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Stability Analysis of Binary Solvent Mixtures for Herbal Phytochemical Extraction

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Abstract

Most of the extraction processes of herbal phytochemicals use solvent mixtures as phytochemical transfer medium. It is very important to predict the stability of solvent mixtures before it is used to extract herbal phytochemicals. In order to prevent any disturbance in the herbal extraction, the solvent mixtures must be in a single-liquid phase (miscible to each other). In this study, the stabilities of five binary solvents (methanol-water, methanol-ethyl acetate, methanol-acetic acid, methanol-n-propioneldehyde, and methanol-isobutylraldehyde mixtures) that could be used in the current extraction processes are evaluated. The main purpose of this study is to evaluate these binary solvents in terms of their stability using Gibbs energy of mixing. The value of the function $\Delta G^{mix}/RT$ is calculated for each solvent mixture. Then, the graph for $\Delta G^{mix}/RT$ versus solvent molar fraction x is plotted. From this plot and the value of function $\Delta G^{mix}/RT$, it can be concluded whether the solvent mixtures is stable or unstable. From the analysis, all five binary mixtures are stable within the selected molar fraction making all mixtures are suitable to be applied in herbal extraction.

1. Introduction

Solvent selection is very important in herbal based industries as it can influence the yield of the final product and subsequently increase their profit. Solvents have been widely used especially in pharmaceutical area. They are used to dissolve the most valuable ingredients such as Active Pharmaceutical Ingredients, API taken from any plant source (herbal plant) to give benefit for health. For instance, herbs were used since ancient time because they are believed to cure diseases. Previously, the whole herbal plant was soaked in the water or boiled to get the benefits from herbal ingredients (phytochemicals). By using this simple method, all water-like phytochemicals (phytochemical and water have almost the same polarity values) from herbal plant will diffuse out from the plant to water medium. This water and phytochemical mixture then is consumed for its beneficial effects.

However, current practitioners have identified which phytochemicals could cure or reduce disease symptoms. Thus, there is a need to extract the targeted phytochemicals from herbal plants. It is very valuable if any solvent/s system can extract the maximum amount of desired phytochemical. Current practice need to use at least six solvents to get the target pure phytochemical from crude extract (Kerton and Marriott, 2013). Thus, it is a need to find the solvent that can reduce the usage of series of solvents to get the target pure phytochemical. In herbal extraction, there are many factors that must be considered before the solvents are chosen such as solvent-phytochemicals solubility, solvent-phytochemicals partition coefficient, solvent boiling point, solvent toxicity, solvent viscosity, solvent density as well as solvent stability as stated by Azmin et al (2015).

Stability of solvent mixtures is an indicator to determine whether the solvent mixtures are miscible, immiscible, or partly miscible to each other. In extraction processes, the solvents stability is very important as it will influence the process and extraction yield. For instance, solvent mixtures that are not stable will split and form two layers of solvents where this phenomenon will affect the extraction yield. Besides that, the removal of solvent from crude extract also will be inefficient.

Previously, the stability of liquid used in varying processes has been studied. For instance, Yunus et al (2014) tested the stability of gasoline and base oil blends for lubrication while Conte et al (2009, 2011), tested the stability of the formulation of paint coating formulation, insect repellent and lotion. Previous work by Azmin et al

(2015) proposed a framework to design the suitable solvent to extract the targeted herbal phytochemical.

The solvent design framework involves five levels. The first level is screening the pure component properties of solvent, the second and third levels are considering linear and non-linear constraints respectively, the fourth level is stability analysis and the fifth level is the cost analysis. The case study presented in the previous work covered from Level 1 to Level 3. Therefore, this work will continue the stability analysis (Level 4) for all solvent mixtures that have been identified in the previous work. The objective of this study is to determine the stability of solvent mixtures whether they are totally miscible, partially miscible or totally immiscible. The stability determination helps in choosing stable solvent mixtures that will not disturb the extraction process of phytochemicals. The more stable the solvent mixture, the fewer disturbances will be occurred in the extraction process.

2.   Materials and Methods

The stability of solvents considered in this study is based on the trend of the Gibbs energy function of mixing (ΔG^{mix}) and its first and second derivatives as a function of solvent composition. The Gibbs energy of mixing is calculated using Pinal et al (1991) model as follows:

$$\frac{\Delta G^{mix}}{RT} = \frac{G^E}{RT} + \sum_{i=1}^{NC} x_i.\ln x_i \qquad (1)$$

where NC is number of solvent candidates; i is pure solvent in solvent mixture; R is gas constant in atm cm³/g mol K; T is temperature in K, x is mole fraction, G^E is the excess Gibbs energy of mixing which is calculated from:

$$\frac{G^E}{RT} = \sum_{i=1}^{NC} x_i.\ln \gamma_i \qquad (2)$$

where γ_i is activity coefficient of component i, estimated using UNIFAC-LLE model by Smith et al (2005) and Fredenslund et al (1975) at 90 ℃, the temperature for extraction process.

According to Smith et al (2005), a stable solvent mixture must fulfill two conditions. First, the solvent mixtures must have the negative value of function $\Delta G^{mix}/RT$ .Second is the plot of $\Delta G^{mix}/RT$ versus mole fraction must appear as U-shape curve (mixtures of type A) shown in Figure 1. Conte et al (2011) represented four types of possible solvent mixtures that can be obtained as shown in Figure 1. These curves are plots of $\Delta G^{mix}/RT$ as a function of x_i, where x_i is composition range from 0 to 1 and the interval is 0.2.

Four types of curves in this graph provide different meanings which are as follows:

1- Mixtures of type A have negative values of the function $\Delta G^{mix}/RT$ and positive value of its second derivative in the entire composition range. These give a meaning that the mixtures are stable and only have one phase (completely miscible) for entire compositions.

2- Mixtures of type B are totally different from mixtures of type A. They have positive value of the function $\Delta G^{mix}/RT$ and negative value of its second derivative in the entire composition range. These types of mixtures are completely immiscible at their entire composition.

3- Mixtures of type C has both miscible and immiscible phase. Miscible mixtures occur at the location where the function $\Delta G^{mix}/RT$ is negative while the immiscible mixtures are when the function is positive. Compositions of two liquid phases are identified by the points at which the function $\Delta G^{mix}/RT$ is zero (immiscibility gap).

4- Mixtures of type D have negative value for the function $\Delta G^{mix}/RT$. However they are a bit complex because the shape of the curve is not as smooth as the curve for the mixtures of type A. It has some deviation from the U-shape graph where the deviation occurs at the point x_1 to x_2 shown in Figure 2. Between these two points, the mixtures will form two split phases (immiscible mixture and not stable) but it does not mean that immiscible mixtures occur starting from composition of x_1 to x_2. The real composition for the mixtures starts to be split is identified by employing the tangent plane at the curve deviation (Conte et al, 2011, Smith et al, 2005) shown in Figure 2. An example of a mixture of type D is binary mixture of ethanol and hexadecane at 298.15 K.

There is one condition in applying tangent plane that is, Tangent Plane Distance, TPD must be more or equal to zero. TPD equation is as follows:

$$TPD = \frac{\Delta G^{mix}}{RT} - (mx + C) \geq 0 \qquad (3)$$

$$y = mx + C \qquad (4)$$

where m is the tangent slope and C is the intercept to the $\Delta G^{mix}/RT$ surface respectively. This TPD corresponds to the distance between the function $\Delta G^{mix}/RT$ and its tangent at every trial composition, x. As shown in Figure 2, the intercept is denoted by C and the slope, m is calculated as follows.

$$m = \sqrt{(Y_1 - Y_2)^2 + (x_2 - x_1)^2} \qquad (5)$$

where Y_1 and Y_2 are the value of $\Delta G^{mix}/RT$ while x_1 and x_2 are molar fraction as shown in Figure 2.

In this study, five binary mixtures are methanol-water, methanol-ethyl acetate, methanol-acetic acid, methanol-n-propioneldehyde, and methanol-isobutylraldehyde. These mixtures are the result from

solvent design framework done by Azmin et al (2015). The stability value using Gibbs energy of mixing for each mixture is calculated using equations 1 and 2. Then the values of Gibbs energy of mixing are evaluated by plotting the curve of $\Delta G^{mix}/RT$ as a function of x_i, (composition range from 0 to 1).

## 3.   Results and Discussion

The result for solvent design framework by Azmin et al (2015) is shown in Table 1. Mole fraction range shown in this table is the composition that satisfied all property constraints in Level 1, 2 and 3 in solvent design framework. However, the stability analysis needs to perform for all composition range (0 to 1) for every solvent mixture. From this result, all solvent mixtures will be analyzed for their stability. Table 2 shows the composition and activity coefficient values for methanol-water, methanol-ethyl actate, methanol-acetic acid and methanol-n-propioneldehyde mixtures and their corresponding values of function $\Delta G^{mix}/RT$. As shown in this table, all the $\Delta G^{mix}/RT$ values for function are negative. It means that the first condition mentioned by Smith et al (2005) has been fulfilled. Smith et al (2005) also stated that in order for the mixture to be stable (one-phase liquid), both conditions must be agreed. The second condition is verified in order to make sure that this solvent mixture is stable before it is used for extraction of herbal phytochemicals. The plots of $\Delta G^{mix}/RT$ versus molar fraction are shown in Figure 3 to 7 for every solvent mixture. The curves for all of these graphs follow type A curve shown in Figure 1. It gives a meaning that, these mixtures are stable and will not split at all composition range. When any of these mixtures is used for herbal extraction, it will not disturb the extraction process and the removal of solvent from crude extract is easier and more efficient.

From Figure 3 to 7, the solvent combinations between methanol and other solvent shows that they are stable in all range of composition, x_i. Methanol and other three solvents (water, etyhl acetate and acetic acid) are polar solvent while the other two, n-propioneldehyde, and isobutylraldehyde are non-polar solvents. Polar solvent (methanol) are attracted to the other polar solvents such as ethyl acetate. It is common situations for polar solvents dissolve polar solvents which lead to a stable solvent combination. Hence, when the stable solvent mixtures are applied to the extraction of herbal phytochemicals it will not cause any disturbance. In the case of interactions between polar (methanol) and non-polar solvent (n-propioneldehyde, and isobutylraldehyde), the non-polar dissolve in the polar solvent because the non-polar chain for aldehyde groups (composed of carbon, methyl and ethyl groups) are short. The tendency of short non-polar groups to dissolve in polar solvent is increased making these mixtures (methanol-n-propioneldehyde and

methanol-isobutylraldehyde) become more stable. Thus, the stability of these mixtures also do not contribute to any disturbance during the extraction of phytochemicals.

Table 1: Result for solvent design framework by Azmin et al (2015)

Solvent 1,S_1	Solvent 2,S_2	Mole fraction range, x_1
Methanol	Water	0.01-0.80
Methanol	Etyhl acetate	0.2-0.20
Methanol	Acetic acid	0.13-0.40
Methanol	n-propioneldehyde	0.01-0.91
Methanol	isobutylraldehyde	0.01-0.92
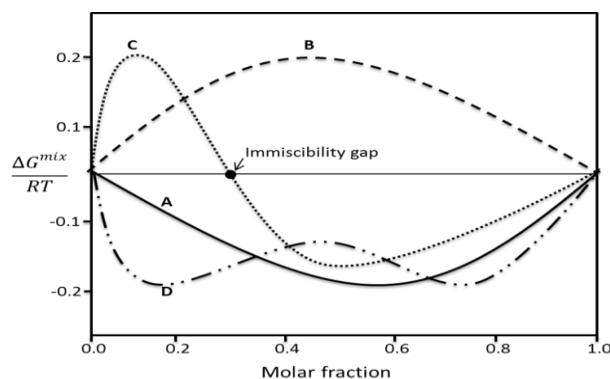
** Mixtures of type A is miscible mixtures, type B is immiscible mixtures, type C is immiscible mixtures at molar fraction 0 to immiscibility gap and miscible mixtures after immiscible gap to molar fraction equal to 1, type D is miscible mixtures except at deviation of U-shape graph.

Figure 1: The most common shapes for the function of $\Delta G^{mix}/RT$ (Conte et al, 2011)
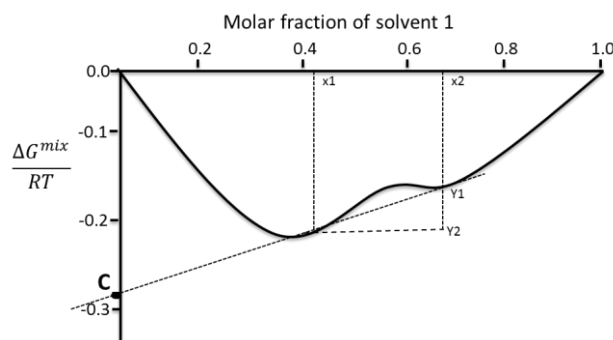

Figure 2: The real immiscibility gap identified by the tangent plane condition

Table 2: Values of molar fraction, activity coefficient and function $\Delta G^{mix}/RT$ for solvent mixtures of methanol-water, methanol-ethyl acetate, methanol-acetic acid, methanol-n-propioneldehyde, and methanol-isobutylraldehyde ,

| Molar fraction for S_1	Molar fraction for S_2	Methanol(1)-water(2)			Methanol(1)-ethyl acetate(2)			Methanol(1)-acetic acid(2)			Methanol(1)- n-propioneldehyde(2)			Methanol(1)-isobutylraldehyde(2)		
x_1	x_2	γ_1	γ_2	$\Delta G^{mix}/RT$	γ_1	γ_2	$\Delta G^{mix}/RT$	γ_1	γ_2	$\Delta G^{mix}/RT$	γ_1	γ_2	$\Delta G^{mix}/RT$	γ_1	γ_2	$\Delta G^{mix}/RT$
0.01	0.99	2.89	1.00	-136.46	3.27	1.00	-133.03	1.01	1.00	-168.67	2.83	1.00	-134.34	2.2522	1.0001	-169.073
0.1	0.9	2.11	1.02	-707.67	2.71	1.01	-650.66	1.01	1.00	-977.48	1.18	1.04	-820.20	1.9911	1.0073	-981.425
0.2	0.8	1.66	1.06	-1061.66	2.24	1.05	-916.53	1.01	1.00	-1503.50	0.97	1.07	-1353.82	1.7532	1.0302	-1510.69
0.3	0.7	1.40	1.12	-1295.07	1.89	1.11	-1054.63	1.01	1.00	-1833.96	0.94	1.09	-1726.04	1.5602	1.0712	-1844.16
0.4	0.6	1.25	1.19	-1442.21	1.62	1.20	-1116.43	1.01	1.00	-2019.52	0.95	1.08	-1955.72	1.4037	1.134	-2031.77
0.5	0.5	1.16	1.27	-1510.40	1.42	1.34	-1123.56	1.01	1.00	-2078.77	0.96	1.07	-2052.39	1.2779	1.2247	-2092.55
0.6	0.4	1.09	1.36	-1496.92	1.26	1.54	-1084.36	1.00	1.01	-2017.70	0.98	1.05	-2018.42	1.1781	1.3529	-2031.76
0.7	0.3	1.05	1.46	-1391.22	1.15	1.84	-997.85	1.00	1.01	-1830.79	0.99	1.03	-1847.98	1.1016	1.5332	-1844.14
0.8	0.2	1.03	1.58	-1171.79	1.07	2.30	-850.92	1.00	1.01	-1499.59	0.99	1.00	-1522.11	1.0463	1.79	-1510.68
0.9	0.1	1.01	1.75	-790.19	1.02	3.02	-600.61	1.00	1.02	-974.55	1.00	0.98	-991.13	1.0121	2.1639	-981.412
0.99	0.01	1.00	2.03	-147.47	1.00	4.08	-126.03	1.00	1.03	-168.27	1.00	0.96	-170.37	1.0001	2.6592	-169.072
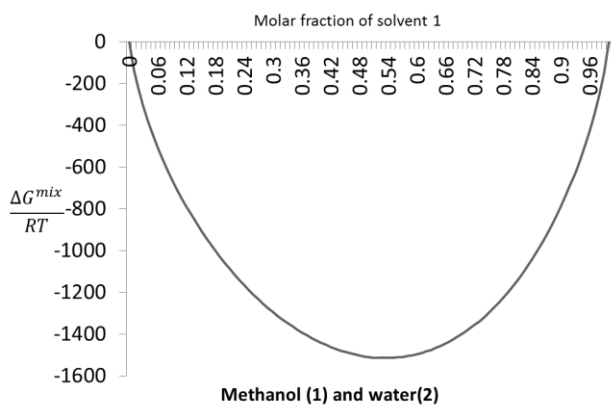
Figure 3: Stability curve of methanol and water mixture.
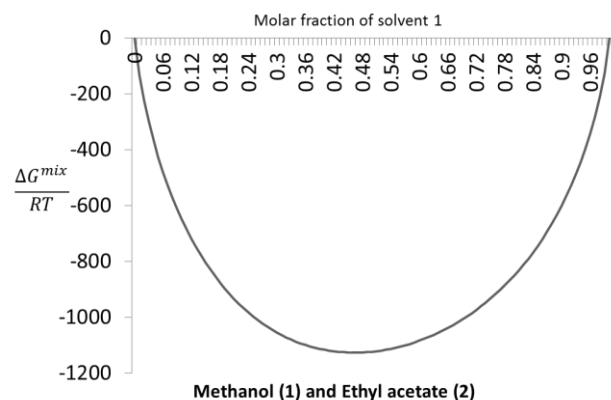

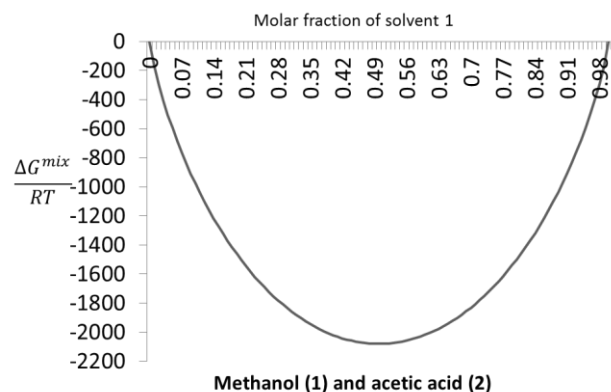**Figure 4**: Stability curve of methanol and ethyl acetate mixture.

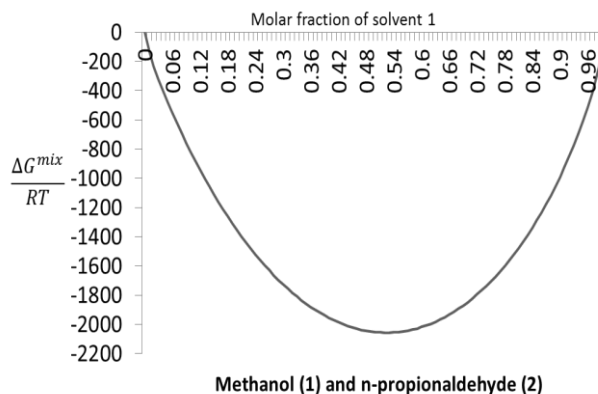**Figure 5**: Stability curve of methanol and acetic acid mixture.

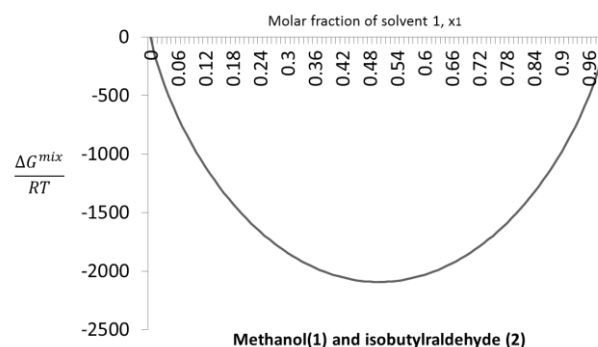**Figure 6**: Stability curve of methanol and n-propionaldehyde mixture

Figure 7: Stability curve of methanol and isobutylraldehyde mixture.

4. Conclusion

The stability test performed for all five binary mixtures (methanol-water, methanol-ethyl acetate, methanol-acetic acid, methanol-n-propioneldehyde, and methanol-isobutylraldehyde) shows that all of the mixtures are stable since they fulfilled both criteria mentioned by Smith et al, 2005. Thus, these mixtures could be used in extraction of herbal phytochemical if the other factors considered in extraction are matching the required properties.

Acknowledgement

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