water are very different for the amorphous and crystalline forms of the same material. Vapor sorption investigations have been used to study many amorphous materials such as lactose³ and salbutamol sulphate⁴ and also the effects of additives such as polyvinylpyrrolidone (PVP) on the crystallization of lactose.⁵

*Corresponding author: Graham Buckton
Facsimile: 0171 753 5858
E-mail: graham.buckton@ulsop.ac.uk

Near-infrared spectroscopy (NIR) is a technique that is becoming increasingly important in the pharmaceutical industry for the identification of actives and excipients. This technique is fast, noninvasive, and does not require sample preparation. It has been used in the past to study physical properties of solid materials such as polymorphism⁶ and the change from amorphous to crystalline lactose.⁷ In this study, the crystallization of amorphous salbutamol sulphate - APG particles was followed using a humidity-controlled microbalance that was linked to an NIR probe. While the sample was exposed to a specific humidity and the sorption/desorption of water was recorded, it was possible to simultaneously obtain NIR spectra in order to study any related physical change(s).

MATERIALS AND METHODS

Materials

Crystalline salbutamol sulphate was supplied by Avocado (Italy).

The "pure" alkylglycoside n-dodecyl β -D-maltoside (C₁₂G₂) was obtained from Sigma (UK) (purity <98%). The technical APG C₁₀ DP2.7 was supplied by Akzo-Nobel (Germany), while C₁₀₋₁₂ DP1.4 and C₁₂₋₁₄ DP1.4 (Glucopon 600) were supplied by Henkel (Germany). Two of the materials (C₁₀ DP2.7 and C₁₂₋₁₄ DP1.4) were dispersions in water and were freeze-dried prior to use to allow the subsequent preparation of solutions of exact known concentrations (it was possible to make solutions at lower concentrations of surfactant).

Spray drying

Microparticles of salbutamol sulphate and salbutamol sulphate-APGs were prepared by spray drying from solution in water, using a Büshi 190 mini spray drier fitted with a 7-mm pneumatic nozzle. A 100-g/L salbutamol sulphate solution in water or in a solution of an APG was spray dried. For each APG, 2 concentrations were selected, 1 above and 1 below the CMC (see figure legends for details of concentrations used for each surfactant). The conditions and spray drying parameters were selected based on the work of Chawla et al:⁸ pump speed, 5 mL/min⁻¹; air-flow rate, 800 L/h⁻¹; aspirator level, 5; inlet temperature, 150°C ($\pm$ 5°C); and outlet temperature, 80°C ($\pm$ 5°C). The material was desiccated immediately after drying. It has been assumed that the final composition of the particles is the same as (or very similar to) the ratio of salbutamol sulphate to APG used in making the spray drying solution, as all of the solution was spray dried.

Assessment of the degree of crystallinity using isothermal microcalorimetry

Isothermal microcalorimetry was used to assess the degree of crystallinity of spray-dried salbutamol

sulphate and salbutamol sulphate-APG microparticles following the method described by Buckton et al.⁹ Spray-dried and feed material were investigated using a Thermal Activity Monitor (TAM, Thermometric, Sweden) at 25°C. About 50 mg of material was accurately weighed and placed into a 3-mL glass ampoule together with a tube containing a saturated solution of sodium chloride (to yield a relative humidity [RH] of 75%). The ampoule was sealed and equilibrated in the calorimeter for 30 minutes before being lowered into the measuring site. The output from the calorimeter was recorded as heat flow (dq/dt = power) as a function of time.

Dynamic vapor sorption combined with near-infrared spectroscopy (DVS-NIR)

Gravimetric studies of spray-dried salbutamol sulphate and salbutamol sulphate-APG particles were undertaken in a humidity-controlled microbalance (DVS, Surface Measurement Systems, UK). The DVS is based on a Cahn microbalance capable of measuring changes in sample mass lower than 1 part per million, placed in an incubator to control the temperature. Mixing dry and saturated vapor gas flows in the correct proportions using mass flow controllers generates the required humidity. The apparatus is computer controlled, allowing a preprogramming of the sorption and desorption isotherms. Samples of about 50 mg were loaded on one side of the pan balance and the program set to control the humidity at 0% for 6 hours (drying phase), then at 75% for 15 hours (to allow crystallization), and then back at 0% for at least 3 hours. At the same time NIR spectra were recorded using a FOSS NIRSystems spectrometer (Eden Prairie, MN, USA) with the fiber-optic probe situated 4 mm below the flat-bottomed pan of the microbalance. Each NIR measurement was the mean of 32 scans over the wavelength range 1100 nm-2500 nm. Spectra were taken every 15 minutes, recorded and analyzed using the Vision software (FOSS NIRSystems).

RESULTS

Isothermal microcalorimeter

The calorimetric data for spray-dried salbutamol sulphate alone and in the presence of APG surfactants exposed at 75% RH are shown in **Figure 1**. A calorimetric response for amorphous material can be described as having an initial disruption caused by lowering the sample into the measuring site, followed by a flat baseline, during which water absorption is balanced by the response for humidity generation from the saturated salt solution. Then an exotherm is detected, caused by the crystallization of the amorphous material. The apparent enthalpies of crystallization (calculated from the area under the peak) for salbutamol sulphate and salbutamol

sulphate - APGs are given in (Table 1). The crystallization exotherm for spray-dried salbutamol sulphate was of similar magnitude to that reported previously by Buckton et al⁹ for the same drug.

Figure 1. Microcalorimeter output (power as function of time) of spray-dried salbutamol sulphate and salbutamol sulphate-APG particles at 75% RH.

Table 1. Apparent Crystallization Enthalpy of Salbutamol Sulphate and Salbutamol Sulphate-APG Particles Obtained from Isothermal Microcalorimetry Data at 75% RH (n = 3)

Material	Crystallization Enthalpy (J/g) (SD)
Salbutamol sulphate	22.3 (0.65)
Salb + C ₁₀ DP 2.7 (0.3 g/l)	21.4 (0.12)
Salb + C ₁₀ DP 2.7 (1.6 g/l)	18.4 (0.26)
Salb + C ₁₀₋₁₂ DP 1.4 (0.15 g/l)	20.6 (0.73)
Salb + C ₁₀₋₁₂ DP 1.4 (0.8 g/l)	18.7 (0.35)
Salb + C ₁₂₋₁₄ DP 1.4 (0.06 g/l)	20.1 (0.65)
Salb + C ₁₂₋₁₄ DP 1.4 (0.3 g/l)	18.1 (0.10)
Salb + C ₁₂ G ₂ (0.08 g/l)	19.4 (0.74)
Salb + C ₁₂ G ₂ (0.8 g/l)	19.9 (0.13)

The microcalorimeter outputs for salbutamol sulphate in the presence of APGs are significantly different from those seen for the drug alone. In the presence of the surfactant, the crystallization peaks have different shapes, and when a low concentration of surfactant is used they show a secondary peak immediately after the crystallization. These differences lead to changes in the area under the crystallization peak, and as a consequence the apparent enthalpies of crystallization are different, as shown in Table 1. Thus the surfactants are either affecting the transition from amorphous to crystalline material, or they influence the other processes that contribute to the calorimetric response, such as the desorption of water during crystallization. As the concentration of surfactant was increased, the area under the peak decreased (Table 1). Given that in each case it is salbutamol sulphate that is crystallizing, it might be assumed that the area under the curve (in J/g of salbutamol sulphate) would be the same, even if the shapes of the thermographs were different. However, it is clear that the different shapes of calorimetric response

(Figure 1) also produce a different area under the curve (Table 1). Under these circumstances, it becomes impossible to use the area under the curve to determine the amorphous content of the salbutamol.

DVS-NIR

The water sorption and desorption data for salbutamol sulphate spray dried alone or in the presence of APGs are shown in Figure 2. For salbutamol sulphate spray dried alone it is possible to observe that as soon as the powder is exposed to 75% RH, there is a rapid uptake of water up to 13% wt/wt, which is then desorbed very slowly. The desorption of water is pseudo zero order and does not change even if the RH is reduced from 75% to 0%. This indicates that it is the movement of water through the solid that is rate limiting, not the concentration difference between the particle surface and the vapor. All of the samples, including salbutamol sulphate with no added surfactant, equilibrate to a very similar maximum water content at 75% RH. However, the rate of water desorption following crystallization is dramatically affected by the surfactants. The release of water from the salbutamol-APG particles is characterized by 2 different desorption rates: in the first part of the desorption curve the release of water is faster than in the second part. These results are summarized in Table 2. The 2 most efficient surfactants in speeding up the release of water (compared with the particle of pure drug) are C₁₀₋₁₂ and C₁₂₋₁₄ DP1.4 at high concentration. C₁₀ DP2.7 and C₁₂ G₂ had the least effect, with water desorption rates being more similar to that of the pure drug, irrespective of the concentration of surfactant that was present in the particles.

Figure 2. Water vapor sorption data of amorphous salbutamol sulphate and salbutamol sulphate-APGs: 6 hours at 0% RH, 15 hours at 75% RH and 6 hours at 0% RH.

Table 2. Vapor Desorption Analysis of Salbutamol and Salbutamol-APG Particles: Values of Slopes in Desorption Curve and % Weight Loss after 2.5 Hours at 75% RH

Material	Apparent Desorption mg/hour	Rate of (part 1)	Apparent Desorption (mg/hour)	Rate of (part 2)	% Weight-loss after 2.5 h at 75% RH
Salbutamol sulphate	N/A		0.16		1.0
Salb+C ₁₀ DP 2.7 (0.3 g/L)	2.9		0.19		3.3
Salb+C ₁₀ DP 2.7 (1.6 g/L)	2.4		0.25		2.0
Salb+C ₁₀₋₁₂ DP 1.4 (0.15 g/L)	2.4		0.26		2.9
Salb+C ₁₀₋₁₂ DP 1.4 (0.8 g/L)	9.7		0.15		9.5
Salb+C ₁₂₋₁₄ DP 1.4 (0.06 g/L)	3.7		0.13		4.6
Salb+C ₁₂₋₁₄ DP 1.4 (0.3 g/L)	10.3		0.15		8.4
Salb+C ₁₂ G ₂ (0.08 g/L)	4.4		0.28		3.1
Salb+C ₁₂ G ₂ (0.8 g/L)	4.5		0.16		2.3

The NIR spectra collected from the probe attached to the DVS are shown in **Figures 3-10**. The spectra have been normalized (standard normal variate) to minimize influences of factors such as particle size and then expressed as the second derivative to enhance resolution. A selection of NIR data that show the spectral changes associated with the crystallization of salbutamol sulphate in the presence of C₁₀ DP2.7 and C₁₂₋₁₄ DP1.4, are shown in **Figures 3-6**. As seen from the DVS data, these 2 surfactants had different effects on the water desorption from the particles, with rapid release seen in the presence of C₁₂₋₁₄ DP1.4. From the spectra, it can be seen that particles containing C₁₂₋₁₄ DP1.4 and C₁₀ DP2.7 had crystallized after 1 and 2 hours, respectively (**Figures 5 and 3**). This can be seen by looking at the 2 groups of peaks between 2050 nm and 2150 nm. These have been modified by the exposure to high humidity and have become very similar to the same peaks in the crystalline form of salbutamol sulphate.

Figure 3. NIR spectra (1800 nm-2200 nm) of spray-dried salbutamol sulphate + C₁₀ DP2.7 after exposure to different RH (SNV second derivative). **Figure 4.** NIR spectra (1250 nm-1650 nm) of spray-dried salbutamol sulphate + C₁₀ DP2.7 after exposure to different RH (SNV second derivative). **Figure 5.** NIR spectra (1800 nm-2200 nm) of spray-dried salbutamol sulphate + C₁₂₋₁₄ DP1.4 after exposure to different RH (SNV second derivative).

Figure 6. NIR spectra (1250 nm-1600 nm) of spray-dried salbutamol sulphate + C₁₂₋₁₄ DP1.4 after exposure to different RH (SNV second derivative).

Figure 8. NIR spectra (1900 nm-2200 nm) of crystalline salbutamol sulphate, spray-dried salbutamol sulphate, spray-dried salbutamol sulphate + C₁₀ DP2.7, C₁₀₋₁₂ DP2.7 and C₁₂₋₁₄ DP1.4 after crystallization in the DVS (SNV second derivative).

Figure 7. NIR spectra (1300 nm-1600 nm) of crystalline salbutamol sulphate, spray-dried salbutamol sulphate, spray-dried salbutamol sulphate + C₁₀ DP2.7, C₁₀₋₁₂ DP2.7 and C₁₂₋₁₄ DP1.4 after crystallization in the DVS (SNV second derivative).

Figure 9. NIR spectra (1800 nm-2000 nm) of SD salbutamol sulphate - C₁₀ DP2.7 particles showing differences in absorbance related to water after different periods of time at 75% RH (SNV second derivative).

Figure 10. NIR spectra (1800 nm-2000 nm) of SD salbutamol sulphate - C₁₂₋₁₄ DP1.4 particles showing differences in absorbance related to water after different periods of time at 75% RH (SNV second derivative).

The uptake and release of water at 75% RH before and after crystallization can be followed at 1940 nm. In the case of C₁₀ DP2.7 after 15 hours the absorbance related to water is still strong (**Figure 3**), while for C₁₂₋₁₄ DP1.4 it has diminished (**Figure 5**), which confirms the water desorption differences observed in the DVS (**Figure 2**).

Spectra for all the samples studied, collected at the end of the DVS run, are shown in **Figures 7 and 8**. All the amorphous materials that have been crystallized have very similar spectra. It is possible to observe similarities in crystalline salbutamol sulphate between 2000 nm and 2200 nm and differences between 1400 nm and 1550 nm. The fact that the final spectra differ from the original spectra for salbutamol sulphate alone could be due to many reasons, including the fact that surfactant could be present giving rise to some different packing geometry, or simply because the final crystallized material was a large fused mass and not a free-flowing powder as was present for the original salbutamol sample. **Figures 9 and 10** show differences in the interaction of water with the different particles. The presence of C₁₀ DP2.7, which results in water desorption at a similarly slow rate to salbutamol sulphate alone (**Figure 2**), has a similar absorbance peak for water (**Figure 9**) as that seen for pure salbutamol sulphate (not shown). C₁₂₋₁₄ DP1.4, which at high concentrations results in extremely fast water desorption, has a spectra with differences in the shape of the peaks related to water (**Figure 10**), which could indicate a different interaction of the material with water compared with the interaction of the sample with C₁₀ DP2.7 present and pure salbutamol sulphate. C_{12G2} and C₁₀₋₁₂ DP1.4 behaved in a similar manner to C₁₀ DP2.7 and C₁₂₋₁₄ DP1.4, respectively, with respect to NIR in the region of 1800 nm to 2000 nm.

DISCUSSION The data collected in the DVS-NIR study helped to explain the results obtained from the isothermal microcalorimeter. The NIR proved that the crystallization event is not affected to such an extent by the presence of the surfactants to give rise to the changes seen in the TAM data between salbutamol sulphate with and without surfactants. Consequently, the major contribution to the differences in the TAM data must be due to the differences observed in the water desorption that follows the crystallization.

The calorimetric crystallization peaks obtained for salbutamol sulphate spray dried with a high concentration of surfactant are of a very different shape than those for the drug alone: they are narrower and "taller" even if they have a smaller area. This is related to the fact that the crystallization peak is in fact the result of numerous events, the largest of which will be the crystallization exotherm and the release of water from the newly formed crystal (endotherm). It is logical that a reduction in water desorption after crystallization would result in a net calorimetric response, which was a larger exotherm. In the presence of the APGs, the endothermic evaporation of water is generally faster leading to the peak returning to baseline quicker and to a smaller net area. In the drug alone, the evaporation of water is extremely slow resulting in a gradual return to an apparent baseline; however, water desorption will continue for many hours, which will be a minor constant endothermic displacement from the baseline that will not be measured easily.

The presence of low concentrations of APGs results in a calorimetric crystallization peak with a shape and area generally intermediate between the drug alone and the drug in the presence of a high amount of surfactant. Also, quite often a secondary peak is present when the surfactant concentration is low. The low concentration was probably due to the fact that the release of water was initially fast but rapidly became slow (**Figure 2**). The changes in the kinetics of the endothermic response will therefore cause the exothermic crystallization peak to be divided into a main peak followed by a second smaller peak.

The DVS-NIR has helped to provide an understanding of the effect of the APG surfactants on the crystallization process of spray-dried salbutamol sulphate. However, it remains unclear why this class of surfactants is causing such big differences in the desorption of water after crystallization.

The slow release of water in spray-dried salbutamol sulphate after crystallization could be a problem in inhalation products. As salbutamol sulphate is micronized prior to use in inhalation products, it can be expected to become partially amorphous. The

amorphous region may or may not have crystallized prior to the production of an inhalation dosage form; however, there is a risk that water could be present in recently crystallized material. The fact that the water is held within the structure of the particles for several days after crystallization could create stability problems for inhalation dosage forms. The APGs, speeding up the desorption of water and allowing in many cases complete release after a few hours, could be a solution to the problem.

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