Determining measured experimental values of density to aid formulation development of new environmentally friendly propellant mixtures with Ethanol

Kindeva DRUG DELIVERY

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Introduction:

- Currently, propellants HFA 134a and HFA 227 are widely used in pMDIs and have very well-known properties that can be factored into formulation development. However, with the current climate change crisis there has been more emphasis on reducing the contribution inhalers have towards CO_2 emissions.
- Research by Dr Alexander J K Wilkinson et al, estimate that pressurised metered dosage inhalers (pMDIs) are contributing towards 3.9% of the National Health Service's (NHS) overall carbon footprint in the UK. [1]
- Kindeva have been working on multiple projects with greener propellants, HFO 1234ze(E) and HFA 152a to assess their suitability to replace the current HFA 134a and HFA 227 as greener alternatives. The GWP of the propellants in question are summarised in Table 1.

Table 1 GWP of current HFA's compared to HFO 1234ze(E) and HFA 152a

Propellant	Formula	GWP	Density at 21°C (g/mL)
HFA 134a	$C_2F_4H_2$	1300	1.222 [2]
HFA 227	C_3F_7H	2900	1.404 [2]
HFA 152a	$C_2H_4F_2$	140	0.910 [2]
HFO 1234ze (E)	$C_3H_2F_4$	<1	1.176 [2]

- A key property of propellants to consider when formulating pressurised metered dosage inhalers (pMDIs) is density. Density has a direct impact on characteristics of the formulation such as flocculation behaviour of suspensions and calculations to determine exact quantities of each component required.
- Density of pure propellant will deviate from it's true value as liquid excipients such as co-solvents are added, a common example being Ethanol. Historically, the relationship between increase in co-solvent % Ethanol and overall formulation density has been well characterised for HFA 134a and HFA 227.
- However, with the change to greener propellants, these density values need to be determined experimentally.

Aim:

- To assess the effect of increasing levels of Ethanol on liquid density of HFA 152a and HFO 1234ze(E) formulations.
- Improve accuracy of theoretical density determination via experimental values.

Methodology:

- Based on Rob Johnson et al [3].
- Propellant was pressure filled into a DH Industries Density Measuring gauge to a specified quantity in grams and the volume recorded after a period of equilibration.
- For all Ethanol containing formulations, Ethanol was pre-dispensed into the inner glass tube of the Density Measuring Gauge to a pre-determined weight, before immediately sealing and pressurising the gauge.

Figure 1: Density Meter Equipment

- Temperature in the laboratory was controlled and remained at 21°C +/- 1°C for the duration of the experiment.
- Experimental values were measured of HFA 134a and HFA 227 as controls and HFA 152a and HFO 1234ze(E) as the propellants of interest.
- Measurements were taken in duplicate with increasing levels of Ethanol, from 0 to 50 % w/w. These experimental data were plotted as individual values vs Kindeva Model data. Vapour pressure values were taken from the Ref prop database at 21°C. [2]
- Results are presented in Figures 2 to 5.

Results/Discussion:

Table 2: Measured Density Values of HFA 152a and HFO 1234ze(E) with increase of Ethanol

	HFA 152a	HFO 1234ze(E)
Ethanol (% w/w)	Average Measured Density (g/mL)	
0%	0.9173	1.1786
20%	0.8972	1.0764
40%	0.8748	0.9870
50%	0.8594	0.9453

Figure 2: Density of HFA 134a

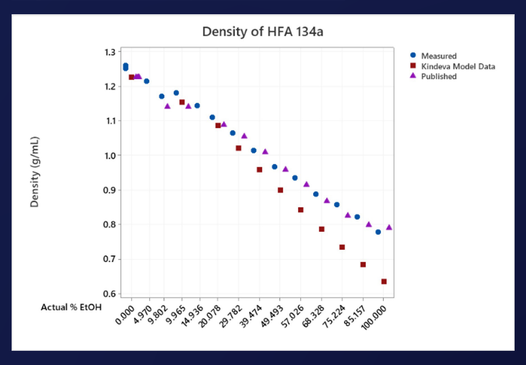


Figure 3: Density of HFA 227

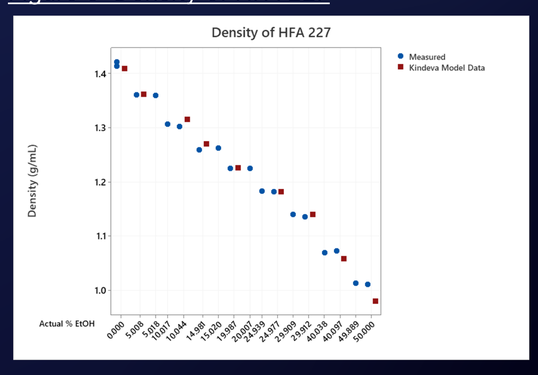


Figure 4: Density of HFA 152a

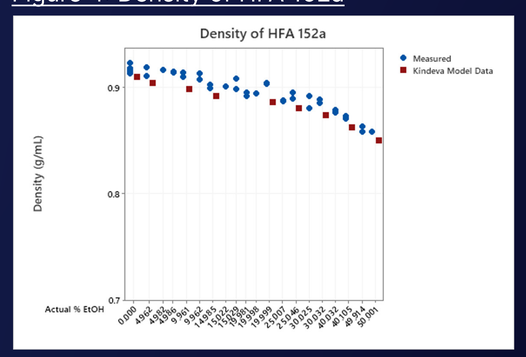
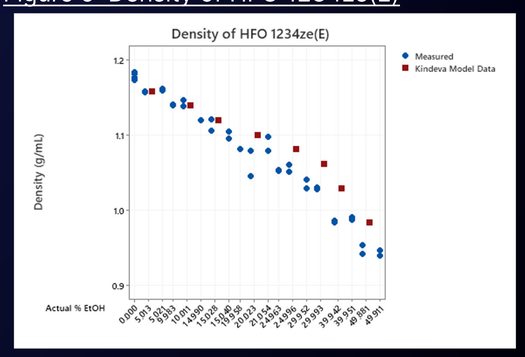


Figure 5: Density of HFO 1234ze(E)



- To verify methodology, published data [3] were plotted against HFA 134a experimentally determined values, which confirmed a strong correlation (r=0.997).
- The historic Kindeva modelled data covering 0 - 20% (w/w) Ethanol with HFA 134a and HFA 227 showed good correlation with experimental data obtained in this study (r=0.998). After 20% Ethanol, the correlation declines.
- In HFA 152a, the density was found to decrease with the addition of Ethnol. Based on the experimentally derived data, a model was determined. Model data and experimental data are closely correlated (r=0.993).
- Kindeva Model Data for HFO 1234ze(E) was not an accurate representation of the experimental values. Therefore, Kindeva are currently working on an alternative model for HFO 1234ze(E).

Conclusion:

- Experimental density values of propellants HFA 152a and HFO 1234ze(E) with increasing levels of Ethanol obtained.
- Increasing Ethanol concentration causes decrease in Density g/mL.
- Historic model was not appropriate for HFA 152a and HFO 1234ze(E).
- Need to re-evaluate new predictive model for HFO 1234ze(E).

References:

[1] Alexander J K Wilkinson, Rory Braggins, Ingeborg Steinbach, James Smith, Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England BMJ Open 2019;9: e028763. doi: 10.1136/bmjopen-2018-028763 (online)
[2] Lemmon, E.W., Bell, I.H., Huber, M.L., McLinden, M.O. NIST Standard Reference Database 23: Reference Fluid Thermodynamic and Transport Properties-REFPROP, Version 10.0, National Institute of Standards and Technology, Standard Reference Data Program, Gaithersburg, 2018. doi: https://doi.org/10.18434/T4/1502528 (online only)
[3] Rob Johnson, Daniel I. Lewis, Paul M. Young, Henk K. Versteeg, Graham Hargrave: Determination of Density and Surface Tension in Ethanol and HFA 134a Mixtures (Article). Respiratory Drug Delivery 2018. (online)

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