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Formulation of solution metered dose inhalers and comparison with aerosols emitted from conventional suspension systems

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Abstract

Micellar solubilisation was used to enhance the solubility of salbutamol (SB) and triamcinolone acetonide (TAA) in chlorofluorocarbon solvents with the aim of formulating solution metered dose inhaler (MDI) products of these drugs. Stable, isotropic solutions of soya phosphatidylcholine (SPC) were obtained in trichlorotrifluoroethane (P113) and a 30:70 mixture of trichlorofluoromethane (P11) and dichlorodifluoromethane (P12) containing water at a maximum level of R (mol water/mol SPC) = 4. The solubility of SB and TAA in both the non-pressurised solvent (P113) and the pressurised mixture (P11/P12) increased proportionately with SPC concentration but was reduced on increasing values of R. The incorporation of a charged lipid, dicetyl phosphate, into the micellar structure promoted the solubilisation of SB in both solvent systems. In SPC solutions, the optimal solubility of either drug was achieved at R value of 0.9. Solution MDI formulations of SB and TAA gave reproducible shot potency throughout the pack-life, comparable to the performance of commercially available suspension products (SB, Ventolin; TAA, Azmacort). In contrast to suspension systems, however, there was no loss of potency in the first spray actuated after storage with SB solution MDIs. The respirable fraction (RF) of drug emitted from solution MDIs was significantly increased by altering the orifice diameter of the actuator. These studies confirmed that the highest RF values (in excess of those achieved with suspension products) were achieved when the MDIs were fired through an actuator with the smallest (0.25 mm) orifice.

Keywords: Metered dose inhaler; Formulation; Micellar solubilization; Aerosol; Solution; Suspension

1. Introduction

The homogeneous nature of metered dose inhaler (MDI) formulations in which the drug is solubilised to form a molecularly dispersed state in the propellant blend may offer certain advantages over the traditional approach of formulating drugs in MDIs as suspensions (Dalby and Byron, 1988; Evans et al., 1991). One of the principal advantages may relate to improved uniformity in unit spray content of the active component (shot potency). In recent years, the phe-

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nomenon of low first spray from suspension MDIs has been reported (Cyr et al., 1991) with evidence to suggest that this may be related to the length of storage time between actuations of the device and the orientation of the canister during that time (Graham et al., 1992). Another key advantage in formulating drugs as solutions in MDIs is the greater opportunity for reducing primary aerosol droplet size by manipulation of the actuator orifice diameter. Compared to suspension MDIs, solution systems may be fired through smaller diameter actuator orifices (Evans et al., 1991). Provided the dissolved non-volatile fraction does not adversely affect propellant evaporation, solution aerosol formulations can lead to a significantly greater extent of lung deposition than is the case for those containing suspended drug particles (Harnor et al., 1993).

Recently, a method of formulating drugs as solutions in an aerosol propellant blend has been demonstrated which involves solubilisation within reverse micelles composed of soya phosphatidylcholine (SPC) (Evans et al., 1990, 1991; Evans and Farr, 1992). One purpose of this investigation was to examine the factors controlling the solubilisation of two therapeutically relevant drugs, salbutamol base (SB) and triamcinolone acetonide (TAA), within reverse micellar systems. The effects of surfactant concentration, surfactant composition and the addition of water on drug solubilisation were studied. Comparisons were made between observations recorded in a model CFC solvent, trichlorotrifluoroethane (P113), and those in a commercially relevant propellant blend (30:70% w/w) of trichlorofluoromethane (P11) and dichlorodifluoromethane (P12).

Optimised MDI formulations containing therapeutically relevant levels of SB and TAA were then assessed for reproducibility of shot potency, and comparison made between the performance of commercially available suspension inhalers and that of the novel solution systems. Using solution MDIs containing salbutamol investigations were also conducted to evaluate the dependence of aerosol characteristics on actuator design.

2. Materials and methods

SPC (Epikuron 200; Lucas Meyer, Germany) was dried by repeatedly dissolving in specially dried methanol (Karl Fischer grade, Fisons, UK) followed by rotary evaporation to a constant weight. Dicetyl phosphate (DCP) was purchased from the Sigma Chemical Co., UK. All CFC solvents/propellants were obtained from ICI (Performance Chemicals), UK. SB and TAA were generous gifts from Armstrong Pharmaceuticals Inc., USA.

2.1. Water solubilisation in SPC micellar systems

SPC solutions were prepared in P113 at concentrations of 0.5, 1.0 and 2.0% w/w. The maximum level of water incorporation at 25° C before phase separation was determined using the method of Evans et al. (1990). Pressurised systems (30:70% w/w P11/P12) were prepared as follows: Aliquots of water were dispensed into clean, dry, plastic-coated glass bottles (20 ml) followed by the addition of SPC, added as a cooled concentrate (20% w/w) in P11. Further P11, in excess of the required weight, was added and allowed to evaporate to the correct weigh before the bottle was sealed with a 50 μl metering valve (Neotechnic Engineering Ltd, UK). The bottles were shaken at 25° C for 24 h after which the required quantity of P12 was pressure filled through the valve. The pressurised units were equilibrated for a further 7 days prior to visual examination to determine the nature of the system, i.e., isotropic or anisotropic. The absolute water concentration of all isotropic systems (pressurised and non-pressurised) was determined using an automatic Karl Fischer titrator (Mitsubishi CA-06 moisture meter) and expressed as a molar ratio of water to SPC (R).

The influence of the incorporation of an anionic lipid on the water solubilising properties of the reverse micelles was examined as a function of the SPC/DCP mole ratio. The calculated amounts of SPC and DCP were dissolved in chloroform and dried to constant weight to form a

thin film which was then used to produce the desired concentrations of surfactant in either P113 or P11/P12.

2.2. Determination of drug solubility in SPC micellar systems

The influence of surfactant concentration, surfactant composition and R on the level of solubilised drug was determined after the addition of excess SB or TAA to the non-pressurised and pressurised solvent systems. At the end of a seven day equilibration period at 25° C, the P113 based systems were filtered through cellulose acetate membrane filters (0.45 μm pore size, Sartorius, Germany), into individual glass round-bottomed flasks, and the solvent evaporated off. The residues were reconstituted in methanol and drug quantification determined by HPLC analysis based on standard Pharmacopoeial methods.

The P11/P12 preparations were filtered under pressure by coupling the donor MDI, containing excess drug in the P11/P12 propellant blend, to a Ministart filter unit (0.45 μm pore size, Sartorius, Germany) by means of a nylon 6 adapter. This was machined to accept the valve stem at one end and to engage the luer fitting of the filter at the other. The valve stem of an empty (receptor) MDI then was coupled to the outlet of the filter and the entire apparatus enclosed in a Perspex tube to ensure the aerosol units were correctly aligned. Downward pressure on the donor MDI opened the continuous valves and the contents flowed through the filter until the vapour pressure within the units was equalised. The weight of filtrate collected in the receptor MDI was recorded, the bottle cooled in a mixture of dry ice and acetone for approx. 10 min, and the valve removed with a tube cutter to allow the liquid propellants to evaporate. Each residue was reconstituted with methanol and the solubilised drug concentration determined by HPLC analysis.

2.3. Preparation of solution MDIs containing salbutamol or triamcinolone acetonide

The solution formulations were packaged in 20 ml anodised aluminium aerosol canisters (Presspart cut edge) and sealed with the 63 μl metering valves (BK 356; Bespak, UK. The calculated quantity of drug was weighed into the aerosol canisters prior to the desired weight of surfactant concentrate. Thereafter, the preparation followed an identical procedure to that detailed for the placebo MDIs described earlier.

2.4. Shot potency determinations

The reproducibility of shot potency was determined at the beginning (SB, shots 10–11; TAA, shots 10–14), middle (shots 100–101, 100–104) and end (shots 200–201, 200–204) of canister life using a collection apparatus based on a 1 l separating funnel (Cyr et al., 1991). The MDI canister was shaken for 10 s and secured in the appropriate actuator (commercial preparations with actuator supplied; solution MDIs with actuators having a 0.53 mm orifice diameter), the stopcock at the neck of the funnel was opened and the vacuum turned on. The MDI was fired and the vacuum was applied for a further 20 s. The MDI was removed and shaken for a further 20 s before repositioning in the actuator and reapplying the vacuum and firing for a second time, this procedure repeated for TAA until five actuations had been collected. The separating funnel was then rinsed with three 10 ml aliquots of methanol, the washings were collected after passage through the cotton wool plug, and made up to a final volume of 50 ml. Drug deposited in the valve stem and actuator were also volumetrically removed with methanol. Drug quantification in each of the collected fractions was determined using the appropriate HPLC method. Throughout the study individual shot weights were also determined by weighing the canisters between actuations.

The phenomenon of low first spray potency following storage of an SB containing MDIs was also investigated in the same apparatus. Potency determinations were made on the selected MDIs (shots 10–12) which were then actuated to waste until the approximate mid-point of the canister life was reached, i.e., shot 100. The MDI valve and actuator were then rinsed with methanol to remove residual drug and stored, undisturbed

(clamped valve down) for 3 h. Individual shot potency determinations using the method described above were then made for the next three shots after 10 s shaking. The time taken for the collection of the three sprays was less than 15 min.

2.5. Assessment of the influence of actuator geometry on respirable fraction of emitted aerosols

The fraction of the emitted aerosol dose that fell within the respirable fraction (RF), i.e., aerodynamic diameter < 5.5 μm was determined using a pre-calibrated multistage liquid impinger (MLI) (Evans et al., 1991). The effect of varying the actuator orifice diameter on the RF of the emitted aerosols from solution MDIs was investigated using a series of actuators having orifices of similar length but with varying diameter (0.62, 0.54, 0.53, 0.47, 0.33 and 0.25 mm) (Bespak, UK).

Initial studies were conducted using the optimised salbutamol solution formulation, with Ventolin fired through its standard actuator serving as a control. Determinations were undertaken between shots 50 and 150 of the pack-life. Five shots were fired into the MLI to ensure sufficient drug deposition on each stage for analysis by HPLC. Three runs were carried out for each of the actuators employed. The actuator providing the highest respirable fraction was then investigated with the optimised TAA solution system, employing the same procedures. In this instance Azmacort was used as the standard.

3. Results and discussion

3.1. Water and drug solubilisation studies

When water was incorporated into SPC solutions in P113 clear isotropic systems were evident up to an R value of 4 irrespective of the concentration of surfactant present. This behaviour was also observed when similar solutions were prepared using the pressurised P11/P12 blend as the solvent. In both P11/P12 and P113 systems, further addition of water to $R \geq 4.5$ resulted in phase separation. When $R > 3.0$ an increase in the viscosity of the solutions was also observed which previously has been attributed to changes in micellar size and shape (Evans et al., 1990). The inclusion of DCP at a mole ratio of 5:95, did not alter the water solubilising capacity of the surfactant solution in P113, however, at greater mole fractions, i.e., 10:90 and 20:80, the level of water inclusion was much reduced before phase separation occurred. It may be speculated that the presence of the negatively charged DCP altered the packing of the SPC molecules in such a way as to exclude water from its preferred sites within the micelle core. As a consequence of these findings the water solubilising capacity of SPC:DCP blends was not examined in the pressurised solvent system.

Solubilisation of SB and TAA in CFC solvents was proportional to SPC concentration (Fig. 1), a probable result of increased micelle numbers providing proportionally more sites for drug solubilisation. Even at the lowest concentration of surfactant investigated, there was a substantial increase in the solubility of either drug over levels determined in solvent alone (SB, 0.007 and 0.053 mg/ml in P113 and P11/P12, respectively; TAA, 0.001 and 0.012 mg/ml). These data demonstrate the importance of micellar solubilisation as a means of enhancing the solubility of drugs in propellant based formulations. Overall, there was good agreement between the solubility behaviour of either drug in each solvent system employed. For SB, there was a small but significant increase in solubility in P11/P12 systems compared to those containing P113. No explanation can be given for this observation due to the lack of a suitable method to determine whether there were any subtle differences in SPC micellar size and shape in the pressurised solvent system compared to those previously reported for P113.

Evans and Farr (1992) have shown using NMR that solubilised SB interacts with the phosphate of the SPC headgroup. This was reconfirmed in this study by demonstrating the effect of incorporating DCP on SB solubilisation in either solvent system (Table 1). The increase in the amount of SB solubilised was linearly related to the mole fraction of DCP, indicating a probable ion pairing interaction between the oppositely charged SB

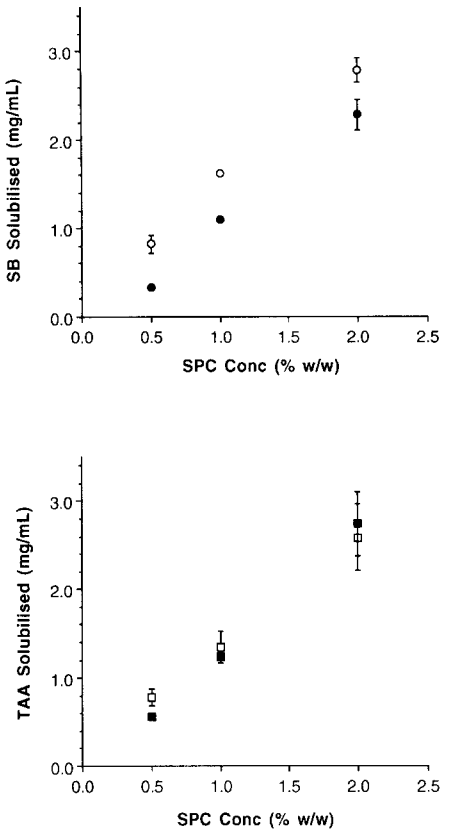

Fig. 1. Solubility of (a) salbutamol and (b) triamcinolone acetonide in chlorofluorocarbon solvents as a function of SPC concentration. Symbols refer to the mean solubilities (±SD, $n = 3$) of salbutamol in P113 (●) and P11/P12, 30/70 (○), and triamcinolone acetonide in P113 (■) and P11/P12, 30/70 (□).

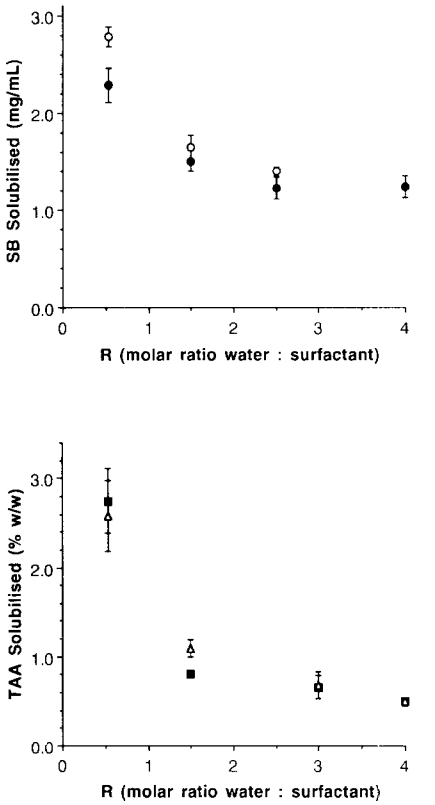

Fig. 2. Solubility of (a) salbutamol and (b) triamcinolone acetonide in chloroflurocarbon solvents as a function of R (water/SPC molar ratio). Symbols refer to the mean solubilities (±SD, $n = 3$) of salbutamol in P113 (●) and P11/P12, 30/70 (○), and triamcinolone acetonide in P113 (■) and P11/P12, 30/70 (∧).

and DCP within the micelle. As before, significantly more SB was solubilised in the P11/P12 solvent system compared to P113. This may be attributed to the difference in dielectric constant between the two solvent systems which could subtly modify the micellar size and shape of SPC in solution (Evans et al., 1988).

In contrast, the incorporation of water into SPC/solvent systems resulted in a reduction of solubilised SB, a phenomenon also observed for TAA (Fig. 2). The reduction in SB solubilisation with increased R has already been attributed to the fact that its preferred sites of interaction become unavailable for binding due to the presence of water (Evans and Farr, 1992). Consequently, the extent of SB solubilised becomes predominantly dependent upon its aqueous solubility as its location is changed from being in close proximity to the polar head groups to one merely dissolved in the freely situated water pool

Table 1
Solubilisation of salbutamol in SPC solutions in P113 and P11/P12 as a function of increasing mole fraction of DCP

Mol% DCP [a]	Amount solubilised (mg/ml) (mean ± SD, $n = 3$)	
	P113	P11/12
0	1.61 (0.26)	2.79 (0.10)
5	1.91 (0.19)	2.87 (0.27)
10	2.38 (0.10)	4.01 (0.33)

[a] The total surfactant concentration was constant at 2% w/w.

Table 2
Composition of pressurised solution MDIs, each containing 220 shots of salbutamol or triamcinolone acetonide

	SB MDI	TAA MDI
Salbutamol (% w/v)	0.159	
Triamcinolone acetonide (% w/v)		0.159
SPC (% w/w)	1.21	1.16
P11 (% w/w)	29.58	29.64
P12 (% w/w)	69.05	69.10
Total weight (g)	19.03	19.03
μg drug/63 μl	100	100

For each formulation, the water content was equivalent to an R value = 0.9.

within the core of the micelle. A similar hypothesis may be proposed for TAA which, despite its greater hydrophobicity (log P 2.53; Goundalkar and Mezei, 1984) compared to SB, may also favour polar headgroup interaction rather than association with the hydrophobic regions of the micelle. Cleary and Zatz (1977) have shown in mixed monolayers of lecithin and hydrocortisone that steroids (such as TAA) having polar headgroups at both ends of the molecule favour a horizontal orientation so that all polar headgroups can remain hydrated. While Fig. 1 and 2 show that SB and TAA appear to be incorporated in SPC micellar systems to a similar extent, this same orientation for TAA in SPC micelles may also serve to explain the lower solubilisation on a molar basis of TAA compared to SB (ratio Mol. Wt TAA/SB = 1.8).

3.2. Formulation testing studies

The results described above permitted the rational determination of the optimum formulation conditions, i.e., surfactant concentration, surfactant composition and R, for the solubilisation of the two model drugs within CFC based MDIs. For the purposes of these investigations the desired (ex-valve) shot potency for SB was 100 μg/63 μl, the same as the world-wide innovator product (Ventolin; Allen and Hanburys Ltd, UK). Using the same volume metering valves, TAA solution MDIs were formulated at a concentration of 100 μg/shot. This concentration was dictated by the maximum desirable concentration of surfactant in the formulation before significant retardation of propellant evaporation occurred following actuation (Evans et al., 1991), and is 50% of that of the appropriate commercial standard (Azmacort). However, Azmacort inhalers are supplied with a spacer device which restricts the drug available to the patient to approx. 100 μg per actuation. The compositions of the actual solution formulations tested are listed in Table 2.

In Table 3, the data for shot potency of SB content of two consecutive sprays for suspension and solution MDIs are compared at pre-determined stages of pack-life. There were no significant differences ($p > 0.05$, two-way ANOVA) between the ex-valve shot potencies of either formulation at any stage of device life. It may be concluded that, under the particular test procedures followed, the solution MDI preparation of SB performed equally as well as the commercial standard, Ventolin, in terms of reproducibility of shot potency. For MDIs containing TAA (Table 4), the units formulated as solutions displayed excellent reproducibility. There was, however, greater variation in ex-valve shot potency for the suspension formulations, highlighted at the mid pack-life testing point (shots 100/104) where the

Table 3
Shot potency analysis of the salbutamol base content of two consecutive sprays at pre-determined stages of MDI life

MDI	Shots 10/11		Shots 100/101		Shots 200/201	
	SB/shot (μg)	Shot wt (mg)	SB/shot (μg)	Shot wt (mg)	SB/shot (μg)	Shot wt (mg)
Ventolin	100.5 (5.27)	85.1 (1.10)	105.2 (1.09)	85.3 (1.30)	106.2 (13.5)	85.1 (0.50)
Solution SB	106.0 (8.38)	89.8 (0.9)	101.2 (2.62)	89.2 (1.70)	102.4 (2.97)	88.5 (0.60)

The table compares mean shot potency (SD) and mean shot weight (SD) for Ventolin and a solution MDI formulation of salbutamol (solution SB).

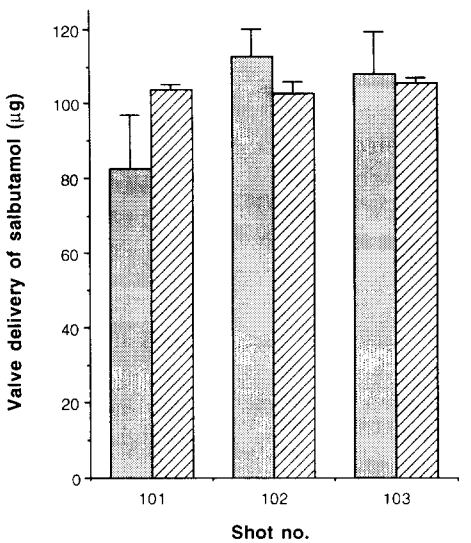

Fig. 3. Comparison of the reproducibility of shot potency of Ventolin (▨) and a solution MDI formulation of salbutamol (⁘) following 3 h storage in a valve inverted orientation (±SD, $n = 3$).

large variability obtained was a result of the dose emitted from one unit varying by > 30% of the nominal value. This observation was not supported by a concomitant variation in shot weight, which was consistent with the data obtained at the other testing points.

A comparison of shot potency variability following 3 h storage of SB MDIs in a valve-down orientation is shown in Fig. 3. The SB solution MDIs maintained a consistent shot potency (and shot weight) throughout the three actuations tested at the midpoint of pack-life, with very little variation between individual MDIs (coefficient of variation was 1.33% for first, 2.74% for second, and 1.36% for third shot). For the suspension products, the mean drug content of the first actuation was statistically lower than that of the two subsequent shots (Duncan's New Multiple Range Test). Although the testing protocols varied in terms of MDI standing time, the level of deficiency in first spray content of SB is similar to that recently reported by Byron (1994). In that paper, it was stated that the lower emitted dose after valve down storage (24 h) was due to the loss of creamed drug out of the metering chamber which, presumably, is replaced by liquid from the bulk of the formulation deficient in suspended drug. The data presented here supports this hypothesis, as certainly there was no loss of prime (indicated by shot weight) over the adopted 3 h duration of storage. Indeed, loss of prime has been shown to be a phenomenon of much longer storage times (Fiese et al., 1988).

The influence of actuator design on the deposition characteristics of aerosols emitted from solution MDIs containing SB is shown in Fig. 4. Consistent with the data published by Evans et al. (1991) for placebo solution MDIs, the proportion of the emitted SB dose contained in the respirable range (i.e., droplets < 5.5 μm) was highly dependent on the orifice diameter (OD) of the actuator through which the MDI was fired (ANOVA; $p < 0.001$). There was a distinct cut-off in the effect of orifice diameter: RF decreased in

Table 4
Shot potency analysis of the triamcinolone acetonide content of two consecutive sprays at pre-determined stages of MDI life

MDI	Shots 10/14		Shots 100/104		Shots 200/204	
	TAA (% valve delivery)	Shot wt (mg)	TAA (% valve delivery)	Shot wt (mg)	TAA (% valve delivery)	Shot wt (mg)
Azmacort	94.1 (7.84)	70.2 (0.19)	84.4 (23.72)	70.5 (1.62)	101.7 (5.46)	69.2 (2.17)
Solution TAA	91.7 (1.31)	89.8 (2.62)	99.6 (9.39)	89.2 (0.31)	101.9 (7.46)	88.5 (0.62)

The table compares mean shot potency (expressed as % of expected valve delivery of TAA (SD)) and mean shot weight (SD) for Azmacort and a solution MDI formulation of TAA (solution TAA).

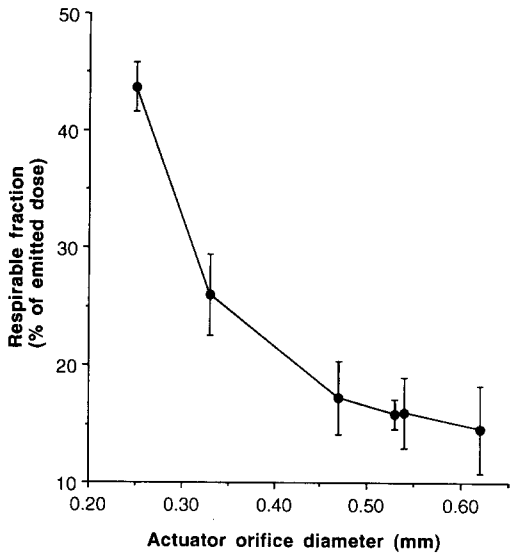

Fig. 4. Respirable fraction (RF) of salbutamol emitted from solution MDI formulations as a function of actuator orifice diameter. Each symbol represents the mean of three replicate determinations (±SD).

the order 0.25 mm OD > 0.33 mm OD > 0.47 mm OD which, in turn, was equivalent to the three other ODs investigated. Thus, an RF of 43.7 ± 2.12%% was achieved using an actuator possessing the smallest orifice diameter investigated (0.25 mm) which compared favourably with the RF achieved for the SB suspension MDI fired through its standard actuator (36.0 ± 1.17%). Also apparent were differences in the relative deposition of the 'non-respirable' proportion of the aerosol dose between the suspension and solution formulations. As a consequence of the small orifice diameter, which produces a wide aerosol cone that favours efficient propellant evaporation, the solution MDIs resulted in a significantly larger actuator deposition at the expense of deposition in the throat (27.7 ± 2.58 and 24.3 ± 3.96%, respectively, for OD = 0.25 mm, 17.4 ± 1.17 and 66.5 ± 5.13%, respectively, for OD = 0.62 mm). This latter observation may be beneficial in cases where it is clinically desirable to reduce unwanted oropharyngeal deposition, e.g., the delivery of inhaled corticosteroids. Similar results to SB are displayed in Table 5 for TAA solution MDIs. While the actuator containing the smallest orifice does retain a high proportion of the non-respirable fraction, deposition in the throat is significantly higher compared to that obtained using the spacer device fitted as standard to Azmacort.

This paper has shown that SB and TAA may be formulated as solutions in MDIs by enhancing their solubility in a propellant blend through the formation of surfactant reverse micelles. There was favourable comparison, in terms of reproducibility of shot potency and the RF of aerosols emitted into a MLI, between the commercially available suspension formulations of these drugs and their novel solution counterparts. However, one potential advantage of solution formulations over suspensions would appear to be the maintenance of drug potency in the first actuation after storage. Solution systems, by definition, are homogeneous, therefore shot potency is a function of individual shot weight. This assumes, of course, that the drug in solution is not susceptible to chemical degradation or to preferential adsorption onto a hardware component of the MDI. These factors must obviously be determined on a case-by-case basis. A thorough investigation of this phenomenon is warranted before solution based systems can be favourably compared with the highly stable environment imparted by the formulation of drugs as non-aqueous suspensions.

The potential advantage of generating finer aerosol sprays (leading to a greater extent of lung deposition) from solution systems compared to suspensions was not overwhelmingly demonstrated in this study. This was because both drugs

Table 5
Comparison of the in vitro aerosol characteristics of a solution MDI of TAA and a suspension formulation (Azmacort)

Formulation	% actuator deposition	% throat deposition	% entering MLI	RF	MMAD
Solution TAA	30.23	22.38	47.39	40.6	3.43
Azmacort	50.30	2.89	45.81	35.3	4.33

required the addition of relatively high amounts of surfactant (> 1% w/w) in order to produce solution formulations. The respirable fraction of an aerosolised drug emitted from an MDI largely depends on the size of the primary aerosol droplets generated in the actuator and the subsequent rate of propellant evaporation. Whereas reduced droplet size was facilitated by use of actuators with a narrow orifice, propellant evaporation would have been impaired by the inclusion of the high levels of SPC. As a result, RFs obtained by both SB and TAA solution MDIs were only marginally higher than those obtained for the appropriate suspension systems. Other drug candidates may require the inclusion of less surfactant for solubilisation with the resultant potential of increasing the efficiency of delivery of aerosolised drug to the lung.

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