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Aerosol Generation by Metered-Dose Inhalers Containing Dimethyl Ether/Propane Inverse Microemulsions

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ABSTRACT

Water soluble compounds were incorporated into metered-dose inhalers (MDIs) by using water-in-propellant lecithin microemulsions, in which dimethyl ether (DME) and propane acted as both continuous phase and propellant. Lecithin, water, and water soluble compounds were added to glass MDI containers, valves were crimped on, and propellants were added using a pressure burette. Aerosols were produced using commercially available actuators, and inertial impaction was used to determine the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and fine particle fraction (FPF) of the resulting aerosols. The DME/propane/lecithin microemulsion MDIs generated aerosols with particle size distributions suitable for pulmonary delivery (eg, MMAD 3.1 μm, FPF 59% for DME with lecithin content 3%, water content 2.5% [wt/wt]). Increasing water concentration (up to 8% wt/wt) was correlated with a reduction in FPF. Freezing and rewarming had no adverse effect on MMAD, GSD, or FPF. Storage of microemulsion samples for up to 3 weeks did not adversely affect the MMAD, GSD, or FPF. This approach may enable the pulmonary delivery of water soluble therapeutic agents via MDIs.

KEYWORDS: microemulsion, lecithin, pulmonary, dimethyl ether, propane

INTRODUCTION

Aerosol delivery of polar low molecular weight molecules and macromolecules (such as peptides) to the lungs is potentially an important alternative to the oral or parenteral routes of administration. Pressurized metered-dose inhalers (MDIs) are most commonly used for the delivery of medicinal compounds to the lungs. However, suspensions of very polar substances in propellants are frequently very unsatisfactory, and methods of solubilization are not common. However, solubilization of polar compounds into dimethyl ether (DME) and DME/propane utilizing lecithin inverse microemulsions has been previously reported by the current authors.[1,2] Water-in-propellant DME/lecithin and DME/propane/lecithin microemulsions were shown to produce aerosols with particle size distributions suitable for pulmonary delivery. The present report extends these previous investigations to include a study of the effect of formulation parameters on aerosols produced by the inverse microemulsions; in addition, several stability issues are addressed.

Any aerosol formulation approach designed to deliver substances to the lungs must ultimately produce a respirable aerosol. Aerosols with a mass median aerodynamic diameter (MMAD) of 1 to 5 μm are considered to be respirable in humans (MMAD is the diameter that divides the particle size distribution in half as a function of mass[3]). The fine particle fraction (FPF) (fraction of particles with an MMAD <5 μm) produced by an MDI depends on both device and formulation variables.[4] Formulation variables include propellant composition,[5,6] drug concentration,[6,7] cosolvent content,[6] and surfactant content.[6,8] Device variables include valve design,[9] metering volume,[5,10] spray orifice diameter,[9] and actuator design.[9,11]

In the following series of experiments, aerosols were produced from MDIs containing lecithin microemulsions, and the MMAD, geometric standard deviation (GSD), and FPF (collectively referred to as "aerosol production parameters") of the aerosols were determined by cascade impaction. Experiments were conducted to determine the effect of propellant composition, water content, storage time, and temperature cycling on the aerosol production parameters of MDIs containing lecithin inverse microemulsions.

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MATERIALS AND METHODS

Propellant Sample Preparation

Lecithin, water, and water-soluble compounds were added to glass MDI containers, valves were crimped on, and propellants were added using a pressure burette. The filling pressure necessary to fill liquid propellant through the valve stem of BK 357 metered valves (Bespak, Apex, NC) exceeded the manufacturer's recommended maximum safety limits of the pressure burette (160 pounds per square inch gauge [psig]). The pressure necessary to fill through the valves was reduced by trimming the lower gasket to half the original thickness (from approximately 1.06 mm to ca 0.5 mm). This modification allowed the valves to be filled at 140 to 160 psig. A BK 632 actuator (0.33 mm orifice) and a BK 357 (50 μL metering volume) were used in all cases. Solvent mixtures are described as DME/propane/water. The ratio of DME to propane is described by the first 2 numbers and always describes the ratio of those propellants. All samples also contained 3% lecithin. The water percentage is a final wt/wt percentage, so for example 60/40/1 contains 3% lecithin, 1% water, and 96% of a 60% DME, 40% propane mixture. The amount of propellant added with the pressure burette was determined by weight, and the samples were made to be accurate to within 1% of the stated composition.

As a tracer for the microemulsion dispersed-phase aqueous content, 5-CF (5-carboxyfluorescein) was incorporated. Polar compounds, such as sucrose, have been associated with the lipid deposit on the same stages as the lipid in reverse micelles, indicating that markers for the internal phase are appropriate probes for following the droplets produced by microemulsion MDIs.[12] Soy lecithin (Phospholipon 100G) was kindly provided by American Lecithin Company (Oxford, CT). The phosphatidylcholine content was 93.6%, and all weights of lecithin were corrected to provide the specified amount of phosphatidylcholine (ie, a 3% lecithin solution contained 3% [wt/wt] of phosphatidylcholine). Solvents and lecithin were handled in a dry box under nitrogen.

Cascade Impaction Method

Particle size analysis was performed using a cascade impactor (Andersen Mark II nonviable inertial sampler, Andersen, Smyrna, GA), which was fitted with a United States Pharmacopeia throat and an AeroChamber spacer (Monaghan Medical Corporation, Plattsburgh, NY) operated at a flow rate of 28.3 L/min. Each MDI was actuated 6 times, with 30 seconds between actuations to ensure thermal reequilibration of the valve. The relative quantity of 5-CF on each impactor stage was determined by washing the impactor plate for that stage with 70% ethanol/30% 50 mM glycine buffer (pH 9.5), adjusting the volume of each rinse to 10 mL, and then determining the optical density of the 5-CF solution using a UV-VIS spectrophotometer (Shimadzu UV160U, Columbia, MD) at 497 nm. Recoveries of 5-CF were in the 92% to 97% range (data not shown).

Calculation of MMAD, GSD, and FPF Using the Cascade Impaction Method

The MMAD was derived from inertial impaction data. The distribution around this median diameter was described assuming a log-normal dispersion of sizes. The GSD was calculated from the particle size at the 84th percentile (by mass) divided by the MMAD. In the present studies, FPF was determined by dividing the mass contained in particles of MMAD equal to 4.7 μm or less by the total mass emitted.

Plume Photography Using UV Light

Long wave UV light was used as shown (**Figure 1**) to illuminate the plume, which contained 5-CF.

Effect of Propellant Composition and Storage on Aerosol Production

Effect of Propellant Composition on the MMAD, GSD, and FPF of Aerosols Issued from DME/Propane/Lecithin Microemulsion MDIs

Propellant samples (100/0/2.5 and 60/40/2.5), crimped with BK 357 valves and containing 5-CF (25 mg/mL in the aqueous phase, pH 8.5), were prepared; and the MMAD, GSD, and FPF for the aerosols generated were determined by the cascade impaction method. In addition, a series of DME microemulsion samples were prepared with varying water content (up to the maximum water solubility, 8%), and the aerosols were evaluated as above. The same amount of 5-CF was included in all the samples (equivalent to 25 mg/mL in the aqueous phase of a 2.5% water sample).

Effect of Cooling and Rewarming on the MMAD, GSD, and FPF of Aerosols Issued from DME/Lecithin Microemulsion MDIs

Propellant samples (100/0/2.5 and 60/40/2.5), crimped with BK 357 valves and containing 5-CF (25 mg/mL in the aqueous phase, pH 8.5), were cooled to +4°C, -20°C,

and -80°C for 48 hours and then returned to room temperature. Aerosols produced by these samples were evaluated for MMAD, GSD, and FPF by cascade impaction.

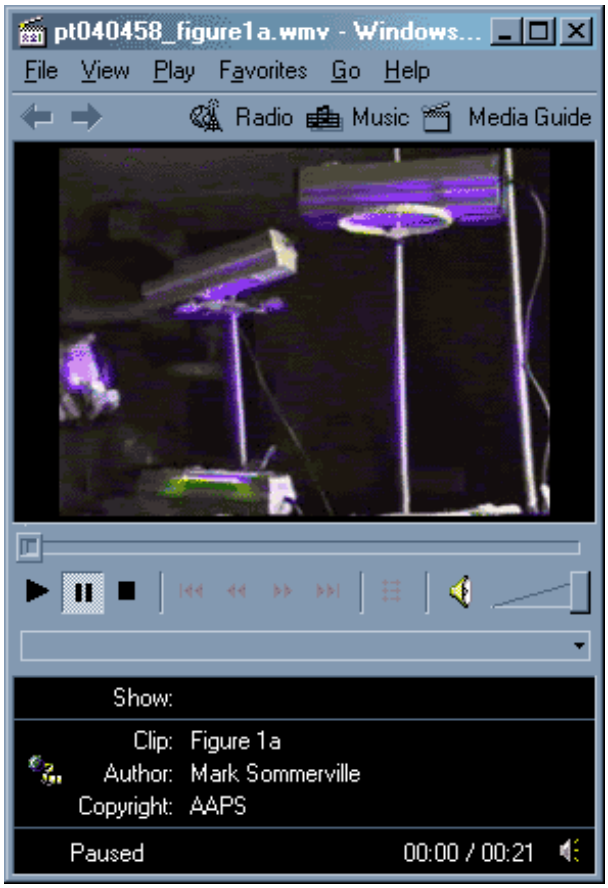

Figure 1. MPEG Visualization of aerosol plumes produced lecithin microemulsion MDIs: A) 100/0/2.5 and 60/40/2.5, B) 100/0/6 and 100/0/8. Plumes from each sample are shown under white light plus ultraviolet light, and then under ultraviolet light alone. Multimedia representation available via online article version.

Effect of Storage Time on the MMAD, GSD, and FPF of Aerosols Issued from DME/Lecithin Microemulsion MDIs

Propellant samples (100/0/2.5 and 60/40/2.5), crimped with BK 357 valves and containing 5-CF (25 mg/mL in the aqueous phase, pH 8.5), were prepared and stored at ambient temperature and humidity. The samples were protected from light by a covering of aluminum foil (light protection was used to prevent 5-CF photobleaching and to eliminate light-induced photochemical reactions of the unsaturated lecithin alkyl chains). MMAD, GSD, and FPF were determined by cascade impaction at 1-week intervals. Time zero samples were measured immediately after manufacture. Storage at elevated temperature was not attempted because of the possible loss of container integrity. Aerosols produced by these samples were evaluated for MMAD, GSD, and FPF using the cascade impaction method.

Hygroscopicity and Physical Stability of DME and DME/Propane Microemulsions

Propellant samples 100/0/0.5 and 60/40/0.5 (each containing 3% lecithin) were stored under 2 conditions, 0% and 75% relative humidity (RH), in sealed desiccators at ambient temperature (23 ± 2°C). The samples were protected from light by a covering of aluminum foil. Zero percent RH was achieved by storing the samples over calcium sulfate (Indicating Drierite, W.A. Hammond Drierite Company, Ltd, Xenia, OH); 75% RH was achieved by storing the samples over saturated sodium acetate solution. The humidity levels were checked using a hygrometer (Traceable Humidity/Temperature Pen, Fisher Scientific, Pittsburgh, PA). After a defined time interval the samples were analyzed for water content. Water content was measured by actuating the samples directly into a Karl Fischer water titration apparatus (Accumet Coulombic CF titrator, Fisher Scientific). An adapter was constructed to introduce the propellant sample from the valve into the titrator as follows. A plastic pipette tip (200 µL, Costar model 4863, VWR Scientific, South Plainfield, NJ) was cut to fit over the end of the valve stem but was kept short enough to allow actuation of the valve. The distal end of the pipette tip was cut such that the outside diameter of the pipette tip, 1.5 mm from the end, fit into a stainless steel Luer lock needle (3-inch, 14-gauge) to achieve a seal. The needle was placed as far into the titrator solution as possible, and directly above the magnetic stirring bar, which was operated at the maximum stirring rate. Actuation was accomplished by depressing the inverted MDI while holding the valve stem stationary with the aid of a hemostat. The mass of each actuation was determined by weighing the MDI before and after actuation. Each sample was tested for water content 5 times; 3 samples were tested for each condition. Aerosols produced by these samples were evaluated for MMAD, GSD, and FPF by the cascade impaction method.

Propellant Loss Measurement

Propellant samples (100/0/2.5 and 60/40/2.5) made with BK 357 valves and containing 5-CF (25 mg/mL in the aqueous phase, pH 8.5) were prepared and stored at ambient temperature and humidity. The samples were pro-

Table 1. Particle Size Parameters (MMAD, GSD, and FPF) of Aerosols Derived from DME/Propane/Water Lecithin Microemulsions*

Sample	MMAD, μm	GSD	FPF (%)	n
100/0/2.5	3.1 (0.22)	1.8 (0.05)	59 (6.2)	8
60/40/2.5	2.7 (0.48)	1.7 (0.08)	69 (6.8)	10

*FPF indicates fine particle fraction; GSD, geometric standard deviation; and MMAD, mass median aerodynamic diameter. SDs are shown in parentheses for n replicates.

tected from light as described above. The mass of the samples was determined periodically to determine propellant leakage rate.

RESULTS AND DISCUSSION

Aerosol Sample Preparation

The optimum crimp height was 7.8 to 7.9 mm. This observation was later confirmed by the valve manufacturer in an independent study (Gordon Bidwell, Bespak Inc; personal communication, March 1999). After propellant addition, the lecithin (etc) typically dissolved quickly (requiring less than a minute), and the samples were immediately available for evaluation.

Effect of Propellant Composition and Storage on Aerosol Production

Effect of Propellant Composition on the MMAD, GSD, and FPF of Aerosols Issued from DME/Propane/Lecithin Microemulsion MDIs

Characterization of aerosols generated by DME and 60% DME/40% propane mixtures containing 3% lecithin and 2.5% 5-CF (25mg/mL, pH 8.5 in the aqueous phase) was undertaken to determine if the aerosol characteristics were suitable for pharmaceutical application. Used as a fluid phase marker, 5-CF was incorporated to facilitate the analysis of the deposition of aerosol droplets deposited in a cascade impactor. The results are shown in **Table 1**.

The MMADs of DME and 60% DME/40% propane lecithin microemulsion MDIs (2.7 and 3.1 μm, respectively) were within the desired range for pharmaceutical application (1-5 μm). DME and DME/propane MDIs produced higher FPFs (59%-69%) compared with commercially available MDI products (10%-50%).[13] The decrease in MMAD and increase in FPF in the 60% DME/40% propane samples versus the DME samples may be explained by the higher vapor pressure of the 60% DME/40% propane propellant mixture (the vapor pressures of DME and propane are 60 and 128 psig at 20°C, respectively). Increased vapor pressure has been correlated with decreases in particle-size output from MDIs.[7,10] Higher vapor pressure results in greater mechanical disruption of the propellant during actuation, and greater evaporation rate of the propellant droplets.[14] The MDIs produced plumes similar to those produced by commercial MDI products (**Figure 1**).

No ballistic component (unevaporated propellant droplets that typically impact the back of the throat) was visible by direct observation or by visualization of the aerosol plume under long wave ultraviolet light. MDIs prepared with 100 mg/mL 5-CF produced aerosols with essentially the same MMAD and FPF as the MDIs containing 25 mg/mL 5-CF (data not shown).

Effect of Water Content on the MMAD, GSD, and FPF of Aerosols Issued from DME/Lecithin Microemulsion MDIs

Increasing the concentration of water in the 100/0 (DME) MDIs (containing 3% lecithin) caused a drop in the FPF (**Figure 2**). The effect on MMAD and GSD was less pronounced. The high water content (6% and 8% water) samples were characterized by high actuator and spacer deposition, thus lowering FPF. Since the MMAD and GSD are only measured on particles that enter the impactor, these parameters did not change significantly, although the fraction of the sample that entered the impactor was reduced significantly. The presence of nonvolatile components may reduce the FPF when present at high concentrations.[10,15] This effect is due in part to a delayed propellant evaporation.[16] Addition of a low volatility component to a formulation not only lowers vapor pressure but also increases the size of the droplets issuing from the actuator.[6]

In the example of a 100/0/2.5 DME/propane/water mixture, stabilized by 3% lecithin, and containing 5-CF at 25 mg/mL in the aqueous phase, approximately 25 μg of 5-CF is delivered with each 50 μL actuation. Hence, it would appear that the technology is suitable for the delivery of drugs that are highly potent and have significant water solubilities.

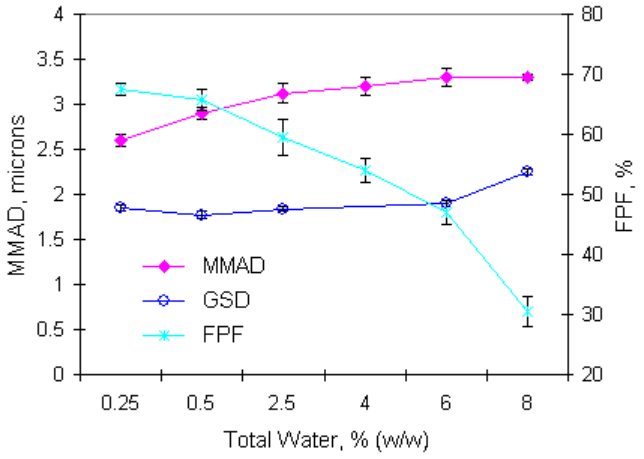

Figure 2. Effect of water content on the parameters describing aerosols (MMAD µm, GSD, and FPF %) issued from MDIs containing lecithin microemulsions in DME (n = 3).

Effect of Cooling and Rewarming on the MMAD, GSD, and FPF of Aerosols Issued from DME/Lecithin Microemulsion MDIs

Propellant samples (100/0/2.5 and 60/40/2.5) containing 5-CF (25 mg/mL in the aqueous phase, pH 8.5) were cooled to +4°C, -20°C, and -80°C for 48 hours, and then returned to room temperature. Cooling to +4°C did not cause precipitation or phase change in the propellant samples. Cooling to -20°C caused a partial precipitation of 5-CF (and, from visual inspection, some lecithin as well). Cooling to -80°C caused a complete precipitation of the 5-CF, along with most or all of the lecithin as well (as judged by visual inspection); however, the propellant remained in the liquid state. Upon warming, and with brief and gentle agitation, the precipitates present in the -20°C and -80°C samples redissolved completely. Reestablishment of homogeneous solutions after precipitation of part or all of the components may be explained by the thermodynamic stability of microemulsions; ie, they form spontaneously. Cooling and rewarming caused no significant change in the MMAD, GSD, or FPF compared with uncycled controls (**Table 2**).

Effect of Storage Time on the MMAD, GSD, and FPF of Aerosols Issued from DME/Lecithin Microemulsion MDIs

The effect of storage at room temperature on the aerosols issued from 100/0/2.5 and 60/40/2.5 MDIs is shown in **Figures 3** and **4**. Storage of up to 3 weeks postmanufacture did not significantly affect the MMAD, GSD, or FPF of these samples. The storage study was discontinued after 3 weeks because approximately 10% of the propellant had escaped, and the resulting increase in solute concentration may have tended to affect the results of further testing. The need to adopt modified valves may have limited the duration of this study. The use of unmodified valves, which would require higher filling pressure, would allow a more thorough storage stability study to be conducted.

Hygroscopicity and Stability of DME and DME/Propane Microemulsions

Storage of 100/0/0 and 60/40/0 samples in a 0% RH atmosphere did not result in the accumulation of water in the propellant MDI samples (**Figure 5**). However, storage of 100/0/0 and 60/40/0 in a 75% RH environment did result in water uptake. The amount of water absorbed by the 100/0/0 samples was greater than that absorbed by the 60/40/0 samples (133% ± 2.4% and 121% ± 2.1% [or 0.21 and 0.10 mg water/g propellant] of

Table 2. Particle Size Parameters (MMAD, GSD, and FPF) of Aerosols Derived from DME/Propane/Water Lecithin Microemulsions Before and After Cooling (48 hours) and Subsequent Rewarming to RT*

Sample	MinTemp	MMAD	GSD	FPF (%)	n
100/0/2.5	control	3.1(0.22)	1.8(0.05)	59(6.2)	8
100/0/2.5	–20°C	3.0(0.15)	1.7(0.05)	58(3.0)	3
100/0/2.5	–80°C	3.1(0.12)	1.8(0.06)	62(3.2)	3
60/40/2.5	control	2.7(0.48)	1.7(0.08)	69(6.8)	10
60/40/2.5	–20°C	2.5(0.05)	1.7(0.0)	72(2.0)	3
60/40/2.5	–80°C	2.6(0.1)	1.8(0.1)	74(1.0)	3

*RT indicates room temperature; Control represents uncooled samples; FPF indicates fine particle fraction; GSD, geometric standard deviation; and MMAD, mass median aerodynamic diameter. SDs are shown in parentheses for n replicates.

original, respectively). This may be due to the more polar 100/0 (DME) propellant being more hygroscopic than the 60/40 DME/propane blend. DME is known to be hygroscopic.[17] Minimization of water uptake in this system could be accomplished by choosing less permeable elastomers, or by storing the microemulsions in a dry atmosphere. Absorption of small amounts of water into anhydrous suspension formulations can be deleterious, because in anhydrous systems water can induce crystal formation, particle aggregation, and Oswald ripening.[6] However, absorption of water would probably not be detrimental to inverse microemulsion formulations, because inverse microemulsions normally contain a significant amount of water.

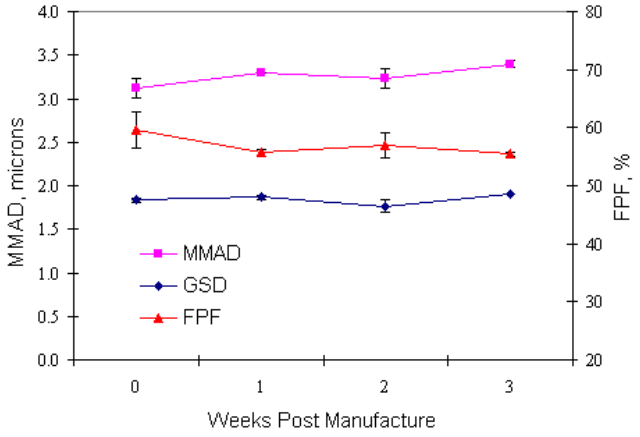

Figure 3. Effect of storage at RT on the parameters describing aerosols (MMAD μm, GSD, and FPF %) issued from MDIs containing lecithin inverse microemulsions in DME (100/0/2.5) (n = 3).

Propellant Loss Measurement

Samples stored over time lost propellant, probably because of permeation of propellant through the elastomer (extracted nitrile) seals. The rate of loss varied between vials but averaged approximately 0.01 to 0.02 g/day. Although this rate of loss permitted experimentation, it is too great for commercial applications. The permeation may be significantly decreased by choosing the correct elastomer. Butyl buna gaskets may prove suitable for this application. Currently, pharmaceutical aerosol valves are not made with elastomers suitable for use with DME. Commercial success of MDIs containing alternate propellants will depend on the selection of appropriate low permeability gaskets.

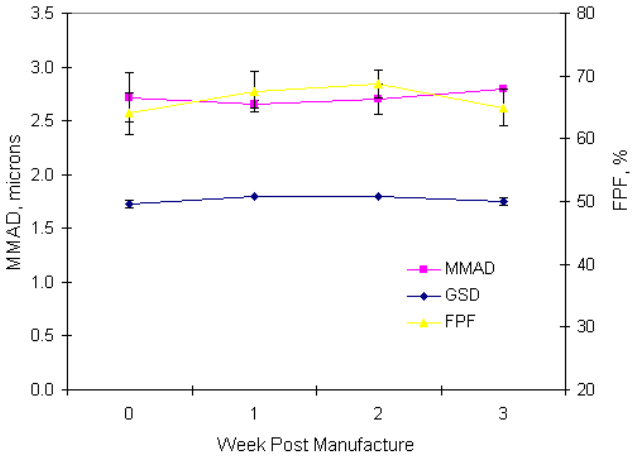

Figure 4. Effect of storage at RT on the parameters describing aerosols (MMAD μm, GSD, and FPF %) issued from MDIs containing lecithin inverse microemulsions in DME/propane (60/40/2.5) (n = 3).

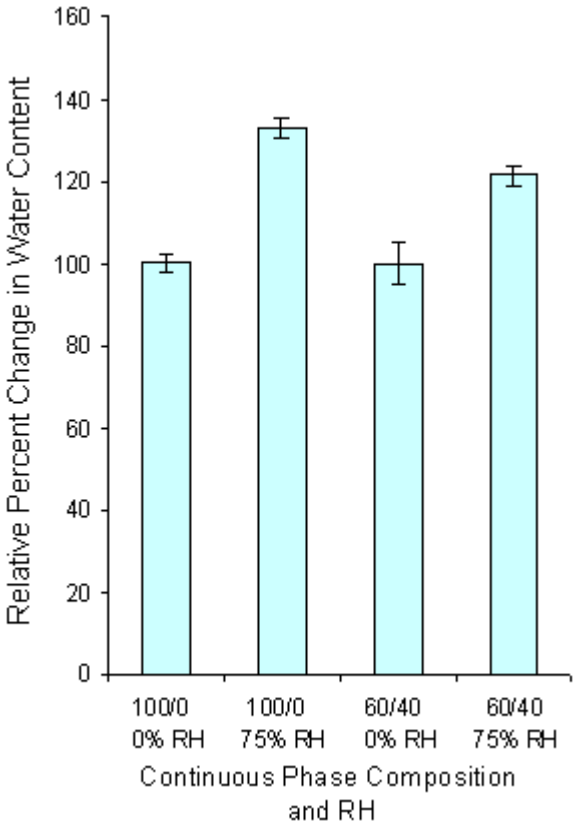

Figure 5. Hygroscopicity of lecithin microemulsions. Samples (100/0/0 and 60/40/0) were stored in 0% and 75% RH atmosphere for 3 weeks (3 samples/condition, 5 water determinations/sample). Percentage change is relative to starting water content (taken as 100%).

CONCLUSION

Water soluble compounds were incorporated into solution phase MDIs, in which dimethyl ether (DME) and propane acted as both continuous phase and propellant. Inertial impaction was used to determine the MMAD, GSD, and FPF of selected microemulsion-based MDIs. The DME/propane/lecithin microemulsion MDIs produced aerosols with particle size distributions comparable to commercial products. Increasing water concentration (up to 8% wt/wt) was correlated with a decrease in FPF.

Storage of microemulsion samples for up to 3 weeks did not adversely affect the MMAD, GSD, or FPF of the aerosols produced from them. Cooling the samples (to a minimum temperature of -80°C) caused precipitation of some or all of the nonvolatile microemulsion components; however, rewarming the samples, followed by gentle agitation, resulted in reformation of the optically clear microemulsion. This treatment had no adverse effect on MMAD, GSD, or FPF. The MDIs prepared with DME were found to absorb moisture, and they slowly lost propellant. Minimization of these effects may be accomplished by appropriate choice of elastomers for the seals and gaskets.

This approach opens exciting possibilities for the pulmonary delivery of highly potent water-soluble therapeutic agents via MDIs.

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