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Measurement and correlation of solute solubility in HFA-134a/ethanol systems

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ABSTRACT

The goals of this study were to determine the solubility values of solid organic solutes in pure HFA-134a and in HFA-134a/ethanol cosolvent systems (0–20%, w/w), and to investigate the relationship between these solubilities and a solute's physico-chemical properties. A direct inject on-line HPLC method was used to determine the solubility of 21 solutes in HFA-134a/ethanol. The samples were allowed to equilibrate for at least 48 h. The filtered sample was injected directly on an analytical HPLC column through a manual injector interface, and analyzed at an appropriate solute wavelength via HPLC. The solutes display diverse physico-chemical properties and yielded solubility values that ranged over four orders of magnitude. In general, a linear–linear solubility relationship was observed as the fraction of ethanol increased. The effects on solubilization ranged from 1.3 to 99.4 times when 20% (w/w) ethanol was introduced, relative to pure HFA-134a. A regression equation utilizing a solute's hydrogen bonding potential resulted in a significant correlation to the slope obtained from a linear model for solubility in HFA-134a with 0–20% (w/w) ethanol, and may be useful for pre-formulation studies.

1. Introduction

The signing of the Montreal Protocol in 1988 resulted in the application of hydrofluoroalkanes (HFAs) as replacements for the ozone depleting chlorofluorocarbon (CFC) propellants (FDA, 21 CFR (2), 2002). One of the most important medical applications of HFAs is in metered dose inhalers (MDIs), a drug delivery device for treatment of lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD). The utilization of HFA propellants in environmentally friendly medication devices has been successful. However, the solubility of some polar and non-polar compounds in HFA-134a is very low, which has become an obstacle for formulation development.

HFA-134a is modestly non-polar (log *P*: 1.1), and has been found to be a poor solvent for polar and even most non-polar organic compounds. Therefore, a cosolvent may be considered for enhancing the solubility of organic compounds in HFAs. Ethanol is widely used as an excipient in pharmaceutical formulations. It is miscible with HFA propellants and has been successfully utilized as a solubilizing agent for the currently marketed solution products, QVAR® (beclomethasone dipropionate) and Aerospan®-HFA (flunisolide). Conversely, the products Proventil®-HFA (albuterol sulfate) and Xopenex®-HFA (levalbuterol tartrate) are stable suspension formulations that also contain ethanol.

A relationship between solubility and fraction cosolvent has previously been reported by Yalkowsky et al. (1972), who presented the classic log-linear relationship for drug solubility in binary aqueous systems. The accuracy of the log-linear model has been proven for many drugs and cosolvents, and the simplicity of the model reflects its utility (Yalkowsky, 1999; Yalkowsky et al., 1976; Li and Yalkowsky, 1998; Yalkowsky and Roseman, 1981). To date, no such relationship has been shown for HFA-134a systems, partly due to the lack of published solubility data.

The effect that ethanol has on product performance when introduced as a cosolvent in HFA-134a based MDIs has been documented by Gupta et al. (2003). They showed that the 'effective solubility' defined as the product of the drug solubility multiplied by the respirable fraction (fine particle mass less than 4.7 μm), had diminishing returns as ethanol concentration increased. The benefit of an increase in drug solubility above 10% ethanol is offset by the decreased respirable fraction (reduced product performance). As a result, the net 'effective solubility' plateaus between ethanol concentrations of 10% and 20% (w/w) (Gupta et al., 2003). Therefore, the practical limitations of cosolvent concentration, as evaluated in this research, are between 0% and 20% (w/w) ethanol.

The objective of this study was to determine the solubility of various solutes in HFA-134a and HFA-134a with ethanol as a cosolvent. The resulting data was evaluated and a relationship between the

Abbreviations: HFA, hydrofluoroalkane; HPLC, high performance liquid chromatography; CFC, chlorofluorocarbon; MDI, metered dose inhaler; COPD, chronic obstructive pulmonary disease; AAE, average absolute error; σ, solubilization power.

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Table 1
Table of 21 solutes used for experimental studies and the respective physical properties

No.	Compound	mp (°C)	log *P*[a]	Molar volume[b] (mole/cm^3)
1	1-Nitronaphthalene[c]	55.0	3.18	143.4
2	2-Naphthyl acetate[c]	68.0	3.43	162.9
3	2-Methoxynaphthalene[c]	72.0	3.36	148.7
4	Naphthalene[c]	80.6	3.45	147.6
5	Phenanthrene[c]	99.5	4.49	199.0
6	2-Naphthol[c]	122.0	2.71	121.4
7	Benzoic acid[c]	122,4	1.88	99.9
8	Progesterone[c]	129.0	4.04	278.3
9	1-Naphthylacetic acid[c]	130.0	2.74	156.0
10	Cholesterol[c]	146.0	9.85	308.1
11	Dehydrocholesterol[c]	149.0	9.50	278.3
12	1-Naphthoic acid[c]	158.0	3.13	139.9
13	Salicylic acid[d]	159.0	2.06	90.9
14	DIM (3,3-diindolylmethane)[d]	164.5	4.67	184.5
15	4-Acetamidoacetophenone[c]	172.0	1.24	372.7
16	Albuterol[e]	185.0	0.11	180.4
17	Anthracene[c]	217.5	4.49	197.0
18	Prednisone[c]	236.0	1.62	250.0
19	Caffeine[c]	238.0	−0.13	105.2
20	Theophylline[c]	273.0	−0.17	160.5
21	Carbendazim[c]	326.0	1.52	120.4

[a] log *P* obtained from ACD lab.
[b] Molar volume calculated using Fedors method (1974).
[c] Sigma–Aldrich (St. Louis, MO).
[d] LKT Laboratories (St. Paul, MN).
[e] Byron Chemical Co. (Long Island, NY).

solubilization efficiency of HFA-134a/ethanol cosolvent systems and the physico-chemical properties of the solutes was determined.

2. Materials and methods

2.1. Materials

Twenty-one solid solutes were selected and purchased from Sigma–Aldrich (St. Louis, MO), LKT Laboratories (St. Paul, MN) and Byron Chemical Co. (Long Island, NY) as shown in Table 1. The propellant 1,1,1,2-tetrafluoroethane (Genetron 134a) was purchased from Honeywell (Morristown, NJ) and the ethanol (200 proof) was purchased from AAPER Alcohol and Chemical Co. (Shelbyville, KY).

2.2. Method

The solubility of 21 solid solutes in HFA-134a and HFA-134a/ethanol was determined using a previously published method (Gupta and Myrdal, 2004a,b, 2005). Solute and cosolvent were placed into safety coated glass MDI vials (RPI international, Mt. Prospect, IL) and crimped with continuous valves (3 M Drug Delivery Systems, St. Paul, MN) using a small scale bottle crimper (model #3000B, Aerotech Laboratory Equipment Company, Maryland, NY). HFA-134a propellant was pressure filled through the valve using a pressure burette (series 3SB Pressure Filler; Aerotech Laboratory Equipment Company). After equilibration for at least 48 h, the filtered sample was injected directly on an analytical HPLC column through a manual injector interface, and analyzed at an appropriate solute wavelength via HPLC.

2.3. Equipment

The instrumentation setup consisted of a Waters 2695 Separations module (Waters, Milford, MA) coupled with a Waters 2487 dual wavelength absorbance detector. The Waters 2695 Separations module was connected with a Rheodyne model 7725 manual sample injector (Rheodyne, L.P., Rohnert Park, CA). The sample loop overflow tubing of the manual injector was interfaced with a pressure regulator (Amtek U.S. Gauge Division, Sellersville, PA) and an adjustable backpressure regulator (Alltech Associates Inc., Deerfield, IL). Ultraviolet detection was performed at appropriate wavelengths and quantitation was conducted based on peak area.

2.4. Multiple linear regression (MLR)

Multiple linear regression (MLR) software (MedCalc Statistical Software, v. 7.4.0) was used to investigate mathematical correlations between physico-chemical properties and the solubility in HFA-134a/ethanol systems. The physico-chemical properties that were examined included melting point, log *P* (ACD/Labs package, release 5.0, Advanced Chemistry Development Inc., Toronto, Ont., Canada), molar volume (Fedors, 1974), molecular weight, number of OH groups, number of COOH groups, number of NH groups, sum of H-accepting groups (i.e. C=O, OH, N, NH) and sum of H-donating groups (i.e. COOH, OH, NH, NH_2).

2.5. Average absolute error

The average absolute error (AAE) was used to check the accuracy of the prediction method and is calculated by Eq. (1):

$$\text{AAE} = \frac{\sum \left|\text{observed} - \text{predicted}\right|}{N} \quad (1)$$

where observed and predicted are the observed and predicted log mole fraction solubilities, respectively, and the *N* is the number of solubility data points. The AAE is the summation of the absolute value of each deviation. An AAE of 0.40 represents an average deviation of a predicted value from the experimental value by a factor of 2.5.

A list of solid solutes used for the solubility evaluation along with their physico-chemical properties is presented in Table 1.

3. Results

3.1. Solubility of solid solutes in HFA-134a/ethanol systems

The solutes used for this study have diverse physico-chemical properties with log *P* values ranging from −0.17 to 9.85 and melting points ranging from 55 to 326 °C. All 21 solutes had measurable solubilities and ranged from 0.0003% to 11.19% (w/w). The average R.S.D. for all 105 average solubility values was 12 ± 10%. In order to evaluate the relationship between ethanol levels and solubility, the solute solubilities (%, w/w) as a function of fraction cosolvent (0–20%, w/w ethanol) are presented in Figs. 1–3. For comparison, Fig. 1 contains compounds having the highest solubilities. Fig. 2 presents the compounds with moderate solubilities and Fig. 3 presents a compilation of those solutes that had the lowest solubilities. Progesterone and 2-naphthol have the highest solubilities, where the solubility values are 11.19% (w/w) and 9.59% (w/w), in HFA-134a with 20% ethanol, respectively. Conversely, anthracene and carbendazim have very low solubilities in HFA-134a with 20% ethanol, 0.019% (w/w) and 0.006% (w/w), respectively.

3.2. Calculation of solubility factor increase

The addition of ethanol resulted in a dramatic increase in solubility for some compounds and a modest increase in solubility for others. The relative solubility enhancement, as a result of the introduced semi-polar cosolvent, can be quantified by the ratio of the solubility obtained with the additional cosolvent (%, w/w) to that

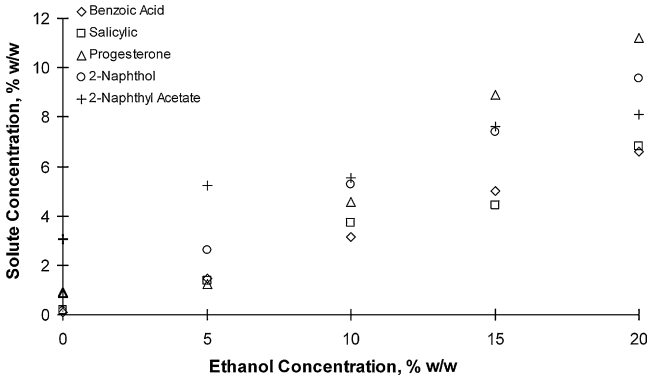

Fig. 1. Solute solubility (%, w/w) in HFA-134a vs. percent ethanol (0–20%, w/w, ethanol) for solutes with the highest solubilities.

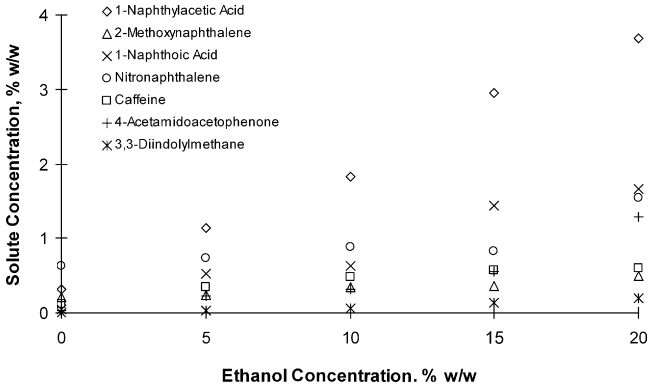

Fig. 2. Solute solubility (%, w/w) in HFA-134a vs. percent ethanol (0–20%, w/w, ethanol) for solutes with moderate solubilities.

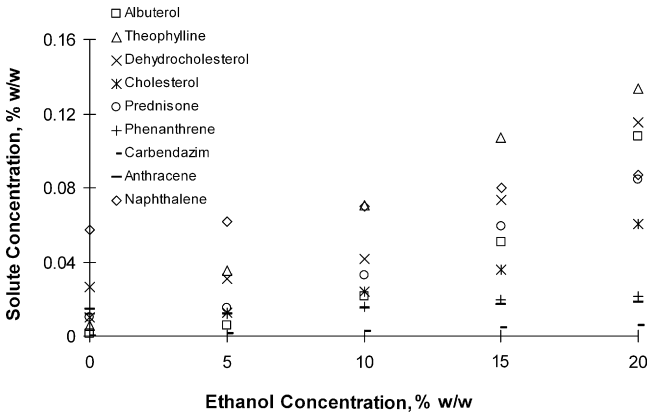

Fig. 3. Solute solubility (%, w/w) in HFA-134a plotted vs. percent ethanol (0–20%, w/w, ethanol) for solutes with the lowest solubilities.

without, i.e. Eq. (2):

$$\text{factor increase} = \frac{\%, \text{w/w}^{\text{HFA/EtOH}}}{\%, \text{w/w}^{\text{HFA}}} \Rightarrow \frac{C^{\text{HFA/EtOH}}}{C^{\text{HFA}}} \quad (2)$$

where $C^{\text{HFA/EtOH}}$ is the total solubility in HFA-134a with 20% (w/w) ethanol and C^{HFA} is the solubility in pure HFA-134a without ethanol. Table 2 shows the solubility factor increase for all 21 compounds, which ranges from 1.2 to 99.4. HFA-134a has a log P of 1.1, and ethanol has a log P of −0.187. Therefore, added ethanol increases the polarity of the HFA-134a solvent.

Hydrogen bonding (hydrogen-bond donors and acceptors) appears to have a significant effect on the solubility factor increase as evidenced by albuterol base, benzoic acid and 2-naphthol. The solutes with no hydrogen bonding functional groups were found to have the lowest factor increase values, such as naphthalene, anthracene and phenanthrene.

Table 2
List of polarity values (log P) for each solute and the factor increase in solubility from 0% to 20% (w/w) ethanol

	log P	Solubility 20% ethanol (log X_2)	Factor increase
Albuterol base	0.11	−3.42	99.4
Benzoic acid	1.88	−1.24	79.1
2-Naphthol	2.71	−1.25	78.3
4-Acetamidoacetophenone	1.24	−2.24	37.7
Salicylic acid	2.06	−1.38	36.5
DIM (3,3-Diindolylmethane)	4.67	−3.19	32.9
Theophylline	−0.17	−3.23	23.1
Carbendazim	1.52	−4.63	18.7
1-Naphthoic acid	3.13	−2.00	13.1
Progesterone	4.04	−1.52	12.7
1-Naphthylacetic acid	2.74	−1.78	11.5
Prednisone	1.62	−3.73	8.4
Cholesterol	9.85	−3.72	5.9
Caffeine	−0.13	−2.49	5.2
Dehydrocholesterol	9.50	−3.62	4.4
2-Naphthyl acetate	3.43	−1.40	2.6
1 -Nitronaphthalene	3.18	−2.13	2.4
2-Methoxynaphthalene	3.36	−2.59	2.3
Phenanthrene	4.49	−4.01	1.8
Naphthalene	3.45	−3.22	1.5
Anthracene	4.49	−4.09	1.3

3.3. Naphthalene series

Among the 21 compounds used in this study, the effects of different functional groups on substituted naphthalene were investigated. The solubility of naphthalene and six naphthalene derived solutes with varied substituents were determined, in order to systematically evaluate the effect of different functional groups on solubility. As shown in Table 3, these naphthalene derivatives have varied solubility responses when going from 0% to 20% ethanol. 2-Naphthol has a factor increase of 78.3, yet naphthoic acid, similar in structure and polarity, has a much lower factor increase of 13.1, while naphthalene itself only increases by 1.5. In order to examine solubility relationships based on structure for the naphthalene

Table 3
List of solutes and slope, σ, values with corresponding R^2 of the line

Compound	Slope (σ)	R^2
2-Naphthol	394.4	1.00
Benzoic acid	386.4	1.00
Albuterol	382.0	0.92
Salicylic acid	169.2	0.97
4-Acetamidoacetophenone	143.0	0.82
DIM (3,3-diindolylmethane)	140.7	0.93
Theophylline	111.9	1.00
Carbendazim	86.0	0.94
1-Naphthoic acid	60.6	0.92
Progesterone	55.3	0.92
1-Naphthylacetic acid	52.6	0.99
Prednisone	32.8	0.93
Caffeine	24.7	0.87
Cholesterol	20.1	0.86
Dehydrocholesterol	13.6	0.83
2-Naphthyl acetate	8.9	0.93
2-Methoxynaphthalene	7.2	0.68
1-Nitronaphthalene	5.2	0.55
Phenanthrene	3.7	0.91
Naphthalene	2.9	0.98
Anthracene	0.9	0.44

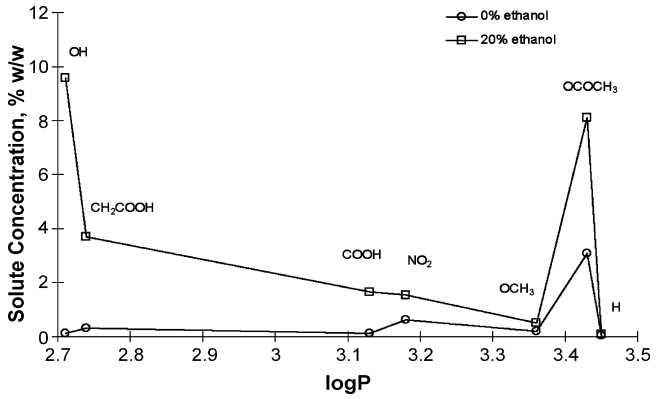

Fig. 4. Solubility of naphthalene and six naphthalene derivatives in 0% and 20% (w/w) ethanol/HFA-134a plotted against the log *P* of each derivative. The substituent for each derivative is indicated for each data point.

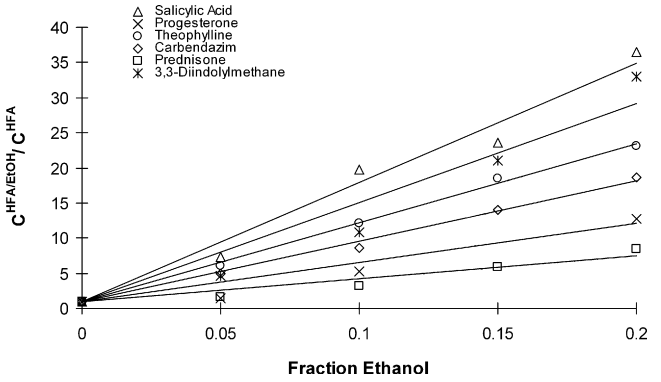

Fig. 5. Normalized solubility ($C^{HFA/EtOH}/C^{HFA}$) from HFA-134a/ethanol propellant systems plotted against the fraction ethanol (%, w/w).

solutes, the % (w/w) solubilities were plotted against the log *P* of each naphthalene substituent (Fig. 4), where H is naphthalene (no functional groups) and OH is 2-naphthol (OH group at two position on naphthalene ring). The *x*-axis is in increasing order of log *P*. The solubility values for both 0% and 20% (w/w) ethanol in HFA-134a are represented. The solubility is always greater at 20% ethanol compared to that at 0%. However, no direct correlation between log *P* and solubility is apparent. Methoxynaphthalene and naphthalene have similar polarities, and the factor increase is similar for these two compounds. In contrast, 2-napthyl acetate which has a log *P* nearly the same as naphthalene, has significantly improved solubility. Clearly, the incorporation of hydrogen-bond accepting and donating functionalities can have a significant affect on cosolvent solubilization.

3.4. Linear relationship

Yalkowsky and Roseman introduced the log-linear model to describe the exponential increase in aqueous solubility for non-polar organic compounds as the cosolvent concentration is increased, as seen in Eq. (3),

$$\log S_m = \log S_w + \sigma f_c \quad (3)$$

where f_c is the fraction of cosolvent in the solute-free solvent mixture, S_m and S_w are the solubilities of solute in water/cosolvent mixtures and in pure water, respectively, and σ is the solubilization power (Yalkowsky and Roseman, 1981). The log-linear model was evaluated to fit the solubility data in HFA-134a. Although very useful for aqueous systems, the log-linear model was not found to be as applicable to HFA-134a/ethanol systems for this particular data set, over the range of ethanol concentrations considered. A linear–linear approach was found to be more appropriate, where an average R^2 value of 0.89 (R.S.D.: 16%) was observed compared to an R^2 of 0.33 (R.S.D.: 49%) for the log-linear model.

To evaluate the solubilization slope, the normalized mole fraction solubility values (i.e. the solute concentration at a given ethanol level over the concentration in pure propellant, $C^{HFA/EtOH}/C^{HFA}$) for all 21 compounds were plotted as a function of fraction ethanol. Fig. 5 illustrates the linear relationship for some select solutes where C^{HFA} and $C^{HFA/EtOH}$ refer to the % (w/w) solubility of the solute in pure HFA-134a and the total solubility with added ethanol, respectively. The normalized % (w/w) solubility reflects the extent of solubilization due to an increase in cosolvent concentration for a linear approach.

This linear relationship for 0–20% ethanol in HFA-134a is consistent with the findings of Banerjee and Yalkowsky (1988) for low cosolvent–water systems. Solubilization in water-rich mixed solvents was found to be linear rather than a logarithmic function of cosolvent up to f_c values between 10% and 20% due to a change in the mechanism of solubilization.

3.5. Calculation of slope

When the extent of solubilization ($C^{HFA/EtOH}/C^{HFA}$) is plotted against the fraction ethanol, the end-to-end slope of the line (intercept set equal to 1) can be defined as σ:

$$\frac{C^{20\%}}{C^{0\%}} = \sigma f_c + 1 \quad (4)$$

where f_c is the fraction cosolvent. The term σ is not related to the crystalline structure of the solute (assuming no degradation, solvation or solvent-mediated polymorphic transitions of the solute occur).

The cosolvent solubilization power, σ, for the solute/ethanol/HFA-134a system was determined for each solute as seen in Table 3. Table 3 also illustrates the suitability of the linear model in HFA-134a/ethanol for each solute based on the corresponding R^2 value, where the average R^2 value is 0.89 (R.S.D. 16%). In aqueous systems, σ can be estimated through a correlation to the solute's polarity, log *P*, in a specific water/cosolvent system as seen in Eq. (5):

$$\sigma = a + b \log P \quad (5)$$

where *a* and *b* are constants that depend only on the cosolvent. In order to determine if σ correlated to a solute's log *P* in HFA-134a/ethanol, a regression approach was used. Fig. 6 shows the relationship between σ and log *P* for each solute, where the R^2 value is 0.151, illustrating that σ does not correlate well to the polarity of a solute in HFA-134a for this data set.

No single parameter was found to correlate with the ethanol solubility end-to-end slopes, σ, so a multiple linear regression (MLR) approach was applied. The σ values were regressed against 19 different physico-chemical properties in order to find predictive correlations for the increase in HFA-134a solubility due to ethanol. The σ of each solute was calculated and plotted against the experimental σ values. Due to the limited number of hydrogen donating solutes in the experimental group (hydrogen donating groups excluded amides and esters), an equation that focused more on specific substituents, OH, COOH and NH, resulted in a significant correlation. Fig. 7 shows the best correlation attained for calculated

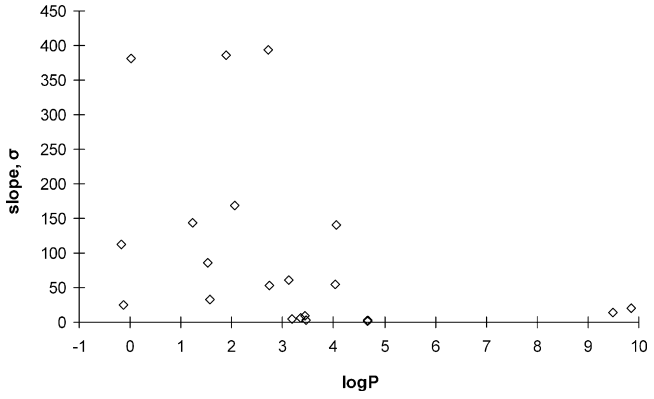

Fig. 6. Relationship between solute log *P* and slope, σ.

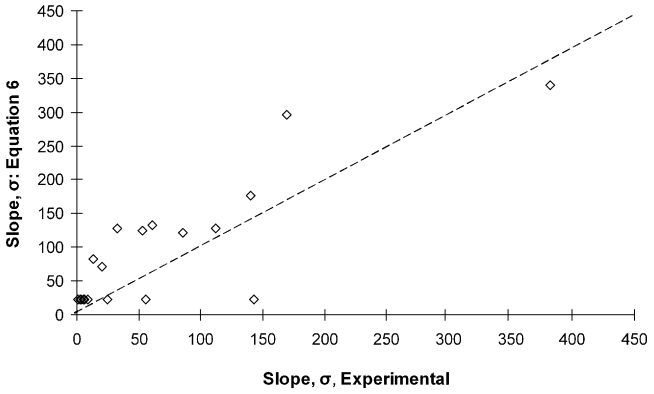

Fig. 7. Relationship between experimental slope, σ, and calculated slope, σ, according to Eq. (6).

σ according to Eq. (6):

$$\sigma = 18985.95\left(\frac{\mathrm{NH}+\mathrm{OH}+\mathrm{COOH}}{\mathrm{MW}}\right)+22.09, \quad p < 0.001, \quad F\text{-ratio} : 19.42 \tag{6}$$

When a regression approach was applied (Eq. (6)), the average absolute error (AAE) (Eq. (1)) of predicting σ was 63.04.

Fig. 7 illustrates that the majority of the solutes have a positive deviation from the line of unity (dashed line), meaning that Eq. (6) over predicts the experimental slope for 15 of the 21 solutes. The solutes that are under predicted show no correlation to log *P*. One solute has an ester group that the regression equation did not take into account, due to the limited data set. Although, there is a high degree of scatter about the line of unity, an improved correlation, compared to Fig. 6, to experimental σ can be seen using Eq. (6), where the hydrogen bond ability of a solute is scaled to molecular weight, resulting in a hydrogen bond density.

4. Discussion

In this study, the equilibrium solubilities of 21 crystalline solutes in HFA-134a with 0–20% (w/w) ethanol were determined by a direct inject on-line HPLC method. The solubility factor increase ranged from 1.2 to 99.4 times when 20% (w/w) ethanol was added compared to pure HFA-134a. Interestingly, the solubility values for every solute investigated increased when ethanol was added. The addition of ethanol significantly increased the solubility of some compounds, such as 2-naphthol, benzoic acid and salicylic acid. However, compounds, such as anthracene and carbendazim have very modest increases in solubility with the addition of ethanol. Solutes with log *P* values higher and lower than both HFA-134a and ethanol were found to have increases in solubility. While a slight trend is observed for solutes with higher log *P* having smaller solubility factor increases, these results suggest that the increase in solubility due to ethanol in HFA-134a is not entirely based on overall solute polarity.

Notably, the resulting solubility curve for each solute investigated in this study is predominately linear from 0% to 20% (w/w) ethanol, with positive slopes. The log *P* of a solute cannot be used to predict either the extent of solubilization by a specific amount of ethanol or the amount of ethanol required to achieve a specific extent of solubilization in HFA-134a. The slope of the line was defined as the cosolvent solubilization power, σ. Preliminary analysis showed that the overall solute's polarity (via log *P*) does not correlate well to the slope, σ, as seen in aqueous systems.

However, a slight trend was observed between σ and a solute's hydrogen bond density where an increase in solubility due to ethanol correlated to a solute's number of hydrogen bond substituents and molecular weight. This simple hydrogen donating equation, involving molecular weight, resulted in a useful correlation (R^2: 0.70). It is apparent from Table 3 that those compounds with OH, COOH and NH groups have higher σ values.

Characterization of the HFA-134a/ethanol systems will be further investigated based on the linear model shown in this work.

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