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RESEARCH PAPER

Influence of Water on the Solubility of Two Steroid Drugs in Hydrofluoroalkane (HFA) Propellants

Robert O. Williams III* and Chengjiu Hu‡

Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712

ABSTRACT

The objective of this research work was to investigate the influence of water level, temperature, and propellant composition on the solubility of two hydrophobic steroid drugs, triamcinolone acetonide (TAA) and beclomethasone diapropionate (BDP). pMDIs containing TAA or BDP, spiked water, and propellant blend with different ratios of HFA 134a and HFA 227 were prepared. The contents of the prepared pMDIs were filtered through a 0.22 mm Acrodisc, syringe filter into a receiving canister after the pMDIs were equilibrated at 15°C, 25°C, 30°C, and 40°C. The drug concentration in the receiving canisters was determined by HPLC and the drug solubility in the propellant blend was calculated. Also, the drug crystal collected on the filter from the donor pMDIs were characterized by x-ray diffraction. The solubility of TAA and BDP varied with propellant composition at all experimental temperatures investigated. The solubility of TAA and BDP increased as the temperature was increased at all propellant compositions and water levels studied, but decreased as the water level in the propellant system was increased at all compositions and temperatures. The x-ray diffraction results indicated that the water in the propellant system had no significant influence on the crystal characteristics of TAA in HFA propellant system, but had a significant impact on the crystal characteristics of BDP was higher than TAA at all propellant compositions, experimental temperatures and water levels investigated. The solubility of TAA and BDP was not only influenced by propellant composition and storage temperature, but also depended on the water level in the propellant system. As a consequence, the crystallinity of the drugs formulated in HFA propellant

*To whom correspondence should be addressed. Fax: (512) 471-7474. E-mail: williro@mail.utexas.edu
‡Present address: DuPont Pharmaceuticals Company, 1000 Stewart Ave., Garden City, NY 11530.

was influenced by the temperature, propellant composition and the water level in the propellant system. The impact of these factors on the crystallinity of formulated drugs.

KEY WORDS: Drug solubility; HFA propellants; pMDI formulations.

INTRODUCTION

Two aspects of pressurized metered dose inhalers (pMDIs) of concern to pharmaceutical formulation scientists are the accuracy and reproducibility of the emitted dose and the stability of the pMDI formulation (1). Each is codependent and affected by both formulation composition and delivery device. The physical and chemical properties of the formulation ingredients affect the stability of the formulation and the accuracy of the delivered dose. In a suspension-based pMDI system, the particle size distribution and the shape of the aerosolized particles emitted are critical factors that determine the deposition pattern in patients. A factor associated with suspension formulations is the physical stability, which is directly influenced by particle dispersion and crystal growth (2–5). Crystal growth occurs as micronized drug particles slowly dissolve and recrystallize onto larger particles.

Similar to the crystal growth observed in aqueous pharmaceutical suspensions (6–9), particle growth of suspended drugs in pMDI propellant systems is an often-encountered problem for suspension-based pMDI systems (4,5,10,11). The adverse consequences of particle growth in pMDI formulations include the physical clogging of the valve or the actuator and the alteration of the aerodynamic characteristics, which may change the site of drug deposition in the respiratory tract. It has been reported that the stability of suspension-based pMDI formulations is sensitive to the presence of moisture in the formulation (11).

Temperature is another important factor that governs the stability of the suspension system by influencing the solubility of drugs in the propellant system. If a small amount of drug is soluble in the liquid propellant, variations in temperature will cause the drug to dissolve and recrystallize during storage. A recent study demonstrated that temperature cycling could promote crystal growth (7). Certainly, 20°C variations in temperature are not improbable during shipping, nor are 40°C variations impossible. If the particles solubilize and recrystallize, then there will be a tendency for the particles to grow and thus produce larger particles. If the particle growth continues, valve malfunctions and inaccurate dosing of drug substance may result.

Chlorofluorocarbons (CFCs) are reported to contribute to the destruction of the ozone layer in the atmosphere and are being replaced with nonchlorinated alternative propelants in pMDIs. The existing CFC-containing pMDI products must be reformulated with alternative propellants (12). Two of the alternatives are tetrafluoroethane (HFA 134a) and heptafluoropropane (HFA 227) (13,14). The physical and chemical properties, such as stability, solvent strength, density, and polarity, of these alternatives are different from those of CFC propellants (15).

HFA 134a and HFA 227 are more polar compounds compared with CFCs. Therefore, the solubility of most drugs in these propellants may be different from their solubility in CFCs depending on the hydrophilicity of the drug. The influence of the polarity of propellants on physical stability of suspended drugs has been investigated. Albuterol, which was physically stable in a CFC propellant blend, experienced a dramatic change in crystal habit in the more polar HFA propellant. Salicylic acid (SA) crystals grown in pure CFC-11 had a much larger axial ratio than those grown in the less polar CFC-12 (4).

The objective of this research work was to investigate the influence of water level, temperature, and propellant composition on the solubility of two hydrophobic steroid drugs, triamcinolone acetonide (TAA) and beclomethasone dipropionate (BDP).

EXPERIMENTAL

Materials

Aluminum aerosol cans (ϕ 23.6 × 60 × 20 mm) with internal epoxy phenolic linings (BASF 6256) were kindly supplied by Cebal S.A. (Bellegarde, France). Clear type-I glass vials (10 ml) were purchased from SGD Pharma (Saint-Gobain Dejonquères, France). Metering valves (100-μl, type DF10/100 RC), 150-μl metering valves (type DF10/150 RC 20 OR), and continuous spray valves (Ariane M) were purchased from Valois of America (Greenwich, CT). The plastic parts and gaskets of the valves were made of acetal resin and chloroprene base rubber, respectively. 1,1,1,2-Tetrafluoroethane (HFA 134a; Dymel®134a, DuPont Chemicals, Wilmington, DE) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227; Solvay Fluorides, Greenwich, CT) were dried by filtering

through a Catch All® filter drier (Sporlan Valve Company, Washington, MO) immediately before filling. Monobasic potassium phosphate, methanol (HPLC grade), and acetonitrile (HPLC grade) were purchased from EM Industries, Inc. (Gibbstown, NJ) and used as received. Phosphoric acid (Mallinckrodt Specialty Chemicals Co., Paris, KY) was used as received. Ethanol (200 proof, Midwest Grain Products of Illinois, Pekin, IL) was used as received. Micronized triamcinolone acetonide USP (TAA; Upjohn Fine Chemicals, Kalamazoo, MI) and micronized beclomethasone dipropionate USP (BDP; Schering-Plough Corp., Kenilworth, NJ) were used as received. Purified water was obtained using a Milli-Q UV plus ultrapure water system (Millipore S.A., Molsheim, France). Acrodisc® CR PTFE syringe filters were purchased from Gelman Sciences (0.22 μm, Ann Arbor, MI). Durapore® membrane filters were purchased from Milipore Corporation (0.22 and 0.45 μm Bedford, MA).

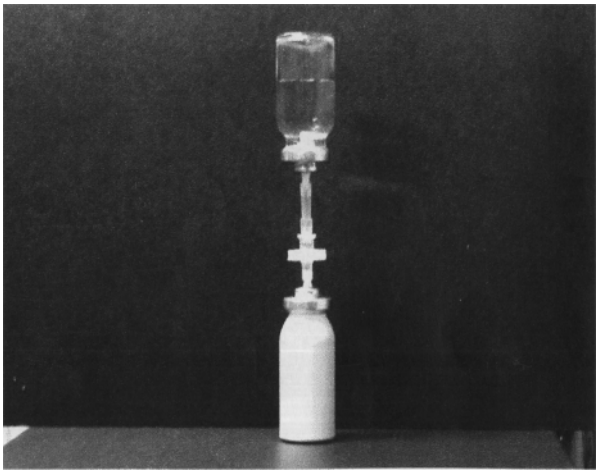

Figure 1. The filtration set up for the solubility determination of TAA and BDP in HFA 134a and 227.

Methods

Preparation of Sample pMDIs for Drug Solubility Study

The continuous spray valves were crimped onto aluminum cans containing excess amounts of TAA or BDP with and without different amounts of spiked water to make the final water concentration in the formulation 500, 1000, 1500, or 2000 ppm using a propellant compressor pump (Pamasol model P2005, Pamasol Willi Mader AG, Pfaffikon, Switzerland). The pMDIs without spiked water were used as control. The weight of the crimped canister was determined before gassing. The crimped canisters were pressure-filled with HFA 134a or HFA 227 through the continuous spray valve in weight ratios (HFA 134a:HFA 227) of 100/0, 75/25, 50/50, 25/75, and 0/100 using a small scale pressure filling machine (Pamasol model P2008, Pamasol Willi Mader AG). The pMDIs were equilibrated in the inverted position on a mechanical shaker at 15, 25, 30, or 40°C for 48 hr. The time to reach equilibrium solubility was experimentally determined to be 48 hr.

Determination of the Solubility of TAA and BDP in HFA 134a or 227

After equilibration for 48 hr at the various storage temperatures, the pMDI canisters were removed and the contents were filtered through 0.22-μm Acrodisc® CR PTFE syringe filters coupled with a plastic adapter into an empty aluminum receiving canister crimped with a continuous spray valve that had been equilibrated at the same temperature (Fig. 1). The receiving canisters containing the filtrate were weighed and then were frozen at -5°C for 10 min. Then the receiving canisters were punctured with a pushpin to slowly evaporate the propellant. Methanol was injected into the receiving canister to dissolve the drug for analysis. The weight of methanol used was determined. The amount of TAA and BDP in the methanol solution was determined by HPLC, and the solubility of TAA and BDP in the propellant systems was calculated.

Assay of TAA and BDP by HPLC

TAA or BDP were assayed by reverse-phase HPLC to determine their solubility in the propellant systems. A Shimadzu HPLC system (Shimadzu Scientific Instruments, Inc., Columbia, MD) equipped with an LC-600 chromatography pump, Sil-9A autoinjector, SPD-6A UV spectrophotometer detector, and a 150 $\times$ 46 mm-Intersil 5-μm ODS-2 column (MetaChem Technologies, Inc., Torrance, CA) was used for the HPLC analysis of TAA and BDP. The mobile phase consisted of 0.025 M potassium phosphate buffer (pH 3.0): acetonitrile (63:37) for the analysis of TAA, and acetonitrile: water (3:2) for the analysis of BDP. The flow rate was 1.5 ml/min, and the detection wavelength was 239 nm for TAA and BDP. The retention time of TAA and BDP was 4.4 and 6.0 min, respectively. The concentrations of TAA and BDP in reconstituted methanol solutions were calculated by comparing their peak areas to the peak areas of their corresponding USP reference standards, which were analyzed concomitantly. The solubility of TAA and BDP was calculated based on their concentration in the methanol solution. The HPLC methods

were validated, and system suitability tests verified that the resolution and reproducibility of the system were adequate for each analysis performed.

X-Ray Diffraction Analysis

Crystallinity of TAA and BDP before and after formulation in propellant HFA 134a or HFA 227 containing water at levels of 158 (control), 500, 1000, 1500, or 2000 ppm were determined using a Philips vertical scanning diffractometer (type 42273, Philips Electronic Instrument, Mount Vernon, NY). First, micronized TAA or BDP (20 mg) was weighed into the aluminum cans. Then, after adding the water into the can, it was crimped with a metering valve and gassed with HFA 134a or HFA 227. The pMDI contents were sonicated for 10 min to disperse the TAA or BDP. The canisters were then mechanically shaken in the inverted position (valve stem down) for 14 days at 25°C/65% RH. At days 7 and 14, the sample pMDIs were removed from the mechanical shaker and placed for 10 min in the upright position (valve stem up) in a −5°C freezer. A pushpin was used to puncture the canisters and evaporate the propellant. The contents in the canister were collected by cutting open the canister. The micronized bulk TAA and BDP were used as the control. The samples were exposed to CuKα radiation under 35 kV and 20 mA over the 2-θ range from 5 to 50° at an increment of 0.05°.

RESULTS

Influence of Propellant Composition on the Solubility of TAA and BDP in the Blend of HFA 134a and HFA 227

The results presented in Figure 2 indicated that solubility of TAA in the binary blends of HFA 134a and HFA 227 at 25°C increased to a maximum at a ratio of 25/75 and then decreased as the proportion of HFA 227 was increased in the propellant system. A similar trend was found for the solubility of TAA in the binary propellant system of HFA 134a and HFA 227 at 15 and 40°C. At 25 and 40°C, the maximal solubility of TAA in the propellant system was found at a HFA 227 composition of 25%. At 15°C, the maximum solubility of TAA in the propellant system was found at HFA 227 composition of 50%. The lowest solubility of TAA was found in pure HFA 227. The solubility of BDP in the binary blend of HFA 134a and HFA 227 increased only slightly to a maximum and then decreased as the proportion of HFA 227 was increased in the system at 25°C (Fig. 3). Also, a similar trend was found

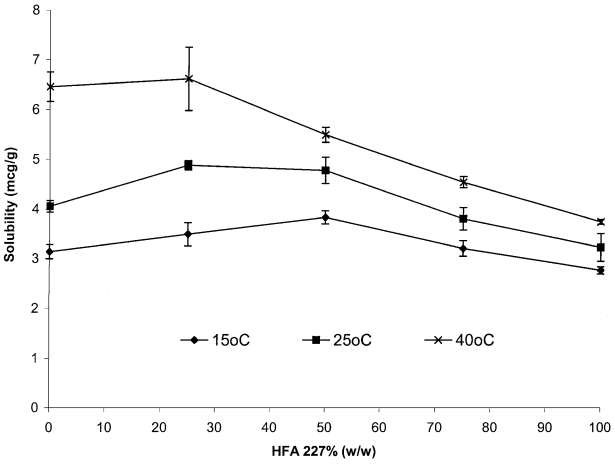

Figure 2. Influence of composition of the binary blend of HFA 134a and 227 on the solubility of TAA.

for the solubility of BDP in the control propellant system at 15°C. However, the solubility of BDP in the binary propellant system at 40°C decreased monotonously as the proportion of HFA 227 was increased in the binary propellant system (Fig. 3) and reached the lowest magnitude as the proportion of HFA 227 was increased to 100%. At 15 and 25°C, the solubility maximum of BDP was found at HFA 227 compositions of 75 and 50%, respectively. The solubility data of TAA and BDP in the binary propellant blend of HFA 134a and 227 indicated that the solubility of these two drugs was significantly influenced by the composition of propellant in the system and the storage temperature.

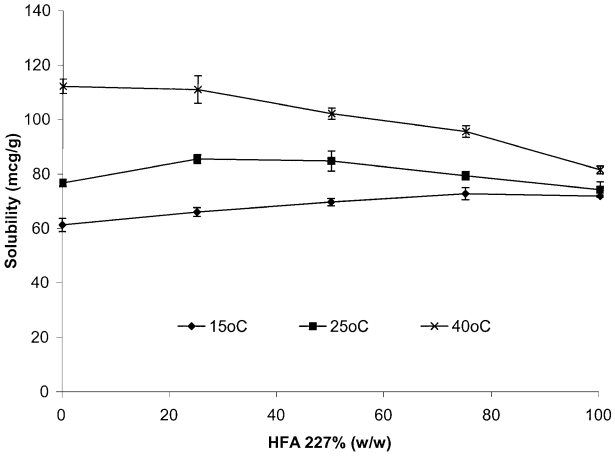

Figure 3. Influence of composition of the binary blend of HFA 134a and 227 on the solubility of BDP.

Influence of Water Level in Propellant System on the Solubility of TAA and BDP in the Binary System of HFA 134a and HFA 227

The influence of water level in the propellant system on the solubility of TAA and BDP in the systems at 25 and 40°C is presented in Figures 4(a), (b) and 5(a), (b) (results at 15 and 30°C are similar and are not shown). As the water level was increased, the solubility of TAA and BDP in most of binary propellant systems investigated decreased significantly at all temperatures investigated (15, 25, 30, and 40°C). However, the solubility of TAA in the propellant system containing 75 and 100% HFA 227 at 40°C decreased slightly as the water level in the propellant system was increased. As the water level was increased above 1000 ppm, the decrease of the solubility of TAA and BDP was not significant, which was more obvious at the lower temperatures (25°C) than at the higher temperature (40°C). The decreased magnitude of the solubility of BDP caused by increasing water level in the propellant system was much greater than that of TAA. At all investigated compositions of the propellant system, the trend of solubility change of TAA and BDP caused by increasing the water level in the propellant system was similar. The results suggested that the change in water level in the propellant system with suspended BDP may significantly influence the physical stability of the BDP formulated in the HFA propellant due to the dissolution and recrystallization of BDP.

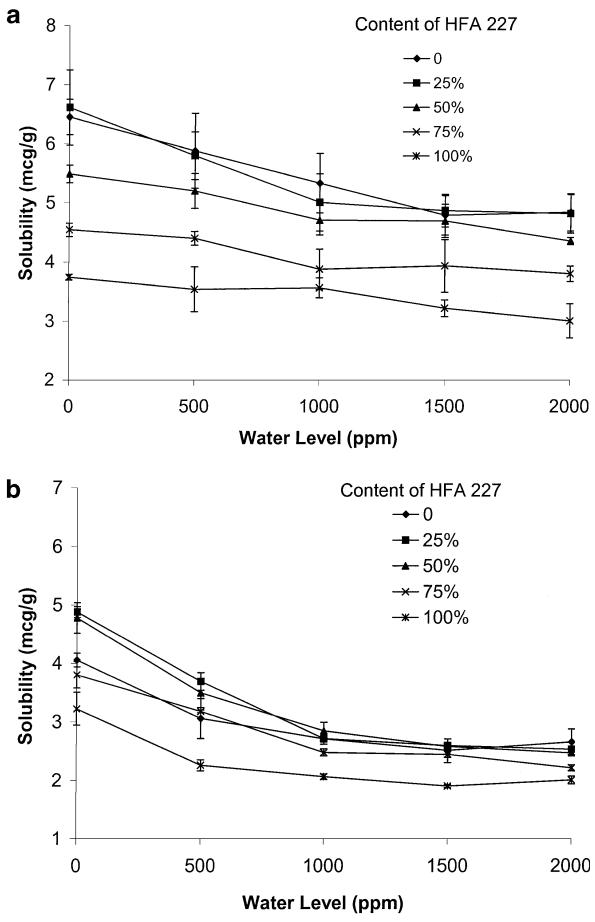

Figure 4. Influence of water level in the binary blend of HFA 134a and 227 on the solubility of TAA at (a) 40°C; (b) 25°C.

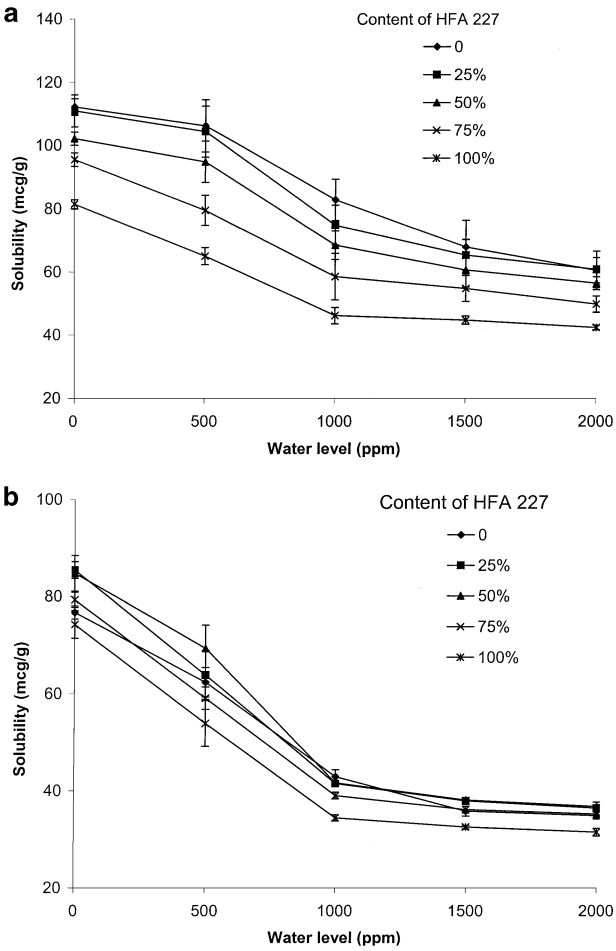

Figure 5. Influence of water level in the binary blend of HFA 134a and 227 on the solubility of BDP at (a) 40°C; (b) 25°C.

Influence of Temperature on the Solubility of TAA and BDP in the Binary Propellant System of HFA 134a and HFA 227

The solubility of TAA and BDP was increased as the temperature was increased at all water levels and propellant compositions investigated as shown in Figures 2–5.

However, the magnitude of the solubility increase was different for TAA and BDP as the temperature was increased. The solubility of BDP at all temperatures, spiked water levels, and propellant compositions was greater than that of TAA at the corresponding conditions. The magnitude of the solubility increase for BDP was also greater than that for TAA as the temperature was increased. This may be because the lower solubility of TAA in HFA propellant system caused the solubility increase for TAA to be insignificant compared with the solubility increase of BDP as the temperature was increased. Therefore, the storage temperature fluctuation may result in physical instability of pMDIs containing BDP and HFA propellants, whereas pMDI formulations containing TAA and HFA propellant may not be affected to a similar extent.

Influence of Water in Propellant on the Crystallinity of Suspended Drugs

The crystallinity of TAA and BDP was examined by x-ray diffractometry. The micronized TAA and BDP were suspended in pMDIs containing control (no spiked water) or 500 ppm water-spiked HFA 134a and HFA 227. The formulated TAA and BDP in pMDIs were recovered at days 7 and 14 (similar results are not shown). The x-ray diffraction patterns of TAA and BDP recovered from various pMDI formulations are presented in Figure 6(a)–(d). The x-ray diffraction patterns of the micronized TAA before and after being suspended in pMDIs containing control or water-spiked HFA 134a or HFA 227 were similar for all samples [Fig. 6(a), (c)]. The main peaks on

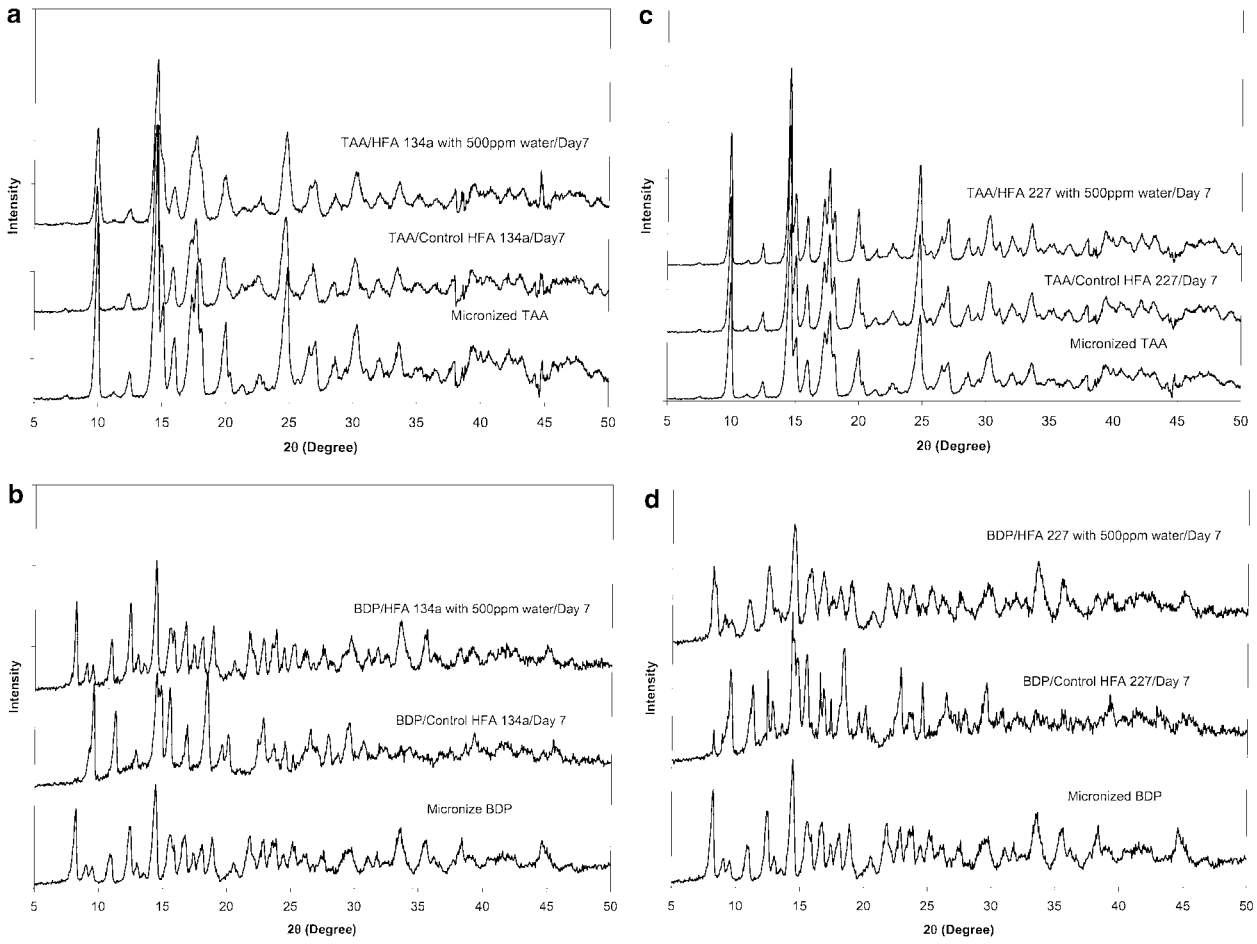

Figure 6. X-ray diffraction pattern of the control and recovered TAA and BDP from HFA 134a- or HFA 227-containing pMDIs with or without 500 ppm spiked water after 7 days' storage. (a) TAA recovered from HFA 134a; (b) BDP recovered from HFA 134a; (c) TAA recovered from HFA 227; (d) BDP recovered from HFA 227.

the x-ray diffraction spectrum were in the same position, independent of the type of propellant, water level in the propellant, or storage time. These results suggested that the crystallinity of TAA was not changed by dispersing the micronized TAA in control or water-spiked HFA 134a or HFA 227. However, one peak ($2\theta = 8^\circ$) observed on the x-ray spectrum of micronized BDP before and after formulation in pMDIs containing 500 ppm water-spiked HFA 134a disappeared or was less intense on the spectrum of BDP recovered from pMDIs containing control HFA 134a [Fig. 6(b)]. The same phenomenon was also observed on the x-ray diffraction spectrum of BDP recovered from formulations containing control HFA 227 and thus was independent of the propellant type and storage time [Fig. 6(d)]. These results suggested that when suspended in control HFA propellant, BDP might have experienced crystal growth and change in crystal habit, which resulted in the disappearance of the peak at 2θ equaling 8°. When water was spiked into the system, the solubility of BDP decreased in the system, which depressed the crystal growth of BDP in the system. These results were in agreement with the results of the particle analysis of the suspended TAA and BDP in HFA-propellant system (16).

DISCUSSION

It is recognized that in pharmaceutical products, the presence of moisture may influence the physical and chemical stability of the formulation, such as changes in disintegration time, hardness, drug release profile, drug crystal growth, conversion of drug polymorphs, hydrolysis, peroxidation, etc. (17–19). Water also interacts with the drug at the molecular level to influence the stability of pharmaceutical products (20,21). Residual water influences the solid-state degradation of drugs in the amorphous state by acting as a reactant, product, reaction medium, or plasticizer in the reactions.

The solubility of a drug in a propellant system determines whether the drug will be suspended or dissolved in the medium and is critical for optimizing the physical and chemical stability of the drug and its bioavailability. Crystallization of dissolved drugs from solution-based pMDIs and crystal growth of drug in suspension by Ostwald ripening are two potential stability concerns for pMDIs when the storage temperature fluctuates (12). It was reported recently that the particle size of crystals suspended in HFA 134a increased sufficiently to change the fine particle fraction (3,10). The dissolution of the suspended drug at concentrations higher than its equilibrium solubility in the propellant blends may be accompanied by crystal growth. The concentration of dissolved drug in propellant may exceed the equilibrium solubility because the smaller particles in the suspension display a high surface curvature allowing drug molecules to escape more easily from their surface or because of lowering of the temperature in a solution pMDI formulation (10). Therefore, the solubility of drug in propellant and its relationship with temperature and composition of the propellant system may be indicative of the chemical and physical stability during shelf life of a pMDI formulation.

Miller (11) suggested that water might act as a cosolvent for the suspended drugs in a pMDI formulation and increase the solvent power of the propellant system. Water may be introduced into the formulation system by the drug itself, excipients, packing materials, or uptake from the environment during storage. The ingress of moisture from the environment during storage into CFC-containing pMDIs has been reported by Miller and co-workers. Some experimental results have confirmed that moisture can be taken up by CFC-based pMDIs through the valve (22,23). Moisture ingress into HFA-containing pMDI was also investigated (16). The existence of trace water in the formulation may not only cause the degradation of active ingredients, e.g., hydrolysis, but it may change the particle size distribution of the drug, which will ultimately influence the accuracy and reproducibility of the delivered dose, drug deposition pattern, and bioavailability (24).

In this study, the water level changes in HFA 134a and HFA 227 altered the solvency of the propellant system and changed the dissolution properties of TAA and BDP. The solubility of TAA in HFA 134a and HFA 227 at 25°C was 4.06 and 3.22 μg/g, respectively. After the introduction of 500 ppm water into the propellant systems, the solubility of TAA in propellant HFA 134a and HFA 227 at the same temperature decreased to 3.06 and 2.26 μg/g, respectively. When the water level was increased to 1000 ppm, the solubility of TAA in propellant HFA 134a and HFA 227 decreased to 2.71 and 2.07 μg/g, respectively. When the water content in the system was increased to greater than 1000 ppm, the solubility of TAA in the system decreased only slightly because the propellant was saturated with water. However, the solubility of BDP in HFA propellant was approximately one order of magnitude greater than that of TAA in the same propellant system. BDP displayed similar trends in solubility to those of TAA as the water level was increased. These results indicated that gradual ingress of moisture into pMDIs during storage could decrease the solubility of TAA and BDP in HFA propellants.

The solubility data of TAA and BDP in the binary propellant blend of HFA 134a and HFA 227 indicated that the influence of composition of propellant system on the

solubility of these two drugs was dependent on the temperature and water level in the propellant system. At each composition investigated, the solubility of TAA and BDP decreased as the concentration of HFA 227 was increased in the binary blend of HFA 134a and HFA 227. The solubility of TAA and BDM in HFA-propellant blends increased linearly as the temperature was increased. The solubility of BDM in all HFA-propellant blends and temperatures investigated were significantly higher than those determined for TAA.

The x-ray diffraction pattern of TAA recovered from pMDIs stored for 1 week suggested that the crystal habit of TAA was not changed by dispersing the micronized TAA in HFA 134a or HFA 227 with or without spiked water. However, one peak ($2\theta = 8^\circ$) observed on the x-ray spectrum of micronized BDP and recovered BDP from the pMDIs containing 500 ppm water-spiked HFA 134a or 227 disappeared or weakened on the spectrum of BDP recovered from pMDIs containing control HFA 134a or 227.

It was reported previously that the fine particle fraction of the emitted aerosol dose from the BDP formulation increased significantly as the water level in the formulation was increased by spiking water into the formulation containing either HFA 134a or HFA 227 (16). Also, the fine particle fraction of TAA from the water-spiked pMDI formulation containing HFA 134a or 227 was not significantly changed compared with the control pMDI. The solubility study and x-ray analysis results presented in this study and the particle size analysis results reported previously are in agreement (16). The partially dissolved BDP in the propellant containing low water content could precipitate out of the propellant and recrystallize onto the suspended particles leading to crystal growth with changes in particle size distribution and crystal habit of BDP. In the propellant system containing a higher water content, the lower solubility of BDP depressed the crystal growth of BDP in the system and the particle size distribution and crystal habit of BDP did not change. In contrast, the solubility of TAA was very low in the HFA-propellant systems containing both high and low water content, and thus the particle size distribution and crystal habit of TAA were not significantly influenced by the water level in the propellant system. These results suggest that crystal growth for certain suspended drugs may occur as moisture gradually ingresses into the pMDIs over time or as the storage temperature fluctuates. Both phenomena may alter drug delivery performance of the pMDIs. Therefore, the issue of moisture uptake into pMDIs, the storage temperature, and the propellant composition must be considered during the development of pMDI formulations and reformulations of CFC-based pMDIs using HFA propellants.

In conclusion, the solubility of TAA and BDP was not only influenced by propellant composition and storage temperature but also changed depending on the water level in the propellant system. As a consequence, the particle size distribution and crystallinity of certain drugs formulated in HFA propellant were influenced by the temperature, propellant composition, and the water level in the propellant system. The impact of these factors on particle size distribution and crystallinity of formulated drugs depended on their influence on the solubility of the formulated drugs. The greater the impact of these factors on the solubility of drug in the HFA propellant system, the greater the tendency of these factors to promote a change in particle size distribution and crystallinity of the formulated drug. Therefore, drug solubility in the propellant system must be quantitatively investigated as a function of propellant composition, water content in the propellant system, and storage temperature to predict the influence of these factors on the physical stability of the formulated drugs in propellant systems. The results of solubility studies can be used to rationalize the necessity of controlling these factors during formulation development, manufacturing, shipping, and storage to maintain desired drug delivery performance.

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