

Ternary Phase Diagram Modeling of Chiral Medetomidine Salts Using NRTL-SAC Model

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Experimental determination of solubility and ternary phase diagram of chiral compound are of tedious and time consuming tasks, and in many cases, there is not enough experimental data for different enantiomeric compositions to access the experimental ternary phase diagram. Using thermodynamic models with predictive capability, having less dependency on experimental data, affords a great advantage for ternary phase diagram modeling of these compounds. In this study, NRTL-SAC model, as one of the known and famous predictive models in the solubility modeling of pharmaceutical compounds, has been applied to ternary phase diagram modeling of chiral medetomidine salts in alcohols. NRTL-SAC molecular parameters of each chiral compound were calculated just by using racemic point solubility data before being used for the solubility prediction of other enantiomeric compositions. The results of thermodynamic modeling and the predictive data are compared with those of the experimental data. Root mean square error (RMSE) is also calculated for each compound. It was observed that, there is a small deviation between predictive and experimental ternary phase diagrams. The eutectic points of chiral compounds in both racemic and conglomerate forms are also well predicted through this method.

Keywords: Medetomidine, Ternary phase diagram, Chiral compounds, NRTL-SAC, Solubility

INTRODUCTION

A significant part of drug molecules are chiral [1] and in many cases only one enantiomer presents the desired pharmaceutical effects whereas the other enantiomer may be inactive or with unwanted effects [2]. Thus, to avoid the undesirable medicinal effects, enantiomeric separation of chiral drugs is necessary. Preferential crystallization is a cheap and effective method for the resolution of enantiomers [3,4]. There are three modes following which the chiral molecules are crystallized [5,6]. More than 90% of all known systems are racemic compound forming system in which, molecules have more attraction to opposite enantiomers and crystal lattice forms a single phase with both enantiomers. Ternary phase diagram of these groups

presents two eutectic points (Fig. 1). Another type is conglomerate forming system (racemic mixture) in which crystal lattice is built with the same enantiomers. In this group, separation of enantiomer is achieved from racemate (50/50: enantiomeric composition with zero enantiomeric excess or $ee = 0$) and seeding with target enantiomer (R or S) is sufficient to preferential crystallization of desired enantiomer (R or S). Ternary phase diagram of this group presents only one eutectic point (Fig. 1). The third group is pseudo racemate system, in which, crystal lattice is formed by both enantiomers without a specified pattern. Knowledge of equilibrium behavior and ternary phase diagram of a chiral compound in a solvent is essential for designing and optimization of separation process [7]. Experimental determination of ternary phase diagram requires many equilibrium data for different enantiomeric compositions. In many cases only a few grams of an expensive compound is

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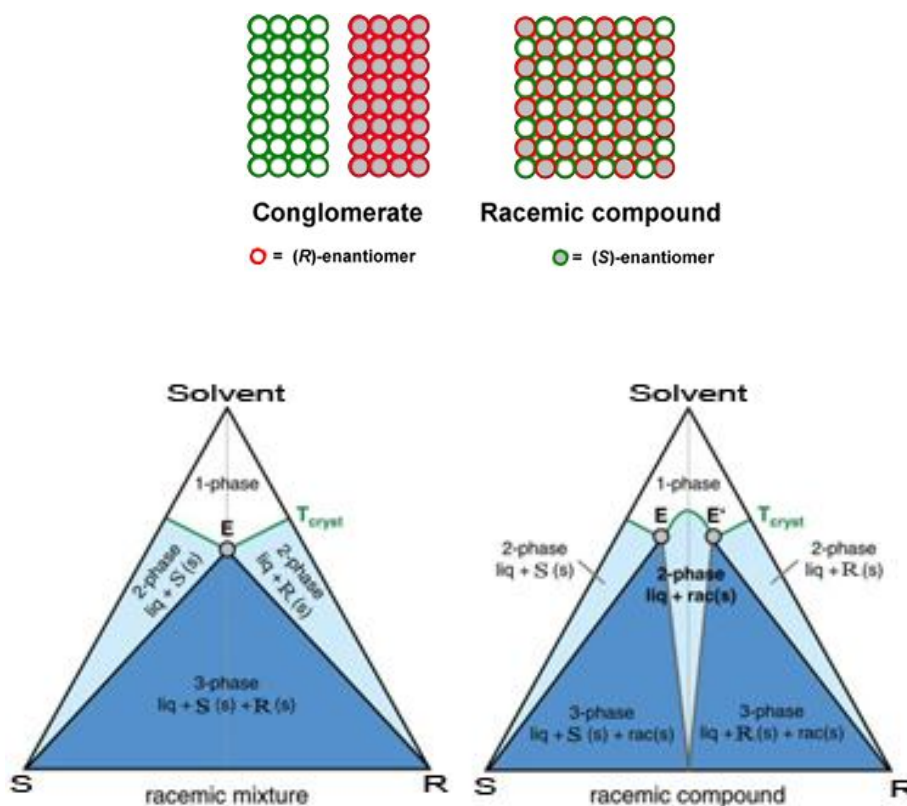


Fig. 1. Crystal packing and ternary phase diagram of chiral compounds.

available or in some cases there is not enough time to determine the experimental solubility of different enantiomeric compositions. Thus, it is desirable to determine the ternary phase diagram of a chiral compound in different solvents without experimental efforts. Thermodynamic activity coefficient models can be used as appropriate tools to achieve this goal.

Activity coefficient models for solubility calculation of compounds can be divided into two groups: Correlative and predictive models.

Correlative models such as Wilson [8], Van Laar [9], NRTL (NonRandom Two Liquid) [10], UNIQUAC (UNIversal QUAsi-Chemical) [11], use experimental equilibrium data for the estimation of adjustable parameters and solubility determination. Solubility modeling of ranitidine hydrochloride has been performed using UNIQUAC model [12].

The predictive models such as Hansen [13], UNIFAC [14], and new developed models such as NRTL-SAC [15], COSMO-SAC [16], predict the solubility using chemical structure of molecules and some of data sets.

Considering the lack of experimental equilibrium data of chiral compounds, the importance of predictive models in ternary phase diagram modeling of these compounds is clear. Chen and Crafts proposed the NRTL-SAC (Non-Random Two-Liquid Segment Activity Coefficient) model based on NRTL [17] for solubility prediction of drugs in pure and mixed solvents [15,18]. It is considered to reduce laboratory time and can provide a practical thermodynamic framework for solubility modeling of drugs [15,19,20].

We have previously reported the thermodynamic modeling and the solubility of pure and racemic forms of chiral ketamine using correlative and predictive models (NRTL and NRTL-SAC) [21]. Comparing the results show

that the average relative deviation error for NRTL-SAC method (15%) is higher than that for NRTL (2%), however this inconvenience is recompensed by the lesser experimental data necessitated for a predictive method such as NRTL-SAC.

Herein, the ternary phase diagram modeling of both medetomidine hydrochloride (Med.HCl) and medetomidine hydrobromide (Med.HBr) in 2-Propanol and medetomidine oxalate (Med.Ox) in ethanol is investigated by NRTL-SAC model.

COMPUTATIONAL METHODS

Solubility

Saturation concentration or concentration at thermodynamic equilibrium is called solubility. According to Prausnitz *et al.* [22], it depends on the ratio of two fugacities by the following equation:

$$\ln \frac{f_2^L}{f_2^S} = \frac{\Delta H_{mel}}{RT_{tp}} \left(\frac{T_{tp}}{T} - 1 \right) - \frac{\Delta C_p}{R} \left(\frac{T_{tp}}{T} - 1 \right) + \frac{\Delta c_p}{R} \ln \frac{T_{tp}}{T} \quad (1)$$

Where

- f_2^L and f_2^S are pure sub-cooled liquid and pure solid fugacities at T.
- ΔH_{mel} is the melting enthalpy.
- ΔC_p is the difference of heat capacities between solid and liquid form of solute at T.
- R is the universal gas constant.
- T_{tp} is the triple point temperature of pure enantiomers.

The ratio of two fugacities can be expressed by the following equation [22],

$$x_2 \gamma_2 = \frac{f_2^S}{f_2^L} \quad (2)$$

where x_2 is the mole fraction of solute in the solvent and can be calculated using solubility data as follows:

$$x_2 = \frac{x}{1+x} \quad (3)$$

$$x = \frac{S \times M_{solvent}}{100 \times M_{solute}} \quad (4)$$

where x is: (moles solute/moles solvent). And then:

where:

• S is the solubility in the terms of grams solute in 100 gram of solvent.

• $M_{solvent}$ and M_{solute} are the solvent and solute molecular mass.

γ_2 is the activity coefficient calculated from activity coefficient models.

Binary Phase Diagram

The binary phase diagram of a chiral system can be generally predicted as a function of enantiomeric composition by Schroder-van Laar equation [4].

$$\ln x = \frac{\Delta H_{mel}}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) \quad (5)$$

Prigogine-Defay equation is used to predict binary curve between two eutectic points of racemic compound [4,23].

$$\ln 4x(1-x) = \frac{\Delta H_{m,rac}}{R} \left(\frac{1}{T_{m,rac}} - \frac{1}{T} \right) \quad (6)$$

NRTL-SAC Model

NRTL-SAC maps the molecules into four conceptual segments, based on the interaction characteristics of molecules in solution. Each molecule can present hydrophobic (X), hydrophilic (Z), polar attractive (Y^+) and polar repulsive (Y^-) segments. Activity coefficient of species I in NRTL-SAC model is written by sum of combinatorial and residual parts as bellow:

$$\ln \gamma_I = \ln \gamma_I^C + \ln \gamma_I^R \quad (7)$$

The residual part, $\ln \gamma_I^R$, is defined as:

$$\ln \gamma_I^R = \ln \gamma_I^{lc} = \sum_m r_{m,I} [\ln \Gamma_m^{lc} - \ln \Gamma_m^{lc,I}] \quad (8)$$

$$\ln \Gamma_m^{lc} = \frac{\sum_j x_j G_{jm} \tau_{jm}}{\sum_k x_k G_{km}} + \sum_{m'} \frac{x_{m'} G_{mm'}}{\sum_k x_k G_{km'}} (\tau_{mm'} - \frac{\sum_j x_j G_{jm'} \tau_{jm'}}{\sum_k x_k G_{km'}}) \quad (9)$$

In the above equation, $\ln \Gamma_m^{lc}$ is the activity coefficient of segment species m in the solution and $\ln \Gamma_m^{lc,I}$ is the activity coefficient of segment species m in component I which can be calculated by the following equations:

$$\ln \Gamma_m^{lc,I} = \frac{\sum_j x_{j,I} G_{jm} \tau_{jm}}{\sum_k x_{k,I} G_{km}} + \sum_{m'} \frac{x_{m',I} G_{mm'}}{\sum_k x_{k,I} G_{km'}} (\tau_{mm'} - \frac{\sum_j x_{j,I} G_{jm'} \tau_{jm'}}{\sum_k x_{k,I} G_{km'}}) \quad (10)$$

$$x_j = \frac{\sum_j x_j r_{j,J}}{\sum_j \sum_i x_i r_{i,I}} \quad (11)$$

$$x_{j,I} = \frac{r_{j,J}}{\sum_i r_{i,I}} \quad (12)$$

where, i, j, k, m and m' are the segment indices in each component, I and J are the component indices, x_j and $x_{j,I}$ are the segment based mole fraction of segment species j in whole solution and only in component I , respectively. G_{ij} and τ_{ij} in Eqs. (9) and (10), are the local binary parameters related to each other by non-random parameter, α_{ij} of NRTL equation with the following equation:

$$G_{ij} = \exp(-\alpha_{ij} \tau_{ij}) \quad (13)$$

The combinatorial term is given by:

$$\ln \gamma_i^C = \ln \frac{\phi_i}{x_i} + 1 - r_i \sum_J \frac{\phi_J}{r_J} \quad (14)$$

where, r_I is total segment number, and ϕ_I is segment mole fraction in the mixture defined by the following equations.

$$r_I = \sum_i r_{i,I} \quad (15)$$

$$\phi_I = \frac{r_I x_I}{\sum_j r_j x_j} \quad (16)$$

RESULTS AND DISCUSSION

NRTL-SAC Molecular Parameters Determination

Experimental binary and ternary phase diagrams of Med.HCl and Med.HBr in 2-propanol showed racemic compound forming system [24,25] while those of Med.Ox in ethanol showed conglomerate behavior [25]. For ternary phase diagram modeling by NRTL-SAC method, molecular parameters for each compound need to be determined *via* experimental data of racemate (50/50: enantiomeric composition with $ee = 0$). Using more experimental data ameliorates the accuracy of these parameters. The solvent used for achieving the molecular parameters is also important. Due to availability of experimental data for racemate, experimental data in racemic point have been used for molecular parameter determination. Thus, the solubility of Med.HCl and Med.HBr in 2-propanol and Med.Ox in ethanol [24,25] is used for parameter determination. The regression was carried out using minimizing root mean square error (RMSE) between experimental and predicted mole fraction using Isqnonlin function of MATLAB software which is suitable for solving the nonlinear least-squares problems. The RMSE is calculated from equation 17,

$$RMSE = \left[\frac{\sum_{i=1}^N (\ln x_i^{\text{exp}} - \ln x_i^{\text{cal}})^2}{N} \right]^{1/2} \quad (17)$$

where, N is the number of experimental data point used for regression, x_i^{cal} is the experimental solute mole fraction and x_i^{exp} is the predicted mole fraction by NRTL-SAC model. Figures 2-4 show the regressed data by isqnonlin function and experimental data points of medetomidine salts. Predicted values for solubility seem to be underestimated at low temperature, and as temperature increases, they seem to come closer to the experimental values or even to be overestimated. This behavior can be attributed to the optimization algorithm and the data fitting way of the parameters. After regression, the NRTL-SAC molecular parameters is determined and presented in Table 1.

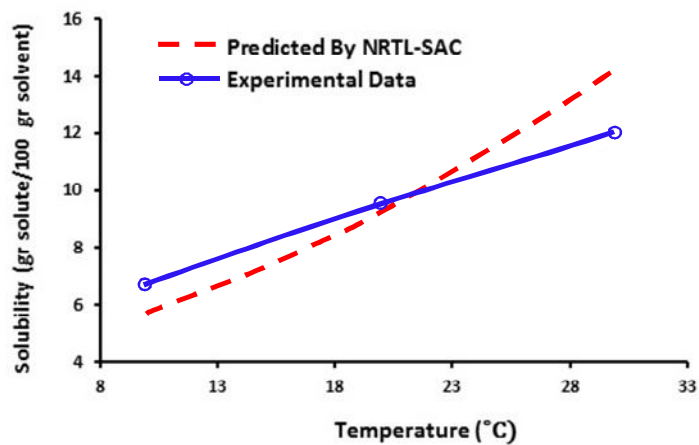


Fig. 2. Experimental and predicted solubility of racemate Med.HBr in 2-propanol.

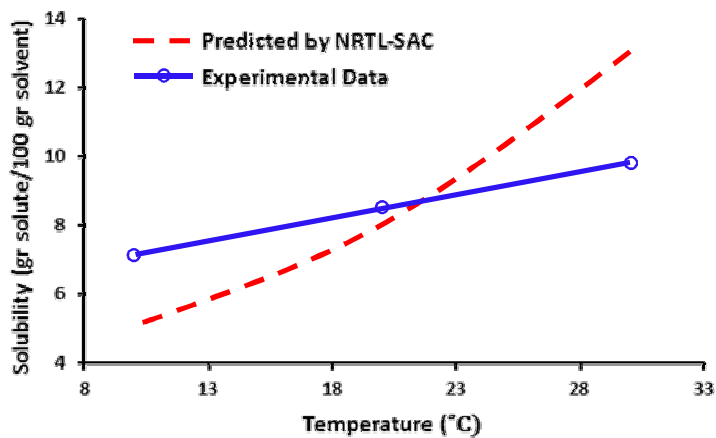


Fig. 3. Experimental and predicted solubility of racemate Med.HCl in 2-propanol.

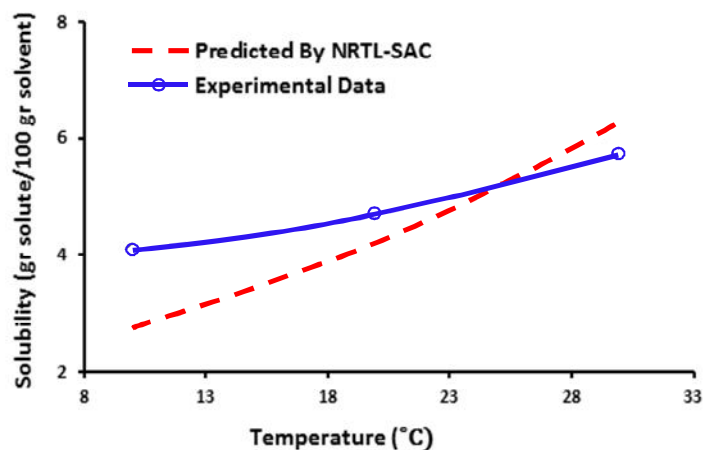


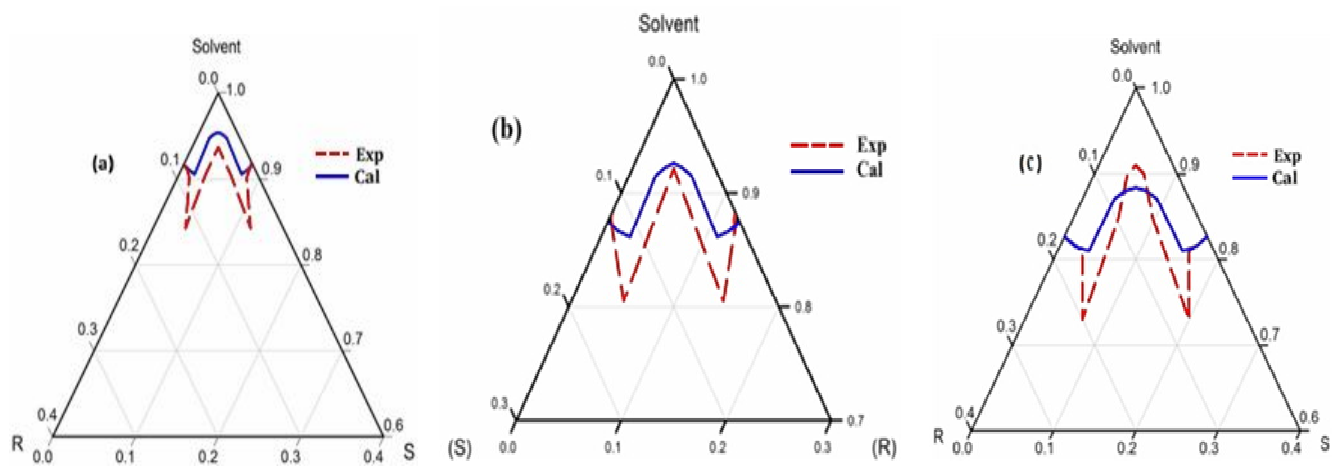
Fig. 4. Experimental and predicted solubility of racemate Med.OX in ethanol.

Table 1. Optimized Segment Number for Solutes

	X	Y ⁻	Y ⁺	Z
Med.HCl	1.8923	0.2303	0.7498	1.5549
Med.HBr	1.0668	0.3345	0.4981	0.9387
Med.Ox	0.0000	0.9400	0.6145	0.0000

Table 2. Calorimetric Data of Medetomidine Salts [24,25]

x_R	T_{IP} (°C)			Δh_{fus} (kJ mol ⁻¹)		
	Med.HCl	Med.HBr	Med.Ox	Med.HCl	Med.HBr	Med.Ox
0	156.0	155.1	175.0	45	28	27.5
0.1	152.0	149.1	167.6	45	28	27.5
0.2	149.8	165.4	161.7	45	34	27.5
0.3	159.4	178.2	154.2	49	34	27.5
0.4	163.5	184.7	145.1	49	34	27.5
0.5	165.0	186.8	135.8	49	34	27.5

**Fig. 5.** Experimental vs predicted ternary phase diagram of Med.HCl in 2-propanol at different temperatures (a: 10 °C, b: 20 °C, c: 30 °C).

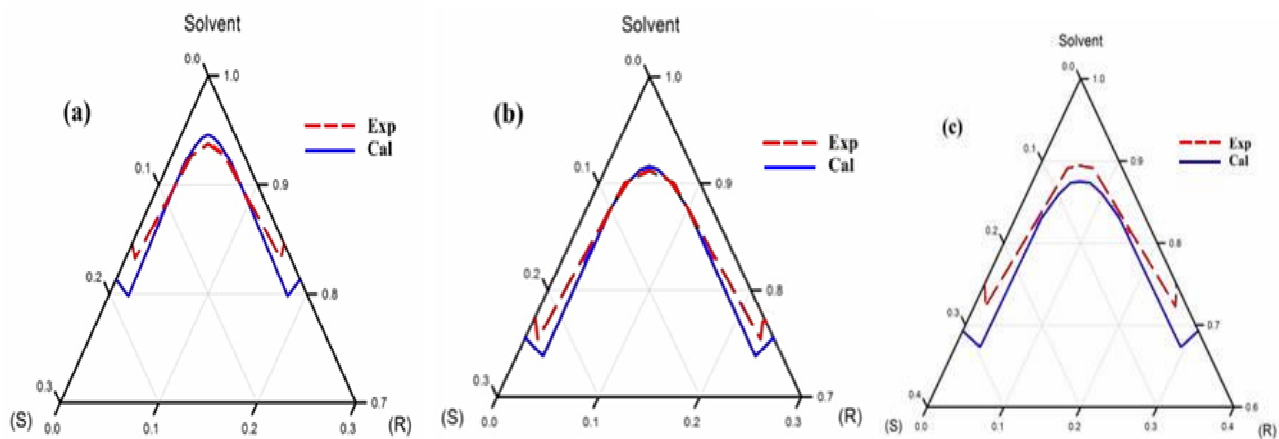


Fig. 6. Experimental vs predicted ternary phase diagram of Med.HBr in 2-propanol at different temperatures (a: 10 °C, b: 20 °C, c: 30 °C).

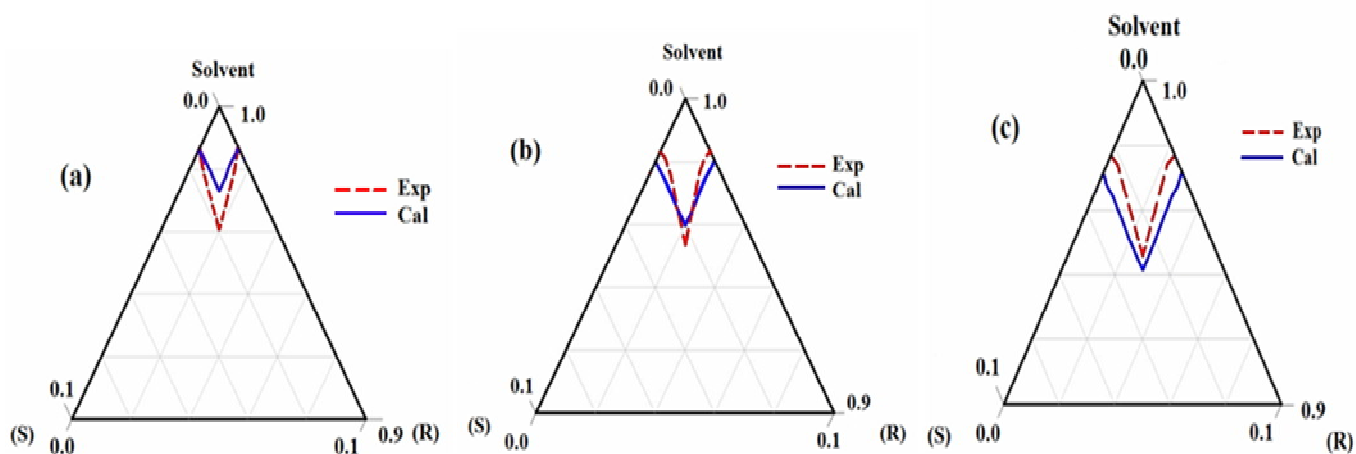


Fig. 7. Experimental vs predicted ternary phase diagram of Med.Ox in ethanol at different temperatures (a: 10 °C, b: 20 °C, c: 30 °C).

Table 3. RMSE for Med.HCl, Med.HBr and Med.OX at 10, 20 and 30 °C

	Med.HCl	Med.HBr	Med.Ox
T = 10 °C	0.38	0.19	0.24
T = 20 °C	0.04	0.08	0.14
T = 30 °C	0.29	0.24	0.20

Ternary Phase Diagram Determination

After determining the NRTL-SAC molecular parameters, the steps below were taken to determine the solubility of other enantiomeric compositions.

1. Guess the initial value for the solubility in a specific enantiomeric composition.
2. Predict the theoretical solubility, determined by NRTL-SAC parameters. Triple point temperature and heat of fusion in this step should be determined by binary phase diagram data. Table 2 shows the experimental binary phase diagram data of medetomidine salts in each enantiomeric composition [24,25].
3. If the predicted solubility is equal to value guessed, assumption is true, if not, the predicted solubility is set based on the value guessed and the procedure is iterated from the first step.

The modeling of ternary phase diagram for each compound is accomplished in enantiomeric compositions of 0.1, 0.2, 0.3, 0.4 and 0.5. The predicted and experimental ternary phase diagram of Med.HCl and Med.HBr in 2-propanol at 10, 20 and 30 °C are respectively presented in Figs. 5 and 6. For both compounds in 2-propanol, eutectic points and enantiomeric compositions are well predicted as to be racemic compound forming systems. The predicted and experimental ternary phase diagram of Med.OX in ethanol at 10, 20 and 30 °C are presented in Fig. 7 showing a conglomerate behavior. RMSE for the three chiral medetomidine salts at 10, 20 and 30 °C (Table 3) presents adequate correlation between the experimental and predicted data.

CONCLUSIONS

There is usually a lack of equilibrium data for ternary phase diagram determination for chiral compound. The use of predictive thermodynamic models can reduce dependency to the experimental equilibrium data. Considering the importance of accessing the ternary phase diagram with fewer amounts of experimental data, NRTL-SAC molecular parameters for chiral medetomidine salts (Med.HCl, Med.HBR and Med.Ox) have been determined using their experimental data (solubility) at racemic point (enantiomeric composition 50/50), and then by an iterative process, having the molecular parameters, the solubility of

other enantiomeric compositions (60/40, 70/30, 80/20, 90/10 and 100/0) have been calculated. Finally, the ternary phase diagrams of medetomidine salts (Med.HCl and Med.HBr in 2-propanol and Med.Ox in ethanol) are determined. RMSE calculated between experimental and predicted data in both racemic and conglomerate systems is relatively small and there is good agreement between experimental and predicted ternary phase diagrams. Main advantage of this method is its simplicity and less need to the experimental data.

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