DETERMINATION AND EVALUATION OF SOLUBILITY PARAMETER OF NORFLOXACIN USING DIOXANE-WATER SYSTEM

P. Sabitha Reddy*, M. Greeshma Haritha and K. Ravindra Reddy

Department of Pharmaceutics, P. Rami Reddy Memorial College of Pharmacy, Kadapa-516003, Andhra Pradesh, India

ABSTRACT
Norfloxacin, a synthetic, broad-spectrum antibacterial agent is an antibiotic in a class of drugs called fluoroquinolones. It is a synthetic chemotherapeutic agent occasionally used to treat various bacterial infections such as common as well as complicated urinary tract infections, gonorrhea, and prostate infections. It is poorly water-soluble drug and has low therapeutic efficacy. One of the important methods to improve the solubility and bioavailability of a less water-soluble drug is by the use of co-solvents. The solubility enhancement produced by binary blends with a co-solvent (dioxane) was studied against the solubility parameter of solvent blends ($\delta_1$) to evaluate the solubility parameter of drug ($\delta_2$). Solubility parameter of drug ($\delta_2$) was evaluated in blends of dioxane-water system. The results obtained were compared with the $\delta_2$ values obtained using Molar Volume Method. The binary blend water-dioxane (60:40) gave maximum solubility with an experimental $\delta_2$ value of 18.04 (Cal/cm$^3$)$^{0.5}$ that was comparable to the theoretical values of 18.04 (Cal/cm$^3$)$^{0.5}$ determined by Molar Volume Method, which is in good agreement with solubility measurement method.

Keywords: Molar volume method, Norfloxacin, solubility parameter.

INTRODUCTION
Norfloxacin, a fluoroquinolone$^{[1]}$, is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, is a second generation synthetic fluoroquinolone (quinolone). Which is used to treat various bacterial infections such as common as well as complicated urinary tract infections, gonorrhea, and prostate infections. Though the molecule is efficacious for urinary tract infections, gonorrhea, and prostate infections, its therapeutic efficacy is hindered due to its poor aqueous solubility. The poor aqueous solubility of Norfloxacin gives rise to difficulties in pharmaceutical formulations meant for oral use, which may lead to variation in bioavailability. 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$^{[2]}$. 
Evaluation of solubility parameter in different solvent blends of various polarities would provide important insight about the solubility of drug. Solubility parameter ($\delta$) is an intrinsic physicochemical property that influences structure activity and transport kinetics of a drug substance [3]. So the present study attempts to determine the solubility parameter of norfloxacin in different blends of dioxane-water. Experimental values obtained were compared with the theoretical values obtained by molar volume method [4]. Dioxane and water were selected based on their Hildebrand values. Water and dioxane exhibit extremities of polarity [5].

MATERIALS AND METHODS

Materials

Norfloxacin, was obtained from Unichem Laboratories, Mumbai, India. 1, 4-Dioxane was obtained from Finar chemicals Ltd, Ahmedabad. 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, Systronics 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. Samson balance, was used for weighing of Norfloxacin.

Methods

Experimental determination of solubility parameter was based upon the maximum solubility of Norfloxacin 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 ($\delta_1$) 10 and 23.4 (cal/cm³)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 2ml.

A quantity of 50mg of norfloxacin 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 24 h at room temperature (~ 25°C). Preliminary studies showed that this time was sufficient to ensure saturation equilibrium [6]. After equilibrium was reached, solutions were filtered through whatman filter paper No. 41 and analyzed after appropriate dilutions with 0.1N Hcl by using UV spectrophotometer at 278 nm [7] ($\lambda_{max}$).
Solubility parameter determination of norfloxacin ($\delta_2$) was achieved by using the solubility measurement method (experimental method) and by theoretical methods, namely, molar volume method. In solubility measurement method, the solubility parameter of Norfloxacin is assumed to be similar to that of the solubility parameter of the solvent ($\delta_1$) in which the drug exhibits maximum solubility. Hence the solubility data (Table 1) obtained by the method described in preceding section was used to determine $\delta_2$

**TABLE 1: MOLE FRACTION SOLUBILITY OF NORFLOXACIN IN BINARY SOLVENT BLENDS**

<table>
<thead>
<tr>
<th>SOLVENT BLEND,WATER: DIOXANE (% v/v)</th>
<th>$\delta_1$ (Cal/cm$^3$)$^{0.5}$</th>
<th>$\Delta\delta$ ($\delta_1$ - $\delta_2$)</th>
<th>SOLUBILITY (g/ml)</th>
<th>MOLE FRACTION SOLUBILITY ($X_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100:0</td>
<td>23.40</td>
<td>+5.30</td>
<td>0.00000307</td>
<td>1.1373637</td>
</tr>
<tr>
<td>90:10</td>
<td>22.60</td>
<td>+4.02</td>
<td>0.00000445</td>
<td>1.4465768</td>
</tr>
<tr>
<td>80:20</td>
<td>20.72</td>
<td>+2.68</td>
<td>0.00001433</td>
<td>1.4465787</td>
</tr>
<tr>
<td>70:30</td>
<td>19.38</td>
<td>+1.34</td>
<td>0.000002031</td>
<td>1.4465790</td>
</tr>
<tr>
<td>60:40</td>
<td>18.04</td>
<td>+0.00</td>
<td>0.00002386</td>
<td>1.44658135</td>
</tr>
<tr>
<td>50:50</td>
<td>16.70</td>
<td>-1.34</td>
<td>0.00000395</td>
<td>1.44658083</td>
</tr>
<tr>
<td>40:60</td>
<td>15.36</td>
<td>-2.68</td>
<td>0.00000618</td>
<td>1.4465806</td>
</tr>
<tr>
<td>30:70</td>
<td>14.02</td>
<td>-4.02</td>
<td>0.00000727</td>
<td>1.4465805</td>
</tr>
<tr>
<td>20:80</td>
<td>12.68</td>
<td>-5.36</td>
<td>0.00000975</td>
<td>1.4465801</td>
</tr>
<tr>
<td>10:90</td>
<td>11.34</td>
<td>-6.7</td>
<td>0.00001171</td>
<td>1.4465799</td>
</tr>
<tr>
<td>0:100</td>
<td>10.00</td>
<td>-8.04</td>
<td>0.00001702</td>
<td>0.3917116</td>
</tr>
</tbody>
</table>

$\delta_1$ = solubility parameter of solvent blend, $\delta_2$ = solubility parameter of drug in solvent blend. The binary solvent blends $\delta_1$ and $\delta_2$ are the corresponding values of equilibrium experimental solubility and mole fraction solubility.

The solubility parameter of Norfloxacin was determined by molar volume method by calculating the mole fraction solubility ($X_2$) of norfloxacin 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 [8], mole fraction solubility,

\[ \phi_i V_i \]

\[ -\log X_i = -\log X_i^i + \frac{(\delta_1 - \delta_2)^2}{2.303RT} \]

Where \( \delta_1 \) and \( \delta_2 \) represent the solubility parameters of solvent and solute, respectively. And \( (X_i^i) \), is ideal mole fraction solubility. A plot of mole fraction solubility of Norfloxacin in the various ratios of the binary mixtures was made against \( \delta \) \((\delta_1-\delta_2)\), difference between solubility parameter of solvent and solute respectively. The solubility parameter of the solvent blend \((\delta_1)\) in which Norfloxacin showed peak mole fraction solubility represents the solubility parameter of Norfloxacin \((\delta_2)\)[9].

RESULT AND DISCUSSION

Solubility of Norfloxacin was evaluated in solvent blends containing water: dioxane for the determination of \( \delta_2 \) as the varying blends of these provided a range of 10.00-23.40 (Cal/cm\(^3\))\(^{0.5}\) of \( \delta_1 \). The peak solubility \((X_2)\) of 0.00002386 g/ml for Norfloxacin was observed in a solvent blend of water: dioxane (60:40) with \( \delta_1 \) of 18.04 (Cal/cm\(^3\))\(^{0.5}\). Thus, the solubility parameter for Norfloxacin can be defined as 18.04 (Cal/cm\(^3\))\(^{0.5}\) as according to the solubility measurement method; \( \delta_2 \) is that value of \( \delta_1 \) at which the drug exhibits maximum solubility. (Table 1) lists the solvent blends, the Hildebrand solubility parameter \((\delta_1)\) of the solvent blends and the experimentally determined solubilities (g/ml) of Norfloxacin.

The molar volume method was used to determine the peak mole fraction solubility of Norfloxacin in various solvent blends and the mole fraction solubilities \( X_2 \) of Norfloxacin and \( \delta \) are tabulated in (Table 1). Peak mole fraction solubility was determined to be 1.446581 in solvent blend (water: dioxane, 60:40) with \( \delta_1 \) value 18.04 (Cal/cm\(^3\))\(^{0.5}\), which is in agreement with the value obtained using solubility measurement
method. A plot of $\delta_1$ and $X_2$ (Figure 1) showed a bell shaped curve suggesting that both at lower and higher values $\delta_1 = 18.04$ (Cal/cm$^3$)$^{0.5}$ the solubility of Norfloxacin decreased. When $\delta$ was plotted against $X_2$ (Figure 2), the solubility parameter of Norfloxacin was confirmed at 18.04 (Cal/cm$^3$)$^{0.5}$ as it is that value of $\delta_1$ at which Norfloxacin exhibited peak mole fraction solubility and $\delta = 0$.

**Figure 1**
Solubility parameter versus mole fraction solubility profile of norfloxacin.

**Figure 2**
Mole fraction solubility versus $(\delta_1-\delta_2)$ profile of Norfloxacin.
CONCLUSION

Therefore, experimentally determined solubility parameter of Norfloxacin in water-dioxane binary solvent system was in good agreement with that of the theoretically determined solubility parameter by Molar volume method. Thus this procedure can be used to predict the solubility of Norfloxacin in pure water or dioxane and in dioxane-water mixtures.

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REFERENCE


For Correspondence:
P. Sabitha Reddy
Email: sabithareddy135@yahoo.co.in