

Determination of Density and Surface Tension in Ethanol and HFA 134a Mixtures

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INTRODUCTION

Recent publications of a transient aerodynamic atomization model have highlighted saturated vapor pressure, density, viscosity and surface tension as key formulation properties governing pressurized metered dose inhaler (pMDI) droplet size [1-3]. Pharmaceutical pMDI formulations frequently use mixtures of propellant and excipients, such as ethanol, but the influence of such co-solvents on the aforementioned properties are not available in the literature. Hence, composition-dependent surface tension and density were experimentally determined for ethanol-HFA 134a mixtures. The expressions developed for density and surface tension are advantageous to understanding transient flows inside the actuator and atomization of pMDI formulations containing ethanol as a co-solvent [2].

MATERIALS AND METHODS

Density

The density of HFA 134a (Mexichem Fluor, Runcorn, UK) and absolute ethanol (Fisher Scientific, Loughborough, UK) mixtures have been determined at $20.2 \pm 0.7^\circ\text{C}$ utilizing a Comes DM density measuring device with Pyrex graduated (± 0.01 mL readability) 46.3 mL inner tube (DH Industries Limited, Laindon, UK). The device (Figure 1) was fitted with a Bepak BK 357 valve (Bepak Limited, King's Lynn, UK) to allow HFA 134a addition using a Pamasol P2016



Figure 1. Comes DM density measuring device with Pyrex graduated 46.3 mL inner tube.

Laboratory Plant (DH Industries Limited, Laindon, UK). A predetermined volume of ethanol was dispensed directly into the inner tube and the mass (± 0.1 g), m_e , recorded by weight difference using a XP6002SDR top pan balance (Mettler Toledo Leicester, UK). Similarly, a pre-determined volume of HFA 134a was filled through the valve and mass, m , quantified by weigh difference (± 0.1 g). All formulations evaluated were mixed by inversion and left to equilibrate for five minutes prior to the determination of the liquid volume, v , using the inner tube graduation marks (± 0.01 mL readability). For each measurement the head space volume, v_h , (calculated as 46.3 mL less the observed liquid volume, v), was multiplied by the density of saturated HFA 134a vapor at 20°C, 0.0278g/mL [4] to give the mass, m_v , of the total HFA 134a vapor within the device (1.041 ± 0.003 g). Air mass trapped within the tube was negligible (<0.055 g). Thus, the mass of HFA 134a within the liquid phase, m_{134a} , was determined as $m - m_v$ (g), giving the density of the liquid phase formulation, ρ , as:

$$\rho = (m_e + m_{134a})/v \quad \text{Equation 1}$$

All formulations are specified as %w/w of the liquid phase components and results presented are an average of duplicate determinations (which were all within $\pm 1\%$).

Surface Tension

A predetermined quantity of ethanol was weighed (0.0001 g readability, Mettler Toledo Leicester, UK) into a pre-tared 15.78 mL aerosol tube (Saint Gobain, UK) containing a new, clean, and dry 0.95mm internal diameter Hirschmann capillary tube (VWR International Limited, Leighton Buzzard, UK). The aerosol tube was crimped with a Bepak BK357 valve and HFA 134a added, through the valve to a predetermined mass (readability 0.0001 g). The duration of the surface tension measurements was considered too short to leach surface active materials from the valve into the propellant/blend. All formulations are specified as %w/w of the liquid phase components and corrected for HFA 134a headspace mass as described in the density section. Surface tension determined at $20.3 \pm 0.7^\circ\text{C}$ by measuring the height of rise, h , of the formulation within the capillary tube using a traveling microscope (readability 0.01mm). Surface tension, γ , was calculated as:

$$\gamma = \frac{\rho g r h}{2} \quad \text{Equation 2}$$

Where, $g = 9.81\text{ms}^{-2}$ and $r = 4.75 \times 10^{-4}$ m, and the glass-liquid contact angle was approximated to 0° . Results presented are an average of duplicate determinations from repeat manufactures of each formulation (which were within $\pm 4\%$).

RESULTS AND DISCUSSION

Figure 2 and Table 1 present the density ($20.2 \pm 0.7^\circ\text{C}$) and surface tension ($20.3 \pm 0.7^\circ\text{C}$) for ethanol and HFA 134a mixtures at 10% w/w intervals. Values determined for the pure components are in excellent agreement (within 0.1% and 2% of published values for density and surface tension measurements respectively [4, 5]).

Analysis of the mixture density results was carried out by considering its reciprocal, the specific volume. If there is no interaction between HFA and ethanol molecules, the volume of the mixture can be assumed to be equal to the sum of the volumes of the constituents. If this assumption is correct, the specific volume V_m of the mixture can be estimated using the following mixing rule:

$$V_m = y_e V_e + (1 - y_e) V_{HFA} \quad \text{Equation 3a}$$

$$\rho_m = 1/V_m \quad \text{Equation 3b}$$

where y_e = mass fraction of ethanol in the mixture, $V_e = 1/\rho_e$ = specific volume of ethanol, $V_{HFA} = 1/\rho_{HFA}$ = specific volume of HFA 134a, and ρ_m = density of the mixture.

The quadratic least-squares fit of the density data in Figure 2 has a sum-of-squares error of 9.9×10^{-4} and a maximum error of 1.4%. The mixing rule (Equation 3a) fits the density data with a sum-of-squares error of 6.1×10^{-5} and a maximum error of 0.5%. This is within the $\pm 1\%$ repeatability of the density measurements.

A similar analysis of the surface tension results was attempted. Based on recommendations in Reid *et al.* [6], the following relationship between surface tension and composition was postulated:

$$\gamma_m^n = x_e \gamma_e^n + (1 - x_e) \gamma_{HFA}^n \quad \text{Equation 4}$$

where x_e = mole fraction of ethanol in the mixture, γ_e = surface tension of ethanol, γ_{HFA} = surface tension of HFA 134a, and γ_m = surface tension of the mixture. Exponent n is adjustable; Reid *et al.* [6] recommend $n = -1$ and $n = -3$. Both values were tried and the latter was found to result in the best model fit to the data, which leads to the following mixing rule for surface tension:

$$\gamma_m^{-3} = x_e \gamma_e^{-3} + (1 - x_e) \gamma_{HFA}^{-3} \quad \text{Equation 5}$$

The quadratic least-squares fit of the surface tension data (Figure 2) has a sum-of-squares error of 3.29 and a maximum error of 7.9%. Equation (5) gives a sum-of-squares error of 1.57 and a maximum error of 5.7%.

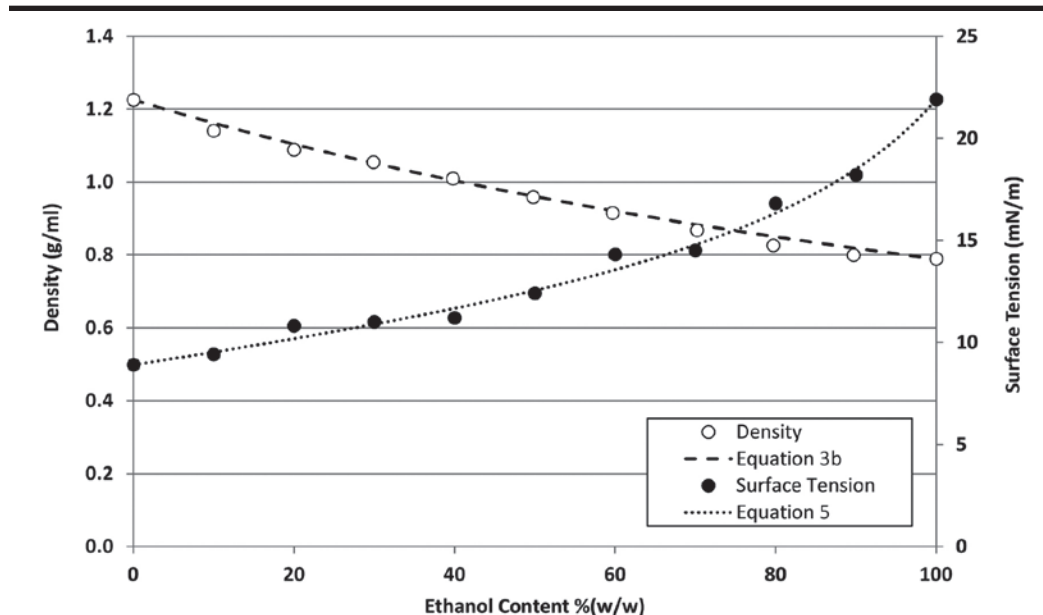


Figure 2. Surface tension ($20.3 \pm 0.7^\circ\text{C}$) and liquid density ($20.2 \pm 0.7^\circ\text{C}$) of ethanol and HFA 134a mixtures.

Table 1.

Liquid density ($20.2 \pm 0.7^\circ\text{C}$) and surface tension ($20.3 \pm 0.7^\circ\text{C}$) of ethanol and HFA 134a mixtures.

| Ethanol %(w/w) | Liquid Density (g/ml) | Ethanol %(w/w) | Surface Tension (mN/m) |
|-------------------|--------------------------|-------------------|---------------------------|
| 0.0 | 1.225 | 0.0 | 8.9 |
| 10.0 | 1.140 | 10.0 | 9.4 |
| 20.0 | 1.088 | 20.0 | 10.8 |
| 29.9 | 1.054 | 30.0 | 11.0 |
| 39.8 | 1.009 | 40.0 | 11.2 |
| 49.8 | 0.958 | 50.0 | 12.4 |
| 59.7 | 0.915 | 60.0 | 14.3 |
| 70.2 | 0.867 | 70.0 | 14.5 |
| 79.7 | 0.826 | 80.0 | 16.8 |
| 89.7 | 0.799 | 90.0 | 18.2 |
| 100.0 | 0.789 | 100.0 | 21.9 |

Finally, it should be noted that Equations 3a, 4, and 5 are model equations. However, while they are not best-fit equations, they manage to describe the behavior of the measured data at least as well as a polynomial best-fit equation. Moreover, Equation 3a involves no adjustable constants and Equation 5 has just one adjustable exponent. Furthermore, the assumed form of these model equations ensures that the density and surface tension of the pure substances are exactly matched with the measured values at $y_e = 0$ and $y_e = 1$. This is a desirable property when data from sources with different levels of confidence are combined (e.g., properties of pure substances known to high accuracy and measurements of mixture properties with higher uncertainty).

CONCLUSIONS

The density ($20.2 \pm 0.7^\circ\text{C}$) and surface tension ($20.3 \pm 0.7^\circ\text{C}$) of ethanol and HFA 134a mixtures have been experimentally determined. Two mixing rules, one for the specific volume of the mixture and one for its surface tension were proposed. These very compact forms managed to capture the behavior of the measured data very efficiently with a minimum number of adjustable parameters.

The expressions found in this work are important for descriptions of internal transient flows within pMDI HFA 134a-ethanol mixtures. The droplet size predicted by the aerodynamic atomization models proposed by Gavtash *et al.* [2, 3] is linearly proportional to surface tension of the mixture. The dependence on liquid density is more complex, but errors in the representation of the density and surface tension could significantly affect the predicted droplet size (estimated error of predicted droplet size up to 20% for ethanol concentration around 10-20% w/w). The resulting theoretical insights into the relationship between droplet size and liquid density and surface tension may also have future benefits through improved control of droplet size in pMDI formulations.

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Notes