



Determination and Evaluation of Solubility Parameter of Aceclofenac Using Dioxane-Water System

Pavan B. Rathi*, Prabhakar S. Panzade, Ashwini U. Patil, Pawan S. Salve
Department of Pharmaceutics, Shri Bhagwan College of Pharmacy, N-6, CIDCO,
Auranagabad-431003, India.

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ABSTRACT

Aceclofenac, non-steroidal anti-inflammatory drug, is a poorly water-soluble drug and has low bioavailability on oral administration. One of the important methods to improve the solubility and bioavailability of a less water-soluble drug is by the use of cosolvents. The solubility enhancement produced by binary blends with a cosolvent (dioxane) was studied against the solubility parameter of solvent blends (δ_1) to evaluate the solubility parameter of drug (δ_2). Solubility parameter of drug (δ_2) was evaluated in blends of dioxane-water system. The results obtained were compared with the δ_2 values obtained using Molar Volume Method and Fedor's Group Substitution Method. The binary blend water-dioxane (10:90) gave maximum solubility with an experimental δ_2 value of $11.34 \text{ (Cal/cm}^3)^{0.5}$ that was comparable to the theoretical values of $11.34 \text{ (Cal/cm}^3)^{0.5}$ determined by Molar Volume Method and $12.08 \text{ (Cal/cm}^3)^{0.5}$ when determined by Fedor's Group Substitution Method, which is still in good agreement with solubility measurement method.

Keywords: Aceclofenac, Fedor's group substitution method, molar volume method, solubility parameter.

1. INTRODUCTION:

Aceclofenac, 2-[(2, 6-dichlorophenyl) amino] phenylacetoxycetic acid, is one of the large series of non-steroidal anti-inflammatory, BCS class II drug [1-3]. It is official in IP, BP, and European Pharmacopoeia [4-6]. Though the molecule is found to be effective orally, its therapeutic efficacy is hindered due to poor aqueous solubility [7]. The poor aqueous solubility and wettability of aceclofenac give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in bioavailability [8-10]. Co-solvency is one of the methods to improve solubility especially in case of liquid formulations. The choice of the appropriate co-solvent is important to obtain maximum solubility of drug [11]. Evaluation of solubility parameter in different solvent blends of various polarities would provide important insight about the solubility of drug [12]. Solubility parameter (δ) is an intrinsic physicochemical property that influences drug action, structure activity, in situ release and transport kinetics of drug substances [13]. Literature survey revealed that solubility parameter of aceclofenac is not estimated by any method till date. So the present study attempts to determine the solubility parameter of aceclofenac in different blends of dioxane-water. Experimental values obtained were compared with the theoretical values obtained by molar volume method and Fedor's group substitution method [14, 15]. Dioxane and water were selected based on their Hildebrand

values [16-18]. Water and dioxane exhibit extremities of polarity [19].

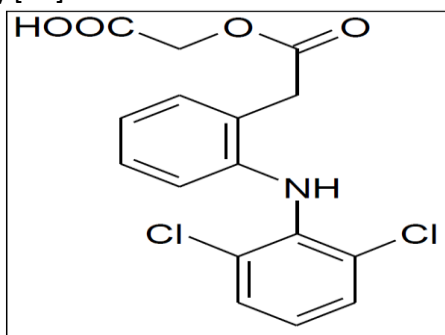


Fig. 1: Structure of Aceclofenac.

2. MATERIALS AND METHOD:

2.1. Materials:

Aceclofenac, obtained as gift sample from Alembic Pharmaceuticals Ltd., Vadodara, India, was purified by recrystallization process. The solvent used for recrystallization of aceclofenac was acetone. 1,4-Dioxane and acetone were purchased from E. Merck, Ltd.; Mumbai, India and Qualigens Fine Chemicals, Mumbai, India respectively. Double distilled water was used for experimental purpose throughout the study. All chemicals and reagents used in the study were of analytical grade and used as such. Double beam UV/Vis spectrophotometer, SICAN 2301, with spectral bandwidth of 2 nm, wavelength accuracy ± 0.5 nm and a pair of 10 mm matched quartz cells was used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of aceclofenac.

2.2. Methods:

2.2.1. Solubility measurements:

Experimental determination of solubility parameter was based upon the maximum solubility of aceclofenac in cosolvent-water blends. For most of cases, 1, 4-dioxane and water were chosen as miscible solvent blends, which provides the two extremes of solubility parameters (δ_1) 10 and 23.4 (Cal/cm^3)^{0.5}, respectively. Binary solvent system was prepared by using dioxane and water, ranging from 0% to 100% respectively, in screw capped vials. The final volume of binary solvent system was kept constant at 5 ml. A slight excess quantity of aceclofenac was introduced into each vial and these were shaken for 3 h by keeping on rotary shaker at constant speed at 150 rpm followed by saturation equilibration for 72 h at room temperature ($\sim 25^\circ$). Preliminary studies showed that this time was sufficient to ensure saturation equilibrium [20]. After equilibrium was reached, solutions were filtered

through Whatman filter paper (No. 41) and analyzed after appropriate dilutions with double distilled water by UV Spectrophotometer at 274 nm (λ_{max}). All experimental results are expressed as the average of at least three determinations. The coefficient of variation ($\text{SD}/\text{mean} \times 100$) was within 2% among replicated samples for the solubility measurements.

2.2.2. Solubility parameter determination:

Solubility parameter determination of aceclofenac (δ_2) was achieved using the solubility measurement method (experimental method) and by theoretical methods, namely, molar volume method and by Fedor's group substitution method proposed by Fedor [21]. In solubility measurement method, the solubility parameter of aceclofenac is assumed to be similar to that of the solubility parameter of the solvent (δ_1) in which the drug exhibits maximum solubility [22]. Hence, the solubility data (Table 1) obtained by the method described in preceding section was used to determine δ_2 .

Solvent blends	δ_1 (Cal/cm^3) ^{0.5}	$\Delta\delta$ ($\delta_1 - \delta_2$)	Solubility (g/ml)	Mole fraction solubility (X_2)
Water:				
Dioxane (%v/v)				
100:0	23.40	+12.06	0.0010523	5.3640E-05
90:10	22.06	+10.72	0.0010610	7.4896E-05
80:20	20.72	+9.38	0.0012606	1.1356E-04
70:30	19.38	+8.04	0.0016915	1.8517E-04
60:40	18.04	+6.70	0.0040567	5.2315E-04
50:50	16.70	+5.36	0.0125333	1.8693E-03
40:60	15.36	+4.02	0.0491500	8.5266E-03
30:70	14.02	+2.68	0.1534583	3.2386E-02
20:80	12.68	+1.34	0.9085417	6.1964E-01
10:90	11.34	+0.00	1.2929167	9.3299E+00
0:100	10.00	-1.34	0.7506250	3.9891E-01

δ_1 = Solubility parameter of solvent blend, δ_2 = Solubility parameter of drug in solvent blend.

The binary solvent blends, δ_1 and $\delta_1 - \delta_2$ and the corresponding values of equilibrium experimental solubility and mole fraction solubility.

Table 1: Mole fraction solubility of aceclofenac in binary solvent blends.

The solubility parameter of aceclofenac was determined by molar volume method by calculating the mole fraction solubility (X_2) of aceclofenac in solvent blends containing water and dioxane in different ratios as shown in Table 1. The mole fraction solubility was calculated by using the equation, mole fraction solubility, $X_2 = \eta_2 / (\eta_1 + \eta_2)$ (1), where η_1 and η_2 are the number of moles of solvent and solute respectively. A plot of mole fraction solubility of aceclofenac in the various ratios of the binary mixtures was made against $\Delta\delta$ ($\delta_1 - \delta_2$), difference between solubility parameter of solvent

and solute respectively. The solubility parameter of the solvent blend (δ_1) in which aceclofenac showed peak mole fraction solubility represents the solubility parameter of aceclofenac (δ_2).

Fedor's group substitution method is based on the determination of solubility parameter of aceclofenac (δ_2) by using the Eqn. $\delta = (\Delta\Delta u / \Delta V)^{0.5}$ (2), in which $\Delta\Delta u$ represents the substituent fragment constant and ΔV represents the fragmental molar volume constant. Further, the solubility parameter of Aceclofenac was determined by dividing the structure of aceclofenac (fig. 1) into different fragments and corresponding values of cohesive energy per mole ($\Delta\Delta u$) and molar volume (ΔV) for each fragment was obtained from literature survey as shown in Table 2.

Drug fragments	No. of Fragments	Cohesive Energy (Cal/mol)	Molar Volume (Cm ³ /mol)
=CH —	[7]	1030	13.5
=C<	[5]	1690	6.5
-O-	[1]	800	3.8
-CO-	[1]	4150	10.8
-Cl	[2]	2760	24
>N-H	[1]	2000	4.5
-CH ₂ -	[2]	1180	16.1
-COOH	[1]	6600	28.5
Conjugation	[6]	400	-2.2
Ring Closure	[2]	250	16
	Total	39990	273.6
	δ_2 (Cal/cm ³) ^{0.5}	$= (39990/273.6)^{0.5}$	$= 12.08$

δ_2 = Solubility parameter of aceclofenac, (Cal/cm³)^{0.5} = Unit of solubility parameter.

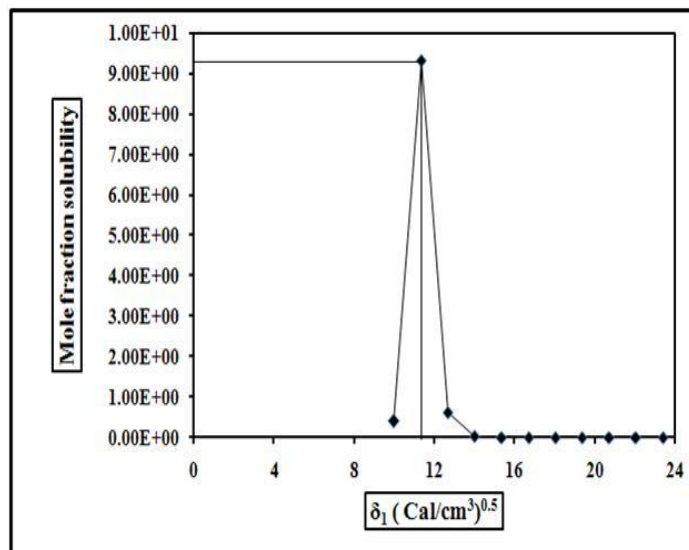
Cohesive energy and molar volume of aceclofenac was obtained by Fedor's group substitution method, which divide the structure into different drug fragments.

Table 2: Calculation Of Solubility Parameter of Aceclofenac by Fedor's Group Substitution Mrthod.

3. RESULTS AND DISCUSSION:

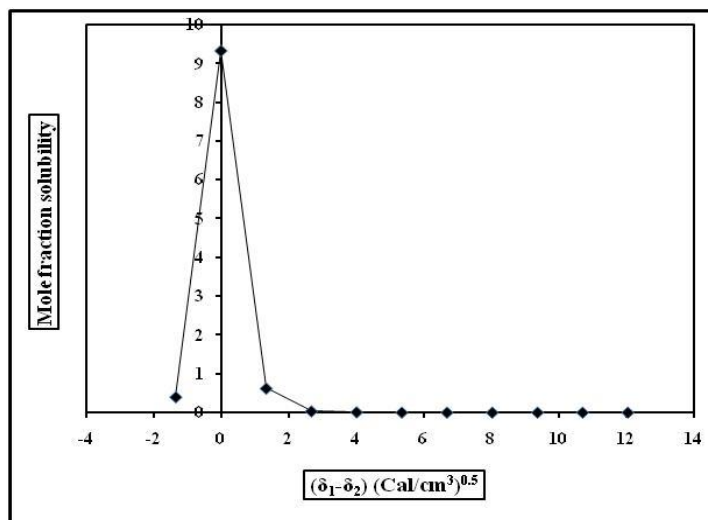
Solubility of aceclofenac was evaluated in solvent blends containing water: dioxane for the determination of δ_2 as the varying blends of these provided a range of 10.00-23.40 (Cal/cm³)^{0.5} of δ_1 . The peak solubility (X_2) of 1.2929167 g/ml for aceclofenac was observed in a solvent blend of water:dioxane (10:90) with δ_1 of 11.34 (Cal/cm³)^{0.5}. Thus, the solubility parameter for aceclofenac can be defined as 11.34 (Cal/cm³)^{0.5} as according to the solubility measurement method; δ_2 is that value of δ_1 at which the drug exhibits maximum solubility. Table 1 lists the solvent blends, the Hildebrand solubility parameter (δ_1) of the solvent blends and the

experimentally determined solubilities (g/ml) of aceclofenac.



The solid line (—) represents highest mole fraction solubility ($X_2=9.3299E+00$) when $\delta_1=11.34$ (Cal/cm³)^{0.5} by molar volume method and Key (— ◆ —) represents experimental solubilities by dioxane-water binary solvent system.

Fig. 2: Solubility parameter versus mole fraction solubility profile of Aceclofenac.



Curve showing mole fraction solubility of aceclofenac (X_2) versus difference between solubility parameter of solvent and solute ($\delta_1 - \delta_2$) and when $\Delta\delta = (\delta_1 - \delta_2) = 0$, then aceclofenac exhibit highest mole fraction solubility by molar volume method.

Fig. 3: Mole fraction solubility versus ($\delta_1 - \delta_2$) profile of Aceclofenac.

The molar volume method was used to determine the peak mole fraction solubility of aceclofenac in various solvent blends and the mole fraction solubility's X_2 of aceclofenac and $\Delta\delta$ are tabulated in Table 1. Peak mole fraction solubility was determined to be 9.3299 in solvent blend (water:dioxane, 10:90) with δ_1 value 11.34 (Cal/cm³)^{0.5}, which is in agreement with the value obtained using solubility measurement method. A plot of δ_1 and mole fraction

solubility (X_2) (fig. 2) showed a bell shaped curve suggesting that both at lower and higher values $\delta_1 = 11.34$ (Cal/cm^3)^{0.5} the solubility of aceclofenac decreased. When $\Delta \delta$ ($\delta_1 - \delta_2$) was plotted against mole fraction solubility (X_2) (fig. 3), the solubility parameter of aceclofenac was confirmed at 11.34 (Cal/cm^3)^{0.5} as it is that value of δ_1 at which aceclofenac exhibited peak mole fraction solubility and $\Delta \delta = 0$. δ_2 determined by the Fedor's group substitution method was found to be 12.08 (Cal/cm^3)^{0.5}, which is still comparable to the value obtained by solubility measurement method and molar volume method.

Therefore, experimentally determined solubility parameter of aceclofenac in water-dioxane binary solvent system was in good agreement with that of the theoretically determined solubility parameter by Molar volume method and by Fedor's group substitution method.

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Conflict of Interest: None Declared

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