Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X

RESEARCH ARTICLE

Received on: 26-11-2013
Accepted on: 25-12-2013
Published on: 18-01-2014

Rathi P. B.*
[1]Shri Bhagwan College of Pharmacy, Dr. Y. S. Khedkar Marg, N-6, CIDCO, Aurangabad, 431005, (M.S.), India
Email: pavanbrathi@gmail.com

QR Code for Mobile users

Conflict of Interest: None Declared !

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

P. B. RATHI*, K. V. DESHPANDE
Department of Pharmaceutics, Shri Bhagwan College of Pharmacy, N-6, CIDCO, Auranagabad-431003, India

Abstract

Nabumetone, 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 11.354 $(Cal/cm^3)^{0.5}$ that was comparable to the theoretical values of 11.354 $(Cal/cm^3)^{0.5}$ determined by Molar Volume Method and 10.1689 $(Cal/cm^3)^{0.5}$ when determined by Fedor's Group Substitution Method, which is still in good agreement with solubility measurement method.

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

Cite this article as:
Rathi PB*, Deshpande KV . Insights Determination and Evaluation of Solubility Parameter of Nabumetone Using Dioxane-Water System. Asian Journal of Biomedical and Pharmaceutical Sciences; 03 (27); 2013; 30-33.

INTRODUCTION:

Nabumetone, 4-(6-methoxy-2-naphthyl)-2-butanone, is one of the large series of non-steroidal anti-inflammatory, BCS class II drug[1-3]. It is official in USP[4-7].Nabumetone is a prodrug that undergoes extensive first pass metabolism to 6-methoxy-2-naphthylacetic acid (6-MNA), the major circulating metabolite. 6-MNA is mainly responsible for the therapeutic efficacy of nabumetone. It decreases prostaglandin synthesis via inhibition of cyclooxygenase, an enzyme involved in the arachidonic acid conversion[8]. Though the molecule is found to be effective orally, its therapeutic efficacy is hindered due to poor aqueous solubility[9]. The poor aqueous solubility and wettability of nabumetone give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in absorption and bioavailability[10,11]. 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[12]. Evaluation of solubility parameter in different solvent blends of various polarities would provide important insight about the solubility of drug[13]. Solubility parameter (δ) is an intrinsic physicochemical property that influences drug action, structure activity, in situ release and transport kinetics of a drug substances[14]. Literature survey revealed that solubility parameter of nabumetone is not estimated by any method till date. So the present study attempts to determine the solubility parameter of nabumetone 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[15,16]. Dioxane and water were selected based on their Hildebrand values[17-19]. Water and dioxane exhibit extremities of polarity[20].

MATERIALS AND METHODS:

Nabumetone, obtained as gift sample from GlaxoSmithKline Pharmaceuticals Ltd. Nasik, India. 1, 4-Dioxane was purchased from Research Lab Fine Chemical Industry, Islampur, India. 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 nabumetone.

Solubility measurements:

Experimental determination of solubility parameter was based upon the maximum solubility of nabumetone 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) 10.01 and 23.45 $(Cal/cm^3)^{0.5}$, 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 2 ml. A slight excess quantity of nabumetone 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 (~ 25^0). Preliminary studies showed that this time was sufficient to ensure saturation equilibrium[21,22]. 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 262 nm (λ_{max}). All experimental results are expressed as the average of at least three determinations. The coefficient of variation (SD/mean*100) was within 2% among replicated samples for the solubility measurements.

Solubility parameter determination of nabumetone (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[23]. In solubility measurement method, the solubility parameter of nabumetone is assumed to be similar to that of the solubility parameter of the solvent (δ_1) in which the drug exhibits maximum solubility[24]. Hence, the solubility data (Table 1) obtained by the method described in preceding section was used to determine δ_2.

Water: 1,4-Dioxane (%v/v)	δ_1 $(Cal/cm^3)^{0.5}$	$\Delta\delta$ (δ_1-δ_2)	Solubility (g/ml)	Mole fraction solubility (X_2)
100:0	23.450	+12.096	1.91E-05	1.51E-06
90:10	22.106	+10.752	5.01E-05	5.48E-06
80:20	20.762	+9.408	1.68E-04	2.34E-05
70:30	19.418	+8.064	5.09E-04	8.64E-05
60:40	18.074	+6.720	1.38E-03	2.74E-04
50:50	16.730	+5.376	3.42E-03	7.84E-04
40:60	15.386	+4.032	8.76E-03	2.28E-03
30:70	14.042	+2.688	1.18E-02	3.42E-03
20:80	12.698	+1.344	1.38E-02	4.40E-03
10:90	11.354	0.000	1.76E-02	6.12E-03
0:100	10.010	-1.344	1.40E-02	5.26E-03

Table 1: Mole fraction solubility of nabumetone in binary solvent blends

δ_1= Solubility parameter of solvent blend, δ_2= Solubility parameter of drug in solvent blend. The binary solvent blends, δ_1 and δ_1-δ_2 and the corresponding values of equilibrium experimental solubility and mole fraction solubility

RESULTS AND DISCUSSION:

The solubility parameter of nabumetone was determined by molar volume method by calculating the mole fraction solubility (X_2) of nabumetone 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 nabumetone in the various ratios of the binary mixtures was made against $\Delta\delta$ (δ_1-δ_2), difference between solubility parameter of solvent and solute respectively. The solubility parameter of the solvent blend (δ_1) in which nabumetone showed peak mole fraction solubility represents the solubility parameter of nabumetone (δ_2).

Fedor's group substitution method is based on the determination of solubility parameter of nabumetone (δ_2) by using the Eqn. $\delta = \left(\Delta\Delta u / \Delta V\right)^{0.5}$ (2), in which $\Delta\Delta u$ represents the substituent fragment constant and ΔV represents the fragmental molar volume constant.

Further, the solubility parameter of nabumetone was determined by dividing the structure of nabumetone (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 of Each Fragment (Cal/mol)	Total Cohesive Energy (Cal/mol)	Molar Volume of Each Fragment (Cm^3/mol)	Total Molar Volume (Cm^3/mol)
=CH —	[6]	1030	6180	13.5	81
=C<	[4]	1690	6760	6.5	26
-O-	[1]	800	800	3.8	3.8
-CO-	[1]	4150	4150	10.8	10.8
$-CH_3$	[2]	1126	2252	33.5	67
$-CH_2-$	[2]	1181	2362	16.1	32.2
Conjugation	[5]	400	2000	-2.2	-11
Ring Closure	[2]	250	500	16	32
	Total	**10628**	**25004**	**98**	**241.8**

$\delta_2 = (25004/241.8)^{0.5} = (103.408)^{0.5} = 10.1689\ (Cal/cm^3)^{0.5}$

Table 2: Calculation of solubility parameter of nabumetone by fedor's group substitution method

δ_2= Solubility parameter of nabumetone, $(Cal/cm^3)^{0.5}$ = Unit of solubility parameter

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

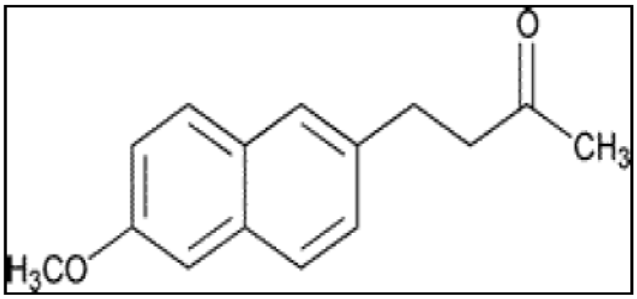

Figure 1: Structure of Nabumetone

Solubility of nabumetone was evaluated in solvent blends containing water: dioxane for the determination of δ_2 as the varying blends of these provided a range of 10.01-23.45 $(Cal/cm^3)^{0.5}$ of δ_1. The peak solubility of 0.0176 g/ml for nabumetone was observed in a solvent blend of water:dioxane (10:90) with δ_1 of 11.354 $(Cal/cm^3)^{0.5}$. Thus, the solubility parameter for nabumetone can be defined as 11.354 $(Cal/cm^3)^{0.5}$ 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 solubility's (g/ml) of nabumetone.

The molar volume method was used to determine the peak mole fraction solubility of nabumetone in various solvent blends and the mole fraction solubility's X_2 of nabumetone and $\Delta\ \delta$ are tabulated in Table 1. Peak mole fraction solubility (X_2) was determined to be 0.00612 in solvent blend (water:dioxane, 10:90) with δ_1 value 11.354 $(Cal/cm^3)^{0.5}$, 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 δ_1 =11.354 $(Cal/cm^3)^{0.5}$ the solubility of nabumetone decreased.

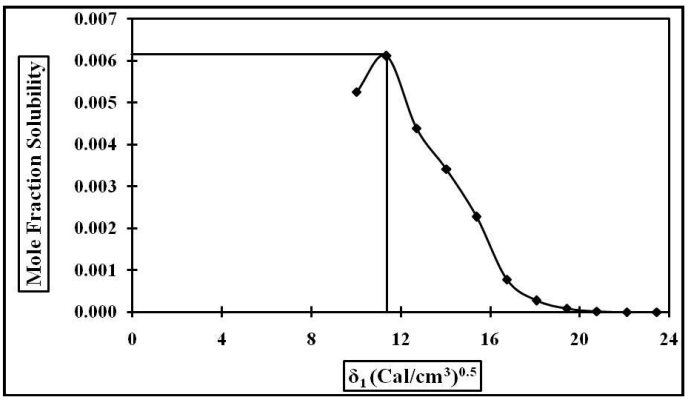

Figure 2: Solubility parameter versus mole fraction solubility profile of nabumetone

The solid line (——) represents highest mole fraction solubility (X_2=6.12E-03) when δ_1=11.354 $(Cal/cm^3)^{0.5}$ by molar volume method and Key (–◆—) represents experimental solubilities by dioxane-water binary solvent system

When Δ δ (δ_1-δ_2) was plotted against mole fraction solubility (X_2) (fig. 3), the solubility parameter of nabumetone was confirmed at 11.354 $(Cal/cm^3)^{0.5}$ as it is that value of δ_1 at which nabumetone exhibited peak mole fraction solubility and Δδ=0. δ_2 determined by the Fedor's group substitution method was found to be 10.1689 $(Cal/cm^3)^{0.5}$, which is still comparable to the value obtained by solubility measurement method and molar volume method.

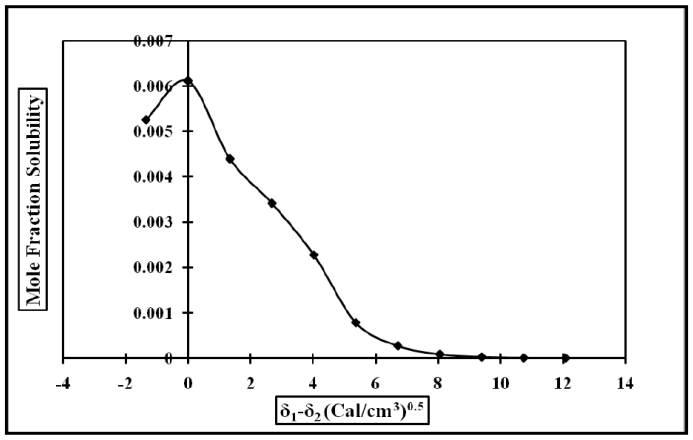

Figure 3: Mole fraction solubility versus (δ_1-δ_2) profile of nabumetone

Curve showing mole fraction solubility of nabumetone (X_2) versus difference between solubility parameter of solvent and solute (δ_1-δ_2) and when Δδ= (δ_1-δ_2)=0, then nabumetone exhibit highest mole fraction solubility by molar volume method

CONCLUSION

Therefore, experimentally determined solubility parameter of nabumetone 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.

ACKNOWLEDGEMENTS

The authors are thankful to M/s. GlaxoSmithKline Pharmaceuticals Limited, Nasik, India for supplying gift sample of nabumetone.

REFERENCES

1. Chelakara LV, Kulkarni SK, Kolwankar DR. Spherical Agglomeration of Mefenamic Acid and Nabumetone to Improve Micromeritics and Solubility: A Technical Note. AAPS PharmSciTech 2006;7: Article 48 E1-E4.
2. Friedel HA, Todd PA. Nabumetone: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Rheumatic Diseases. Drugs 1988;35:504-24.
3. Margarita V, Javier T, Licesio J. Encapsulation of Nabumetone by means of Drug:(Beta-Cyclodextrin)2:Polyvinylpyrrolidone ternary complex formation. J Lum 2007;126: 297–302.
4. United States Pharmacopoeia, USP 31/NF, Volume 326, US Pharmacopoeial Convention, Inc., Rockville, 2008; 2743-4.
5. Mohite AH. Development of UV-spectroscopic method for Nabumetone in Tablet Formulation. J Pharm Res 2009;2:1221-3.
6. Rote R. Development and Statistical Validation of Spectrophotometric Methods for the Estimation of Nabumetone in Tablet Dosage Form. E J Chem2010;7:1463-7.
7. Lakshmi PB. Development and Validation of Nabumetone by Isocratic RP- HPLC Method. Int Res J Pharm App Sci 2012;2:92-8.
8. Kamila K, Malgorzata B, Maria K. Analysis of Nabumetone in Human Plasma by HPLC -Application to single dose Pharmacokinetic Studies. J Pharm Biomed Ana 2003;32:323-8.
9. Patil P, Gupta VRM. Application of Spherical Agglomeration Technique to improve Micromeritic Properties and Dissolution Characteristics of Nabumetone. Int Res J Pharm 2012;3:156-62.
10. Rao KP, Kamamia EK. Characterisation of Nabumetone Microcrystals prepared by Solvent Evaporation Method. Int J Res Pharm Biomed Sci 2011;2:1346-9.
11. Shingade G. Development of Nabumetone Topical Gels: Effect of Formulation variables on the Release of Nabumetone. World J Pharm Research 2012;1:776-85.
12. Etman MA, Salama RO, Shamsedeen MA, El-Kamel A.Solubilization of Etodolac for Parenteral Administration. Indian J Pharm Sci 2001;63:459-67.
13. Rathi PB. Determination and Evaluation of Solubility Parameter of Satranidazole Using Dioxane-Water System. Indian J Pharm Sci 2010;72:671-4.
14. Greenhalgh DJ, Williams AC, Timmins P, York P. Solubility Parameters as Predictors of Miscibility in Solid Dispersions. J Pharm Sci 1999;88:1182-90.
15. Kuksal K, Pathak K. Use of Solubility Parameter to Design Dry Suspension of Cefaclor as a Dual Pack System. Indian J Pharm Sci 2008;70:609-13.
16. Barton AFM. CRC Handbook of Solubility Parameters and other Cohesion Parameters, 2nd ed. New York: CRC Press; 1983. p. 7-59, 157-85.
17. Rathi PB, Mourya VK. Extended Hildebrand Solubility Approach: Satranidazole in Mixtures of Dioxane and Water. Indian J Pharm Sci 2011;73:315-9.
18. Martin A, Wu PL. Extended Hildebrand Solubility Approach: Hydroxybenzoic acid in Mixtures of Dioxane and Water. J Pharm Sci 1983;72:587-92.
19. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences, 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 245-6, 595-6.
20. Martin A, Wu PL, Velasquez T. Extended Hildebrand Solubility Approach: Sulfonamides in Binary and Ternary Solvents. J Pharm Sci 1985;74:277-82.
21. Martin A, Newburger J, Adjei A. Extended Hildebrand Solubility Approach: Solubility of Theophylline in Polar Binary Solvents. J Pharm Sci 1980;69:487-91.
22. Rathi PB. Solubility Prediction of Satranidazole in Propylene Glycol-Water Mixtures Using Extended Hildebrand Solubility Approach. Indian J Pharm Sci 2011;73:670-74.
23. Barra J, Bustamante P, Pena MA. Partial solubility parameters of naproxen and sodium diclofenac. J Pharm Pharmacol 1998;50:975-82.
24. Hancock BC, York P, Rowe RC. The use of solubility parameters in pharmaceutical dosage form design. Int J Pharm 1997;148:1-21.