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A Thermodynamic Framework to Predict Thermophysical Properties that Control pMDI Aerosol Generation

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SUMMARY

Activity coefficient models are introduced to provide a thermodynamic framework for simultaneously predicting multiple thermophysical properties of relevance to pressurized metered dose inhaler (pMDI) aerosol formation. The UNIFAC and UNIQUAC models are discussed in the context of calculation of saturated vapor pressure, surface tension and liquid viscosity using molecule and functional group interaction parameters. New interaction parameters are generated and presented for HFA134a/ethanol mixtures using experimental data for saturated vapor pressure, surface tension and viscosity. The UNIFAC model is shown to give adequate predictivity and can be used when no experimental data is available. Better predictions were obtained with the UNIQUAC model, which is most useful when high-quality measurement data is obtained. The use of these models for flexible

thermophysical property prediction of low-GWP formulations is discussed, with potential developments to improve model fits and better utilize the experimental data.

INTRODUCTION

Hydrofluoroalkanes (HFA) HFA134a and HFA227ea are currently used as propellants in pressurized metered dose inhalers (pMDIs). These propellants have high global warming potentials (GWP) [1] and are scheduled to be phased down under the Kigali Amendment to the Montreal Protocol [2]. This has stimulated development of new pMDI products based on lower GWP propellants including HFA152a [1] and the hydrofluoroolefin (HFO) HFO1234ze(E) [3].

Ideally, new low-GWP pMDI products will demonstrate equivalent aerosol performance to the original HFA-based products by matching the aerodynamic particle size distribution (APSD). During the transition from chlorofluorocarbon (CFC) to HFA propellants, reformulation was required using non-volatile excipients such as ethanol, polyethylene glycol (PEG) etc. The replacement of HFAs with low-GWP propellants may also involve formulation changes. An understanding of the thermophysical properties of propellant-excipient mixtures is essential to predict complex phenomena that occur during aerosol formation, such as flash boiling, atomization, droplet break-up and collision, bubble growth and coalescence [4].

The pMDI formulation expands as it flows through the actuator and exits the spray orifice, experiencing rapid changes of pressure and temperature. Differential evaporation of formulation constituents will cause composition changes. To predict aerosol formation accurately, formulation thermophysical properties, such as saturated vapor pressure, surface tension and viscosity, are needed across a range of compositions, temperatures, and pressures. This is challenging, because pMDI formulations are non-ideal multicomponent liquids: strong molecular interactions between hydrofluorocarbons (HFCs) (including HFAs and HFOs) and ethanol and

other polar molecules make simple averaging rules for physical properties inaccurate. An important aspect of next-generation propellant research will be the collation of high-precision physical property datasets [5-16], to inform formulation design and validate aerosol formation models. A rational framework to minimize the effort necessary to make confident predictions of the thermophysical properties that are most influential in aerosol formation could potentially facilitate new product development.

This article introduces the UNIFAC (UNIQUE Functional-group Activity Coefficients) and UNIQUAC (UNIVERSAL QUASI-Chemical Activity Coefficients) models for the computation of molecular interactions present in a mixture. UNIFAC and UNIQUAC provide a general framework based on pure component properties and pre-generated interaction parameters to predict vapor-liquid equilibrium (VLE) and mixture properties. The techniques have been successfully applied in the automotive and petrochemical industry where they are used to predict the properties of complex hydrocarbon mixtures. Here, we explain the basis of UNIFAC and UNIQUAC and demonstrate the usefulness of these techniques in the context of respiratory drug delivery using HFA134a/ethanol mixtures as an illustrative example.

THEORETICAL BACKGROUND – ACTIVITY COEFFICIENTS MODELS

The saturated vapor pressure (SVP) and VLE of a non-ideal liquid mixture, such as HFA/ethanol, is poorly predicted by Raoult's Law [14,17]. Improved prediction is possible at pressure and temperature conditions relevant to pMDI operation, using a modified Raoult's Law:

$$y_i p_{vap} = \gamma_i x_i p_{vap,i} \quad (1)$$

where γ_i is the activity coefficient for species i ; x_i , y_i are the liquid and vapor mole fraction respectively for species i ; $p_{vap,i}$ is the pure component SVP of species i ; and p_{vap} is the total mixture SVP. Activity coefficients depend on temperature, pressure, and composition so that Equation (1) accurately describes the experimental VLE.

The activity coefficient accounts for the presence of repulsive or attractive intermolecular forces between formulation constituents. Models of varying complexity are available to describe the temperature-, pressure- and composition-dependence of activity coefficients [18]. Two models that are sufficiently general to be appropriate for pharmaceutical formulations are UNIFAC [19] and UNIQUAC [20], which are outlined in Figure 1. A preliminary application of UNIFAC to HFA134a/ethanol mixtures has been described [21]. In UNIFAC, activity coefficients γ_i are modelled via the interaction between common organic functional groups present in molecules in the liquid phase. The functional groups are classified by molecular interaction behavior. For example, for the system HFA134a/ethanol, HFA134a contains $-\text{CH}_2\text{F}$ and $-\text{CF}_3$ groups; ethanol contains $-\text{CH}_3$, $-\text{CH}_2-$, and $-\text{OH}$ groups, with $-\text{CH}_3$ and $-\text{CH}_2-$ grouped together.

The activity coefficient γ_i is a sum of combinatorial and residual contributions. The former are identical for UNIFAC and UNIQUAC, containing van der Waals group volume (R_k) and surface area (Q_k) parameters, which are found in [18]. Parameter $v_k^{(i)}$ denotes the number of occurrences of functional group k in species i . The residual contributions differ for the two models. The UNIFAC model can be used when there is no pre-existing VLE data of a new formulation mixture at all. A

standard set of predetermined Interaction Parameters a_{mn} quantify interaction between the m^{th} and n^{th} functional groups present in the liquid phase. Their values were determined in the original work [19] and subsequently optimized [22,23] using UNIFAC predictions of large sets of VLE data.

Activity Coefficient for species i : $\gamma_i = \exp(\ln \gamma_i^{\text{Comb}} + \ln \gamma_i^{\text{Res}})$

Combinatorial component: $\ln \gamma_i^{\text{Comb}} = \ln \frac{\phi_i}{\Phi_i} + \frac{z}{2} \ln \frac{\Phi_i}{\phi_i} + \frac{\phi_i}{\Phi_i} \sigma_{ii}$

Group segment fraction: $\Phi_i = \frac{\sum_k \sigma_{ik} \nu_k}{\sum_k \sigma_{ik} \nu_k}$, Group surface area fraction: $\phi_i = \frac{\sum_k \sigma_{ik} \nu_k}{\sum_k \sigma_{ik} \nu_k}$

Group volume and surface area in species i : $\nu_k = \sigma_{ik} \nu_k$, $\sigma_{ik} = \sigma_{ik}$

Molecule size parameter: $z = \frac{\sum_k \nu_k}{\nu} - \nu - 1$ Coordination Number: $z = 10$

| | |
|---|---|
| <p>UNIFAC Residual component</p> $\ln \gamma_i^{\text{Res}} = \sum_{\text{All Groups}} \nu_k \ln \Gamma_{ik} - \ln \Gamma_{ii}$ $\ln \Gamma_{ik} = \nu_k \ln \left[1 - \frac{\sum_{m,n} \nu_m \nu_n \Psi_{mn}}{\sum_{m,n} \nu_m \nu_n} \right]$ $\Psi_{mn} = \exp \left[- \frac{a_{mn}}{\nu_m} \right]$ | <p>UNIQUAC Residual component</p> $\ln \gamma_i^{\text{Res}} = \sum_{\text{All Groups}} \nu_k \ln \Gamma_{ik} - \ln \Gamma_{ii}$ $\ln \Gamma_{ik} = \nu_k \ln \left[1 - \frac{\sum_{m,n} \nu_m \nu_n \tau_{mn}}{\sum_{m,n} \nu_m \nu_n} \right]$ |
|---|---|

Figure 1: Equations describing the UNIFAC and UNIQUAC models

Kleiber [23] carried out a program of work on liquid mixtures containing HFCs. HFC functional group sub-divisions in UNIFAC were refined based on electronegativity and on case-by-case observation of the quality of fit to data. This generated a set of new a_{mn} to contribute to the UNIFAC model with relevance to pMDI propellant mixtures. The behavior of the HFA152a molecule was found sufficiently different from other HFAs for Kleiber to have placed it in its own group.

The UNIQUAC model is used when partial VLE (or SVP) data exists for the mixture in question; or, at least, for all binary pairs of constituents. Best fits to these data are used to obtain the interaction coefficients τ_{ij} of the UNIQUAC residual contribution. The model often gives better predictions of SVP than UNIFAC, since the calculated γ_i are based on experimental data of the mixture itself. Computational time for UNIQUAC fitting is much shorter but parameters can only be used for a specific liquid system. Other liquid properties also depend on mutual interactions between the chemical species that can be described in terms of activity coefficients. In this work, mixture surface tension σ_m is predicted using a method outlined by Sprow and Prausnitz and described in Equation 2 [24]:

$$\sigma_m = \sigma_i + \frac{RT}{A_i} \ln \ln \frac{x_i^\sigma \gamma_i^\sigma}{x_i \gamma_i}, \quad (2)$$

where R is the universal gas constant and T is the absolute temperature. With N species in a mixture, there are N equations and N unknowns x_i^σ representing the surface composition of each species. The equations are solved iteratively, with constraint $\sum_i x_i^\sigma = 1$. The surface activity coefficients γ_i^σ are calculated using x_i^σ . The parameter A_i is surface partial molar area, estimated from methods in [18] and [25].

Liquid viscosity is predicted in this work using the UNIMOD [26] and GC-UNIMOD [27] methods. UNIMOD directly uses the τ_{ij} parameters output from the UNIQUAC model, GC-UNIMOD directly uses the a_{mn} parameters output from the UNIFAC model.

UNIFAC and UNIQUAC model fitting was performed for the system HFA134a/ethanol, across existing vapor pressure and surface tension datasets shown in Table 1, using the equations in Figure 1. Vapor pressure was measured [17] directly from canister headspace to a precision of 0.05 bar with a diaphragm pressure gauge, for mixtures with 10 – 90% w/w ethanol. To represent the range of conditions encountered during formulation flow through a pMDI, low and high canister temperatures were created using an ice bath and a calibrated environmental chamber. Surface tension was measured [28] for mixtures with 10 – 90% w/w ethanol by a capillary rise method at $20.3 \pm 0.7^\circ\text{C}$, with repeatability within 4% and pure component measurements within 2% of published values. Liquid viscosity was measured [29] using a falling sphere inclined viscometer, for 20 – 90% w/w ethanol at $20.4 \pm 1.2^\circ\text{C}$, with repeatability within 2.3% and pure component measurements within 1.2% of published values.

Table 1: Experimental data for UNIFAC and UNIQUAC parameter generation

| Physical Property | Actual Temperatures Investigated ($^\circ\text{C}$) | Ethanol Weight Fractions Investigated | Source |
|---------------------------------|---|---------------------------------------|--------|
| Vapor Pressure, $p_{vap,Exp}$ | -16.6, -11.3, 0.3, 20.0, 30.0 | 0 – 100%, 10% intervals | [17] |
| Surface Tension, σ_{Exp} | 20.3 | 0 – 100%, 10% intervals | [28] |
| Viscosity, μ_{Exp} | 20.4 | 0%, 20 – 100%, 10% intervals | [29] |

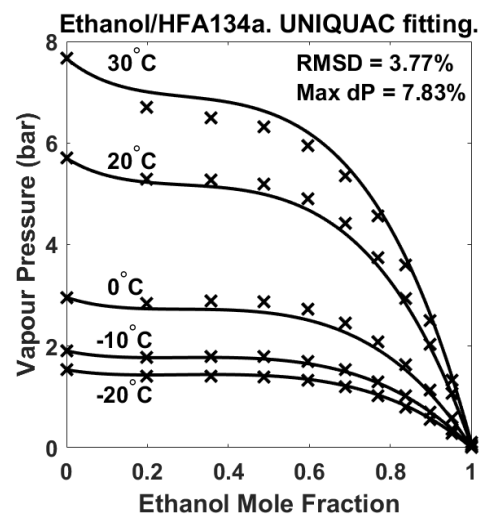
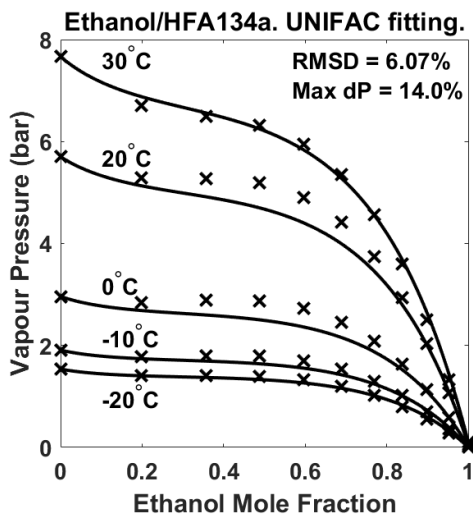
A least squares optimization was used to minimize the sum of squares of the normalized deviation between experimental and fitted datapoints. Equal weighting was used for SVP and surface tension datapoints. A satisfactory viscosity data fit was achieved without inclusion of viscosity datapoints in the optimization. The final UNIFAC interaction parameters between the m^{th} and the n^{th} group are given in

Table 2; the UNIQUAC parameters are $\tau_{12} = 2409.9$, $\tau_{21} = -132.3$, component 1 being HFA134a. Figure 2 shows experimental and fitted data for each property, for UNIQUAC and UNIFAC models. The uncertainty of the data fitting is shown in Figure 2 via root-mean-square deviation (RMSD) calculated as

$$RMSD = \sqrt{\frac{1}{N} \sum_i \frac{(P_{i,Exp} - P_{i,Calc})^2}{P_{i,Exp}^2}}$$
 and maximum relative error.

Table 2: UNIFAC interaction parameters generated in this study, using Kleiber's group sets [23]. Existing data in *italic* [22,23], data from this work in **bold**.

| | | Group n | | | |
|------------|-------------------------|-----------------------|---------------|-----------------------|-------------------------|
| a_{mn} | | CH _n group | OH group | CF ₃ group | CH ₂ F group |
| Group m | CH _n group | 0 | 986.50 | 33.51 | 134.38 |
| | OH group | 156.4 | 0 | 11.95 | 531.28 |
| | CF ₃ group | 87.26 | 845.06 | 0 | 245.25 |
| | CH ₂ F group | 35.69 | 441.36 | -11.44 | 0 |



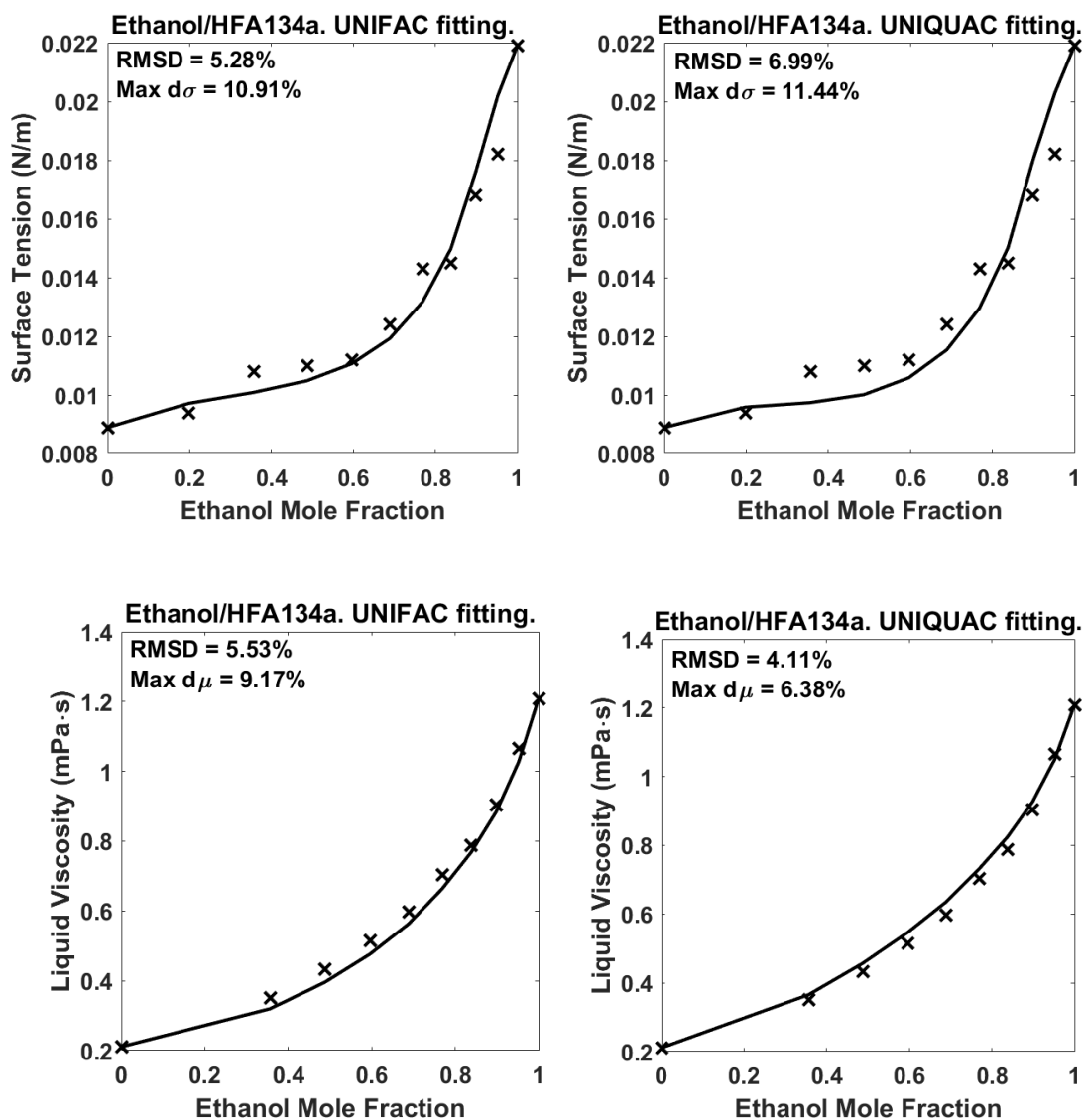


Figure 2: Data fit for UNIFAC model (left) and UNIQUAC model (right) with relative RMSD and maximum relative error

The results of Figure 2 demonstrate the ability of activity coefficient models to capture the non-ideal behavior of HFA/ethanol mixtures. For SVP predictions, the departure from Raoult's Law is represented across the range of temperatures relevant for pMDIs, as well as the inflection point and local maximum in SVP at intermediate ethanol content. The largest relative errors were observed at close to 0.6 ethanol mole fraction for UNIQUAC and at the highest ethanol mole fractions for UNIFAC.

The nonlinear trend of surface tension and viscosity with ethanol content is captured well. The surface tension fit is satisfactory. Improvement might be sought by refitting the parameter A_i from Equation (2) for pMDI formulation mixtures, which were not included in the original study [25]. The maximum deviations and RMSD for viscosity were similar in magnitude to the data fit from tuned phenomenological models in [29]. UNIFAC, or UNIQUAC in contrast, can represent these physical properties with one set of parameters, without the need to select from different mixing rules for each property. As anticipated, the UNIQUAC model gave a closer fit to experimental data for SVP and viscosity in comparison to UNIFAC but a poorer fit to the surface tension data.

Ordinarily, vapor composition y_i or activity coefficients γ_i would be included in the fitting function [23,30]. It would be preferable to predict y_i or γ_i accurately as well as p_{vap} because thermophysical properties predicted under the same framework also use γ_i ; see Equation (2). Considering Equation (1), it is possible to obtain an accurate fit for p_{vap} with less accurate values obtained for y_i or γ_i . It is recommended therefore in future experimental studies that y_i be measured alongside vapor pressures, to prevent errors in thermophysical property prediction.

CONCLUSIONS

Theoretical approaches to predict thermophysical properties of pMDI formulations were not widely used during the 1990's CFC-HFA transition. Differences discovered in the properties of these superficially similar classes of propellants required the development of new technology platforms including solution formulations. Facing the transition to products with low-GWP propellants, it may be useful to be able to

predict the effect of formulation composition on aerosol formation, via SVP, surface tension and viscosity.

The UNIFAC and UNIQUAC models provide physically-based capability by modelling interactions between the key functional groups of liquid formulation constituents. Future work is needed to inform revision of the functional group classifications to enable accurate prediction of properties known to influence pMDI aerosol formation.

The present work has shown how SVP, surface tension and viscosity of HFA/ethanol mixtures can be predicted with 5-10% accuracy across a range of compositions and temperatures using a modest set of experimental data. Once interaction parameters are generated, the UNIFAC model finds greatest use to predict properties outside of the range of existing experimental data, for example, at alternative temperature conditions or with multiple constituents. The UNIQUAC model provides a more accurate prediction where high-quality experimental data exists. The semi-empirical nature of the UNIFAC/UNIQUAC framework provides a flexible route to maximize the knowledge of thermophysical properties from programs of experimental work on novel low-GWP propellant formulations.

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