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Influence of formulation additives on the vapor pressure of hydrofluoroalkane propellants

Robert O. Williams III *, Jie Liu

College of Pharmacy, University of Texas at Austin, Mailstop A1920, Austin, TX 78712-1074, USA

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Abstract

The influence of propellant composition and addition of formulation additives to pressurized metered dose inhalers on the vapor pressure was investigated. The vapor pressure was determined for each propellant blend of HFA 134a and HFA 227, and for formulations containing triamcinolone acetonide and ethanol at 6°C, 16°C, 25°C, and 42°C. The results indicated that the vapor pressure increased linearly as the mol fraction of HFA 227 was increased, and that the propellant system obeyed Raoult's Law at all temperatures investigated. The vapor pressure decreased with the addition of ethanol. The enthalpy of vaporization of the propellant blends was estimated from the Clausius-Clapeyron equation. © 1998 Elsevier Science B.V. All rights reserved.

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Hydrofluoroalkanes (HFA 134a and HFA 227) are replacing chlorofluorocarbons (CFCs) as propellants for pressurized metered dose inhalers (pMDI) because of ozone-depleting properties of CFCs (June et al., 1994). The vapor pressure of propellants is a critical physico-chemical property that influences the performance of a pMDI, such as aerosol droplet velocity and dose delivery characteristics (Rance, 1974). The aerosol droplet velocity increases with increasing vapor pressure (Rance, 1974) resulting in greater shear forces to reduce the droplet size (Harnor et al., 1993) and inertial impaction in the mouth and oropharynx region (Gonda, 1992; Newman et al., 1982; Harnor et al., 1993). In pMDI formulations, the vapor pressure is manipulated by varying the molar ratio between propellants with high and low vapor pressures.

In the present study, the influence of pMDI formulation additives, including the propellant composition, the active ingredient, ethanol and inert suspended particles, on the vapor pressure of the HFA propellant systems was investigated as a

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* Corresponding author. Tel.: +1 512 4714681; fax: +1 512 4717474; e-mail: williro@mail.utexas.edu

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function of temperature. The enthalpy of vaporization (ΔH) was calculated for pure HFA 134a, pure HFA 227 and each propellant blend.

pMDIs were assembled using Pamasol crimping and filling equipment (Pamasol Willi Mader AG, Pfäffikon, Switzerland). The desired weight of HFA 134a (Dymel 134a; DuPont Chemicals, Wilmington, DE) or HFA 227 (Hoechst, Germany) was filled through continuous spray valves (Valois of America, Inc., Greenwich, CT). Air was depleted from each empty aerosol can (Cebal S.A., Bellegarde, France) prior to crimping by dispensing an aliquot of the propellant mixture containing the corresponding molar composition into the can. The molar ratios of HFA 134a to HFA 227 investigated were 1:0, 0.84:0.16, 0.63:0.37, 0.37:0.63 and 0:1. TAA (The Upjohn Co., Kalamazoo, MI), microcrystalline cellulose (MCC, Avicel® PH101, FMC Corporation, Philadelphia, PA) and ethanol (McCormick Distilling Co., Inc., Weston, MO) were used as received. The influence of ethanol on the vapor pressure of the propellant system was investigated by adding ethanol alone to each propellant blend at concentrations of 2.37% w/w, 3.95% w/w, 7.9% w/w and 11.85% w/w. The concentrations of TAA and MCC in the formulations were both 0.3% w/w, and the level of ethanol used in the these formulations was 2.37% w/w. TAA also was suspended alone in HFA 134a and HFA 227 at increasing levels of 0.1% w/w, 0.3% w/w, 1.0% w/w and 3.0% w/w. The vapor pressure was measured using a pressure test gauge (Pamasol Willi Mäder AG) at temperatures of 6, 16, 25 and 42°C. The pMDIs were equilibrated at the test temperatures for 6 h before determining the vapor pressure. Each determination was conducted on replicates of five canisters, except for the formulations containing TAA or MCC, for which the measurement was performed on three canisters. A Student's t-test was used to determine the statistical significance of the linear correlation at the 95% confidence level, as well as the statistical significance of the differences among the acquired data. The true density of TAA and MCC was determined by helium pycnometry (Micromeritics® AccuPyc 1330, Norcross, GA), and the determination was performed in triplicate.

The results presented in Fig. 1 show the vapor pressure of the propellant blends as a function of the mol fraction of HFA 227 at different temperatures. The gas phase that existed in the aerosol canister was composed of HFA 134a and HFA 227 vapor because air was depleted from the empty can prior to assembly of the pMDI. Therefore, the headspace pressure approximated the vapor pressure of the formulation contained in the aerosol canister. The vapor pressure of the pure HFA 134a and HFA 227 determined at 6, 16, 25 and 42°C in the study was compared to the reported values as shown in Table 1, and the determined values approximately agreed with the reported values, confirming the accuracy of the measurements in this study. As shown in Fig. 1, the vapor pressure increased significantly as the temperature was increased, and decreased linearly as the mol fraction of HFA 227 was increased. This was because HFA 227 has a lower vapor pressure than HFA 134a at any given temperature. A linear relationship was found between the vapor pressure and the mol fraction of HFA 227.

According to Raoult's Law (Atkins, 1982), for a system composed of HFA 134a and HFA 227:

$$P_{134a} = P^{\circ}_{134a}X_{134a} \tag{1}$$

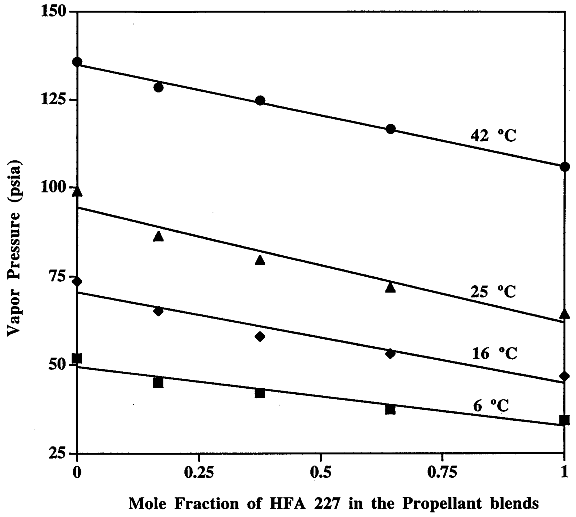

Fig. 1. Plot of vapor pressure versus mol fraction of HFA 227 for pure propellant systems composed of HFA 134a and HFA 227 at 6, 16, 25, and 42°C.

Table 1
Comparison of the vapor pressure determined for pure HFA 134a and pure HFA 227 with the reported values at different temperatures

Temperature (°C)	HFA 134		HFA 227	
	Measured vapor pressure (psia)	Reported vapor pressure[a] (psia)	Measured vapor pressure (psia)	Reported vapor pressure[b] (psia)
6	51.9 (2.2)[c]	52.736	34.2 (0.8)	34.810
16	73.7 (0.6)	73.459	46.7 (0.6)	49.749
25	98.9 (3.8)	96.606	64.4 (0.8)	66.109
42	135.8 (3.6)	152.039	105.9 (0)	107.634

[a] From Therrmodynamic Properties of HFC-1334a, Du Pont Chemicals, Wilmington, DE.
[b] From The Technical Information of HFA 227, Hoechst Chemicals, Germany.
[c] Standard deviation shown in parentheses.

$$P_{227} = P^{\circ}_{227} X_{227} \quad (2)$$

$$P = P_{134a} + P_{227} = P^{\circ}_{134a} X_{134a} + P^{\circ}_{227} X_{227}$$
$$= P^{\circ}_{134a} + (P^{\circ}_{227} - P^{\circ}_{134a}) X_{227} \quad (3)$$

where P_{134a} and P_{227} are the partial vapor pressures of HFA 134a and HFA 227, respectively, X_{134a} and X_{227} are the mol fractions of each component, and $X_{134a} + X_{227} = 1$. The vapor pressures of the pure components are given by P°_{134a} and P°_{227}. P is the total vapor pressure of the solution mixture. An ideal solution requires complete uniformity of attractive forces between molecules of HFA 134a and HFA 227 in the system. Ideal solutions are typically formed by mixing substances with similar properties, and is confirmed by determining the total vapor pressure of the mixture over the range of mol fractions for each component. The solutions form an ideal mixture if Raoult's Law is obeyed (Martin, 1993). Therefore, according to Raoult's Law, mixtures of HFA 134a and HFA 227 behaved as ideal solutions at all temperatures investigated.

The vapor pressure of the propellant blends containing increasing levels of ethanol was investigated at different temperatures. Ethanol was added to the propellant blends at concentrations ranging from 2.37% w/w to 11.85% w/w. The influence of ethanol on the vapor pressure at 25°C is shown in Fig. 2. The addition of ethanol decreased the vapor pressure of the propellant system at 25°C, and the magnitude of the change was increased as the level of ethanol was increased. A similar pattern was found at 6, 16 and 42°C. Ethanol is miscible with the propellants in the concentration range investigated in this study (Byron and Blondino, 1996a,b; Lostritto, 1996). Ethanol was added to the propellant blends as a less volatile solute, therefore, the presence of ethanol in the propellant system decreased the vapor pressure. Ethanol is commonly used as a dispersing aid or a cosolvent in pMDI formulations to facilitate manufacturing or to improve the homogeneity of the formulation (Dalby et al., 1996). However, as indicated by these results, the addition of ethanol is associated with decreases in propellant vapor pressure, and may result in larger aerosol droplets and greater oropharyngeal deposition (Newman et al., 1982; Gonda, 1992; Harnor et al., 1993). Therefore, to obtain improved physical stability of the formulation, the tendency to decrease the vapor pressure should be accounted for when selecting the appropriate ethanol level in a pMDI formulation.

TAA is suspended in the propellants with ethanol as a processing aid to prepare suspension-based pMDI formulations for treating asthma. The influence of TAA on the total vapor pressure of the propellant system in this formulation was investigated. MCC is insoluble and non-reactive in most organic solvents (Wade and Weller, 1994). It was used in this study as an inert material to be suspended in a similar manner as TAA in the propellant systems. The influence of MCC on the vapor pressure of the propellant blends also was

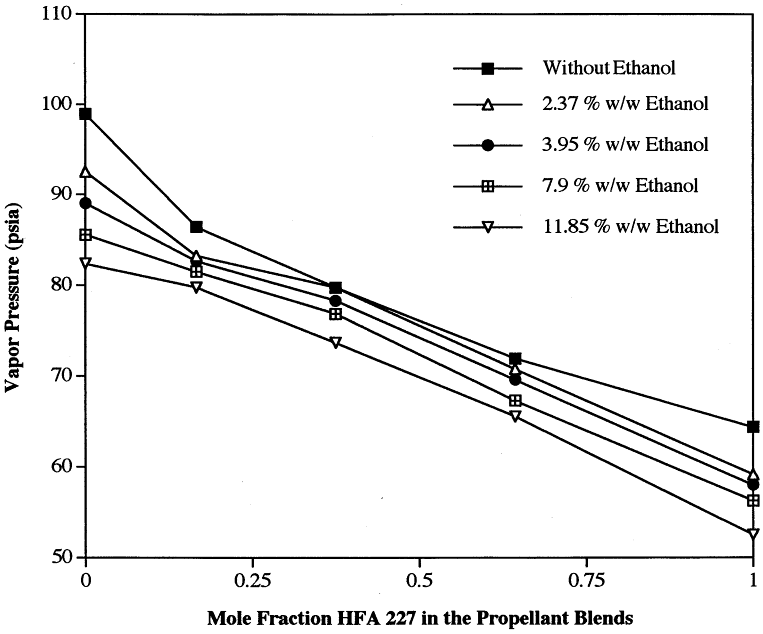

Fig. 2. The vapor pressure of HFA 134a and HFA 227 blends at 25°C in the presence of increasing levels of ethanol.

investigated and compared with the TAA formulation. As shown in Fig. 3, the addition of TAA slightly decreased the vapor pressure of HFA 134a at 16°C and 25°C, but did not significantly influence the vapor pressure of HFA 134a at 6°C and 42°C or the vapor pressure of HFA 227 at all temperatures investigated. A similar trend also was found for MCC suspended in the propellant. Therefore, no significant differences were found between the vapor pressure in the absence, and in the presence, of either TAA or MCC. The true density of TAA was 1.32 g/cm^3 (the relative standard deviation (R.S.D.) = 0.03%), and the true density of MCC was 1.55 g/cm^3 (R.S.D. = 0.03%). Therefore, the influence of suspended particles on the vapor pressure of the propellant was independent of the true density of the suspended particles.

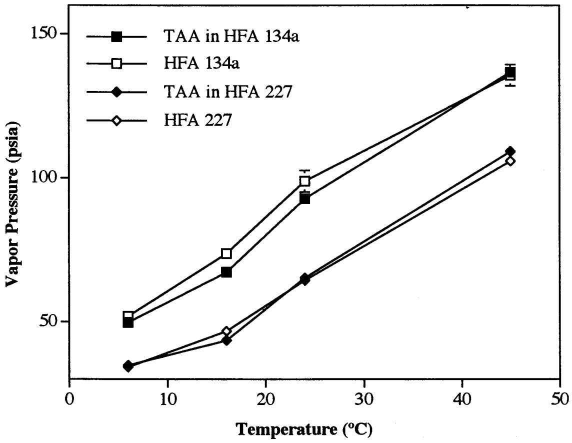

Fig. 3. Influence of triamcinolone acetonide (0.3% w/w) on vapor pressure of pure HFA 134a and pure HFA 227 as a function of temperature.

In a two-phase system composed of vapor and liquid phases, if the vapor obeys the ideal gas law to a good approximation, _H can be estimated from the Clausius-Clapeyron equation (Martin, 1993):

$$\frac{\mathrm{d}P}{\mathrm{d}T}=\frac{P\cdot\Delta H}{R\cdot T^2} \qquad (4)$$

and integrated assuming ΔH is constant,

$$\ln P=\frac{\Delta H}{RT}+C \qquad (5)$$

Table 2
Calculation of parameters according to the Clausius-Clapeyron equation

Mol fraction		Slope	ΔH (kJ/mol)	r^2
HFA 134a	HFA 227			
1	0	2353	19.56	0.976
0.84	0.16	2561	21.29	0.989
0.63	0.37	2685	22.32	0.995
0.37	0.63	2792	23.22	0.997
0	1	2794	23.23	0.993

where P is the vapor pressure of the system at an absolute temperature T. In this study, ΔH was calculated from the slope of the plot of $\ln P$ versus T. The values of the slope, r^2, and ΔH are listed in Table 2. Each r^2 was statistically significant ($p > 0.01$), indicating a linear correlation between $\ln P$ and $1/T$, and a good fit of the Clausius-Clapeyron equation. The vapor pressure at any given temperature can be estimated for each propellant blend based on ΔH.

In conclusion, the vapor pressure of HFA 134a and HFA 227 blends was experimentally determined as a function of temperature. The vapor pressure of the propellant blends increased linearly as the mole fraction of HFA 227 was increased, and the increase in vapor pressure obeyed Raoult's Law at all temperatures investigated. Addition of ethanol decreased the vapor pressure of the propellant because ethanol was a less volatile solute in the propellant system. The suspended particles caused slight changes in the vapor pressure of HFA 134a at 16°C and 25°C, but no changes in the vapor pressure of HFA 227 at these temperatures.

References

Atkins, P.W., 1982. Physical Chemistry, 2nd ed., W.H. Freeman, San Francisco.

Dalby, R.N., Hickey, A.J., Tiano, S.L., 1996. Medical devices for the delivery of therapeutic aerosols to the lungs. In: Hickey, A.J. (Ed.), Inhalation Aerosols: Physical and Biological Basis for Therapy. Marcel Dekker, New York, pp. 441–473.

Byron, P., Blondino, F., 1996a. Metered dose inhaler formulations which included the ozone-friendly propellant HFC 134A and a pharmaceutically acceptable suspending, solubilizing, wetting, emulsifying or lubricating agent. US Patent 5,492,688, Feb. 1996.

Byron, P., Blondino, F., 1996b. Pharmaceutically acceptable agents for solubilizing, wetting, emulsifying, or lubricating in metered dose inhaler formulations which use HFC-227 propellant. US Patent 5,508,023, Apr. 1996.

Gonda, I., 1992. Targeting by deposition. In: Hickey, A.J. (Ed.), Pharmaceutical Inhalation Aerosol Technology, Marcel Dekker, New York, pp. 155–185.

Harnor, K.J., Perkins, A.C., Wastie, M., Wilson, C.G., Sims, E.E., Feely, L.C., Farr, S.J., 1993. Effect of vapor pressure on the deposition pattern from solution phase metered dose inhalers. Int. J. Pharm. 95, 111–116.

June, D.S., Schultz, R.K., Miller, N.C., 1994. A conceptual model for the development of pressurized metered-dose hydrofluoroalkane-based inhalation aerosols. Pharm. Technol. 18, 40–52.

Lostritto, R.T., 1996. A non-empirical model describing the phase behavior of propellant vehicles. Pharm. Res. 13 (suppl.), 177.

Martin, A., 1993. Physical Pharmacy, 4th ed., Lea&Febiger, Philadelphia.

Newman, S.P., Morén, F., Pavia, D., Corrado, O., Clarke, S.W., 1982. The effects of changes in metered volume and propellant vapour pressure on the deposition of pressurized inhalation aerosols. Int. J. Pharm. 11, 337–344.

Rance, R.W., 1974. Studies of the factors controlling the action of hair sprays. III. The influence of particle velocity and diameter on the capture of particles by arrays of hair fibres. J. Soc. Cosmet. Chem. 25, 545–561.

Wade, A., Weller, P.J., (Eds.), 1994. Handbook of Pharmaceutical Excipients, 2nd ed., American Pharmaceutical Association, Washington, DC.