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# Solubility and thermodynamic analysis of aceclofenac in different {Carbitol + water} mixtures at various temperatures

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## Abstract

The solubility and thermodynamic properties of the anti-inflammatory drug aceclofenac (ACF) have been assessed in a range of {2-(2-ethoxyethoxy)ethanol (Carbitol) + water} combinations at temperatures ranging from 298.2 K to 318.2 K and atmospheric pressure of 101.1 kPa. The shake flask method was employed to determine the solubility of ACF, and various models including “van’t Hoff, Apelblat, Buchowski-Ksiazczak  $\lambda h$ , Yalkowsky-Roseman, Jouyban-Acree, and Jouyban-Acree-van’t Hoff models” were used to validate the results. The computational models demonstrated a strong correlation with the experimental ACF solubility data, as indicated by the error values of < 3.0%. In the compositions of {Carbitol + water}, the ACF mole fraction solubility was enhanced by temperature and Carbitol mass fraction. The solubility of ACF in mole fraction was found to be lowest in pure water ( $1.07 \times 10^{-6}$  at 298.2 K), and highest in pure Carbitol ( $1.04 \times 10^{-1}$  at 318.2 K). Based on the positive values of the calculated thermodynamic parameters, the dissolution of ACF was determined to be “endothermic and entropy-driven” in all of the {Carbitol + water} solutions that were studied. It was also observed that enthalpy controls the solvation of ACF in solutions containing {Carbitol + water}. ACF-Carbitol had the strongest molecular interactions in contrast to ACF-water. Based on the results of this study, Carbitol holds significant potential for enhancing the solubility of ACF in water.

**Keywords** Aceclofenac, Carbitol, Computational models, Cosolvent mixtures, Molecular interactions, Solubility

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used treatments to allviate pain and inflammation within the human body [1]. One such NSAID, oral aceclofenac (ACF), has been proposed as a treatment for osteoarthritis (OA) and rheumatoid arthritis (RA) [2, 3]. Besides its application in RA and OA, it also possesses antipyretic, analgesic, and anti-inflammatory properties [3, 4]. Chemically, it is known as [(2-{2, 6-dichlorophenyl} amino) phenylacetoxyacetic acid] (Fig. 1A) [5]. ACF is reported to be practically insoluble in water, leading to low bioavailability upon oral administration [4, 5]. The log P and pK<sub>a</sub> values of ACF are reported to be 2.17 and 3.46, respectively [5, 6]. Due to its low water solubility,

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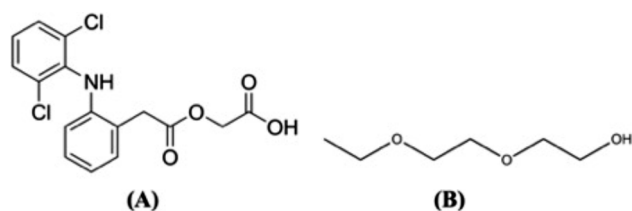
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**Fig. 1** Molecular structures of (A) aceclofenac (ACF) (taken from <https://en.wikipedia.org/wiki/Aceclofenac>) and (B) Carbitol (taken from [https://en.wikipedia.org/wiki/2-\(2-Ethoxyethoxy\)ethanol](https://en.wikipedia.org/wiki/2-(2-Ethoxyethoxy)ethanol))

designing (feasible/viable) commercial oral formulations are challenging. ACF belongs to biopharmaceutical classification system (BCS) class II drug, which means it shows low solubility and high permeability [6]. Due to its association to BCS class II, it results in poor dissolution rate and low bioavailability from commercial tablets after oral administration.

Drugs' solubility data are crucial for pharmaceutical industries [7, 8]. Researchers can use these data to make better-informed decisions, especially in drug research and development, where data can be used to enhance the quality of medicinal compounds and increase the success rate of clinical trials [9]. Additionally, dose prediction is improved when *in vivo* pharmacokinetics are predicted using solubility data [10, 11]. Several formulation-based approaches such as cyclodextrin complexation [12, 13], solid dispersions [14], chitosan nanoparticles [15], nanocrystals [16–18], Soluplus®-nanocomposites [19], microemulsions [4], nanoemulsions [20], PEGylated solid-lipid microparticles homolipid-based solidified micellar solution [21], self-emulsifying drug delivery systems [22], ACF-salt formation [5], and sonoprecipitation [23] approaches have been attempted into the literature to improve ACF solubility in an aqueous media. One technique that has been researched in the area of drug discovery [11] to improve the solubility of pharmaceuticals is the cosolvency strategy [24–27]. In order to improve ACF solubility in the current study, the cosolvent 2-(2-ethoxyethoxy)ethanol (Carbitol) [Fig. 1B] was employed. By using Carbitol to boost ACF solubility, several ACF issues, including those with solubility, dissolution rate, absorption, and bioavailability, can be fixed. Carbitol has its main applications in topical/transdermal drug delivery systems. In addition, its application in transdermal delivery of ACF using nanoemulsion approach has been proved in our previous publication [20]. Therefore, the solubility data obtained in this work would be helpful mainly in the development of topical/transdermal drug delivery systems. Solubility data is a vital physicochemical attribute for many industrial operations, including manufacturing, dosage form design, and other applications [28–30]. The solubility data for ACF in water and cosolvent combinations has not yet been sufficiently

established. However, the solubility of ACF in neat water at an ambient temperature of 298.2 K and neat Carbitol at 310.2 K has been reported by many researchers [18, 20, 22, 23, 31]. Additionally, ACF's solubility data and thermodynamic properties in four pharmaceutically significant solvents—buffers (pH 2.0 and 7.4), 1-octanol, and hexane at 293.15–313.15 K—have been reported [32].

Due to its complete miscibility with water, Carbitol is frequently used as a cosolvent to enhance solubility [33–35]. Carbitol has shown to improve the solubility of various poorly soluble medications, including tadalafil, flufenamic acid, sunitinib malate, ketoconazole, cinnarizine, meloxicam, sulphadiazine, and phenytoin [33–42]. Carbitol is a FDA approved excipient for the use in oral, topical, and injectable dosage forms. It has good biocompatibility. Many commercial products intended for oral and injectable applications to human body have been approved and commercialized [43]. There are currently no known solubility data for ACF in any of the {Carbitol+water} combinations. As a result, the aim of this study was to determine the solubility and thermodynamic parameters of ACF in various {Carbitol+water} compositions, including pure Carbitol and water, at the temperatures ranging from 298.2 K to 318.2 K under atmospheric/ambient pressure. The temperature range under investigation was chosen at random intervals of 5.0 K. The temperature range from 298.2 K to 318.2 K was kept such that the highest temperature that was studied, 318.2 K, should not have been higher than the boiling temperatures of the solvents that were studied and the melting temperature of ACF, which is 426 K [32]. The boiling temperatures of Carbitol and water are 475.1 K and 373.2 K, respectively. The greatest temperature that was investigated, 318.2 K, was lower than the melting temperature of ACF and the boiling temperatures of water and Carbitol. Consequently, the temperature range of the current work remained within the aforementioned range. The data collected during the study's data gathering phase may benefit the purification of the intended medication, ACF, as well as pre-formulation analysis and development of topical dosage forms.

## Experimental

### Materials

ACF was obtained from “E-Merck (Mumbai, India)”. Carbitol was obtained from “Sigma Aldrich (Mumbai, India)”. Purified/deionized water was obtained from “Milli-Q unit (Lyon, France)”. Table 1 contains the combined data for all materials.

### Determination of ACF solubility in {Carbitol + water} mixtures and neat solvents

To determine the mass of each {Carbitol+water} combination, an Electronic Analytical Balance (Radwag,

**Table 1** Combined data for all materials used

Material	Molecular formula	Molar mass (g mol <sup>-1</sup> )	CAS	Purification method	Mass fraction purity	Analysis method	Source
ACF	C <sub>16</sub> H <sub>13</sub> Cl <sub>2</sub> NO <sub>4</sub>	354.19	89796-99-6	None	>0.98	HPLC	E-Merck
Carbitol	C <sub>6</sub> H <sub>14</sub> O <sub>3</sub>	134.17	111-90-0	None	>0.99	GC	Sigma Aldrich
Water	H <sub>2</sub> O	18.07	7732-18-5	None	-	-	Milli-Q

Mumbai, India) was utilized, which has a sensitivity and accuracy of 0.10 mg. A range of {Carbitol+water} compositions ( $m=0.0-1.0$ ) were examined. For every cosolvent composition, three replications were made [33]. A shaking flask methodology was used to determine the solubility values of ACF in varied {Carbitol+water} compositions ( $m=0.1-0.9$ ) and pure Carbitol ( $m=1.0$ ) and pure water ( $m=0.0$ ) at five different temperatures and fixed atmospheric pressure [44]. In essence, triplicates of each cosolvent mixture and neat solvent were combined with additional ACF crystals in unknown proportions. A total of five minutes was spent vortexing each mixture. The resultant mixes were shaken continuously for 72 h at 100 rpm in an isothermal water bath (Nirmal International, New Delhi, India) to reach equilibrium [20]. The samples were taken out of the shaker and centrifuged at 5000 rpm for 30 min at 298.2 K after they had reached equilibrium. The uncertainty in the temperature of the water bath was found to be 0.13 K. Preliminary tests were conducted to optimize the equilibrium time of 72 h. ACF solubility was assessed under preliminary trials at several time intervals: 24, 48, 72, 96, and 120 h. Since the solubility of ACF did not significantly change after 72 h, this period was chosen as the equilibrium. Spectrophotometric analysis was used to detect the ACF concentration at 274 nm following the separation and, if necessary, dilution of the supernatants [20]. The ACF calibration curve was plotted and found to be linear in the range of 2–20  $\mu\text{g g}^{-1}$ , with determination of coefficient ( $R^2$ ) value of 0.9997. ACF experimental mole fraction solubility ( $x_e$ ) values were computed using standard equations published in the literature [33–35].

#### Hansen solubility parameters (HSPs) of ACF and numerous {Carbitol+water} mixtures

The degree to which a medicine dissolves in binary or pure solvent compositions is closely connected to its HSP. A medication is said to be most soluble in a solvent when its HSP is similar to that of the solvent [45]. Therefore, this work computed HSP for ACF, neat Carbitol, neat water, and various {Carbitol+water} combinations free of ACF. The value of total HSP ( $\delta$ ) for ACF, neat Carbitol, and neat water was computed using Eq. (1) [46, 47]:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

Where,  $\delta$ ,  $\delta_d$ ,  $\delta_p$ , and  $\delta_h$  represent the total, dispersion, polar, and hydrogen-bonded HSPs, respectively. The

values of HSP were derived using “HSPiP software (version 6.0.04, Louisville, KY, USA)” by entering the simplified molecular input line entry system (SMILES) of ACF, neat Carbitol, and neat water into the HSPiP software [47]. The SMILES for ACF, neat Carbitol, and neat water were taken from their PubChem database.

The HSP for different {Carbitol+water} mixtures free of ACF ( $\delta_{\text{mix}}$ ) was calculated using Eq. (2) [48]:

$$\delta_{\text{mix}} = \alpha \delta_1 + (1 - \alpha) \delta_2 \quad (2)$$

Where,  $\alpha$  is the volume fraction of Carbitol in {Carbitol+water} compositions,  $\delta_1$  is the HSP of Carbitol, and  $\delta_2$  is the HSP of water.

#### Ideal solubility ( $x_{\text{idl}}$ ) and activity coefficient ( $\gamma_i$ ) data to derive molecular interactions

Using Eq. (3), the  $x_{\text{idl}}$  of ACF at five distinct temperature was calculated [49]:

$$\ln x_{\text{idl}} = \frac{-\Delta H_{\text{fus}}(T_{\text{fus}} - T)}{RT_{\text{fus}}T} + \left(\frac{\Delta C_p}{R}\right) \left[\frac{T_{\text{fus}} - T}{T} + \ln\left(\frac{T}{T_{\text{fus}}}\right)\right] \quad (3)$$

Where  $T$  is the absolute temperature,  $T_{\text{fus}}$  is the melting/fusion temperature of ACF,  $R$  is the universal gas constant,  $\Delta H_{\text{fus}}$  is the enthalpy of ACF fusion, and  $\Delta C_p$  is the difference between ACF's molar heat capacity in its liquid and solid states [50].

Reference [32] provided the  $T_{\text{fus}}$  and  $\Delta H_{\text{fus}}$  values for ACF, which are 426 K and 49.30 kJ mol<sup>-1</sup>, respectively. Equation (4) was used to get the value of  $\Delta C_p$  for ACF [50]:

$$\Delta C_p = \frac{\Delta H_{\text{fus}}}{T_{\text{fus}}} \quad (4)$$

After computation, the ACF  $\Delta C_p$  value came out to be 115.72 J mol<sup>-1</sup> K<sup>-1</sup>. Now, the  $x_{\text{idl}}$  values for ACF were computed using Eq. (3). Equation (5) was used to derive the  $\gamma_i$  values for ACF in all {Carbitol+water} compositions and neat solvents [49, 51]:

$$\gamma_i = \frac{x_{\text{idl}}}{x_e} \quad (5)$$

The molecular foundation of the interactions between the solute and solvent was characterized by means of ACF  $\gamma_i$  data.

### Computational models

Meaningful forecasts and validations require computational validation of experimentally determined solubility data [46, 47]. The experimental solubility data from ACF were correlated using six different computational models: “van’t Hoff, Apelblat, Buchowski-Ksiazczak  $\lambda h$ , Yalkowsky-Roseman, Jouyban-Acree, and Jouyban-Acree-van’t Hoff models” [38, 52–57]. Equation (6) was used to estimate the “van’t Hoff model solubility ( $x^{\text{van't}}$ )” of ACF in varied {Carbitol+water} compositions including pure solvents [38]:

$$\ln x^{\text{van't}} = a + \frac{b}{T} \quad (6)$$

Where the model parameters from Eq. (6) that are determined by the least squares approach are denoted by  $a$  and  $b$  [33]. The root mean square deviation (*RMSD*) was used to link the values of  $x_e$  and  $x^{\text{van't}}$  for the ACF. A formula taken from the literature [58] was used to compute the *RMSD*. Equation (7) was used to estimate the “Apelblat model solubility ( $x^{\text{Apl}}$ )” of ACF in cosolvent mixtures and neat solvents [52, 53]:

$$\ln x^{\text{Apl}} = A + \frac{B}{T} + C \ln(T) \quad (7)$$

Where the model parameters from Eq. (7) that are determined by the “nonlinear multiple regression analysis” of ACF experimental solubility data mentioned in Table 2 are denoted by  $A$ ,  $B$ , and  $C$  [33]. The *RMSD* was used to link the values of  $x_e$  and  $x^{\text{Apl}}$  for the ACF. Equation (8) has been utilized to estimate the “Buchowski-Ksiazczak  $\lambda h$  solubility ( $x^{\lambda h}$ )” of ACF in varied {Carbitol+water} compositions including pure solvents [54, 55]:

$$\ln \left[ 1 + \frac{\lambda (1 - x^{\lambda h})}{x^{\lambda h}} \right] = \lambda h \left[ \frac{1}{T} - \frac{1}{T_{\text{fus}}} \right] \quad (8)$$

Where the model parameters from Eq. (8) are denoted by  $\lambda$  and  $h$ .

It is impossible to get the solubility data of drugs in the cosolvent mixtures at different solvent combinations since Eqs. (6–8) explain solubility data at different temperatures in a specific solvent combination [57, 58]. These forecasts need the use of cosolvency approaches like “Yalkowsky-Roseman, Jouyban-Acree, and Jouyban-Acree-van’t Hoff models” [56–60]. Equation (9) was used to estimate the “logarithmic solubility of Yalkowsky-Roseman model ( $\log x^{\text{Yal}}$ )” for ACF in binary {Carbitol+water} compositions [56]:

$$\log x^{\text{Yal}} = w_1 \log x_1 + w_2 \log x_2 \quad (9)$$

Where,  $w_1$  is the mass fraction of Carbitol,  $w_2$  is the mass fraction of water, and  $x_1$  and  $x_2$  are the solubility of ACF in Carbitol and water, respectively. Equation (9) connects drug solubility data at a given temperature in different solvent mixtures.

Equation (10) was used to estimate the “Jouyban-Acree model” solubility of ACF ( $x_{mT}$ ) at different {Carbitol+water} compositions and temperature [57]:

$$\ln x_{m,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \left( \frac{w_1 \cdot w_2}{T} \right) \sum_{i=0}^2 J_i (w_1 - w_2)^i \quad (10)$$

Where,  $J_i$  is the model parameter from Eq. (10), and  $x_{1T}$  and  $x_{2T}$  are ACF solubility in Carbitol and water, respectively. Equation (11) can be used to describe the trained version of Eq. (10) for the current data set by entering the  $J_1$  value (11):

$$\ln x_{m,T} = w_1 \ln x_1 + w_2 \ln x_2 + \frac{21076 w_1 w_2}{T} \quad (11)$$

When determining the ACF solubility in various {Carbitol+water} compositions at the specified temperature, the ACF solubility values in pure Carbitol and water must be utilized as input data. To get around this restriction, the “Jouyban-Acree-van’t Hoff model” (Eq. 12) can be created using Eqs. (6) and (10) [57]:

$$\ln x_{m,T} = w_1 \left( A_1 + \frac{B_1}{T} \right) + w_2 \left( A_2 + \frac{B_2}{T} \right) + \left[ \frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \right] \quad (12)$$

Where the model parameters in Eq. (12) are  $A_1$ ,  $B_1$ ,  $A_2$ ,  $B_2$ , and  $J_i$ . The trained version of Eq. (12) for the current data set can be stated by Eq. (13):

**Table 2** Experimental ( $x_e$ ) and ideal solubility ( $x_{\text{id}}$ ) data of ACF in binary {Carbitol+water} mixtures (carbitol mass fraction  $m=0.0-1.0$ ) at 298.2–318.2 K and 101.1 kPa

$m^a$	$x_e^b$	T=298.2 K	T=303.2 K	T=308.2 K	T=313.2 K	T=318.2 K
0.0		$1.10 \times 10^{-6}$	$1.40 \times 10^{-6}$	$1.80 \times 10^{-6}$	$2.30 \times 10^{-6}$	$3.00 \times 10^{-6}$
0.1		$3.40 \times 10^{-6}$	$4.23 \times 10^{-6}$	$5.35 \times 10^{-6}$	$6.71 \times 10^{-6}$	$8.46 \times 10^{-6}$
0.2		$1.07 \times 10^{-5}$	$1.30 \times 10^{-5}$	$1.60 \times 10^{-5}$	$1.97 \times 10^{-5}$	$2.46 \times 10^{-5}$
0.3		$3.28 \times 10^{-5}$	$3.92 \times 10^{-5}$	$4.74 \times 10^{-5}$	$5.72 \times 10^{-5}$	$6.87 \times 10^{-5}$
0.4		$1.00 \times 10^{-4}$	$1.22 \times 10^{-4}$	$1.45 \times 10^{-4}$	$1.72 \times 10^{-4}$	$2.02 \times 10^{-4}$
0.5		$3.14 \times 10^{-4}$	$3.61 \times 10^{-4}$	$4.21 \times 10^{-4}$	$4.82 \times 10^{-4}$	$5.62 \times 10^{-4}$
0.6		$9.73 \times 10^{-4}$	$1.12 \times 10^{-3}$	$1.27 \times 10^{-3}$	$1.45 \times 10^{-3}$	$1.63 \times 10^{-3}$
0.7		$3.02 \times 10^{-3}$	$3.32 \times 10^{-3}$	$3.68 \times 10^{-3}$	$4.08 \times 10^{-3}$	$4.51 \times 10^{-3}$
0.8		$9.31 \times 10^{-3}$	$1.02 \times 10^{-2}$	$1.13 \times 10^{-2}$	$1.21 \times 10^{-2}$	$1.34 \times 10^{-2}$
0.9		$2.91 \times 10^{-2}$	$3.08 \times 10^{-2}$	$3.25 \times 10^{-2}$	$3.47 \times 10^{-2}$	$3.66 \times 10^{-2}$
1.0		$8.93 \times 10^{-2}$	$9.27 \times 10^{-2}$	$9.65 \times 10^{-2}$	$1.00 \times 10^{-1}$	$1.04 \times 10^{-1}$
$x_{\text{id}}$		$6.98 \times 10^{-3}$	$8.80 \times 10^{-3}$	$1.10 \times 10^{-2}$	$1.38 \times 10^{-2}$	$1.72 \times 10^{-2}$

<sup>a</sup>The uncertainties  $u$  are  $u(T)=0.13$  K,  $u(m)=0.0007$ , and  $u(p)=2$  kPa, and <sup>b</sup>the relative uncertainty  $u_r$  in solubility is  $u_r(x_e)=0.03$

$$\ln x_{m,T} = w_1 \left( 0.06340 - \frac{739.72}{T} \right) + w_2 \left( 2.4198 - \frac{4824.3}{T} \right) + \frac{20142w_1w_2}{T} \quad (13)$$

### Thermodynamic parameters for ACF dissolution behavior

The mean harmonic temperature ( $T_{\text{hm}}$ ) was used to calculate all of the apparent thermodynamic parameters of the ACF [49]. The  $T_{\text{hm}}$  was derived using the stated Eqs. [49, 57]. We have determined the  $T_{\text{hm}}$  for ACF to be 308 K. Through an apparent thermodynamic study, a number of thermodynamic parameters were derived. To calculate these parameters, the “van’t Hoff and Gibbs equations” were utilized. The apparent standard enthalpy ( $\Delta_{\text{sol}}H^0$ ) data for ACF at  $T_{\text{hm}} = 308$  K in cosolvent compositions and neat solvents were computed using Eq. (14) [49, 61]:

$$\left( \frac{\partial \ln x_e}{\partial \left( \frac{1}{T} - \frac{1}{T_{\text{hm}}} \right)} \right)_P = -\frac{\Delta_{\text{sol}}H^0}{R} \quad (14)$$

The “ $\Delta_{\text{sol}}H^0$ ” for ACF was derived by the constructed “van’t Hoff” curves between  $\ln x_e$  of ACF and  $1/T - 1/T_{\text{hm}}$ . The van’t Hoff curves for ACF in

cosolvent compositions and pure solvents are displayed in Fig. 2.

Additionally, using the Krug et al. approach [61], Eq. (15) was used to estimate the apparent standard Gibbs energy ( $\Delta_{\text{sol}}G^0$ ) for ACF in varied {Carbitol+water} compositions and pure solvents at  $T_{\text{hm}} = 308$  K.

$$\Delta_{\text{sol}}G^0 = -RT_{\text{hm}} \times \text{intercept} \quad (15)$$

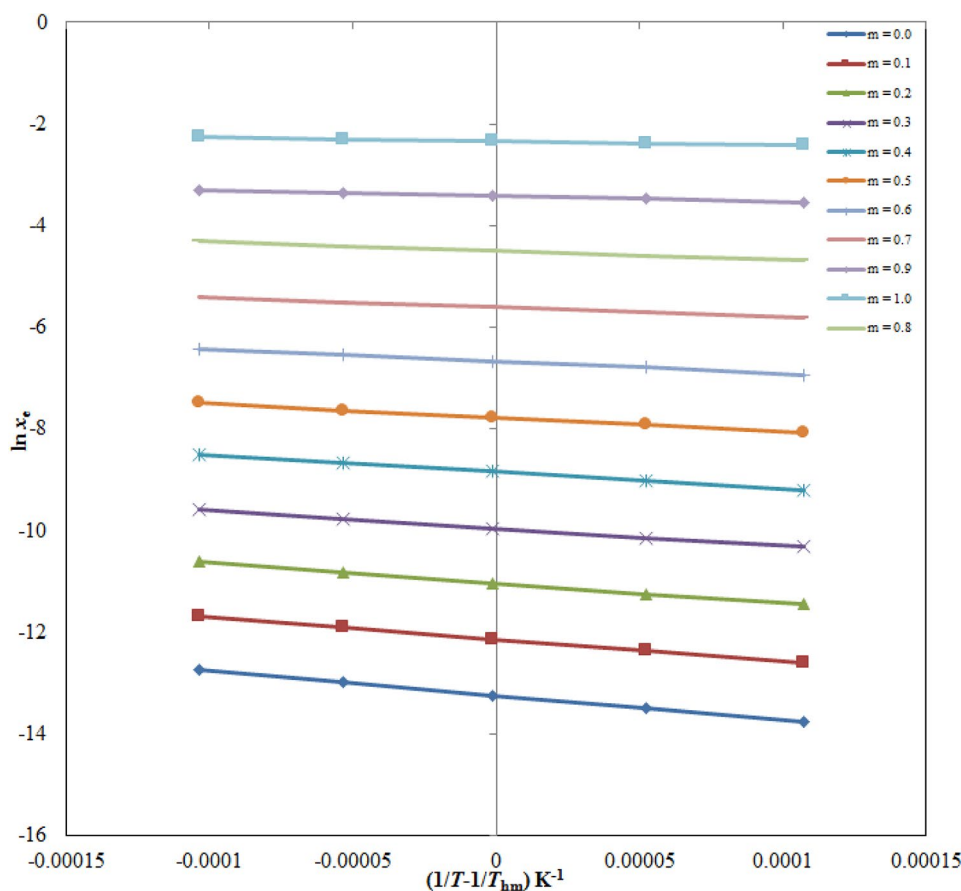
In which the “van’t Hoff plots” displayed in Fig. 2 were utilized to derive ACF intercept values in varied {Carbitol+water} compositions and pure solvents.

The apparent standard entropies ( $\Delta_{\text{sol}}S^0$ ) for ACF in varied {Carbitol+water} compositions and pure solvents were obtained using Eq. (16) [49, 61, 62]:

$$\Delta_{\text{sol}}S^0 = \frac{\Delta_{\text{sol}}H^0 - \Delta_{\text{sol}}G^0}{T_{\text{hm}}} \quad (16)$$

### Enthalpy-entropy compensation analyses

As previously mentioned [33], an enthalpy-entropy compensation analysis was carried out to evaluate the solvation behaviour of ACF in neat solvents and cosolvent



**Fig. 2** van’t Hoff curves for ACF constructed between  $\ln x_e$  and  $1/T - 1/T_{\text{hm}}$  for ACF in binary {Carbitol+water} mixtures to derive thermodynamic properties



combinations. For this experiment, weighted graphs of  $\Delta_{\text{sol}}H^\circ$  vs.  $\Delta_{\text{sol}}G^\circ$  were created at  $T_{\text{hm}} = 308$  K [34, 35].

## Results and discussion

### ACF measured solubility data and literature comparison

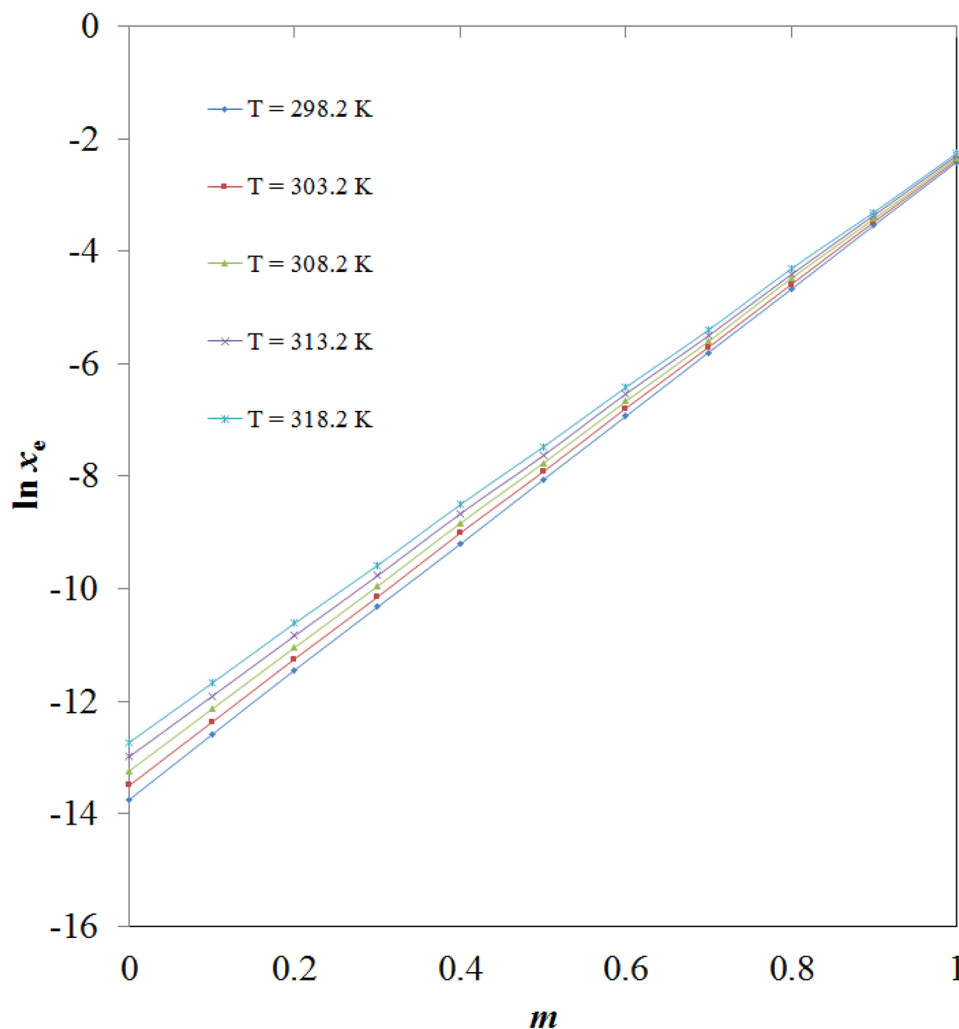
Table 2 summarizes the experimental ACF solubility values in binary {Carbitol+water} compositions and pure solvents at five distinct temperatures and atmospheric pressure.

Regarding ACF's solubility in binary {Carbitol+water} mixtures at different temperatures, there is no report available. Nonetheless, numerous researchers have reported ACF solubility values in pure water and Carbitol [18, 20, 22, 23, 31]. Samal et al. [31] observed that ACF's solubility in pure water at 298.2 K was  $88.6 \mu\text{g mL}^{-1}$ , which translates to  $4.51 \times 10^{-6}$  in mole fraction. However, Narayan et al. [18] observed that ACF's solubility in pure water at 298.2 K was  $20 \mu\text{g mL}^{-1}$  (equivalent to  $1.02 \times 10^{-6}$  in mole fraction). On the other hand, Desai et al. [23] found that ACF's solubility in pure water at 298.2 K was  $150 \mu\text{g mL}^{-1}$  (equivalent to  $7.63 \times 10^{-6}$  in mole fraction). The recorded mole fraction solubility of ACF in neat water ( $1.10 \times 10^{-6}$  at 298.2 K) in the present work was found to be closed with that reported by Narayan et al. [18]. However, it was deviated significantly with those reported by Samal et al. and Desai et al. [23, 31]. Shakeel et al. [20] found that the solubility of ACF in pure Carbitol at 310.2 K was  $289.5 \text{ mg mL}^{-1}$  (equivalent to  $9.88 \times 10^{-2}$  in mole fraction). However, Jianxian et al. [22] found that ACF's solubility in pure Carbitol at 310.2 K was  $205.5 \text{ mg mL}^{-1}$  (equivalent to  $7.22 \times 10^{-2}$  in mole fraction). This study did not directly record the ACF solubility in pure Carbitol at 310.2 K. The line shown between ACF  $\ln x_e$  and  $1/T$  was interpolated to get the mole fraction solubility of ACF in pure Carbitol at 310.2 K. In the current work, it was found that the ACF mole fraction solubility in pure Carbitol at 310.2 K was  $9.82 \times 10^{-2}$ . It was discovered that the ACF solubility in mole fraction in neat Carbitol ( $9.82 \times 10^{-2}$  at 310.2 K) that was recorded in this work and that reported by Shakeel et al. [20] were closed. It did not, however, closely resemble the report by Jianxian et al. [22]. There could be a number of reasons for the variation in ACF solubility values in neat water and neat Carbitol, including the analysis method, equilibrium time, and shaking speed throughout the experiment. The ACF solubilities in pure Carbitol and water were generally estimated to be greatest and least, respectively. Because Carbitol has a weaker polarity than water, it may be the reason why ACF dissolves more completely in neat Carbitol [33–35]. Intermolecular interactions between the -OH group of Carbitol (Fig. 1B) and the C=O, -COOH, -Cl, and -NH groups of ACF (Fig. 1A) may also be the cause of the greater solubility of ACF in Carbitol. Both temperature

and the mass fraction of Carbitol improved the solubility of ACF in binary {Carbitol+water} mixtures significantly as mentioned in Table 2 ( $p < 0.05$ ). ACF solubility in logarithmic mole fractions was also examined as a function of Carbitol mass fraction at five different temperatures. Figure 3 includes the summary of the results. The solubility of ACF increased linearly with the Carbitol mass fraction in all {Carbitol+water} mixtures across all tested temperatures ( $p < 0.05$ ). These findings suggest that ACF is essentially insoluble in water and freely soluble in Carbitol. As a result, water was chosen as the antisolvent and Carbitol as the ideal solvent for ACF. The ACF solubility in mole fractions rose dramatically to neat Carbitol when compared to neat water. Therefore, ACF can be dissolved in an aqueous medium like water by using Carbitol as a cosolvent. All things considered, Carbitol can be employed as a cosolvent in ACF dosage form development and pre-formulation studies, especially in the case of liquid dosage forms.

### Evaluation of HSPs

Because HSPs provide a quantitative evaluation on the degree of interaction between the solute and the solvent, they are a valuable tool for determining miscibility or solubility [45]. Similar HSPs indicate that solutes and solvents may probably dissolve in one another [46]. The same polarity of the solvent and the solute are further demonstrated by the same HSPs. Thus, the HSPs of ACF, pure Carbitol, and pure water were computed in this study. There are several uses for the HSPs estimation in various research domains [45, 46]. The main objective of the current endeavor was to gather information about the solubility of the solvent and solute. Using HSPiP software, the  $\delta$  value for ACF was predicted to be  $24.10 \text{ MPa}^{1/2}$ , indicating low polarity. The HSPiP software indicates that pure Carbitol ( $\delta_1$ ) and pure water ( $\delta_2$ ) have HSP values of  $21.40 \text{ MPa}^{1/2}$  and  $47.80 \text{ MPa}^{1/2}$ , respectively. For binary {Carbitol+water} compositions without ACF ( $\delta_{\text{mix}}$ ), the HSP range was found to be between 24.04 and  $45.16 \text{ MPa}^{1/2}$ . It was found that the  $\delta_{\text{mix}}$  values in {Carbitol+water} compositions declined as the mass proportion of Carbitol rose. Consequently,  $m=0.1$  and  $m=0.9$  yielded the highest and lowest  $\delta_{\text{mix}}$  values, respectively. It was discovered, nevertheless, that the ACF solubility values were enhanced by reducing the  $\delta_{\text{mix}}$  values. The pure Carbitol ( $\delta_1=21.40 \text{ MPa}^{1/2}$ ) and ACF ( $\delta=24.10 \text{ MPa}^{1/2}$ ) HSPs were frequently close to each other. Additionally, the studies showed that ACF dissolves more readily in pure Carbitol. Thus, these results were in good agreement with the ACF solubility data from the experiments utilizing combinations of {Carbitol+water}.



**Fig. 3** Impact of Carbitol mass fraction ( $m$ ) on logarithmic ACF solubility values ( $\ln x_e$ ) at five different temperatures ranged from 298.2 K to 318.2 K

**Table 3** ACF activity coefficients ( $\gamma_i$ ) data at 298.2–318.2 K in different {Carbitol + water} compositions ( $m=0.0$ – $1.0$ )

$m$	$\gamma_i$				
	T=298.2 K	T=303.2 K	T=308.2 K	T=313.2 K	T=318.2 K
0.0	6535	6406	6205	6038	5840
0.1	2050	2080	2070	2060	2040
0.2	652.1	674.6	690.7	702.1	700.2
0.3	212.9	224.6	233.0	241.8	250.8
0.4	69.55	72.02	75.93	80.39	85.18
0.5	22.24	24.34	26.21	28.65	30.65
0.6	7.175	7.849	8.708	9.544	10.58
0.7	2.307	2.650	3.002	3.390	3.819
0.8	0.7497	0.8663	0.9786	1.142	1.287
0.9	0.2401	0.2855	0.3395	0.3984	0.4706
1.0	0.0781	0.0948	0.1144	0.1379	0.1649

#### Molecular interactions based on $x_{idl}$ and $\gamma_i$

Table 2 has the  $x_{idl}$  data for ACF. The derived values for ACF's  $x_{idl}$  ranged from  $6.98 \times 10^{-3}$  to  $1.72 \times 10^{-2}$ , at 298.2–318.2 K. The  $x_{idl}$  levels of ACF were substantially

greater than the  $x_e$  data in neat water. At every temperature that was examined, the  $x_e$  values of ACF were higher than the  $x_{idl}$  values of pure Carbitol. Since ACF dissolves more readily in pure Carbitol, this cosolvent is appropriate for ACF solubilization. Table 3 displays the  $\gamma_i$  data for ACF in a variety of {Carbitol+water} mixtures, including pure solvents, at 298.2–318.2 K. At every temperature examined, the ACF's  $\gamma_i$  value in pure water achieved its maximum value. However, the ACF  $\gamma_i$  was lowest in pure Carbitol at all temperatures considered. Compared to pure water, the  $\gamma_i$  values for ACF were considerably lower in pure Carbitol. The largest  $\gamma_i$  for ACF in pure water could be explained by its lowest water solubility. These results indicate that compared to the ACF-water combination, the ACF-Carbitol combination shows more molecular solute-solvent interactions.

#### Computational analysis of ACF solubility

Six different computational methods, such as the “van't Hoff, Apelblat, Buchowski-Ksiazczak  $\lambda h$ ,

**Table 4** Results for the “van’t Hoff model” with model parameters ( $a$  and  $b$ ),  $R^2$ , and  $RMSD$  for ACF in binary {Carbitol+water} compositions ( $m=0.0-1.0$ )\*

$m$	$a$	$b$	$R^2$	Overall $RMSD$ (%)
0.0	2.4198 (0.000)	-4824.3 (0.000)	0.9996	
0.1	1.9455 (0.002)	-4338.7 (0.000)	0.9993	
0.2	1.7479 (0.009)	-3938.2 (0.000)	0.9983	
0.3	1.4894 (0.002)	-3526.0 (0.000)	0.9994	
0.4	1.9006 (0.000)	-3310.2 (0.000)	0.9996	
0.5	1.1803 (0.003)	-2759.2 (0.000)	0.9992	0.86
0.6	1.2488 (0.000)	-2439.8 (0.000)	0.9997	
0.7	0.58250 (0.015)	-1905.6 (0.000)	0.9988	
0.8	1.0552 (0.009)	-1709.9 (0.000)	0.9969	
0.9	NS	-1100.1 (0.000)	0.9989	
1.0	NS	-739.72 (0.000)	0.9988	

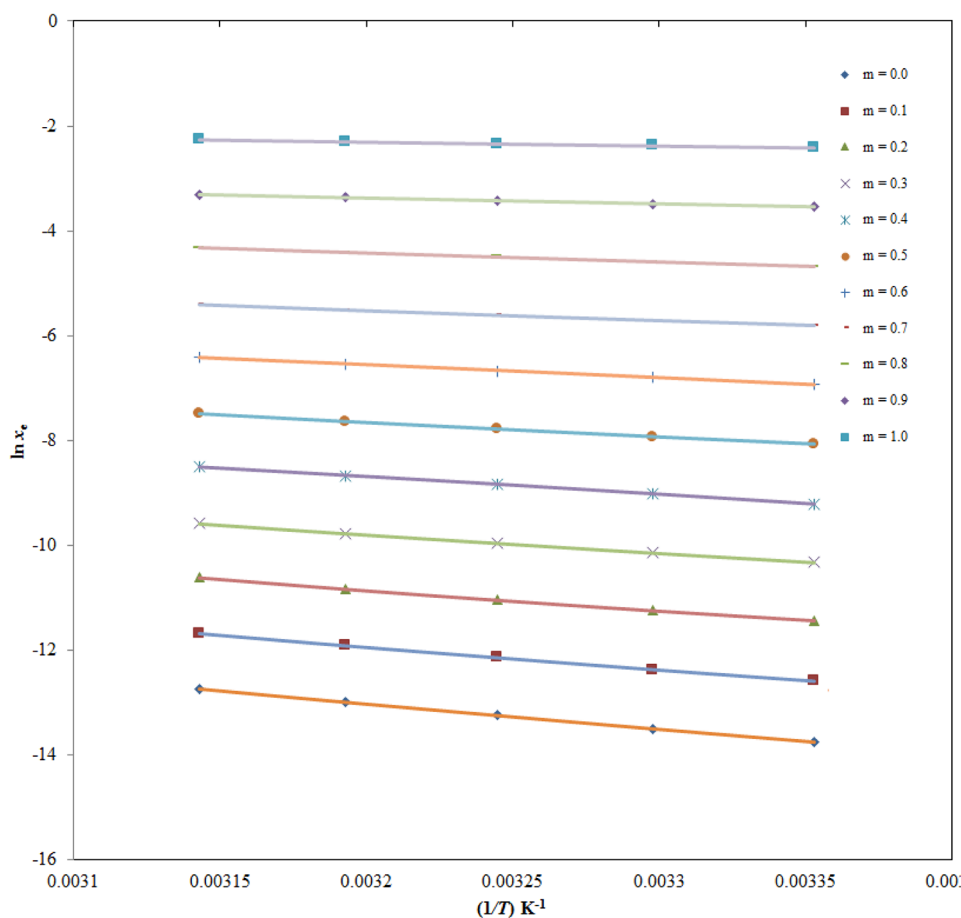
\*Values in parenthesis are significant p values and NS is non-significant

Yalkowsky-Roseman, Jouyban-Acree, and Jouyban-Acree-van’t Hoff models” [38, 52–57], were used to connect the solubility data of ACF. Table 4 presents the results of the model fitting using the “van’t Hoff model”. The overall  $RMSD$  of this model was predicted to be

0.86%. The results showed that the ACF  $R^2$  for pure solvents and all {Carbitol+water} compositions fell between 0.9969 and 0.9997. The experimental solubility data from the ACF in varied {Carbitol+water} compositions, including neat solvents, showed a strong correlation with the “van’t Hoff model” predictions.

The experimental and Apelblat solubility data for ACF in a range of {Carbitol+water} compositions including pure water and Carbitol, are graphically compared in Fig. 4. The outcomes displayed in Fig. 4 showed a robust connection between the experimentally measured solubility data of ACF and the “Apelblat model”. Table 5 presents the results of the correlation using the “Apelblat model”. The overall  $RMSD$  of this model was predicted to be 0.48%. The outcomes showed that ACF  $R^2$  for pure solvents and all {Carbitol+water} compositions fell between 0.9972 and 0.9999. The experimental solubility data from the ACF showed a strong correlation with the predictions of the “Apelblat model” in a range of {Carbitol+water} compositions and neat solvents.

Table 6 presents the results of the correlation using the “Buchowski-Ksiazaczak  $\lambda h$ ” model. The overall  $RMSD$  for

**Fig. 4** Graphical association between the “Apelblat model” and experimental ACF solubility values ( $x_e$ ) in a range of {Carbitol+water} compositions ( $m=0.0-1.0$ ) as a function of  $1/T$ ; solid lines represent the ACF solubility values from the “Apelblat model” and symbols represent the ACF  $x_e$  values



**Table 5** Results of the “Apelblat model” with model parameters (A, B, and C),  $R^2$ , and  $RMSD$  for ACF in binary {Carbitol + water} compositions ( $m = 0.0–1.0$ )\*

m	A	B	C	$R^2$	Overall RMSD (%)
0.0	-219.55 (0.020)	NS	32.971 (0.019)	0.9999	
0.1	-289.16 (0.018)	9009.0 (0.038)	43.238 (0.017)	0.9999	
0.2	-417.81 (0.007)	15,306 (0.010)	62.313 (0.006)	0.9999	
0.3	-201.39 (0.078)	NS	8.9253 (0.077)	0.9999	
0.4	NS	NS	NS	0.9998	
0.5	NS	NS	NS	0.9997	0.48
0.6	NS	NS	NS	0.9998	
0.7	-160.82 (0.049)	NS	23.973 (0.048)	0.9998	
0.8	NS	NS	NS	0.9972	
0.9	NS	NS	NS	0.9993	
1.0	-63.729 (0.028)	2185.8 (0.049)	9.4747 (0.028)	0.9999	

\*Values in parenthesis are significant p values and NS is non-significant

**Table 6** Results of “Buchowski-Ksiazaczak  $\lambda h$  model” with model parameters ( $\lambda$  and  $h$ ),  $R^2$ , and  $RMSD$  for ACF in binary {Carbitol + water} compositions ( $m = 0.0–1.0$ )\*

m	$\lambda$	h	$R^2$	Overall RMSD (%)
0.0	7.9047 (0.000)	610.32 (0.000)	0.9996	
0.1	7.2393 (0.000)	599.29 (0.000)	0.9993	
0.2	6.4966 (0.000)	606.19 (0.000)	0.9983	
0.3	5.7874 (0.000)	609.27 (0.000)	0.9994	
0.4	4.8698 (0.000)	679.74 (0.000)	0.9996	
0.5	4.2968 (0.000)	642.15 (0.000)	0.9992	2.48
0.6	3.4783 (0.000)	701.43 (0.000)	0.9997	
0.7	2.8906 (0.000)	659.24 (0.000)	0.9988	
0.8	1.9587 (0.000)	872.97 (0.000)	0.9969	
0.9	1.4336 (0.000)	767.36 (0.000)	0.9990	
1.0	0.67300 (0.000)	1099.1 (0.000)	0.9988	

\*Values in parenthesis are significant p values

this model was predicted to be 2.48%. The results showed that ACF  $R^2$  for pure solvents and all {Carbitol + water} compositions fell between 0.9969 and 0.9997. In varied {Carbitol + water} compositions and neat solvents,

**Table 7** Results of “Yalkowsky-Roseman model” for ACF in binary {Carbitol + water} compositions ( $m = 0.1–0.9$ ) at five different temperatures ranged from 298.2 K to 318.2 K

m	Log $x^{val}$					Overall RMSD (%)
	T = 298.2 K	T = 303.2 K	T = 308.2 K	T = 313.2 K	T = 318.2 K	
0.1	-5.47	-5.38	-5.27	-5.17	-5.07	
0.2	-4.98	-4.89	-4.80	-4.71	-4.62	
0.3	-4.49	-4.41	-4.32	-4.24	-4.16	
0.4	-4.00	-3.93	-3.85	-3.78	-3.71	
0.5	-3.50	-3.44	-3.38	-3.31	-3.25	1.91
0.6	-3.01	-2.96	-2.90	-2.85	-2.80	
0.7	-2.52	-2.48	-2.43	-2.39	-2.34	
0.8	-2.03	-1.99	-1.96	-1.92	-1.89	
0.9	-1.54	-1.51	-1.48	-1.46	-1.43	

**Table 8** Results of “Jouyban-Acree” and “Jouyban-Acree-Van’t Hoff” models for ACF in different {Carbitol + water} compositions\*

System	Jouyban-Acree	Jouyban-Acree-van’t Hoff
		$A_1$ NS
{Carbitol + water}	$J_1$ 21,076 (0.002)	$B_1$ -739.72 (0.000)
$RMSD$ (%)	0.38	$A_2$ 2.4198 (0.000)
		$B_2$ -4824.3 (0.000)
		$J_1$ 20,142 (0.001)
		0.42

\* Values in parenthesis are significant p values and NS is non-significant

there was a strong connection between the experimental solubility data from the ACF and the predictions of the “Buchowski-Ksiazaczak  $\lambda h$ ” model.

The correlation results utilizing the “Yalkowsky-Roseman model” are shown in Table 7. The overall  $RMSD$  of this model was predicted to be 1.91%. In all of the {Carbitol + water} compositions, there was a strong connection between the experimental solubility data from the ACF and the predictions of the “Yalkowsky-Roseman model”.

Additionally, the solubility data of ACF was linked with “Jouyban-Acree and Jouyban-Acree-van’t Hoff models” in several {Carbitol + water} mixes at numerous temperatures and cosolvent compositions [57]. Table 8 displays the results of the correlation between the “Jouyban-Acree and Jouyban-Acree-van’t Hoff models”. The models predictions indicated that the overall  $RMSDs$  for the “Jouyban-Acree and Jouyban-Acree-van’t Hoff models”, which are 0.38% and 0.42%, respectively, have an exceptional relationship. All models showed a significant correlation overall, as indicated by low  $RMSD$  values. It was impossible, however, to compare the error levels of each model to each other. The error levels of all investigated models were within a narrow range of the experimental uncertainties. This outcome demonstrated that each model examined was capable to reproduce the solubility data from the experiments with the lowest possible degree of error.

### Thermodynamic assessment for ACF dissolution

The van't Hoff approach was utilized to calculate the  $\Delta_{\text{sol}}H^\circ$  values for ACF in binary {Carbitol+water} compositions as well as pure solvents. As seen in Table 9,  $R^2 > 0.99$  was predicted for the linear van't Hoff curves of ACF in varied {Carbitol+water} compositions and Carbitol and water (Fig. 2). Table 9 displays the results for all thermodynamic parameters as well. The ACF  $\Delta_{\text{sol}}H^\circ$  values varied between 6.15 and 40.61 kJ mol<sup>-1</sup> in varied {Carbitol+water} compositions and neat solvents. The ACF  $\Delta_{\text{sol}}G^\circ$  values varied between 5.98 and 33.90 kJ mol<sup>-1</sup> in varied {Carbitol+water} compositions and neat solvents. The  $\Delta_{\text{sol}}H^\circ$  and  $\Delta_{\text{sol}}G^\circ$  data for ACF showed that the compound underwent “endothermic dissolution” in varied {Carbitol+water} compositions, including neat solvents [34, 35]. The ACF  $\Delta_{\text{sol}}S^\circ$  values varied between 0.55 and 20.31 J mol<sup>-1</sup> K<sup>-1</sup> in varied {Carbitol+water} compositions and neat solvents. The  $\Delta_{\text{sol}}S^\circ$  values for ACF indicated that the compound underwent “entropy-driven” ACF dissolution in varied {Carbitol+water} compositions, including neat solvents [34]. It has now been discovered that the dissolution of ACF was “endothermic and entropy-driven” in varied {Carbitol+water} compositions, including neat solvents [34, 35].

### Enthalpy-entropy compensation analyses

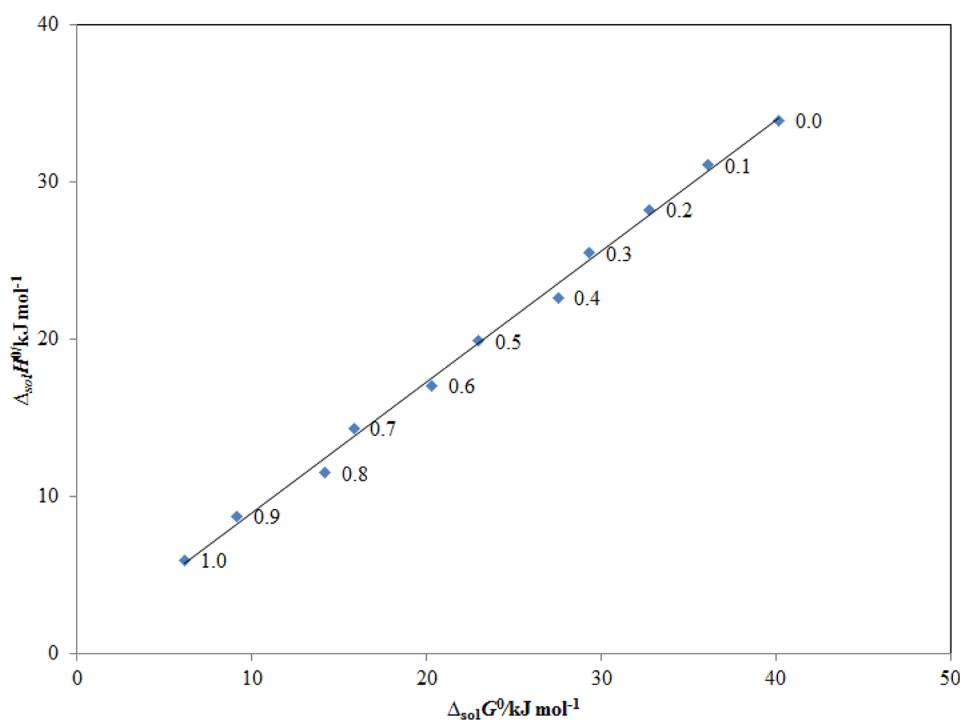
An enthalpy-entropy compensation analysis was performed to investigate the solvation behavior of ACF in different {Carbitol+water} compositions and pure

**Table 9** Apparent thermodynamic parameters ( $\Delta_{\text{sol}}H^\circ$ ,  $\Delta_{\text{sol}}G^\circ$ , and  $\Delta_{\text{sol}}S^\circ$ ) and  $R^2$  values for ACF in binary {Carbitol+water} compositions ( $m=0.0-1.0$ )<sup>c</sup>

m	$\Delta_{\text{sol}}H^\circ/\text{kJ mol}^{-1}$	$\Delta_{\text{sol}}G^\circ/\text{kJ mol}^{-1}$	$\Delta_{\text{sol}}S^\circ/\text{J mol}^{-1} \text{K}^{-1}$	$R^2$
0.0	40.61	33.90	20.31	0.9997
0.1	36.12	31.08	16.35	0.9993
0.2	32.78	28.26	14.68	0.9984
0.3	29.35	25.49	12.52	0.9995
0.4	27.55	22.65	15.92	0.9995
0.5	22.97	19.91	9.92	0.9992
0.6	20.31	17.08	10.47	0.9997
0.7	15.86	14.34	4.92	0.9989
0.8	14.23	11.51	8.84	0.9970
0.9	9.15	8.76	1.28	0.9990
1.0	6.15	5.98	0.55	0.9989

<sup>c</sup>The relative uncertainties are  $u(\Delta_{\text{sol}}H^\circ)=0.047$ ,  $u(\Delta_{\text{sol}}G^\circ)=0.046$ , and  $u(\Delta_{\text{sol}}S^\circ)=0.060$

solvents. Figure 5 presents the results. Figure 5 demonstrates that ACF yields a straight  $\Delta_{\text{sol}}H^\circ$  vs.  $\Delta_{\text{sol}}G^\circ$  curve with a slope  $> 1.0$  and an  $R^2 > 0.99$  in all {Carbitol+water} compositions and pure solvents. Based on these results, it is expected that the ACF solvation-driven process is enthalpy-driven in all {Carbitol+water} compositions and pure solvents. This ACF solvation mechanism can be explained by the fact that ACF solvates more efficiently in neat Carbitol molecules than in neat water molecules [33, 34]. Consequently, the molecular interaction between ACF-Carbitol was stronger than the ACF-water. ACF solvated similarly to that reported for flufenamic acid,



**Fig. 5**  $\Delta_{\text{sol}}H^\circ$  vs.  $\Delta_{\text{sol}}G^\circ$  enthalpy-entropy compensation graph for ACF solubility in varied {Carbitol+water} compositions ( $m=0.0-1.0$ ) at  $T_{\text{hm}} = 308 \text{ K}$

sinapic acid, sunitinib malate, cinnarizine, and tadalafil in a number of {Carbitol+water} compositions and pure solvents [33–35, 38, 42].

## Conclusions

This study investigated the solubility of ACF in several Carbitol aqueous solutions, including neat solvents, at different temperatures and fixed pressures. Temperature and Carbitol mass percentage fluctuations were seen in the ACF solubility values across all cosolvent combinations, including neat solvents. For each temperature under investigation, the solubilities of ACF were found to be highest in neat Carbitol and lowest in neat water. Experimentally obtained ACF solubility data showed good agreement with six distinct computational models for all {Carbitol+water} compositions, including pure solvents. In pure solvents and various {Carbitol+water} combinations, all thermodynamic data, including  $\Delta_{\text{sol}}H^\circ$ ,  $\Delta_{\text{sol}}G^\circ$ , and  $\Delta_{\text{sol}}S^\circ$ , were found to be positive, indicating “endothermic and entropy-driven” ACF dissolution. The ACF solvation behavior was driven by enthalpy in neat solvents as well as in all cosolvent combinations. The information gained from this investigation could be helpful for designing dosage forms, recrystallization, purification, and pre-formulation assessment for the ACF.

## Abbreviations

ACF	Aceclofenac
NSAIDS	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
RA	Rheumatoid arthritis
BCS	Biopharmaceutical classification system
m	Carbitol mass fraction in {Carbitol + water} mixtures
$x_e$	Mole fraction solubility of ACF
HSP	Hansen solubility parameter
$\delta$	Total HSP
$\delta_d$	Dispersion HSP
$\delta_p$	Polar HSP
$\delta_h$	Hydrogen-bonded HSP
$\delta_{\text{mix}}$	HSP for different {Carbitol + water} mixtures free of ACF
$\alpha$	Volume fraction of Carbitol in {Carbitol + water} compositions
$\delta_1$	HSP of pure Carbitol
$\delta_2$	HSP of pure water
SMILES	Simplified molecular input line entry system
$x_{\text{idl}}$	Ideal solubility
$\gamma_i$	Activity coefficient
T	Absolute temperature
$T_{\text{fus}}$	Melting/fusion temperature of ACF
R	Universal gas constant
$\Delta H_{\text{fus}}$	Enthalpy of ACF fusion
$\Delta C_p$	Difference between ACF's molar heat capacity in its liquid and solid states
$x^{\text{van't}}$	Van't Hoff model solubility
a and b	Model parameters of Van't Hoff model
$x^{\text{Apl}}$	Apelblat model solubility
A, B, and C	Model parameters of Apelblat model
RMSD	Root mean square deviations
$x^{\text{lh}}$	Buchowski-Ksiazczak lh model solubility
$\text{land h}$	Model parameters of Buchowski-Ksiazczak lh model
$x^{\text{Yal}}$	Yalkowsky-Roseman model solubility
$w_1$	Mass fraction of Carbitol
$w_2$	Mass fraction of water

$x_1$	Solubility of ACF in Carbitol
$x_2$	Solubility of ACF in water
$x_{m,T}$	Jouyban-Acree model solubility of ACF
$x_{1,T}$	Solubility of ACF in Carbitol at temperature T
$x_{2,T}$	Solubility of ACF in water at temperature T
$J_i$	Jouyban-Acree model parameter
$A_1, B_1, A_2, B_2, J_1$	Jouyban-Acree-van't Hoff model parameters
$T_{\text{hm}}$	Mean harmonic temperature
$\Delta_{\text{sol}}H^\circ$	Apparent standard enthalpy
$\Delta_{\text{sol}}G^\circ$	Apparent standard Gibbs energy
$\Delta_{\text{sol}}S^\circ$	Apparent standard entropy
$R^2$	ACF coefficient of determination

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## Author contributions

Faiyaz Shakeel: Conceptualization, Methodology, Investigation, Funding acquisition, Visualization, Resources, Software, Supervision, Project administration, Writing original draft; Ramadan Al-Shdefat: Data curation, Formal analysis, Validation, Writing, review, and editing; Mohammad A. Altamimi: Investigation, Formal analysis, Validation, Software, Writing, review, and editing; Usama Ahmad: Conceptualization, Methodology, Investigation, Data curation, Validation, Writing, review, and editing.

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## Data availability

Data are available on reasonable request from the corresponding author.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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