 Thermodynamic, Computational Solubility Parameters in Organic Solvents and In Silico GastroPlus Based Prediction of Ketoconazole

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ABSTRACT: The study aimed to select a suitable solvent capable to solubilize ketoconazole (KETO) and serve as a permeation enhancer across the skin. Experimental solubility and Hansen solubility parameters were obtained in ethanol, dimethyl sulfoxide (DMSO), ethylene glycol, oleic acid, span 80, limonene, eugenol, transcutol (THP), labrasol, and propylene glycol. Thermodynamic functional parameters and computational models (van’t Hoff and Apelblat) validated the determined solubility in various solvents at $T = 298.2 \text{ K to 318.2 \text{ K}}$ and $P = 0.1 \text{ MPa}$. The HSPIP software estimated the solubility parameters in the solvents. The maximum mole fractional solubility values of KETO were found to be in an order as oleic acid ($8.5 \times 10^{-3}) > \text{limonene} (7.3 \times 10^{-3}) > \text{span 80} (6.9 \times 10^{-2}) > \text{THP} (4.9 \times 10^{-2}) > \text{eugenol} (4.5 \times 10^{-3})$ at $T = 318.2 \text{ K}$. The results of the apparent thermodynamic analysis confirmed that the dissolution rate was endothermic and entropy driven. The GastroPlus program predicted significantly high permeation of KETO ($79.1\%$) in human skin from the KETO-THP construct as compared to drug solution ($38\%$) and excellent immediate release from THP-solubilized construct ($90\% < 1 \text{ h}$). Hence, THP could be a better option for topical, transdermal, and oral formulation.

INTRODUCTION

The incidence of fungal infections occurred about 40 million in developing and under developing nations as per global estimates. Chemically, ketoconazole (KETO) is an azole type ($\pm$) (cis-1-acetyl-4-[4-2,4-dichlorophenyl-2-(1H-imidazol-1-ylmethyl)-1,3-dioxalan-4-ylmethoxy]phenyl]-piperazine) antifungal drug for local and systemic treatments.1 Azole molecules are the first choice option to treat cutaneous and systemic fungal infections. However, the drug possesses poor aqueous solubility (0.04 mg/mL at 25 °C), high partition coefficient ($\log P = 4.31$), and limited oral bioavailability.2 The drug is reported to treat several cutaneous fungal infections such as (a) onychomycosis (nail fungal infection), (b) psoriasis, (c) dermatitis, and (d) fungal infections (Candida species and Cryptococcus neoformans) associated with other diseases (human immunodeficiency virus).3 The poor aqueous solubility challenged the drug for parenteral, oral, and topical delivery to treat these fungal infections. A high oral dose owing to limited aqueous solubility results in dose-related toxic side effects. Therefore, topical and transdermal delivery could be a suitable alternative using a suitable permeation enhancer. Hossin et al. investigated the nail–drug interaction (affinity) using Hansen solubility parameters, which can assist formulation scientists to design a suitable carrier or solvent selection (DMSO, N-methyl pyrrolidone, ethanol, and ethylene glycol) for topical application with improved efficacy.4 Hashemzadeh and Jouyban studied the binary system of ethanol + water mixture for improved solubility of KETO at various temperatures using a Jouyban–Acree model of co-solvency.2 Moreover, authors reported that KETO exhibited the maximum mole fractional solubility (0.117) at 308.2 K when the mass fraction of ethanol in water was 0.8.5 They also reported KETO molar solubilities of $1.40 \times 10^{-5}$ and $2.90 \times 10^{-5}$ at 293.2 and 308.2 K in water, respectively.2 Jouyban et al. explored the solubility of KETO in various polyethylene glycol-200 + water binary systems at various temperature range (298.2–318.32 K) wherein the computational models (Jouyban–Acree and van’t Hoff models) were the best fit to the experimental solubility data within acceptable range of mean relative deviation (MRD) values.6 In further development, polyethylene glycols (of various molecular weights such as 200, 400, and 600) were used for the solubility study of KETO as binary as well as ternary with ethanol or water at 298.2 K. Soltanpour and...
Nazemi investigated that the binary mixture of ethanol + water showed relatively less molar solubility (0.041–3.071) over explored mass fractions (0.1–0.9), whereas the binary mixture of the PEG + water system exhibited higher molar solubility (0.065–3.86 for PEG200, 0.04–9.87 for PEG400, and 0.145–10.71 for PEG600) at the same mass fraction and experimental temperature (298.2 K). They also studied that the binary system of ethanol + PEG revealed increased solubility with increase in the PEG molecular weight (PEG600 > PEG400 > PEG200). Considering these, there are several safe and biocompatible permeation enhancers, which may be explored for solubilizing KETO, which can assist enhanced permeation across the stratum corneum (SC) after topical or transdermal application. These are ethanol, propylene glycol, labrasol, transcutol, eugenol, limonene, span 80, oleic acid, ethylene glycol, and DMSO (dimethyl sulfoxide). KETO (bearing two pKa values such as 2.94 and 6.51) solubility in acetate buffer (pH = 5.0) was reported to be 0.3 mg/mL, and the solubility was increased to 4.6 mg/mL by fabricating as KETO succinate co-crystals. KETO is a weakly basic molecule.

No studies have been conducted for Hansen solubility, thermodynamic parameters, computational validation, and the GastroPlus-based in silico prediction of ketoconazole for topical or transdermal delivery employing these permeation enhancers. Based on experimental solubility values, the GastroPlus software can be applied to predict in vivo performance of the drug solution in a particular solvent (permeation enhancer) responsible for maximized solubility depending on the experimental solubility, Hansen solubility (HSPiP software), and thermodynamic parameters. Moreover, the software can predict the effect of physicochemical properties of the drug for improved permeation across the human skin. Thus, the solubility of KETO in these permeation enhancers and their validation parameters (thermodynamic and computational models) are required in pre-formulation study.

In this study, HSPiP assisted to select the most relevant organic solvent (permeation enhancers) based on three solubility parameters (three-dimensional Hansen solubility and space parameters), which are designated as δ_d as the dispersion parameter, δ_p as the polarity parameter, and δ_h as the hydrogen parameter. The solubility study was conducted over various temperature range (T = 298.2 to 318.2 K) and fixed pressure (P = 0.1 MPa). The study was performed at a temperature below its melting point (146.7 °C) (Figure 1B). These parameters were modeled to correlate the experimental solubility data. Furthermore, the apparent thermodynamic analysis and computational models regressed the experimental data and validated the studied solubility models, respectively. Molecular interaction between the drug and solvents was also studied. Finally, the GastroPlus simulation and prediction modules investigated major factors affecting the solubility of the drug and pharmacokinetic parameters when formulated for oral or topical delivery in the best solvent.

**RESULTS AND DISCUSSION**

**Characterization of KETO in the Solid Phase.** KETO is a highly crystalline compound with poor aqueous solubility. The pure drug and equilibrated KETO (with methanol) were characterized for solid phases using a differential scanning calorimeter (DSC), and the result (thermogram) is illustrated in Figure 1B. A characteristic endothermic peak indicated a fusion temperature (T_fus) along with the marked value of the
Table 1. Mole Fractional Experimental Solubility ($x_i$) of Ketoconazole at Varied Temperatures $T = 298.2−318.2$ K and Pressure = 0.1 MPa

| solvent         | 298.2 K | 303.2 K | 308.2 K | 313.2 K | 318.2 K |
|-----------------|---------|---------|---------|---------|---------|
| ethanol         | $2.1 \times 10^{-4}$ | $2.8 \times 10^{-4}$ | $3.7 \times 10^{-4}$ | $4.9 \times 10^{-4}$ | $5.6 \times 10^{-4}$ |
| DMSO            | $2.5 \times 10^{-4}$ | $2.9 \times 10^{-4}$ | $3.4 \times 10^{-4}$ | $4.2 \times 10^{-4}$ | $4.9 \times 10^{-4}$ |
| ethylene glycol | $0.2 \times 10^{-4}$ | $0.3 \times 10^{-4}$ | $1.0 \times 10^{-4}$ | $1.3 \times 10^{-4}$ | $1.7 \times 10^{-4}$ |
| oleic acid      | $5.8 \times 10^{-3}$ | $6.3 \times 10^{-3}$ | $6.9 \times 10^{-3}$ | $7.5 \times 10^{-3}$ | $8.5 \times 10^{-3}$ |
| span 80         | $4.7 \times 10^{-3}$ | $5.1 \times 10^{-3}$ | $5.7 \times 10^{-3}$ | $6.2 \times 10^{-3}$ | $6.9 \times 10^{-3}$ |
| limonene        | $5.1 \times 10^{-3}$ | $5.5 \times 10^{-3}$ | $6.1 \times 10^{-3}$ | $6.8 \times 10^{-3}$ | $7.3 \times 10^{-3}$ |
| eugenol         | $3.5 \times 10^{-3}$ | $3.7 \times 10^{-3}$ | $4.1 \times 10^{-3}$ | $4.2 \times 10^{-3}$ | $4.5 \times 10^{-3}$ |
| THP             | $3.2 \times 10^{-3}$ | $3.4 \times 10^{-3}$ | $3.9 \times 10^{-3}$ | $4.3 \times 10^{-3}$ | $4.9 \times 10^{-3}$ |
| labrasol        | $2.8 \times 10^{-3}$ | $3.1 \times 10^{-3}$ | $3.5 \times 10^{-3}$ | $3.9 \times 10^{-3}$ | $4.4 \times 10^{-3}$ |
| propylene glycol| $0.1 \times 10^{-4}$ | $1.2 \times 10^{-4}$ | $1.6 \times 10^{-4}$ | $2.3 \times 10^{-4}$ | $2.8 \times 10^{-4}$ |

$x_i^{10}$

Table 2. Various Hansen Solubility ($x_i$) Parameters of KTZ in Various Permeation Enhancers (Solvents)

| solvent         | $\delta_d$ | $\delta_p$ | $\delta_h$ | $\delta$ | $\delta_u$ | $\Delta\delta$ | $\Delta\delta^+$ |
|-----------------|-------------|-------------|-------------|----------|------------|----------------|------------------|
| ketoconazole     | 21.6        | 11.9        | 6.2         | 25.4     | 15.9       | 2.20           | 16.64            |
| ethanol         | 15.3        | 8.9         | 19.1        | 25.1     | 11.0       | 4.47           | 16.89            |
| DMSO            | 10.2        | 16.8        | 10.2        | 24.8     | 6.6        | 2.61           | 17.33            |
| ethylene glycol | 17.2        | 11.1        | 26.4        | 35.8     | 22.6       | 0.18           | 25.67            |
| oleic acid      | 16.1        | 7.3         | 5.8         | 17.2     | 6.6        | 2.61           | 17.33            |
| span 80         | 16.2        | 6.5         | 7.1         | 19.7     | 6.72       | 2.9            | 17.16            |
| limonene        | 17.2        | 2.1         | 4.3         | 18.9     | 5.92       | 2.91           | 10.41            |
| eugenol         | 19.4        | 7.2         | 12.9        | 22.9     | 5.14       | 0.41           | 12.65            |
| THP             | 16.3        | 7.1         | 10.2        | 21.8     | 4.13       | 2.51           | 2.93             |
| labrasol        | 15.8        | 4.1         | 8.7         | 20.1     | 9.32       | 3.96           | 10.00            |
| propylene glycol| 17.1        | 10.1        | 21.8        | 28.1     | 18.00      | 0.42           | 25.50            |

IPA = isopropyl alcohol; IPM = isopropyl myristate; THP = transcutol HP; EA = ethyl acetate.
ethanol were found to be $2.1 \times 10^{-4}$, $2.8 \times 10^{-4}$, $3.7 \times 10^{-4}$, $4.9 \times 10^{-4}$, and $5.6 \times 10^{-4}$ at $T = 298.2 \, \text{K}$, $T = 303.2 \, \text{K}$, $T = 308.2 \, \text{K}$, $T = 313.2 \, \text{K}$, and $T = 313.2 \, \text{K}$, respectively. Recently, the drug molar solubility values in ethanol were reported to be $2.2 \times 10^{-3}$, $2.6 \times 10^{-3}$, and $2.9 \times 10^{-3}$ at $T = 298.2 \, \text{K}$, $T = 303.2 \, \text{K}$, and $T = 308.2 \, \text{K}$, respectively. The slight differences at the corresponding temperatures may be due to differences in pressure (0.1 MPa). However, the differences in the molar solubility with the increase in temperature were not significant, which are in accordance with the reported pattern. Hashemzadeh and Jouyban did not investigate the molar solubility of KETO in ethylene glycol and propylene glycol are 1.7 MPa1/2.

The drug was poorly water soluble being crystalline in nature. Therefore, the increased drug solubility may be correlated with the lipophilic–lipophilic-enabled (solute–solvent) interaction (like dissolves like). On the other hand, labrasol, ethanol, propylene glycol, and ethylene glycol exhibited quite lower values of $x_d$ which are due to the high polarity $\delta_p$ of solvents. Oleic acid and span 80 showed similar values of HSPs parameters, which may be a reason for closeness in experimental solubility ($x_e$), space parameter ($\delta_s$), and total solubility ($\Delta \delta_s$) values as shown in Table 2. Oleic acid and propylene glycol are 1.7 $\times$ 10−4 and 2.8 $\times$ 10−4, respectively, which may be due to higher values of $\delta_p$ (26.4 for ethylene glycol and 21.8 for propylene glycol) compared to KETO (6.2). This may have led to limited interaction (hydrogen bonding interaction) between the drug and solvent resulting least solubility (Tables 1 and 2). Ethylene glycol showed an approximate value of the Hansen solubility parameters ($\delta_p$, 11.1), which was close to that of the drug (11.9). However, the drug was found to be the least soluble, which may be due to weak dispersion in the solvent ($\delta_p$ = 17.2). In this context, the drug was found maximally solubilized in oleic acid due to poor solubility of the solvent and hydrophobic–hydrophobic facilitated interaction. Thus, the solvents such as oleic acid, THP, span 80, and limonene can be proposed as suitable solvents for developing formulation intended for transdermal or topical delivery of rifampicin working as a carrier as well as permeation enhancer if laden with the drug.

**Solubility Parameters of KETO and Studied Solvents using Various Models.** We used all of the HSPs parameters for the drug and solvents as shown in Table 2. The value of $\delta$ of KETO was predicted to be 25.4 MPa1/2 and polarity parameter was estimated to be 11.9 MPa1/2 suggesting weak interaction with hydrophilic/polar solvents. Therefore, the drug was found to have maximum $x_d$ data in a permeation enhancer with high hydrophilicity and low polarity ($\delta_p$) (oleic acid, THP, span 80, and limonene). It is noteworthy that calculated values of $R_u$ for oleic acid (6.6), span 80 (6.7), limonene (5.92), eugenol (5.14), and THP (4.13) were <10.0 MPa1/2, suggesting augmented miscibility of the drug in these solvents. In general, the value of $R_u$ of <10.0 MPa1/2 is considered as “good soluble” or “miscible of solute”.

However, there are contradictory findings among the literature values. Few authors correlated this value as soluble (around 10 MPa1/2). In the other case, the values of $R_u$ for limonene, eugenol, THP, span 80, and oleic acid are in the range of 5.6–8.0 MPa1/2 and these could be considered as the most suitable permeation enhancers for topical or transdermal delivery. There are few reports where authors could not find any values of the $R_u$ value close to 5.6 MPa1/2 in all explored solvents. However, they agreed and defined the solubility of the solute as soluble considering the $R_u$ value of 8.0 close to 5.6 MPa1/2. Thus, THP, limonene, span 80, oleic acid, and eugenol can be considered as a first series of solvents for good solubility/miscibility of KETO among them. Furthermore, the values of other parameters such as $\Delta \delta^*$ and $\Delta \delta$ were estimated in the solvents. The value of $\Delta \delta$ ranged from 0.18 to 4.74 MPa1/2 for the studied solvents, which indicated within the acceptable range (<10.0 MPa1/2). This parameter ($\Delta \delta$) was minimum for ethylene glycol (0.18 MPa1/2), propylene glycol (0.42 MPa1/2), and eugenol (0.41 MPa1/2), as shown in Table 2. As per the literature, the value of $\Delta \delta$ of <7.0 MPa1/2 was considered as the most soluble or miscible of a solute in a given solvent. Considering the values of $R_u$ and $\Delta \delta$, limonene, eugenol, and THP are the most preferred solvents being capable of solubilizing hydrophobic KETO. In the case of propylene glycol and ethylene glycol, the values of $\Delta \delta$ are the least but the $R_u$ values are quite high. This might be due to the fact that the dispersion ability of the drug as observed in the $\delta_p$ of the Hansen solubility parameter for eugenol ($\delta_p = 19.0$) is the closest value to KETO (21.6). Similarly, the $\Delta \delta^*$ values of KETO were determined using van Krevelen and Hoftyzer equations. However, the value of $\Delta \delta^*$ of <5.0 MPa1/2 is good for improved solubility or miscibility. The values of $\Delta \delta^*$ are found to be >10.0 MPa1/2 in all explored permeation enhancers except THP (2.93 MPa1/2) as shown in Table 2. A solvent is selected with the lowest value of $\Delta \delta^*$ of the Hansen solubility parameter. The estimated values of $\Delta \delta^*$ were observed to be 2.93, 10.0, and 10.41 MPa1/2 for THP, labrasol, and limonene, respectively, wherein the THP exhibited the minimum value. Thus, these Hansen solubility parameters ($R_u$, $\Delta \delta^*$, and $\Delta \delta$) are in an acceptable range as compared to other solvents, which showed good solubility of KETO in THP. Thus, THP could be considered as the most suitable solvent (permeation enhancer), whereas ethylene glycol is the solvent with poor solubility of KETO. There is a correlation that exists between the solubility of a solute in a solvent and their solubility parameters. In addition, several factors are responsible for KETO solubility in the solvent and these are the molar mass volume and molecular interaction (inter and intra). The objective of the study was to select a permeation enhancer with dual functionality (permeation enhancer and carrier) in developing topical or transdermal formulation. Therefore, considering Hansen solubility parameters and space parameter ($R_u$), THP could be the best permeation enhancer and suitable solvent when fabricated in a nanocarrier system intended for topical or transdermal delivery.

**Estimation of Ideal Solubility ($x^{idl}$) and Activity Coefficient ($Y_i$).** These values were estimated to identify the most suitable solvent responsible for maximum solubility of KETO and serving as the potential permeation enhancer. Moreover, the estimated value of $Y_i$ assists to find a molecular interaction between the solute and the solvent. Initially, the $x^{idl}$ of KETO was estimated to calculate the value of the activity coefficient. Tables 1 and 3 summarize the values of $x^{idl}$ and $Y_i$ of KETO in various permeation enhancers, respectively. The ideal solubility values ($x^{idl}$) of KETO were found to be 0.38 $\times$ 10−3 to 1.37 $\times$ 10−3 at $T = 298.2$ to 318.2 K (Table 1). The experimental solubility $x_e$ of KETO in oleic acid was found to be significantly ($p < 0.05$) higher than the ideal solubility ($x^{idl}$) values at $T = 298.2$ and 303.2 K, whereas this pattern decreases beyond the temperature of 303.2 K (Table 1). Ethanol, DMSO, ethylene glycol, and propylene glycol showed experimental solubility values of KETO lower than the ideal value.
solvents suitable for KETO solubilization. The estimated values of activity coefficient ($\chi_i$) of KETO at varied temperatures ($T = 298.2−318.2$ K) are tabulated in Table 3. The values were in the range of 0.75–1.87, 1.0–1.98, and 0.11–1.18 in limonene, eugenol, and THP, respectively. Moreover, the $\chi_i$ values were relatively higher in DMSO, ethylene glycol, propylene glycol, labrasol, and ethanol as compared to THP, limonene, and eugenol estimated at $T = 298.2$ K, 303.2, 308.2, 313.2, and 318.2 K. That may rationalize that these three solvents might have maximized the solute–solvent molecular interaction, which can be ordered as “KETO-THP > KETO-limonene > KETO-Eugenol” combination. Improved solubilization in THP may be attributed to formation of intermolecular hydrogen bonding between the hydroxyl group of THP and the imidazole nitrogen atom. Conclusively, THP, limonene, and eugenol may be the most preferred solvents to solubilize KETO.

### Table 3. Activity Coefficient ($\chi_i$) of Ketoconazole at Varied Temperatures ($T = 298.2−318.2$ K)\(^{\text{a}}\)

| solvent      | 298.2 K | 303.2 K | 308.2 K | 313.2 K | 318.2 K |
|--------------|---------|---------|---------|---------|---------|
| ethanol      | 1.81    | 1.89    | 1.98    | 2.05    | 2.44    |
| DMSO         | 1.52    | 1.83    | 2.16    | 2.41    | 2.79    |
| ethylene glycol | 1.93    | 3.65    | 7.35    | 7.75    | 8.06    |
| oleic acid   | 1.65    | 1.84    | 1.76    | 1.84    | 2.61    |
| span 80      | 0.80    | 1.04    | 1.28    | 1.62    | 2.21    |
| limonene     | 0.74    | 0.96    | 1.20    | 1.48    | 1.87    |
| eugenol      | 1.00    | 1.43    | 1.69    | 1.85    | 1.98    |
| THP          | 0.11    | 0.56    | 0.88    | 1.03    | 1.18    |
| labrasol     | 1.35    | 1.71    | 2.10    | 2.58    | 3.11    |
| propylene glycol | 3.80    | 4.43    | 4.59    | 4.83    | 4.98    |

\(\text{DMSO} = \text{dimethyl sulfoxide}; \text{THP} = \text{transcutol HP.}\)

![Figure 2. Correlation of ln$x$ values of ketoconazole with the Apelblat model in various organic solvents as a function of 1/T.](https://dx.doi.org/10.1021/acsomega.0c06234)

### COMPUTATIONAL VALIDATION

The objective of the study was to investigate a suitable permeation enhancer working as a solvent to solubilize KETO and a potential skin permeation when formulated as topical or transdermal formulation. Therefore, experimental solubility data were generated at various temperatures (selected based on Hansen solubility parameters). The data needed to be validated using two known validation computational models such as the Apelblat model and van’t Hoff model. Using both of them, a graphical correlation was established between the ln$x$ and ln$x$\(^{\text{apl}}\) of KETO as a function of 1/T (Figure 2). The computational validation results are presented in Table 4, which corroborated a good correlation between ln$x$ and ln$x$\(^{\text{apl}}\) (Figure 2). Moreover, the estimated values of the percent relative mean square deviation (%RMSD) and overall %RMSD of the drug in all studied solvents were 0.011–0.848 and 0.136, respectively (Table 4). In Table 4, the values of $A$, $B$, and $C$ represent the Apelblat solubility parameters, which were estimated using the Apelblat equation. To analyze this model for each solvent, the value of $\rho^2$ (regression coefficient) was found to be $\geq 0.99$, vindicating a good correlation of ln$x$ of KETO in all studied solvents.

Similar experimental analysis was carried out using the van’t Hoff model wherein a graphical correlation between ln$x$ and ln$x$\(^{\text{van}}\) as a function of 1/T was demonstrated, suggesting a good correlation (Figure 3). Likewise, the estimated values of the %RMSD, overall %RMSD, model parameters ($a$ and $b$), and regression coefficient are presented in Table 5. The estimated values of %RMSD and overall %RMSD were found to be 0.011–0.178 and 0.0478, respectively (Table 5) for all studied solvents. The estimated values of $\rho^2$ in each solvent were found to be $\geq 0.09$. Thus, both models validated the experimental solubility data studied in various solvents at varied temperatures by establishing a good graphical correlation and estimating model parameters.

**Thermodynamic Parameters.** Thermodynamic functional parameters are required to explain the mechanistic view of KETO solubility in individual solvent at various temperatures. These function parameters are based on physical changes (events) and represented as $\Delta_{\text{sol}}G^0$, $\Delta_{\text{sol}}H^0$ and $\Delta_{\text{sol}}S^0$. The computational validation results are presented in Table 4, which corroborated a good correlation between $\ln x$ and $\ln x^{\text{apl}}$ (Figure 2). Moreover, the estimated values of the percent relative mean square deviation (%RMSD) and overall %RMSD of the drug in all studied solvents were 0.011–0.848 and 0.136, respectively (Table 4). In Table 4, the values of $A$, $B$, and $C$ represent the Apelblat solubility parameters, which were estimated using the Apelblat equation. To analyze this model for each solvent, the value of $\rho^2$ (regression coefficient) was found to be $\geq 0.99$, vindicating a good correlation of $\ln x$ of KETO in all studied solvents.

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In a mathematical equation. We rationalized the process of KETO solubility in studied solvents by thermodynamic analysis and using three thermodynamic solubility function parameters. These functional parameters were estimated for KETO in various solvents and are presented in Table 6. The calculated values of $\Delta_{sol}G^\circ$, $\Delta_{sol}H^\circ$ and $\Delta_{sol}S^\circ$ were found in the range of 1195.7–10820.7, 13071.9–22501.2, and 28.4–56.92 kJ mol$^{-1}$, respectively, in the investigated solvents. It is apparently clear from the result that oleic acid, span 80, limonene, eugenol, and THP showed relatively low values of the free energy ($\Delta_{sol}G^\circ$) of dissolution as compared to other solvents. Similarly, limonene, eugenol, and THP showed the values of $\Delta_{sol}S^\circ$ to be 27.07, 22.34, 20.2 kJ mol$^{-1}$, respectively, which were the minimum values.

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$$\Delta_{sol}S^\circ$$ in a mathematical equation. We rationalized the process of KETO solubility in studied solvents by thermodynamic analysis and using three thermodynamic solubility function parameters. These functional parameters were estimated for KETO in various solvents and are presented in Table 6. The calculated values of $\Delta_{sol}G^\circ$, $\Delta_{sol}H^\circ$ and $\Delta_{sol}S^\circ$ were found in the range of 1195.7–10820.7, 13071.9–22501.2, and 28.4–56.92 kJ mol$^{-1}$, respectively, in the investigated solvents. It is apparently clear from the result that oleic acid, span 80, limonene, eugenol, and THP showed relatively low values of the free energy ($\Delta_{sol}G^\circ$) of dissolution as compared to other solvents. Similarly, limonene, eugenol, and THP showed the values of $\Delta_{sol}S^\circ$ to be 27.07, 22.34, 20.2 kJ mol$^{-1}$, respectively, which were the minimum values.

<Figure 3. van’t Hoff plot for ketoconazole plotted between ln$x$ and $(1/T - 1/T_{hm})$ for the drug in various organic solvents.>
values among them. These solvents can be ordered for $\Delta_{\text{sol}} S^\circ$ as limonene > eugenol > THP, suggesting THP as the most suitable solvent for KETO. The estimated values of $\Delta_{\text{sol}} S^\circ$ were the maximum in ethanol, DMSO, ethylene glycol, and propylene glycol, which indicated that these solvents could be considered as solvents for poor solubility of KETO due to hydrophilicity and high polarity solvent resulting in weak solute–solvent molecular interaction (Table 6). As per the concept of thermodynamics, a reaction or a process is said to be spontaneous (negative free energy) when the change in free energy $\Delta_{\text{sol}} G^\circ$ decreases. Thus, KETO solubilization in limonene, THP, and eugenol was a spontaneous process resulting in a significant change in $\Delta_{\text{sol}} G^\circ$, providing a suitable thermodynamic environment for increased solubility.20 In addition, the lower values of $\Delta_{\text{sol}} S^\circ$ for THP, limonene, and eugenol further supported a reasonable explanation for the increased solubility of KETO in these permeation enhancers. It is quite interesting to note that the negative enthalpy values of dissolution in limonene, eugenol, and THP may be due to the possible hydrophobic interaction with the non-polar functional groups (methyl, methylene, and aromatic rings) of KETO as shown in Figure 1A.21 Apart from these, there are several factors responsible for the solubility of KETO in these solvents or permeation enhancers. These are physicochemical behavior of the solute and solvent, hydrogen bond formation with non-polar groups of the drug, solute–solvent interaction, and co-solvency using a binary mixture of organic solvent with water. Very recently, it was reported that ethanol used as co-solvent with water increased the solubility of KETO due to breaking the ordered structure of water stabilized with hydrogen bonding around the non-polar groups of KETO, which caused increased values of enthalpy and entropy of the system.20

**GastroPlus Prediction Studies.** The software program is basically to simulate *in vitro* data and prediction of *in vivo* performance based on the input parameters (Table 7). We added the values of *in vitro* drug release in *in vitro* data tab for pure KETO and THP-solubilized drug. Neat KETO (suspension) exhibited % drug releases of 8.4, 12.0, 25.1, 31.6, and 39.9% at the time points of 0.5, 1, 2, 4, and 8 h, respectively, in phosphate buffer solution (pH 7.4). Similarly, THP-solubilized KETO exhibited % drug releases of 25.7, 56.9, 67.3, 75.2, and 87.7% at the same time points. The release data was also modeled for the Weibull release distribution pattern using the GastroPlus simulation. The results are illustrated in Figure 4A,B. Figure 4A and Figure 4B shows the *in vitro* release pattern of the neat KETO suspension and THP-solubilized drug (10 mg/mL), respectively. The neat KETO suspension and THP-solubilized drug revealed maximum drug releases of 39.9 and 87.7% at the end of 8 h, respectively. The Weibull-modeled graph (single Weibull) showed that the release distribution followed a sigmoidal pattern as evidenced with shape factors (b shape values) of 1.47 and 1.57, for suspension and THP-solubilized KETO (blue solid lines of Figure 4A,B). It is obvious from the release graphs that this model may not be the only prefect release model to confirm immediate and controlled release behavior of the drug. However, all of the other parameters affecting the drug release (such as pH, amount, pKa, polarity, logP, density, and temperature) should be figured out and controlled.22,23

Furthermore, the software PBPK model predicted the amount of the drug permeated across human skin (70 Kg) when applied to the skin (arm). The predicted values of KETO cream (considering pure drug = 0.2 mg) and THP-solubilized KETO (0.2 mg as solution) are illustrated in Figure 4C and 4D, respectively where the neat drug cream and THP-solubilized KETO showed 38.0% and 79.1%, respectively. This may be correlated with improved solubilization and permeation potential of THP explored for several poor soluble drugs. This skin penetration and permeation may be attributed to the facilitated drug partitioning and diffusion. The THP is reported as the most suitable skin permeation enhancer possibly due to capable of increasing flux (21 times higher) and diffusion coefficient (17 times) higher than the hydrated skin.23

The neat KETO is a hydrophobic and weak water soluble molecule. However, THP-solubilized KETO was anticipated to have high permeation across human skin on topical application and enhanced absorption through intestinal membrane when administered oral. Therefore, the software based prediction study suggested that the dissolution rate (0.1 mg as input parameter of topical dose) of the drug and skin absorption (at pH 5.6 as simulated pH of human skin) was within 1 h as shown in Figure 5. The inset graph of Figure 5 depicted the immediate absorption (*in vivo*) profile of THP-solubilized KETO when administered orally. This could be possible due to improved drug solubility and enhanced permeation attributed to the solvent (THP).22 However, the preclinical study using a suitable animal requires generating a complete proof of concept for topical/transdermal/oral formulation of KETO using THP as a solvent and permeation enhancer.

**Significance of the Explored Permeation Enhancers.** In this study, the term “solvent” was used collective for the organic solvent, lipid, and surfactants responsible for improved solubilization and skin permeation if laden with the drug. KETO is a choice drug for several topical fungal diseases, which need to be addressed with new excipients exhibiting dual functionality such as solubilization as well as skin permeation. Based on the Hansen solubility parameter, 10 solvents were predicted for KETO solubility and possible interaction. The solubility experimental data were validated using thermodynamic functional terms and computational models. Thus, the result of this study would assist formulation scientists (transdermal and topical) during the preliminary study for the selection of the organic phase considering the solubility and skin permeation enhancer. We found limonene (terpene),

---

**Table 7. Summary of the Input Parameters of Ketoconazole for the GastroPlus-Based Prediction Study**

| input parameters         | value                          |
|--------------------------|--------------------------------|
| empirical formula        | C_{26}H_{28}Cl_{2}N_{4}O_{4}   |
| molecular weight (g/mole)| 531.04                         |
| melting point (°C)       | 146                            |
| log P value              | 4.35                           |
| pKa                      | 3.96 (amine) and 6.74 (imine)   |
| aqueous solubility (mg/mL at 25 °C) | 0.24                        |
| apparent permeability (×10^{-4} cm/s) | 0.75                             |
| dosing volume (mL)       | 1.0                            |
| dose (mg)                | 2.0                            |
| body weight (Kg)         | 60.0                           |
| total clearance (L/h)    | 8.66                           |
| elimination half-life (h) | 8.0                            |
| volume of distribution (L/Kg) | 0.36 (25.41 L)                |
| protein binding capacity (%) | 84                        |
| simulation time (h)      | 12                             |
eugenol, and THP as the most suitable solvents (permeation enhancer) intended for topical and transdermal formulation. In several literature studies, these excipients are well established for the skin permeation potential of poor soluble drugs. There is scarcity of in vivo data in human to establish a direct correlation with in vitro findings. However, we predicted in vitro release kinetics, the drug absorption across human skin (left arm), and compared between the neat drug and THP-solubilized KETO using the GastroPlus predictive modules.

CONCLUSIONS
KETO is extremely poorly soluble in water and a well-established antifungal candidate to control cutaneous fungal infections. Data of experimental and Hansen solubility parameters suggested that several permeation enhancers can be a suitable option for the drug solubilization and skin permeation enhancing effect. The thermodynamic functional parameters and computational models validated the experimental solubility carried out at varied temperature. No transformation occurred in KETO extracted from methanol as evidenced by the DSC result. Two models such as the van’t Hoff and Apelblat were employed to validate the results of experimental solubility. All of the solvents exhibited a significant ($p < 0.05$) proportional relationship of the experimental solubility values with temperature. This may be rationalized that these three solvents were found to have maximum solute–solvent molecular interaction, which can be ordered as KETO-THP > KETO-limonene > KETO-Eugenol combination at $T = 318.2$ K as compared to other combinations. The GastroPlus program software predicted a maximized drug content permeated (THP solubilized) in human skin as compared to the drug solution. Moreover, there was a good correlation between in vitro drug dissolution and permeation (absorption across the skin) when predicted for

Figure 4. GastroPlus-based simulation and prediction study: (A) In vitro drug release behavior and Weibull model distribution of neat ketoconazole suspension (blue line for sigmoidal release pattern), (B) in vitro drug release behavior and Weibull model distribution of THP solubilized ketoconazole (blue line for sigmoidal release pattern) in buffer solution (pH 7.4), (C) skin absorption of neat ketoconazole from suspension, and (D) skin absorption of THP-solubilized ketoconazole.
solution.25 mobile phase was adjusted to 9.0 using a 0.01 N NaOH sensitivity of the analysis was 0.005 to 0.010 using a reverse phase C18 column (150 mm adopted as per the reported method.24 Analysis was performed Waters, Empower 2 software, USA), and the procedure was validated HPLC (high-performance liquid chromatography, reagents were of analytical grade. purchased from Merck Chemicals Mumbai, India. All of the oleic acid, eugenol, limonene, DMSO, and ethanol were Saint Priest Cedex France). Span 80, ethanol, ethylene glycol, from Gatte

Thu 30th, 2019 GMT

Figure 5. GastroPlus-based prediction of a relationship between dissolution and skin permeation of ketoconazole dissolved in THP. The inset of the figure predicted the plasma concentration time profile of THP solubilized ketoconazole when administered orally (0.1 mg).

EXPERIMENTAL METHODS

Materials. KETO was procured from Sigma-Aldrich, (India). Transcutol HP and labrasol were obtained as ex gratia from Gattefosse (36 chem de Genas-BP 603-F-69804 Saint Priest Cedex France). Span 80, ethanol, ethylene glycol, oleic acid, eugenol, limonene, DMSO, and ethanol were purchased from Merck Chemicals Mumbai, India. All of the reagents were of analytical grade.

Analytical Methodology. The drug was assayed using a validated HPLC (high-performance liquid chromatography, Waters, Empower 2 software, USA), and the procedure was adopted as per the reported method.24 Analysis was performed using a reverse phase C18 column (150 mm x 46 mm, 5 μm), at a flow rate of 1 mL/min and UV detector at 254 nm. The mobile phase was composed of acetonitrile, water, and diethylamine (70:30:0.05, v/v). The mobile phase was sonicated, and then used in the system using 10 μL as the injection volume (sample). The set run time was 10 min with a constant operating temperature of 20 ± 1 °C (Figure 1C). The sensitivity of the analysis was 0.005 to 0.010 μg/mL with a regression coefficient (r2) of 0.9999. The final pH of the mobile phase was adjusted to 9.0 using a 0.01 N NaOH solution.

Differential Scanning Calorimeter: Thermal Analysis. In order to observe any possible transition in analytical solvent, pure KETO was completely recovered from the equilibrated KETO in methanol (slow evaporation method) and assessed for thermal parameters (fusion temperature and enthalpy) using a DSC method (DSC-50, Shimadzu, Japan). This analysis was conducted to find probable chances of transition in the explored organic solvents, possible impurities, and drug degradation over the studied temperature range. An accurately weighed amount (4.0 mg) of both samples (pure and recovered) were transferred into an aluminum pan, sealed (hermatically), and then kept in the furnace chamber (sample holder). The samples were heated at the heating rate of 10 °C/ min till 200 °C followed by cooling after completion of heating (nitrogen flow of 20.0 mL/min) for the next sample. The result of DSC was presented in DSC spectral peaks containing the values of endothermic peaks and fusion enthalpy (ΔHfusion J/g). The DSC cell was calibrated using indium (melting point of 156.8 °C and ΔHfusion of 28.71 J/g).

Solubility Assessment. The experimental solubility (xE) of KETO was studied in PG (propylene glycol), labrasol, THP (transcutol HP), eugenol, limonene, span 80, oleic acid, ethylene glycol, DMSO, and ethanol, which are of GRAS (generally regarded as safe) organic solvents and major skin permeation enhancer in topical formulations. The study was performed at five temperature points (T = 298.2, 303.3, 308.2, 313.2, and 318.2 K) and constant pressure (0.1 MPa) following the reported method. In brief, the weighed amount of KETO was added to 5 mL of each organic solvent separately followed by shaking in a water bath shaker for 12 h (Remi Equipment Pvt. Ltd., Mumbai, India). The study was continued till equilibrium was attained between the dissolved and undissolved KETO. The dissolved content (μg g−1) was estimated using validated HPLC at a λmax of 254 nm. Analysis was carried out in triplicate (n = 3) for mean and ± SD values.

Experimental solubility (xE) = \[ \frac{m_1 M_2}{m_2 M_1} \]  (1)

where m1 and M1 are the mass and the molar mass of KETO, respectively. Similarly, m2 and M2 represent the mass and the molar mass of the solvent, respectively.

Solubility Parameters. Hildebrand and Scott introduced the idea of the solubility parameters based on the solubility behavior of the solute in a specific solvent.26 Hildebrand and Scott considered that the inherent cohesive energy (criterion of attractiveness) of any solute is a necessary factor to separate molecules or ions or atoms from the parent compound and is related to the solubility parameters.27 It is noticeable that the solubility of any solute is maximum when the difference between the polarity parameter of the solute (δp) and the
solvent is approximately zero \[ \Delta(\delta^m - \delta^e) = 0 \]. The Hildebrand principle could be applied to the simple liquid mixture being used in pharmaceutical manufacturing such as oral solution, parenteral product, and topical formulation (solution). However, this concept does not fit for the complex pharmaceutical mixture based products. For this, the principle was further extended by establishing new approach named as the Hansen approach to understand the complex mixture and associated interactions between the solute and the solvent. Theoretically, the Hansen theory depends upon the divided associated interactions between the solute and the solvent. Thus, there are various established approaches based on the concept of solubility parameters responsible for main interactions between the solute and organic solvent.

In a new approach, the three-dimensional Hansen solubility parameter (3D-HSP, \( \delta \)) was obtained by the sum of the square of the individual parameters:

\[
\delta^2 = (\delta_d)^2 + (\delta_p)^2 + (\delta_h)^2
\]

(3)

Thus, 3D-HSP (\( \delta \)) of KETO and individual solvent was calculated using HSPiP software (version 5.0.1, Louisville, KY, USA) using eq 3. The individual parameters such as dispersion, polarity, and hydrogen bonding are indicated as \( \delta_d \), \( \delta_p \), and \( \delta_h \) respectively, which are three prime Hansen solubility parameters responsible for main interactions between the solute and organic solvent.

During product development and generation proof of concept, researchers and formulation scientists need to understand the basic fundamental working in the solubility concept. Researchers need to understand the maximum probable miscibility of a polymer or an active drug or solute in a particular solvent/excipient. Furthermore, Greenhalgh established a new model for the miscibility of two substances, which was based on the differences of \( \Delta \delta \) (the total solubility parameters). This can be calculated using eq 7:

\[
\Delta \delta = (\delta_t - \delta_s)
\]

(7)

In this model, it was established that two substances or compounds are said to be completely miscible when \( \Delta \delta \leq 7.0 \) MPa\(^{1/2}\) and immiscible when \( \Delta \delta \geq 10.0 \) MPa\(^{1/2}\). It is crucial to divide \( \Delta \delta \) into its components (\( \delta_d \), \( \delta_p \), and \( \delta_h \)), and the major limitation of this approach is the estimation of partial solubility.

Ideal solubility (\( x_{\text{ideal}} \)) and activity coefficient (\( \gamma \))

Fundamentally, a compound or substance or solute is considered in an equilibrium state of an ideal solution. Moreover, the free energy (\( G \)) or partial molar G of any compound or substance (crystalline solute) must be equal to the saturated solution of the same solute, which can be expressed as eq 8:

\[
G_{\text{solute}} = G_{\text{solution}}
\]

(8)

In the case of an irreversible process, the total energy of such process is the sum of all involved reversible processes between the same points (Kirchoff’s law). That is why the irreversible enthalpy (at temperature \( T \) as melting point of the solute) represents the sum of all reversible enthalpies. The \( x_{\text{ideal}} \) of any solute in a particular organic solvent or permeation enhancer can be presented as eq 9:

\[
\text{Rln} x_{u, \text{ideal}} = -\Delta H_m \left( \frac{T_m - T}{T_m \times T} \right) + \Delta C_{pm} \left( \frac{T_m - T}{T} \right)
\]

\[
- \Delta C_{pm} \times \ln \frac{T_m}{T}
\]

(9)

where \( \Delta H_m \) and \( \Delta C_{pm} \) are the enthalpy of melting, the difference of the molar heat capacity of the solid state with that of the liquid state, and the fusion temperature of the solute, respectively.

Mathematically, the value of \( \Delta C_{pm} \) can be estimated using eq 10:

\[
\Delta C_{pm} = \frac{\Delta H_m}{T_m}
\]

(10)

where the values of \( T_m \) and \( \Delta H_m \) were estimated to be 419.0 K and 57.28 kJ mol\(^{-1} \), respectively (Figure 1B) by DSC analysis. Thus, the calculated value of \( \Delta C_{pm} \) for pure KETO was 43.79 J mol\(^{-1} \) K\(^{-1} \) using eq 10. Notably, it is obvious from eq 9 that an ideal solubility or the crystal–liquid solubility ratio is dependent upon the melting point of the solute only and the solvent has no effect. The values of \( x_{\text{ideal}} \) and activity coefficient (\( \gamma \)) of KETO were estimated in various solvents using eqs 9 and 11, respectively.

Activity coefficient (\( \gamma \))

\[
\text{Activity coefficient (} \gamma \text{)} = \frac{x_{\text{ideal}}}{x}
\]

(11)
COMPUTATIONAL VALIDATION

In the present study, the experimental solubility was estimated in various organic solvents (permeation enhancers), which need to be validated using computational validation models. These models (Apelblat model and van’t Hoff model) are based on a thermodynamic concept.\textsuperscript{31,32} The apelblat solubility ($x^{apl}$) of KETO was calculated using eq 12:

$$\ln(x^{apl}) = A + B/T + C \ln(T)$$

(12)

where $A$, $B$, and $C$ are the Apelblat solubility parameters estimated from the experimental solubility data (Table 1) using the nonlinear multivariate regression analysis method. The $x^p$ values of KETO in various solvents were modeled with the $x^{spl}$ data using relative means square deviation (% RMSD) and regression $r^2$ values (Figure 2). The % RMSD values can be estimated using eq 13

$$\text{RMSD} = \left[ \frac{1}{N} \sum_{i=1}^{N} \left( \frac{x^{apl} - x_p}{x_p} \right)^2 \right]^{1/2}$$

(13)

where $N$ is the number of experimental data points in the current study. Similarly, the van’t Hoff model solubility was estimated using eq 14

$$\ln(x^{van}) = a + \frac{b}{T}$$

(14)

where $a$ and $b$ are the van’t Hoff solubility parameters at temperature $T$ and estimated by plotting the $\ln(x_p)$ value of KETO as function of $1/T$ (K).

Thermodynamic Parameter Assessment. It was required to assess the thermodynamic terms (Gibbs free energy, enthalpy, and entropy) for KETO in each solvent at the studied temperature. Generally, up to now, explanation of thermodynamic function parameters (terms) for the noted molecule was lacking in the literature. Therefore, these functional parameters as validation tools for the experimental solubility have been taken into consideration and there are the scarcity of quantitative thermodynamics data for the drug in previous reports. In this study, an attempt has been made to fill this gap for the assessment of the solubility parameters. Fundamentally, a solution is said to be an ideal solution when the change of entropy, volume, and energy on mixing is null. Therefore, thermodynamic functional parameters of the solubilized KETO in a particular solvent forming a non-ideal solution can be used to characterize them, which are apparent standard dissolution enthalpy ($\Delta_H^o$), apparent standard dissolution entropy ($\Delta_S^o$), and apparent standard Gibbs free energy ($\Delta_G^o$). These parameters were estimated through the apparent thermodynamic analysis method for KETO in a particular organic solvent over the explored temperature range. Moreover, the values of these parameters ($\Delta_H^o$, $\Delta_G^o$, and $\Delta_S^o$) were determined using the van’t Hoff and Krug models.\textsuperscript{33} It was required to estimate the value of $\Delta_H^o$ for KETO in an individual solvent at mean harmonic temperature ($T_{hm} = 305.0$ K) using the van’t Hoff analysis model (eq 15):\textsuperscript{29}

$$\frac{\partial \ln(x_p)}{\partial \left( \frac{1}{T} - \frac{1}{T_{hm}} \right)} = \frac{\Delta_H^o}{R}$$

(15)

where $R$ and $T_{hm}$ are the gas constant ($8.314 \text{ J K}^{-1} \text{ mol}^{-1}$) and the mean harmonic temperature, respectively. The enthalpy of dissolution ($\Delta_H^o$) was calculated using the van’t Hoff plot. Moreover, the value of $\Delta_G^o$ for KETO was calculated using the Krug et al.\textsuperscript{33} analysis model (eq 16) in each organic solvent at $T_{hm}$:

$$\Delta_G^o = -RT_{hm} \times \text{intercept}$$

(16)

The intercept value was estimated from the van’t Hoff plot in each solvent (Figure 3).

Similarly, the $\Delta_S^o$ value of KETO was calculated using eq 17:\textsuperscript{33}

$$\Delta_S^o = \frac{\Delta_H^o - \Delta_G^o}{T_{hm}}$$

(17)

GastroPlus Prediction Software: In Silico Study. The GastroPlus software (version 9.7, Simulation Plus, Inc., Lancaster, USA) simulates in vitro data to in vivo performance using the ACAT (advanced compartmental absorption and transit) model based on physiological-based oral absorption model comprising nine compartmental segments of gastrointestinal tract (GIT). The software estimates and predicts pharmacokinetic parameters using PKPlus modules based on the input parameters. The program provides three tabs (compound, physiological, and pharmacokinetics tabs) for data input before analysis. There are several by-default parameters, literature-based input values, and experimental data, which are processed for simulation and prediction. The PSA module (parameter sensitivity analysis) predicts the effect of physiochemical properties (solubility, particle size, shape, density, pH, pKa, logP, etc.) of the compound, the effect of the physiological condition (intestinal transit time, volume, fast and fed condition), and effect of formulation (nanoeffect, particle size, permeability coefficient) on PK parameters.

In this study, a prediction study was carried out using the experimental data, ADMET predictor module-based suggested values, and literature data. The permeation enhancer or solvent exhibiting maximum solubility of KETO was used as a new construct and compared to pure KETO for oral as well as transdermal delivery. The input parameters of the drug are presented in Table 5 obtained from various literature sources. For prediction of transdermal performance, a new additional route module was used.

Statistical Analysis. All of the experiments were repeated to get mean and standard deviation values. Data were statistically analyzed using the Kruskal–Wallis analysis and Dunn’s test. MINITAB (version 15.0, free trial version) was employed to run nonlinear regression analysis using experimental values. The HSPiP software (version 5.2.06) estimated the Hansen solubility parameters of KETO and organic solvents. The value was considered significant at $p < 0.05$ in the study.

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