Saturated vapour pressure (SVP) measurement of ethanol/HFA binary mixtures

B. Gavtash[1], **B. Myatt**[1], **H. O'Shea**[2], **F. Mason**[2], **D. Lewis**[2], **T. Church**[2], **H.K. Versteeg**[1], **G. Hargrave**[1], **G. Brambilla**[3],

[1] Wolfson School of Mechanical and Manufacturing Engineering, Loughborough University, Loughborough, LE11 3TU, United Kingdom

[2] Chiesi Limited, Bath Road Industrial Estate, Chippenham, Wilts, SN14 0AB, United Kingdom

[3] Chiesi Farmaceutici SpA, Via Palermo, 43122 Parma, Italy

Summary

Addition of ethanol to propellant based formulations of pMDIs results in saturated vapour pressure alteration which is understood to have an impact on the droplet size of the resulting aerosol cloud [1, 2, 3, 4]. Accurate and simple methods of estimating the saturated vapour pressure are important in developing the next generation of pMDI formulations. Here we report the results of a series of vapour pressure measurements of ethanol/HFA134 and ethanol/HFA227 binary mixtures over a wide range of ethanol concentration and temperature. The outcome shows strong departure from Raoult's law. An empirical expression is developed to capture the nonlinear behaviour of vapour pressure in a compact set of equations as follows:

$$\Pi_v^*(x_{eth}, T) = \frac{P_{mix}(x_{eth}, T) - P_{eth}(T)}{P_{HFA}(T) - P_{eth}(T)} = (1 - x_{eth})[1 + ax_{eth} + bx_{eth}^2 + cx_{eth}T + dx_{eth}^3 + ex_{eth}^2 T + fx_{eth}T^2] \qquad 1$$

Where $P_{mix}(x_{eth}, T)$ denotes the saturated vapour pressure of a mixture of HFA and ethanol with mole fraction x_{eth} at temperature T. $P_{HFA}(T)$ and $P_{eth}(T)$ are SVP values of pure HFA and ethanol respectively, which are functions of temperature only. Coefficients in $a - f$ in equation 1 are propellant dependent and are tabulated as follows:

Coefficient	a	b	c	d	e	f
HFA134	-57.73	4.325	0.4202	0.01125	-0.005239	-0.000759
HFA227	0.613	-6.784	0.171	-2.666	0.03957	-7.149×10^{-5}

Introduction

Most established chlorofluorocarbon (CFC) pMDIs, were developed as suspensions in which the active pharmaceutical ingredient (API) is dispersed in the liquefied propellant system with the aid of a surfactant. Later on and as required by Montreal protocol in 1989, conventional propellants were substituted by hydrofluoroalkane (HFA) propellants such as HFA227 and HFA134. Due to poor solubility of many drugs in these HFA propellants, ethanol is commonly used as cosolvent. However, addition of ethanol changes the performance of a formulation. It is known that saturated vapour pressure (SVP) of a formulation is altered by addition of ethanol which in turn influences the atomisation process. This affects the size of the emitted droplets and, hence, the respirable dose [1, 2, 3, 4]. The science in this area is empirical and theoretical approaches are limited by the lack of a comprehensive database. In this paper, we report the findings of a series of experiments to measure the vapour pressure of HFA134/ethanol and HFA227/ethanol mixtures over a wide range of ethanol concentration and temperature. We also represent a compact relationship that captures the functional relationship between SVP and these variables.

Experimental procedure

MDI canisters containing a wide range of ethanol concentrations (10%-90% w/w) in HFA 227 and HFA 134 were manufactured. Predetermined quantities of ethanol were weighed into tared cut edge C128 aluminium cans (Presspart). The headspace of all MDI canisters (containing bulk formulation) was purged with HFA spray shots prior to placing and crimping each MDI valve to reduce the chance of any air presence inside the cans which may modulate the vapour pressure. Using Pamasol P2016 laboratory scale, crimping and filling equipment, the cans were sealed with BK 357 continuous spray valves (Bespak, UK) and filled to pre-specified weights with propellant. After the filling stage, the cans were weighted once more to ensure the predetermined weight and hence correct formulation composition was achieved. The sealed cans were then placed in trays and the faulty ones (cans with leakage problem or incorrect weight) were inverted. These cans are marked with "X" in figure 1 and were discarded from the experiment next phase. For high temperature (20°C and 30°C) measurement, the cans were left to equilibrate for minimum of 60 mins within a calibrated environmental chamber (Westech, UK) prior to measurement.

The 60 min period was chosen for the purpose of MDI hardware and formulation equilibrium and exceeded the 30 min equilibrium period that had been found to be adequate in a previous study[1].

For 0°C temperature, a standard ice bath was prepared. For measurements at -10°C and -20°C, NaCl/ice cooling baths were employed with the weight ratios of approximately 1:9 and 1:3, respectively. Cooling bath temperatures were monitored during the measurements using two calibrated Hanna HI147-00 thermometers.   One was placed to monitor the temperature adjacent to the canister shell while the other one monitored the tray side temperature. Immediate action was taken to reduce the impact of small temperature variations by addition of extra ice.

		Cooling bath			Environmental chamber	
Target Temperature (℃)		-20	-10	0	20	30
Measurement temperature (℃)	**HFA134**	-16.6	-11.3	0.3	20	30
	HFA227	-17.0	-11.8	0.2		

Table 1. Comparison between target temperature and achieved temperature during measurement
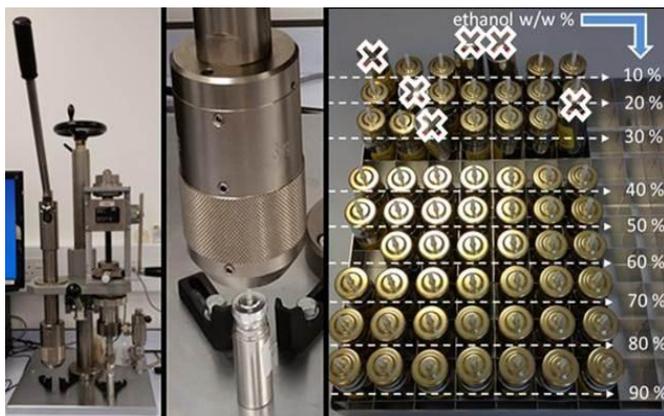

Figure 1. Can manufacturing using Parmasol P2016 Lab scale

Figure 2. Cooling baths used for low temperature measurement

Measurements of the pressure in the canister headspace where conducted using a MMD-30E electronic diaphragm gauge (0-30 bar) readable to 0.05 bar. For each canister, five readings were taken with at least 120 s rest before repeating the measurement. The electronic pressure gauge depressed the canister valve for 5 s to provide enough time for the vapour to fill the diaphragm space uniformly and to establish a steady reading. The reading was then recorded and the whole process was repeated on two further canisters with the same ethanol concentration and an average vapour pressure determined. During low temperature measurement, a fixed target temperature could not always be met as a result of ice melting with a typical variation of 2-3°C. Thus, the measurement temperature is reported as the averaged value (see table 1).

Result and Discussion

Vapour pressure data for HFA134 and HFA227 is presented with respect to ethanol mole fraction in figure 3a-b. Boundary values of the curves (corresponding to pure HFA and ethanol from NIST database [9]) are included in the figures. The straight red line in Figure 3 indicates Raoult's law of vapour liquid equilibrium (VLE) [8], which assumes a linear relationship between the saturated vapour pressure and the molar concentration of ethanol. Graphs show that an increase of ethanol concentration causes a decrease in vapour pressure. Figure 3 shows positive deviation from Raoult's law, i.e. the actual SVP values are significantly above the red lines, suggesting that Raoult's law is inadequate for pMDI formulations as supported by other work [5]. Raoult's law is valid for mixtures of non-interacting molecular species. Positive deviation indicates net repulsive forces between the molecular species, resulting in larger amounts of HFA entering the vapour phase and, hence, higher SVP values.   Figure 4a-b show a comparison of our measured values of SVP of HFA 227/ethanol and HFA 134/ethanol blends with published data from the literature. The comparison shows consistent trends with respect to ethanol composition. Additionally magnitude of the current measurement with respect to temperature is in good agreement with previous studies.

To develop empirical equations of vapour pressure from data, measured values presented in figure 3 are non-dimensionalised to normalise the effect of temperature so SVP values can be reproduced on similar scale. The function is formulated as shown in equation 1:
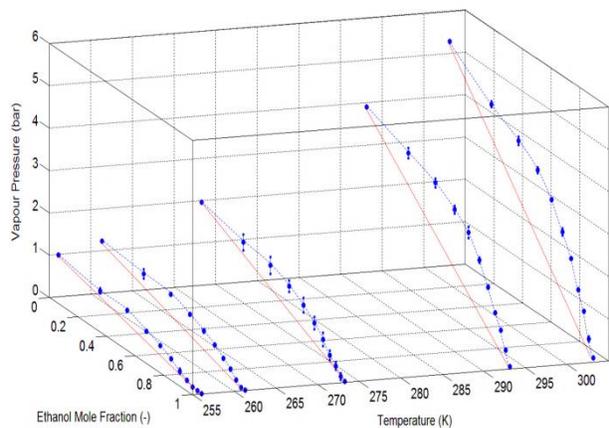
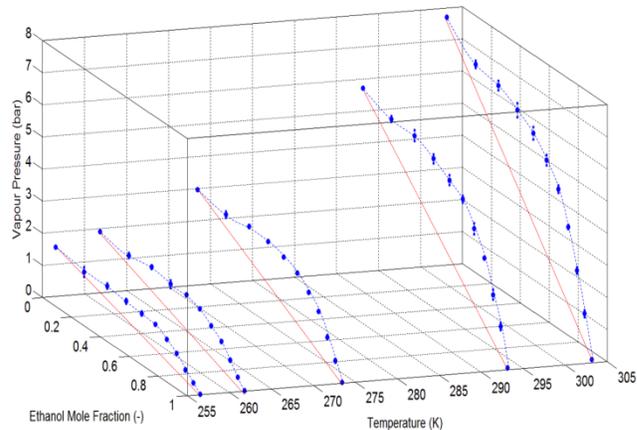**Figure 3a. SVP values of ethanol/HFA227 mixture**

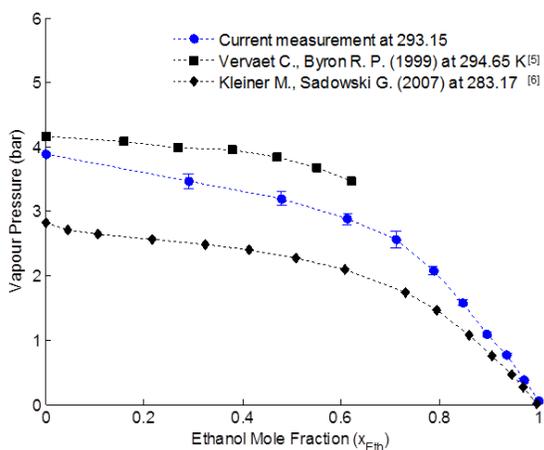**Figure 3b. SVP values of ethanol/HFA134 mixture**

Figure 4a. Comparison of current SVP values with available data for ethanol/HFA227
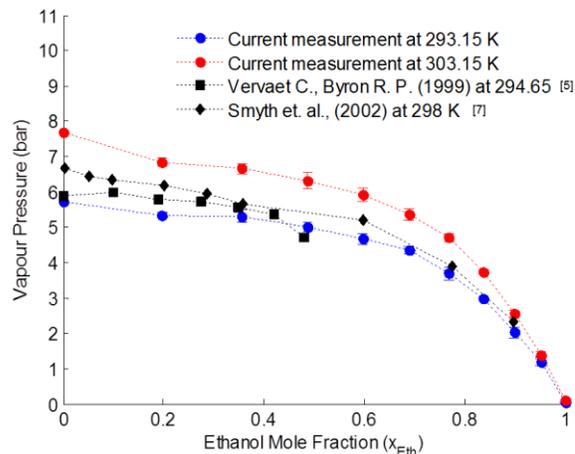

Figure 4b. Comparison of current SVP values with available data for ethanol/HFA134
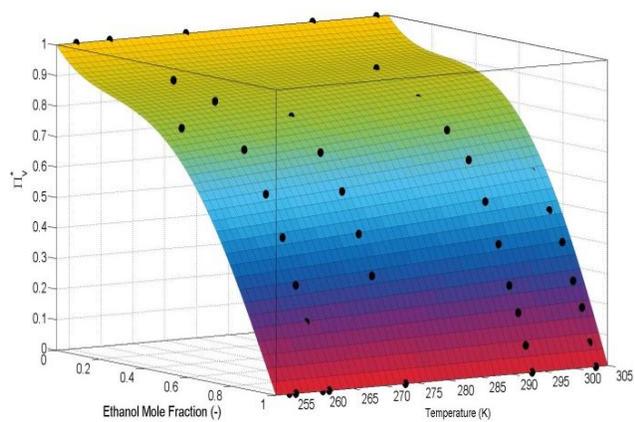

Figure 5a. Non-dimensional SVP representation and surface fit for ethanol/HFA227 mixture
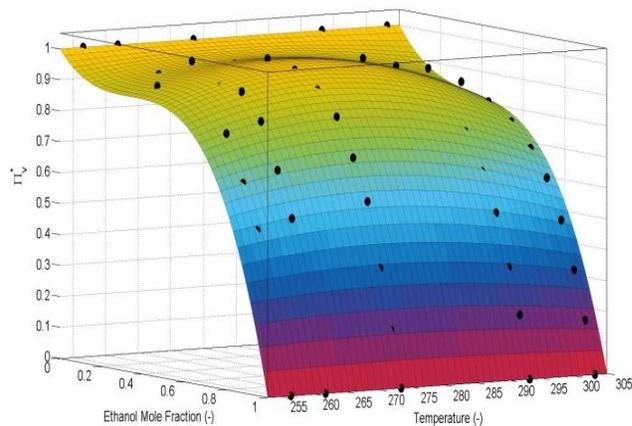

Figure 5b. Non-dimensional SVP representation and surface fit for ethanol/HFA134 mixture

$$\Pi_v^*(x_{eth}, T) = \frac{P_{mix}(x_{eth}, T) - P_{eth}(T)}{P_{HFA}(T) - P_{eth}(T)} = (1 - x_{eth})[1 + ax_{eth} + bx_{eth}^2 + cx_{eth}T + dx_{eth}^3 + ex_{eth}^2 T + fx_{eth}T^2]$$

2

Where $P_{mix}(x_{eth}, T)$ denotes the saturated vapour pressure of a mixture of HFA and ethanol with mole fraction x_{eth} at temperature T. $P_{HFA}(T)$ and $P_{eth}(T)$ are SVP values of pure HFA and ethanol respectively, which are functions of temperature only. The advantage of current non-dimensional representation is to automatically incorporate exactly the SVP values for the pure substances, which are known to very high accuracy. This practice also improves the fitting by eliminating the large differences in HFA134 and HFA227 pressures as temperature varies. This data representation is shown in Figure 5. Function coefficients for each propellant/ethanol mixture are summarised in table 2. The goodness of the fits, judged by coefficient of multiple determinations, R^2 is 0.98 and 0.97 for HFA 227 and HFA 134 respectively. The fitted surface for each propellant/ethanol blend is illustrated in Figure 5a-b. Coefficients in $a - f$ in equation 1 are propellant dependent and are tabulated as follows:

Coefficient	a	b	c	d	e	f
HFA134	-57.73	4.325	0.4202	0.01125	-0.005239	-0.000759
HFA227	0.613	-6.784	0.171	-2.666	0.03957	-7.149×10^{-5}

Table 2. Departure function coefficient for HFA134 and HFA227 based formulation

The developed expression is much more compact and easy to handle comparing to the previous similar work[2] which makes it useful to be used in formulation design, numerical models and optimisation tools.

Conclusion

A comprehensive data set of vapour pressure of HFA/ethanol binary mixtures was presented. It is observed that SVP of these mixtures is poorly described by Raoult's law due to interactions between the polar species HFA and ethanol. A new empirical SVP model was proposed to capture nonlinear SVP behaviour and automatically include the saturated vapour pressures of pure HFA and ethanol, which are known to very high accuracy.

1. Clark, A.R. PhD thesis, Loughborough University of Technology, Loughborough, UK, 1991.
2. Mason F, Lewis DA, Gavtash B. Empirical Equations for Predicting the Vapour Pressure of HFA 134a or HFA 227ea Systems containing Ethanol. In: *Drug Delivery to the Lungs 24*. Vol ; 2013:153-156.
3. Gavtash, B., Versteeg HK, Hargrave, G.K., Lewis, D, Church, T., Brambilla, G.: *Linear Instability Sheet Atomisation (LISA) model to predict drplet size issued from a pMDI*. In: ILASS – Europe 2014, 26th Annual Conference on Liquid Atomization and Spray Systems, Sep. 2014, Bremen, Germany.
4. Williams RO, Liu J: *Influence of formulation additives on the vapour pressure of hydroalkane propellants*,International Journal of Pharmaceutics 1998; 166 pp.99-103.
5. Vervaet C, Byron PR: *Drug-surfactant-propellant Interactions in HFA-formulations*, International J. of Pharmaceutics 1999; 186 pp.13- 30.
6. Kleiner, M. Sadowski. G.: *Modelling vapor-liquid equilibria of ethanol + 1,1,1,2,3,3,3,-heptafluoropropane binary mixtures using PC-SAFT*, Fluid Phase Equilibria 2007; 260, pp. 190-194.
7. Smyth, H., Mejia-Millan, E., & Hickey, A.,: *The effect of ethanol on solvency, vapor pressure, and emitted droplet size of solution metered dose inhalers containing HFA1 34a*. In: Respiratory Drug Delivery VIII, pp. 735-738, 2002.
8. Reid, R.C., Prausnitz, J.M., Poling, B.E.,: *The Properties of Gases and Liquids*, McGraw-Hill, Ed. 4, 1987.
9. National Institute of Standards and Technology (NIST),: *NIST Chemistry WebBook*, 2015. [Online]. Available: http://www. http://webbook.nist.gov/chemistry/fluid/ [Accessed: 01-April-2015].