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RESEARCH PAPER

Study of Solubility of Steroids in Hydrofluoroalkane Propellants

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ABSTRACT

The solubility of prednisone, hydrocortisone 21–acetate, hydrocortisone, dexamethasone, betamethasone 17–valerate, and danazol in hydrofluoroalkane (HFA) 134a and HFA 227 was determined at 5°C and 25°C. It was found that the solubility of steroid in HFA propellants was related to the melting point and the lipophilicity of the steroid. The solubility of the steroids in the binary system of HFA propellants and ethanol also was investigated in the study. Ethanol significantly increased the solubility of the steroids in HFA propellant. The magnitude of increase was related to the solubility of the corresponding steroid in ethanol alone.
Key Words: *HFA 134a; HFA 227; Steroids; Solubility.*

INTRODUCTION

A variety of drugs has been formulated into pressurized metered-dose inhaler (pMDI) delivery systems. Two types of pMDI formulations are suspension-based formulations, in which the drug particles are dispersed in the volatile propellant system, and solution-based formulations, in which either the drug is dissolved in the propellant or a combination of the propellant and an acceptable cosolvent, typically ethanol (1), is used. The type of formulation is dictated by the solubility of a drug in the propellant system. The solubility of a drug in the propellant system also relates to the physical stability of the formulation, drug propensity for polymorph interconversion, crystal growth potential, and solvate or clathrate formation, which are all among the issues to be addressed during the early stage of pMDI formulation development (1). As hydrofluroroalkanes (HFAs) became the major substitutes for chlorofluorocarbons (CFCs) as the propellant used in pMDI dosage forms (2), any information pertaining to the solubility characteristics of a specific drug in HFA would greatly benefit the formulation and

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reformulation process of a pMDI with the new propellants.

Ethanol is used in pMDI formulations as a cosolvent to increase the solubility of a drug in the propellants when formulating a solution-based pMDI (3). Ethanol is sometimes added as a dispersing aid to facilitate the dispersion of drug particles in the propellants during the manufacturing process when a suspension-based pMDI is formulated (1). However, in this case, any increase in drug solubility that may result from the presence of ethanol could be deleterious to the physical stability of the suspension due to crystal growth of the drug particles (4). Therefore, it is critical to understand the solubility characteristics of a drug in the binary solvent system composed of propellant and ethanol in order to use ethanol as a formulation ingredient appropriately.

The objective of this study was to investigate the solubility of a homologous series of steroids in HFA 134a, HFA 227, and a binary system of the propellants and ethanol.

MATERIALS AND METHODS

Materials

The following steroids were investigated in this study: prednisone, hydrocortisone, hydrocortisone 21–acetate, dexamethasone, betamethasone 17–valerate (Spectrum Chemical Manufacturing Corp., Gardena, CA), and danazol (Sigma Chemical Co., St. Louis, MO). Anhydrous ethanol was purchased from McCormick Distilling Company, Incorporated (Weston, MO). All chemicals were used as received. Tetrafluoroethane (HFA 134a and Dymel 134a; DuPont Chemicals, Wilmington, DE) and heptafluoropropane (HFA 227 and Solkane 227 Pharma; Solvay Fluorides, Greenwich, CT) were filtered through a refrigeration filter-drier (type C082, Sporlan Valve Co., Washington, MO) prior to use to eliminate moisture.

Determination of Equilibrium Solubility in Propellant

Excessive amounts of steroid were weighed and placed into aerosol glass vials (SGD Pharma, Paris, France). Continuous spray valves (Valois of America, Greenwich, CT) were crimped using Pamasol crimping and filling equipment (models P2005 and P2008, Pamasol Willi Mader AG, Pfaffikon, Switzerland). An aliquot of 10 g of HFA 134a or HFA 227 was filled into the aerosol canister immediately following crimping of the valve. Prior to crimping, 1 ml of anhydrous ethanol (7.89% w/w) was added to the vial prior to prepare the binary solvent systems containing propellant and ethanol. The assembled glass aerosol vials containing the drug were used as the donor vials, and they were stored in an upright position (valve stem up) on a horizontal shaker at 5°C or 25°C and were protected from light. The receiver canister consisted of a continuous spray valve crimped onto an aluminum aerosol can (Cebal SA, Bellegarde, France).

The time required to reach dissolution equilibrium for each drug was determined. The solubility was determined after the samples were stored for 48, 72, and 96 hr at 5°C and 25°C. The gas-tight filtration apparatus used to separate the liquid phase from the remaining undissolved drug is shown in Fig. 1. The donor vial was mounted onto the top of the apparatus. Pressure was applied to the donor vial to actuate the continuous spray valve, causing the liquid phase to flow freely through the filter housing containing a 0.22-μm membrane filter (type GV, Milli-

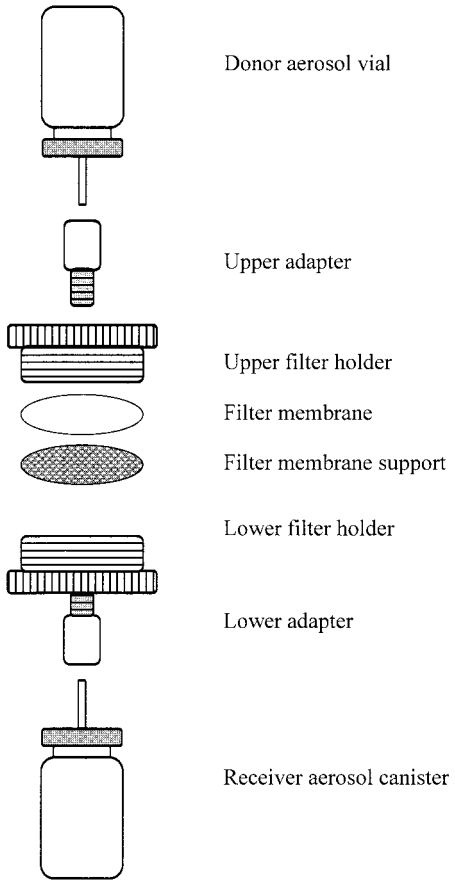


Figure 1. Schematic illustration of the filtration apparatus.

pore Corp., Bedford, MA) into a receiver canister. The filtration apparatus was designed to be a closed gas-tight system during the test procedure. The receiver canister was weighed before and after the filtering procedure so that the weight of the liquid that passed through the membrane could be determined. The canister was maintained in a freezer at 0°C for 20 min and then immediately punctured at the neck. The propellant was subsequently allowed to evaporate at 25°C. Ethanol was added to the can to dissolve the drug residues after the propellant was completely vaporized, and the drug concentration was determined using ultraviolet (UV) spectroscopy. The assay was determined at a wavelength of 240 nm for hydrocortisone, betamethasone 17–valerate, dexamethasone, prednisone, and hydrocortisone 21–acetate and at 286 nm for danazol. The solubility of drug in the propellant system was expressed as micrograms of drug per gram of solvent. Each determination was conducted in replicates of five.

Suitability Study of the Filtration Apparatus

An experiment was conducted to validate the filtration apparatus and the technique associated with operating the apparatus. A solution aerosol standard was formulated using 50 mg danazol, 1 ml ethanol, and 10 g HFA 134a. The solution was contained in an aluminum aerosol canister crimped with a continuous spray valve as the donor. The donor canisters were stored at 5°C and 25°C for 24 hr to equilibrate at each temperature. The empty receiver canisters also were equilibrated at the corresponding temperature for 24 hr prior to filtering. Afterward, half of the total amount of the formulation was transferred from the donor into a receiver aerosol canister using the filtration apparatus described above. Both the donor and the receiver canisters were weighed before and after filtering so that the weight of the formulation remaining in the canister after filtering could be determined. After filtering, both the donor and the receiver canisters were cooled to 0°C in a freezer, immediately punctured, and brought back to 25°C to evaporate the propellant slowly. The drug content was determined using the same method described above. The drug concentration in each canister was expressed as micrograms of drug per gram of formulation. The drug concentration in the donor canister was compared to that in the corresponding receiver canister to establish the suitability of the filtration apparatus. This study was conducted in replicates of five at each temperature condition.

Determination of Solubility in Ethanol

The solubility of drug in ethanol alone was determined. Excessive amounts of drug were admixed with 5 ml of ethanol in a clear glass vial fitted with a screw cap. The samples were stored on a shaker at 5°C and 25°C and protected from light. After dissolution equilibrium was reached, the ethanol solution was filtered through a 0.22-μm membrane filter (type GV, Millipore Corp.). The filtrate was collected and diluted with ethanol for quantitation by UV spectroscopy as described above.

Statistical Analysis

The data were compared using one-way analysis of variance (ANOVA) to evaluate the differences. Results were judged to be significant based on the 95% probability values ($p < .05$).

RESULTS AND DISCUSSION

The filtration apparatus employed in this study was constructed based on the design previously developed by Dalby, Phillips, and Byron (5), which was used to determine the solubility of salicylic acid in CFC 11. Compared to the apparatus used by Dalby et al., modifications were made so that the current apparatus was suitable for HFA propellant systems that possess a higher vapor pressure than CFC 11. A glass aerosol vial was used as the donor on the top, and an aluminum aerosol canister was used as a receiver at the bottom so that it would resist the force exerted on the canister. Both the donor and the receiver were held and compressed by hand when filtering the suspension of drug in HFA propellant. The apparatus operated in such a way that the continuous valves of both the donor vial and the receiver canister were open as they were compressed toward each other; consequently, the contents in the donor vial passed through the valve into the filter assembly, where the undissolved drug particles were blocked by the filter membrane, and the solution was forced through the filter membrane into the receiver canister through its valve. Maintaining a good seal to prevent the leakage of the propellant was critical to the accuracy and consistency of the results. A study was conducted to examine the suitability of the filtration apparatus used in this study to ensure the good sealing and proper operational techniques; in that study, danazol solution in HFA 134a was filtered through the apparatus, and the concentrations of the solutions in the donor and the receiver were compared afterward. The results

showed that the quantity of the drug recovered from the donor vial and from the receiver canister differed by 5.8% at 5°C and 2.9% at 25°C. The relative standard deviation of the determinations was 4.8% at 5°C and 3.8% at 25°C. The trivial differences in the drug concentration between the donor vial and the receiver canister indicated that the solution in the donor vial could be transferred accurately into the receiver vial, and that there was no significant amount of drug being lost due to leakage of propellant during the filtration process. Therefore, a gastight system was properly maintained. The low variation among replicates of determinations suggested that the apparatus operating technique was consistent and reproducible. Therefore, the filtration apparatus and the technique used to operate the apparatus were suitable for filtering HFA solutions accurately and reproducibly from the donor to the receiver canister in this study.

However, a close examination of the thermodynamics involved during the filtration process revealed a defect in this apparatus. Solubility is an equilibrium parameter, which implies that, as the equilibrium is disturbed, the solubility will change accordingly. At the moment that the continuous valve of the donor vial was compressed and opened to the filtration assembly, the head space pressure inside the donor vial was instantaneously decreased, thus perturbing the equilibrium between the liquid and vapor phases of the propellant. As a result, the dissolution equilibrium of the drug in the propellant was altered, and the amount of drug dissolved was decreased as the propellant liquid phase was vaporized. Therefore, the results from the filtration process would underestimate the solubility of the drug in the propellant. However, difficulty in handling the highly volatile propellant systems hindered the development of experimental procedures to determine accurately the solubility of the drug in the propellant. No previous study has been reported regarding determination of drug solubility in volatile propellant, except for the one designed by Dalby et al. (5), discussed above. With the apparatus developed in this study, no more than 5 sec was required to complete the filtration process, thus disturbance to the dissolution equilibrium of drug in propellant occurred over a very short period of time. Therefore, it could be justified to use the simple and quick method reported in this study to estimate the drug solubility in propellant. The solubility of prednisone, hydrocortisone, dexamethasone, hydrocortisone 21–acetate, betamethasone 17–valerate, and danazol in HFA propellants was determined at 5°C

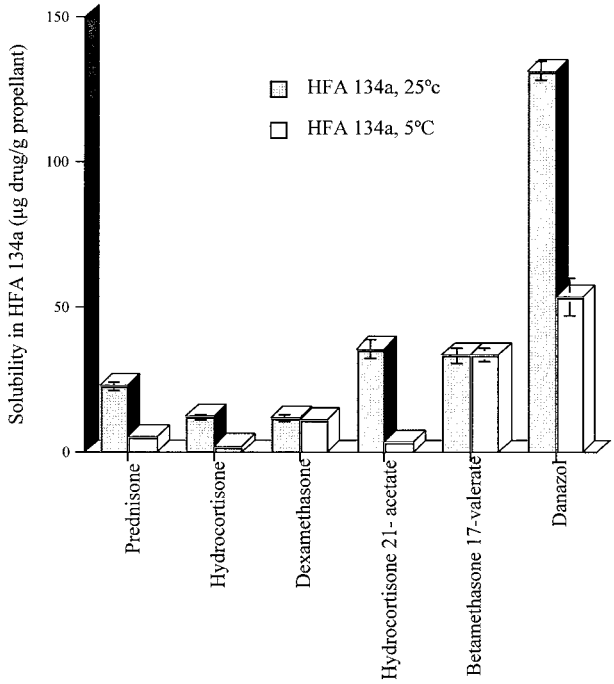


Figure 2. Solubility of steroids in HFA 134a at 5°C and 25°C expressed as micrograms of drug dissolved per gram of propellants ($n = 5$).

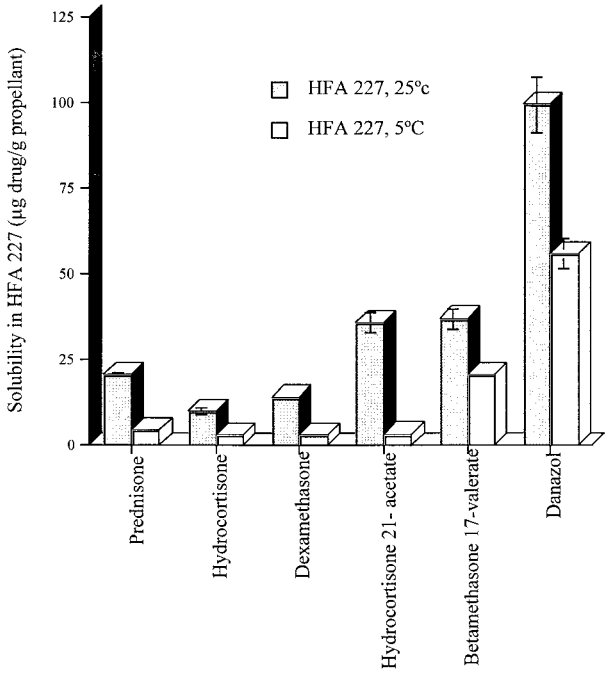


Figure 3. Solubility of steroids in HFA 227 at 5°C and 25°C expressed as micrograms of drug dissolved per gram of propellants ($n = 5$).

Table 1

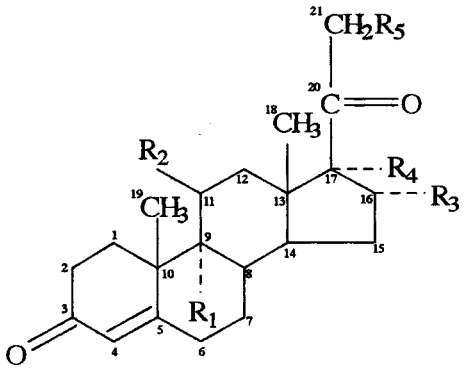
Physical Properties of the Steroids Investigated

Compound	Log *P*	Melting Point	Molecular Weight
Prednisone	1.36	233	358.44
Hydrocortisone 21–acetate	1.5	223	404.51
Hydrocortisone	1.55	219	362.47
Dexamethasone	1.89	270	392.47
Betamethasone 17–valerate	3.60	183	476.58
Danazol	4.53	225	337.46

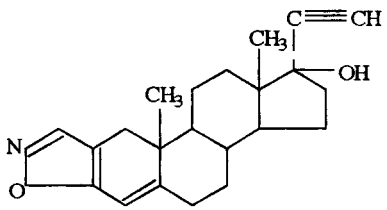
and 25°C. A time period of 72 hr was required to reach equilibrium before the mixture of excessive drug and propellant was filtered and assayed.

The solubility for each steroid investigated is presented in Figs. 2 and 3. Danazol showed the maximal solubility in both HFA 134a and HFA 227 among the steroids investigated in this study, and it was followed by hydrocortisone 21–acetate and betamethasone 17–valerate. Prednisone, hydrocortisone, and dexamethasone showed considerably less solubility in both HFA 134a and HFA 227 than danazol.

The physicochemical properties of the steroids investigated are summarized in Table 1 (6). The structures of the steroids investigated in this study are shown in Fig. 4, and the table in Fig. 4 summarizes the substitution



The General Structure of Steroids



Danazol

Compound	$\Delta^{1,2}$ [a]	R_1	R_2	R_3	R_4	R_5
Prednisone	+	H	OH	H	OH	OH
Hydrocortisone	-	H	OH	H	OH	OH
Dexamethasone	+	F	OH	CH_3	OH	OH
Hydrocortisone 21-acetate	-	H	OH	H	OH	$OCOCH_3$
Betamethasone 17-valerate	+	F	OH	CH_3	$OCO(CH_2)_2CH_3$	OH

[a]. $\Delta^{1,2}$ indicates the double bond between C1 and C2. "-" means no double bond between C1 and C2, and "+" means double bond existing between C1 and C2.

Figure 4. The structures of the steroids. The structures listed in the table represent the substitution groups (R_1–R_5) of each steroid.

Table 2

Solubility of the Steroids in Ethanol at 5°C and 25°C

Compounds	Solubility in Ethanol (mg/ml) 5°C	25°C
Prednisone	3.07	3.69
Hydrocortisone 21–acetate	1.51	2.74
Hydrocortisone	13.39	15.40
Dexamethasone	16.31	18.85
Betamethasone 17–valerate	49.39	72.41
Danazol	23.73	28.07

groups for each steroid. Although the compounds studied are structurally similar, the difference in their substitution groups resulted in different hydrophilicity/lipophilicity. According to the study by Caron and Shroot (7), the introduction of a double bond between C1 and C2 (prednisone, dexamethasone, and betamethasone 17–valerate), the substitution of the hydrogen atom by a fluorine at C9 (dexamethasone and betamethasone 17–valerate), or the presence of a hydroxyl group at C11 does not have a significant effect on the hydrophilicity/lipophilicity of the compound. However, changing a hydroxyl group at C16 (hydrocortisone) to a methyl group (dexamethasone) resulted in an increase in lipophilicity, and the esterification of the hydroxyl group at the C17 position of betamethasone 17–valerate resulted in an even larger increase in the lipophilicity. For danazol, the presence of the ethynyl group at C17 and the addition of a five-member heterocyclic ring to C2 and C3 positions further increased the lipophilicity, resulting in danazol being the most lipophilic compound in the series investigated in this study. The influence of molecular structure on the physicochemical properties of the compound also is manifested in the great difference in the melting point of the compound. Betamethasone 17–valerate presents the lowest melting point due to its bulky valerate substitution group. A compound that has a low melting point typically indicates that the compound crystals are bound together by weaker forces, which consequently results in higher solubility in solvents (8). Therefore, the solubility of steroids in HFA propellants is related to hydrophilicity/lipophilicity and the melting point of the corresponding compound. As a result, danazol, being the most lipophilic steroid among the drugs investigated, presented the greatest solubility in HFA propellants. Betamethasone 17–valerate showed greater solubility in HFA 134a and HFA 227 than prednisone, hydrocortisone, and dexamethasone due its greater lipophilicity and lower melting point.

A significantly higher solubility was observed at 25°C compared to 5°C for most of the steroids investigated. The difference in solubility determined at 25°C and 5°C was caused by a combined effect of temperature and pressure. Generally speaking, solubility increases with temperature. In addition, vapor pressure of the propellant increases with temperature, so the higher head space pressure at the higher temperature would enhance the drug solubility as well. Also, it was found that the magnitude of the solubility of each steroid was similar for HFA 134a and HFA 227, with the solubility in HFA 134a being slightly larger in most cases. This suggested that HFA 134a and HFA 227 possessed similar solubilizing power for the steroids investigated.

Ethanol is miscible with HFA 134a and HFA 227 over a broad range of concentrations (9,10). The solubility of the compounds in ethanol was determined at 5°C and 25°C; the results are presented in Table 2. The solubility

Table 3

Solubility of Steroids in HFA Propellant in the Presence of Ethanol (7.89% w/w) at 5°C and 25°C

Compound	Solubility in Ethanol/HFA 134a (μg drug per g solvent) 5°C	25°C	Solubility in Ethanol/HFA 227 (μg drug per g solvent) 5°C	25°C
Hydrocortisone	134.38	190.08	147.19	175.24
Dexamethasone	99.81	133.51	77.52	145.71
Betamethasone 17–valerate	2549.71	2635.55	2730.67	2733.35
Danazol	640.02	1077.90	633.23	816.36

of steroids in ethanol was considerably greater than that in HFA propellant.

The solubility of the steroids in the binary cosolvent system consisting of an HFA propellant and ethanol (7.89% w/w) was determined in this study. The presence of ethanol significantly increased the solubility of all steroids investigated (Table 3). The magnitude of increase was more significant for the lipophilic drugs betamethasone 17–valerate and danazol compared to hydrocortisone and dexamethasone. The solubility of steroid in the binary solvent systems of HFA propellants and ethanol was plotted against the solubility of steroid in ethanol (Figs. 5 and 6). It was observed that the solubility in the binary solvent systems increased as the solubility in ethanol alone increased. Therefore, the solubility in ethanol was indicative of the influence of ethanol on solubility of drug in HFA propellant. Greater solubility of the steroid in ethanol suggested that ethanol could be used as an effective cosolvent to enhance the solubility in HFA propellants for a drug. However, ethanol is not suitable for use as a dispersing aid in a suspension-based formulation if the drug has considerable solubility in ethanol since the increased drug solubility in HFA propellant due to the addition of ethanol could promote crystal growth and physical instability of a suspension-based pMDI formulation. Therefore, incorporation of ethanol in a pMDI formulation should take these factors into consideration.

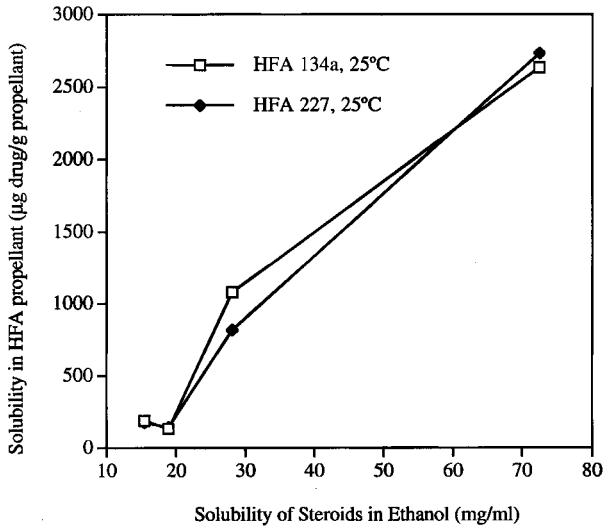


Figure 5. Solubility of steroids in HFA propellants in the presence of ethanol (7.89% w/w) plotted against solubility of corresponding steroid in ethanol at 25°C.

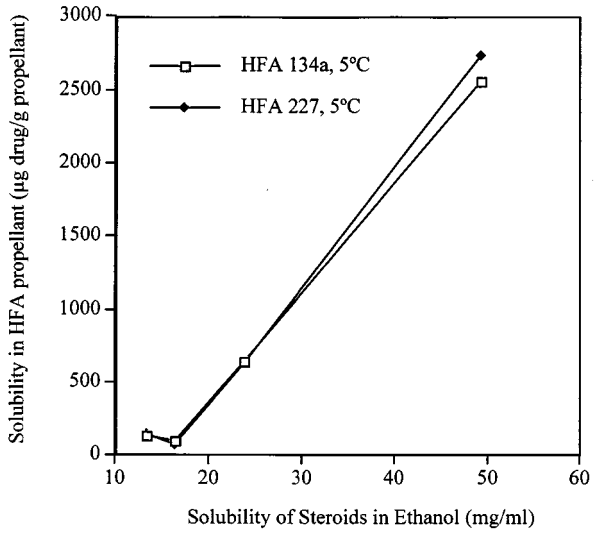


Figure 6. Solubility of steroids in HFA propellants in the presence of ethanol (7.89% w/w) plotted against solubility of corresponding steroid in ethanol at 5°C.

CONCLUSION

In conclusion, the solubility of a series of steroids in HFA propellants was determined. It was found that the steroid solubility in HFA propellants could be related to the melting point and the lipophilicity of the drug. A lower melting point or greater lipophilicity resulted in greater solubility in the HFA propellants. The solubilization power of HFA 134a and HFA 227 was similar for the steroids investigated, as indicated by the similar magnitude of solubility. The influence of ethanol on the solubility of the steroids in HFA propellant also was investigated. Ethanol dramatically increased the solubility of all steroids investigated, and the magnitude of the increase in solubility was related to the solubility of the drug in ethanol alone.

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