

Propellant and formulation properties for next-generation pMDIs: Measurement, representation and prediction

As pMDIs with low global warming potential are introduced and the need for accurate thermophysical property prediction grows, models that use activity coefficient are promising.

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Context

The hydrofluoroalkanes (HFAs) currently used as propellants in pressurized metered dose inhalers (pMDIs) are expected to be phased-out of use. This is due to the Kigali amendment to the Montreal Protocol [1], which targets scheduled reduction of certain fluorinated gases due their high global warming potential (GWP) and impact on climate change. Although in the pharmaceutical industry, the contribution of HFA gases to overall greenhouse gas emissions is small, for pMDI producers, there is a need to avoid increased costs as the supply of specific HFAs becomes reduced and interest grows in decreasing greenhouse gas emissions and their impact on climate change.

Potential replacement propellants include HFA152a and the hydrofluoroolefin HFO1234ze (which has a carbon/carbon double bond). HFA152a is currently being evaluated with respect to a variety of criteria, including patient safety and manufacturing process safety [2]. Its performance as a pMDI aerosol propellant is being predicted by companies and researchers [3, 4].

This is a large undertaking for the industry as a whole. The fundamental thermophysical and aerosol formation properties of pMDI formulations will change when HFA134a and HFA227ea are phased-out. However, if a new propellant is introduced for a current product, it is desirable to achieve very similar aerodynamic particle size distribution (APSD) and

fine particle fraction (FPF), as well as to provide a very similar and satisfactory experience for patients.

Simultaneously, there has been an increase in the use of computational fluid dynamics (CFD) and other predictive modeling tools [5]. For the pharmaceutical industry, crucially, this includes a greater awareness, understanding and availability of specialist CFD that can predict multi-phase flow, with detailed turbulence modeling (for example, Large-Eddy Simulation), cavitation [5] and non-equilibrium phase change [6]. There is also, of course, ever increasing simulation power and access to high performance computing (HPC) that can offer more numerous, faster and more detailed simulations.

In this article, the fundamental thermophysical properties that control the complex internal flow and aerosol formation process in a pMDI will be examined, from the perspective of their measurement, representation, and prediction. Accurate knowledge and understanding of these properties, potentially in comparison with predictive simulation tools, will contribute to the effective development of next-generation pMDI formulation. Activity coefficient models that enable simultaneous description and prediction of important formulation thermophysical properties will also be presented. The performance of these models is demonstrated using existing data for HFA134a/ethanol mixtures, to show their potential application alongside experimental property data collection involving future propellants.

Table 1

Formulation physical properties and characteristics relevant to pMDIs, and the phenomena that are dependent on them

Formulation physical property	Phenomena dependent on this property
Density	Atomization Loss of prime Internal two-phase flow Liquid/Surface interaction
Saturated vapor pressure (SVP)	Atomization Internal two-phase flow Droplet evaporation/Particle drying
Surface tension	Atomization Loss of prime Liquid/Surface interaction
Liquid viscosity	Atomization Liquid/Surface interaction
Thermal conductivity	Temperature reduction Liquid/Surface interaction
Specific heat capacity	Temperature reduction
Mass diffusion coefficients	Canister sealing Bubble growth Droplet evaporation/Particle drying
Enthalpy of vaporization	Temperature reduction Droplet evaporation/Particle drying
Contact angle	Particle cohesion and adhesion

Formulation and aerosol behavior

MDI formulations are a multi-component mixture, including active ingredients (APIs), propellant, co-solvent, excipients and surfactants. The formulations interact with a variety of metal, polymer elastomer materials and coatings used in MDI canister and valve hardware. Additionally, in experimental work, there may be a dummy or placebo API in the mixture, or tracer compounds to facilitate a certain experimental technique. Next-generation formulations, for example containing HFA152a, will have as yet unknown final constituents and composition.

The aerosol performance (e.g., flow rate, aerosol temperature and aerodynamic particle size distribution) of these multi-component solution- and suspension-formulations is influenced strongly by the thermophysical properties of the liquid phase. These properties govern the complex internal flow behavior that is a precursor to atomization and aerosol formation, understanding of which has recently been improved through optical [7] and X-ray phase contrast imaging [8]. Table 1 lists various physical properties and characteristics relevant to pMDIs and the phenomena that are dependent on or controlled by them.

In particular, the formulation saturated vapor pressure (SVP), strongly affected by the addition of ethanol, has great influence in the overall efficiency of atomization and resultant particle or droplet size distribution. It has been observed that the addition of ethanol, which reduces overall formulation SVP, has tended to increase droplet size metrics [3]. However, addition of ethanol has also been noted to stabilize the internal two-phase flow process and result in a lower Sauter Mean Diameter [7].

The properties in Table 1 should be known relatively accurately for a multi-component formulation. This enables comparison of one formulation's specifications against another, either an existing specification with that of a next-generation, or two different versions of the same formulation (e.g., with concentration of ethanol varied). These properties are also entered into empirical equations (e.g., that of Clark [9]), for one-dimensional (1-D) modeling [10] and 3-D CFD modeling. In the latter, multi-component fluid property evaluation is often handled automatically by proprietary industrial software, sometimes using mixing rules designed for ideal mixtures [10]. The properties of multi-component liquids are often not well represented by a simple weighted

average of the pure component properties. This is particularly true of so-called non-ideal liquids, of which ethanol/HFA mixtures are an example. Therefore, obtaining experimental mixture property data is a must.

Furthermore, physical properties are temperature-dependent (and to a lesser extent, pressure-dependent). This is not just important because pMDIs are used in various climates around the world. The pMDI two-phase flow through the metering chamber, into the expansion chamber and then out of the orifice as an aerosol, goes through rapid transient temperature change. Firstly, cooling due to flash evaporation and expansion of the propellant, then heating once most of the propellant has vaporized, leaving behind less volatile or solid components. In addition, the temperature at a fixed location will vary throughout the event, as solid walls reach equilibrium temperature and flow transients settle.

The liquid-phase composition will also change markedly as the dose process occurs, varying both temporally and spatially. Therefore, the liquid properties will vary, impacting the tendency to boil, atomize, form and grow bubbles, etc., as controlled by the properties and processes in Table 1.

Physical properties are typically measured at atmospheric pressure (close to 100 kPa) or at formulation vapor pressure, whichever is greater. The expansion chamber sump pressure inside the actuator reduces during pMDI actuation from a value close to the formulation saturated vapor pressure down towards atmospheric pressure by the end of dosing [3]. The pressure inside the free aerosol is essentially atmospheric.

Therefore, the formulation mixture takes a temperature, pressure and composition trajectory as it is transformed into an aerosol; meaning that properties that control aerosol formation are also varying throughout. The effects of this can be incorporated into CFD and 1-D modeling, which requires knowledge of the temperature-, pressure- and composition-dependence of properties and proper implementation of these in the model.

The models that attempt to predict, for example, the growth of instabilities in liquid surface in the actuator orifice during the atomization process, require that liquid physical properties be evaluated at the conditions in the orifice. For a solution formulation, this may be a liquid that is rich in ethanol and at a cooler than ambient temperature. The predictions from models are therefore only as reliable as the data that goes into them.

Measuring thermophysical properties

Some data already exist: HFA152a was evaluated with respect to many physical properties for consideration as a propellant and a refrigerant during

the CFC to HFA transition in the 1990s [11, 12]. HFO1234ze has been also evaluated as a refrigerant for many applications [13].

Available data from existing work typically relates to pure component properties. However, as discussed, the modeler and designer of a pMDI system needs information about temperature- and composition-dependent formulation mixture properties, with propellant plus ethanol being a key mixture.

Accurate room temperature HFA134a/ethanol mixture properties have been recently obtained for density, surface tension and liquid viscosity [14, 15], across a wide range of mixtures, from pure ethanol to pure HFA134a. These studies used mechanical methods: the height of capillary rise for surface tension and the falling ball method for liquid viscosity. Other methods can be used as well, including, for surface tension, direct force measurements via an immersed rod, ring or plate (e.g., the Wilhelmy plate method); the droplet shape fitting method for suspended or sessile droplets (requiring imaging of the droplet with a camera); or bubble pressure methods. For liquid viscosity, vibrating-wire viscometers or various proprietary rheometry instruments may also be used.

However, such data are required across a wide range of temperatures. Temperature-controlled mechanical measurements are possible using existing instruments, including those described here. Alternatively, an optical test method can be used, which employs a laser-based technique to probe a small volume of formulation fluid held in an optical test cell under well-controlled conditions. Two techniques that achieve this are surface light scattering (SLS) and dynamic light scattering (DLS). Both techniques are non-invasive and highly precise since they rely on photon correlation spectroscopy and are therefore relatively insensitive to noise and fluctuations in signal intensity. The SLS technique can be used for simultaneous measurement of surface tension and liquid viscosity, whereas DLS leads to measurements of mixture mass diffusivity and thermal diffusivity if combined with *in situ* refractive index measurement. Optical and laser-based techniques have advantages in that they are more easily applied at conditions differing from ambient; for example, below 0°C and at several atmospheres of pressure, as needed for pMDI formulation property measurement.

Physical properties of pMDI formulations typically are more strongly influenced by temperature and chemical composition than pressure. However, with a purpose-built optical cell for laser-based measurement, it would be possible to condition fluid mixtures to different pressures if desired.

Specific mixtures that support development of a particular product (e.g., containing active or dummy pharmaceutical ingredients) can rapidly be tested

using either a proprietary instrument or laser-based test system. A range of compositions and temperatures can be tested, and a suitable number of repeat measurements can be made to generate a dataset that can support decision-making or be used as input for a model or model-fitting exercise.

Property modeling: Representation and prediction

Once property data has been measured, or if existing data has been identified, it will then need to be recalled: for comparison of two or more formulations, or as input into a simulation exercise. Of course, this can include the need to evaluate a property at a temperature or composition that was not part of the matrix of experimental conditions. Two families of expressions are typically fitted to experimental data to provide a continuous function of temperature, composition, pressure or other independent variables, to represent the thermophysical property. These are known as empirical (or phenomenological) models and physically-based models. Importantly, any function used must minimize the error between the actual experimental property data and representations of the property by the function. An example of a phenomenological model to represent the SVP of HFA134a/ethanol mixtures across the full composition range and at pMDI relevant temperatures is shown in Figure 1, from reference 16. The normalized SVP is represented by a polynomial in both ethanol mole fraction and temperature with 6 fitted coefficients, which fits closely to the experimental datapoints from that work and provides useful interpolation and extrapolation. However, this empirical expression does not provide any

underlying insight into the behavior of the mixtures and the reason for the departure from ideal behavior. It is also not predictive, in the sense that it could not be generalized to mixtures with additional or alternative components—new experiments would be necessary.

Physically-based models, on the other hand, utilize an expression that incorporates some of the underlying physics and/or chemistry of the mixture to represent the thermophysical property. While these still have fitted parameters that allow the expression to adequately represent experimental data, the values of these parameters can have fundamental physical meaning relating to the theories underpinning them. In addition, these expressions can become predictive if the physically-based model is well-matched to the behavior of the mixture. This means that it still gives reliable physical property values if there is little or no experimental data for a mixture at a condition of interest.

In engineering CFD packages, properties of mixtures will typically be calculated from simple mixing rules or empirical relationships [10]. These may not be based on any experimental evidence, and if they are, they will only be strictly valid for the range of experimental conditions.

Saturated vapor pressure (SVP)

As previously discussed, the SVP is one of the most important properties of a formulation of which to have good knowledge and understanding. If a liquid mixture or solution contains molecules that do not interact, then a suitable expression for the mixture SVP is Raoult's law, given in Equation 1:

$$SVP = \sum_i x_i P_{vi} \quad (1)$$

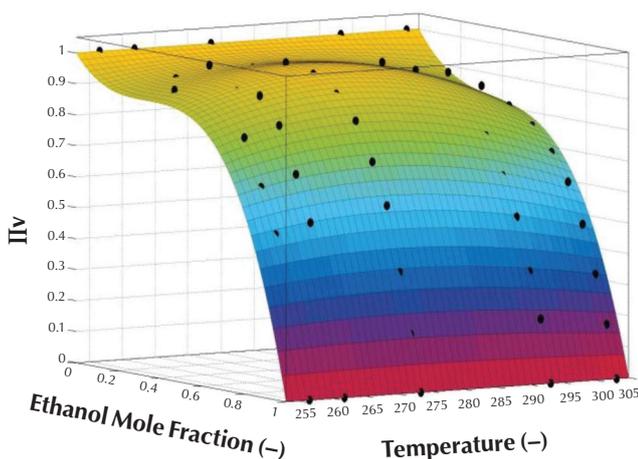
in which x_i is the mole fraction of species i in the mixture and P_{vi} is the SVP of the pure species i at the temperature of interest. For solution formulations containing HFAs and ethanol, Equation 1 is not suitable because it would predict a flat, inclined surface, rather than a curved surface, for Figure 1. Instead, the modified Raoult's law is needed, given in Equation 2:

$$SVP = \sum_i \gamma_i x_i P_{vi} \quad (2)$$

where γ_i is the activity coefficient for species i in the mixture. This is now an appropriate physically-based model, since it is based on the thermodynamic equilibrium between the vapor and liquid phases in a two-phase system, under the simplifications of an ideal vapor phase and an incompressible liquid phase [17] and the activity coefficients have physical meaning beyond the scope of Equation 2.

Figure 1

Normalized saturated vapor pressure for HFA134a/ethanol mixtures: Experimental data points and empirical surface fitted to those. From reference 16, used with permission.



Activity coefficients provide a thermodynamic basis for molecular interactions that cause deviation in mixture behavior and properties in liquid systems, and vapor/liquid, liquid/liquid and solid/liquid systems. They are related to the excess Gibbs free energy G_E generated when a solution is created, due to any molecular interactions, over and above that of an ideal, non-interacting mixture:

$$RT \ln \gamma_i = \frac{\partial G_E}{\partial n_i} \quad (3)$$

where R is the universal gas constant, T the mixture temperature, and n_i the number of moles of species in the mixture. Therefore, activity coefficient values greater than 1 indicate that the presence of molecules of species i causes repulsive interaction in the mixture, whereas a value less than 1 indicates these molecules tend to attract the other molecules in the mixture (leading to $G_E < 0$).

Various models exist to describe activity coefficients as well as to fit SVP or vapor/liquid equilibrium experimental data. In this article, UNIQUAC (Universal Quasi-chemical Activity Coefficients) and UNIFAC (UNIQUAC Functional-group Activity Coefficients) are used, which are described in more detail in reference 18. Both models use properties of the functional groups present in mixture components. UNIQUAC only requires two parameters per pair of components in the mixture and can accurately represent activity coefficients and SVP data, even for highly non-ideal mixtures (compared to the 6 coefficients required for the fit in Figure 1). UNIFAC is a predictive model that uses pure component properties only and a set of predetermined functional group interaction parameters, which are available for some HFA/ethanol mixtures [18].

Other thermophysical properties

Since molecular interactions also control other liquid mixture and solution properties, activity coefficients can be successfully used to represent or predict those properties. For example, the same numerical UNIQUAC parameters can be used in a modified model, suitable for liquid viscosity prediction, known as UNIMOD (Modified UNIQUAC) [19]. Calculated activity coefficients (from any model) can be used to determine mixture surface tension, with the Sprow and Prausnitz method [20], and liquid mass diffusion coefficients, using methods discussed in detail in reference 21.

Simultaneous representation or estimation of all these properties is possible, either by using the activity coefficients estimated from SVP experimental data, or by incorporating all the data and physical property models into an overall thermodynamic framework—as shown in recent papers presented at RDD2021 [18] and DDL2020 [22]. In addition,

liquid mixture miscibility and solid phase solubility can be estimated using the same framework, potentially with modified versions of UNIFAC and UNIQUAC models described in reference 17.

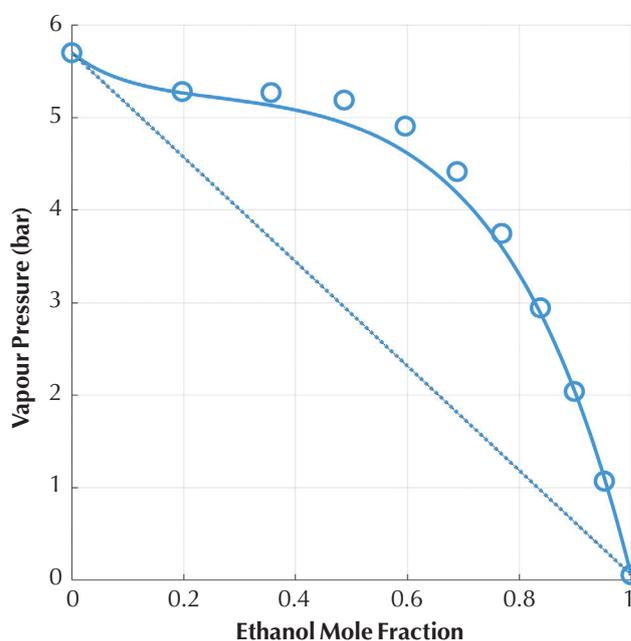
Sample formulation property results

Next, sample results are presented that demonstrate the property framework approach for SVP, surface tension and viscosity, to show the quality of representation of the data and, in the case of viscosity, the predictive power of the approach. Experimental data from references 14, 15 and 16 was used, and the UNIFAC and UNIQUAC model parameters were selected to optimally fit these models to these data in a least squares sense.

To demonstrate the need for an expression for SVP that incorporates the non-ideal behavior, Figure 2 compares the result of an HFA134a/ethanol mixture SVP from Raoult's law (Equation 1)—the dotted straight line—with that from the modified Raoult's law (Equation 2) using the UNIFAC model for activity coefficients—the solid line. The UNIFAC predetermined interaction parameters for the molecules HFA134a and ethanol are presented in full in reference 18, having been calculated from both SVP and surface tension experimental data. These can now be used for SVP prediction at alternate temperatures or with additional formulation constituents present, without further experimental data.

Figure 2

Saturated vapor pressure (SVP) measurement [16] and UNIFAC prediction for HFA134a/ethanol mixtures, at 20.0°C.



The ability of the UNIQUAC model to predict physical property data is shown in Figure 3, where UNIQUAC parameters previously generated solely from fitting to experimental SVP data [16] are used directly in the UNIMOD model for viscosity. The experimental data has a maximum of 2.3% relative standard deviation, from 10 repeats, and the maximum deviation of the UNIMOD prediction from the experimental data is 4.9%, with a root mean square deviation of 3.5%.

Figure 4 shows the effect of incorporating both SVP data into the fitting process (as standard) and desired thermophysical property data (here, surface tension is shown). When the parameters are solely from the SVP, the fit is not satisfactory, with the root mean square deviation at 7.5%. When the surface tension data was incorporated into the fitting process, this was reduced to 5%. This fitting approach was then used to generate all the data presented in reference 18, to ensure a better representation of the surface tension data. There was no adverse effect on the quality of the prediction of the viscosity.

The fitted expressions that generated the examples shown in this article could readily be used in conjunction with 1-D modeling or CFD modeling to provide predictions of SVP, surface tension and liquid viscosity at all temperature and composition conditions encountered in such a model.

Conclusion and next steps

The need for accurate thermophysical property prediction for diverse formulation mixtures is expected to grow, as next-generation formulations with low global warming potential (GWP) are introduced and as usage of predictive simulation increases during pMDI development. This need can be supported by appropriate experimental measurement campaigns for formulation mixtures, spanning the full range of temperature, pressure and composition that will be encountered by pMDI internal flows and aerosols.

A promising set of methods for representing and predicting many of these mixture thermophysical properties is a framework of physically-based models that use activity coefficients to describe non-ideal molecular interactions in the liquid phase, which can affect such properties. These models are particularly useful for solution formulations containing ethanol.

Future work would require current and new experimental data for new propellants, e.g., HFA152a, with ethanol and other important constituents, to generate activity coefficient models that describe the physical property behavior of these mixtures. This may involve searching for the most suitable activity coefficient model that best describes the measurement data and underlying physics and chemistry. This ultimately could lead to a property prediction tool that can be integrated, with confidence, in one-dimensional and three-dimensional CFD simulations, including usage at conditions outside the range of existing experimental data.

Figure 3

Liquid viscosity measurement [15] and UNIMOD prediction (using UNIQUAC parameters) for HFA134a/ethanol mixtures, at 20.4°C.

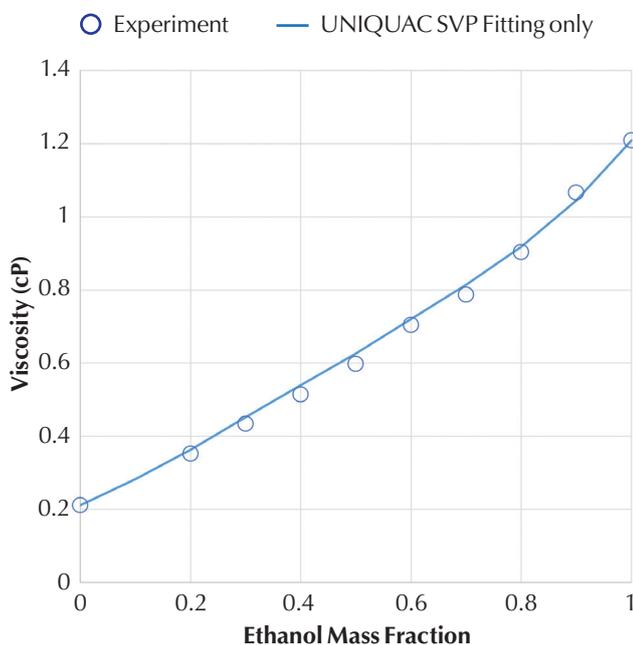
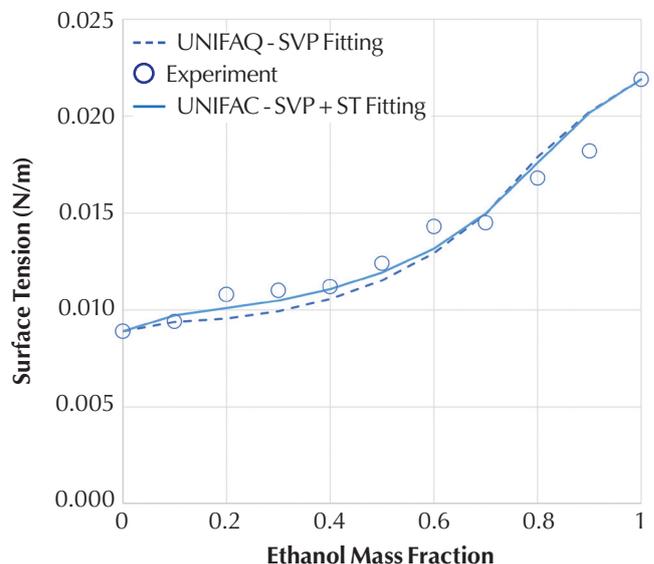


Figure 4

Surface tension measurement [14] and UNIFAC prediction for HFA134a/ethanol mixtures, at 20.3°C. Parameters were generated solely from SVP data or from SVP and surface tension data.



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