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A Novel Apparatus for the Determination of Solubility in Pressurized Metered Dose Inhalers

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ABSTRACT The accurate solubility of salbutamol sulfate, budesonide, and formoterol fumarate dihydrate in hydrofluoroalkane propellant 134a at 25°C for 24 h, are reported. The authors describe a novel reusable in-line pressurized solubility apparatus containing an integral filter holder and a continuous decrimpable valve for the determination of drug/excipients solubility in pressurized metered dose inhalers. The solubility was determined by high-performance liquid chromatography. Solubility of salbutamol sulfate was determined as being below the detection limits while budesonide and formoterol fumarate dihydrate solubility were 23.136 ± 2.951 $\mu g.g^{-1}$ and 0.776 ± 1.023 $\mu g.g^{-1}$, respectively ($n = 3$). This novel solubility apparatus offers an improved ease of use and potential higher analytical throughput.

KEYWORDS pMDI, Solubility, HFA, Salbutamol sulfate, Budesonide, Formoterol fumarate dihydrate

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INTRODUCTION

Pressurized metered dose inhalers (pMDI) are currently the most common form of respiratory device in use (Smyth, 2005). They rely on supercritical liquid propellants (chlorofluorocarbons or hydrofluorocarbons [HFA]) to produce high-energy atomization of therapeutic or prophylactic material, which is coordinated with patient inhalation.

The formulation of pMDI systems can be separated into two categories: suspension or solution based systems (Williams et al., 2001). Suspension-based systems contain a micronized drug suspended in propellant with or without physical-stabilizing agents. In comparison, solution-based systems require the drug to be solubilized in the propellant with or without cosolvents, nonvolatile additives, and chemical stabilizers.

The in situ determination of drug solubility in suspension- or solution-based pMDI systems is clearly of importance. For example, the potential solubilization of suspended drug particles may result in chemical degradation of the dissolved molecules. Furthermore, the potential for dissolution of smaller particulates (through the Kelvin effect [Wilson, 1994]), due to their larger surface area to volume ratio, and potential crystal growth of large particulates (Oswald ripening [Oswald, 1896]) that are thermodynamically favored, may result in particles outside the size range for inhalation therapy (>5 μm) (Johnson, 1996; Pritchard, 2001). In comparison, the measurement of drug solubility in cosolvents and/or nonvolatile additives is of major importance when developing solution-based systems. Factors such as temperature, water ingress, storage time, and environmental cycling conditions may all influence drug solubility.

Previously, Dalby et al. (1991) described an apparatus for the determination of salicylic acid solubility in mixtures of chlorofluorocarbons and demonstrated how limited solubility can result in Oswald ripening. A schematic of the original apparatus described by Dalby et al. (1991) is shown in Fig. 1. Williams et al. (1999) modified the apparatus for the measurement of steroid solubility in hydrofluorocarbon-based systems. More recently, Gupta and Myrdal (2004) compared a novel method for the determination of solubility of beclomethasone dipproprionate with Dalby's method and found the two methods to be in good agreement.

Although the technique described by Dalby et al. (1991) was a powerful tool for determination of solubility in pMDI systems, limitations in the experimental apparatus existed. For example, the seal between the two connecting pMDI canisters and filter must be firmly secure. In addition, the experimental apparatus required transfer of the parent suspension into receiving container, followed by venting of the propellant and removal of the valve with consequent crimp assembly and disassembly (through can cutting) for each solubility study.

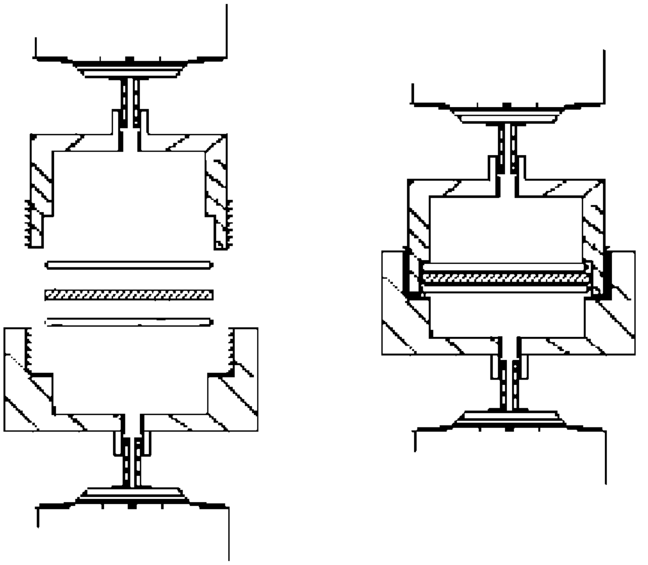

FIGURE 1 External Solubility Filter, Consisting of Two Leak-Proof Couplings, One Connected to the Valve Stem of the Aerosol Unit Containing the Suspension Formulation to be Sampled (Top of the Filter Unit), and the Other to an Airtight Receiving Container (Bottom of the Filter Unit) as Described by Dalby et al. (1991).

The Gupta and Myrdal (2004) apparatus, which uses a direct injection from a pMDI vial into the needle injector port of a manual HPLC injector, is surely a very robust and accurate technique, but it uses a similar external filter as in the Dalby method, suggesting similar technical problems (Gupta and Myrdal, 2005).

Here the authors describe a reusable pMDI solubility apparatus that contains an integral filter holder. The device can be used in conjunction with a pressurized, reusable, reciprocal (similar to the method described previously [Dalby et al., 1991; Williams et al., 1999; Gupta & Myrdal, 2004]) and/or in conjunction with a dose uniformity or impinger apparatus (as conducted in this study). Furthermore, the authors have used high-performance liquid chromatography for drug content determinations. Previous investigations using UV for solubility determination suggested pMDI valve component extractables influenced the measured drug absorbance (Dalby et al., 1991).

MATERIALS AND METHODS

Materials

Drugs investigated were micronized salbutamol sulfate (β_2 bronchodilator agonist), micronized budesonide (corticosteroid), and micronized formoterol fumarate dihydrate (β_2 adrenoreceptor agonist), and were used as supplied (AstraZeneca, R&D Charnwood, UK). 1,1,1, 2-Tetrafluoroethane (Zephex 134a; Ineos Fluor, Cheshire, UK) was used as propellant. Continuous valves (BK 357; Bespack Europe Limited, Norfolk, UK) were used in the developed apparatus. The apparatus was pressure-filled using a manual Pamasol Laboratory plant 02016 (Pamasol Willi Maäden AG, Pfaffikon, SZ). All solvents were supplied by BDH (Poole, Dorset, UK) and were of analytical grade. Water was prepared by reverse osmosis (MilliQ, Molsheim, France).

Apparatus and Chromatographic Conditions

A schematic diagram of the solubility apparatus is shown in Fig. 2A. The apparatus consists of a primary

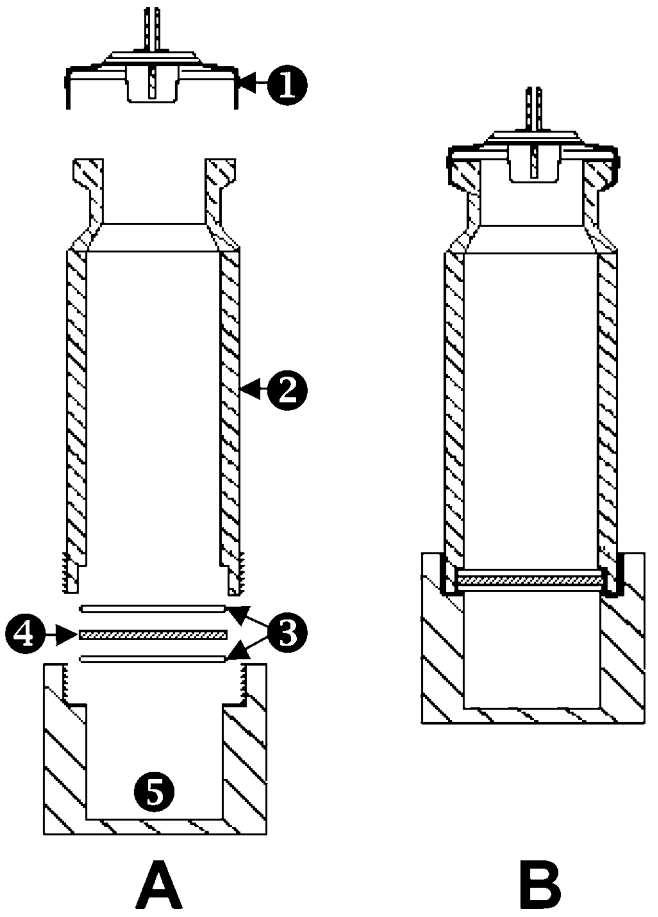

FIGURE 2 (A) Developed In-Line Solubility Apparatus Components, Where: 1, Standard pMDI Valve (Bespak BK 357); 2, Primary Casing for Solublized Drug; 3, O-Ring Supports; 4, Filter; 5, Secondary Casing (Drug Under Investigation Is Weighed Into This Compartment). (B) Assembled Solubility Apparatus.

and secondary stainless steel casing between which a stainless steel frit (0.1 μm) is sandwiched between two slit O-rings. A saturated solution was prepared by adding excess drug to the secondary casing, which was then assembled as shown in Fig. 2B. A standard continuous pMDI valve (BK-357, Bespak Ltd. Norfolk, UK) was crimped to the primary casing and the apparatus accurately filled with approximately 7 g of HFA 134a (INEOS Fluor Ltd., Cheshire, UK) using a manual fill Pamasol laboratory plant, (Pfäffikon, Switzerland). The solubility apparatus was kept shaking in a water bath at 25°C for 24 h prior to analysis. Drug solubility was determined using the twin stage impinger (TSI) sampling apparatus (Copley Instruments Ltd., Nottingham, UK).

After considering the possibility of overloading the collector device after firing to exhaustion the pMDI canister, the TSI, being an impinger, was chosen as the collector device, since all three drugs may present high solubility in the mobile phase used for the experiments.

The TSI was used as a simple dose collection device and contained 7 mL of mobile phase in stage one and 30 mL of mobile phase in stage two. Mobile phase compositions were 8:92 % v/v acetonitrile/MilliQ water (0.4 M orthophosphoric acid buffer) for salbutamol sulfate, 40:60 % v/v acetonitrile/MilliQ for budesonide, and 40:60 % v/v acetonitrile/MilliQ (2.3 mM orthophosphoric acid buffer) for formoterol fumarate dihydrate, respectively. The equilibrated solubility apparatus was connected to a standard pMDI actuator (fitted with a 0.30 mm diameter orifice), which was fired to exhaustion in the TSI apparatus at 60 L.min^{-1}. Mass of the solubility apparatus was recorded before and after firing. Vaporization of propellant during firing would have been accompanied by a decrease in temperature that could have affected solubility, but envisaging low solubility of the compounds analyzed, the canister was fired to exhaustion to ensure samples were above the detection limits of the systems.

The TSI components, actuator, and upper/lower casings of the solubility device were rinsed into separate volumetrics with appropriate mobile phase and made to volume.

Chemical analyses were performed using a reverse-phase Jasco model HPLC (Jasco Corporation, Tokyo, Japan) equipped with an autosampler. Data were recorded and integrated using AZUR-OSIRIS Chromatography Software V 3.0 (Datalys, St. Martin d'Hères, France). A Sphereclone ODS (Phenomenex, Torrance, CA) 5-μm packing HPLC column was used for salbutamol sulfate analysis. A Supelcosil LC-SI (Supelco Inc., Bellefonte, PA) 5-μm packing HPLC column was used for both budesonide and formoterol fumarate dihydrate, respectively. Flow rate was set at 0.75 mL.min^{-1} for salbutamol sulfate and 1.5 mL.min^{-1} for budesonide and formoterol fumarate dihydrate, respectively. Ultraviolet absorbance wavelength was set at 223 nm for salbutamol sulfate, 248 nm for budesonide, and 218 nm for formoterol fumarate dihydrate. Summary of the material and methods for HPLC drug analysis can be found in Table 1.

Stock solutions of salbutamol sulfate, budesonide, and formoterol fumarate dihydrate were prepared in mobile phase. Samples were sequentially diluted in the appropriate mobile phase to fit within the linearity region of the HPLC analysis (typically ~0.5 μm.mL^{-1}

TABLE 1 HPLC Conditions for the Drug Materials Under Analysis, Where Column Temperature=25°C and Injection Volume=100 µL

Drug	HPLC column	Mobile phase	Flow rate (mL.min^{-1})	UV Absorbance wavelength (nm)	Retention time (min)
Salbutamol sulfate	Sphereclone™ ODS, 5 µm packing, 25 cm × 0.32 mm	8:92 % v/v CH_3CN/H_2O (0.5 M orthophosphoric acid buffer)	0.75	223	~8
Budesonide	Supelcosil™ LC-SI, 5 µm packing, 5 cm × 4.6 mm	40:60 % v/v CH_3CN/H_2O	1.5	248	~6
Formoterol fumarate dihydrate	Supelcosil™ LC-SI, 5 µm packing, 5 cm × 4.6 mm	40:60 % v/v CH_3CN/H_2O (2.3 mM orthophosphoric acid buffer)	1.5	218	~8

– 10 µm.mL^{-1}, $R^2 > 0.999$). Quantitation was based on peak area, using a standard curve, which was prepared daily. Solubility of each drug in HFA 134a was determined by dividing the total drug mass recovery from the upper casing and all TSI and actuator components by the initial HFA 134a mass added. In addition, the total recovered drug was compared to the initial weighed drug for mass balance. The analytical peaks for all three drugs were well resolved from the solvent front.

RESULTS AND DISCUSSION

Salbutamol sulfate, budesonide, and formoterol fumarate dihydrate were chosen for their popularity in inhalation-based systems. Solubility values for the salbutamol sulfate, budesonide, and formoterol fumarate dihydrate are shown in Table 2.

Significant differences ($p < 0.05$. ANOVA) in the solubility of each drug were observed; however, the processing method did not affect the solubility in HFA 134a. Previous studies from Dickinson et al. (2000) found the solubility of salbutamol to be <4 µg.g^{-1}. In the current investigation solubility of salbutamol sulfate was found to be below the limit of detection of the HPLC technique.

In general, the solubility of budesonide (~23 µg.g^{-1}) using the new apparatus suggested similar values to previous studies using steroids (Williams et al., 1999), approximated as 20–45 µg.g^{-1} (from graphical data). Formoterol fumarate dihydrate was found to have a solubility of 0.776 ± 1.023 µg.g^{-1}. Recovery efficiency was greater than 95% across all drugs examined. The authors suggest also referring to Rogueda (2005), a very comprehensive summary of various drugs' solubility in HFAs propellant. Furthermore, it is interesting to note that multiple peaks that did not correlate to the drug standard peak were observed during HPLC analysis. It is speculated that such peaks are related to valve extractables (Howlett et al., 2002) and without resolution would clearly contribute to the measurement errors observed by Dalby et al. (1991).

TABLE 2 Summary Table of Solubility Values for Drug Materials and Relative Mass Balance (n = 3, ± SD)

Drug	Solubility of drug in propellant (µg.g^{-1})	Mass balance % ± SD
Salbutamol sulfhate	<0.000*	99 ± 2.3
Budesonide	23.136 ± 2.951	101 ± 1.7
Formoterol fumarate dihydrate	0.776 ± 1.023	95 ± 2.0

*Below limit of detection.

CONCLUSIONS

The determination of drug solubility in pressurized systems is clearly important for both suspension- and solution-based pMDIs. In this study, a rapid, convenient, and accurate apparatus for the determination of drug solubility in HFA propellants was developed. The investigated modified solubility apparatus demonstrated similar findings to previous studies (Dalby et al., 1991; Williams et al., 1999), but overcame previous system problems such as possible drug loss due to leakage during the quantitative transfer of contents, while offering improved ease of use; the novel method presented allows the pMDI to be fired directly into a collection device and hence does not require the MDI vial to be opened, eliminating the need for additional sample manipulations and reduces analysis time. The novel apparatus, being "self-contained," does not require any of these transfer steps, therefore reducing the operational errors, which directly results in consistent and reproducible results.

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