RESEARCH PAPER

Accepted 28 November 2002
Revised 29 October 2002
Received 4 October 2001
Indian J. Pharm. Sci., 2003, 65(1): 58-61

Solubilization of Nimesulide; Use of Co-solvents

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Solubility of nimesulide in various solvents and solvent-co-solvent mixtures was determined in relation to the development of parenteral formulations. Solubility was low in aqueous solvents. Solubility increased on solubilization of drug in semi-polar solvents and non-ionic surfactants. Solubility increased drastically (>70 mg/ml) when polyethylene glycol 300 and polyethylene glycol 400 were used as solvents. The minimum concentration of polyethylene glycol required for solubility to be greater than 50 mg/ml was found to be 80%. It was recommended that solvent containing 90% polyethylene glycol and 10% co-solvent (alcohol, propylene glycol, Tween 80 and Brij 30) with solubility greater than 65 mg/ml can be used in parenteral formulations of nimesuilde. Alternatively 8% co-solvent can be mixed with 2% benzyl alcohol which acts as an anaesthetic agent.

Nimesulide, 4-nitro-2-phenoxy methane sulfonanilide, is a highly effective non-steroidal antiinflammatory and analgesic drug with high gastrointestinal tolerability and minimum drug related side effects[1]. It is not only a superior antiinflammatory drug, it can also act as anticancer agent, help prevention of premature labour and even retard Alzheimer disease[2]. Further no clinically significant drug interactions have been reported for nimesulide[3]. The drug is however, beset with the disadvantage of poor water solubility. The very poor aqueous solubility and wettability of the drug gives rise to difficulties in the design of pharmaceutical formulations and leads to variable bioavailability.

An attempt has been made by a number of workers to increase the solubility of nimesulide. Various methods such as crystallization by solvent change[4], preparation of inclusion complexes with β-cyclodextrin[5], nimesulide-L-lysine-cyclodextrin complexes[6] have been used. Present paper is an effort to increase the solubility of nimesulide using a series of solvents and solvent-co-solvent mixtures. The work is significant in relation to development of parenteral formulations of nimesulide, since parenteral route requires injection of a small volume of concentrated drug solution. At present nimesulide is available mainly in solid and liquid dosage forms for oral administration. Although nimesulide has no problem in absorption from the gastrointestinal route[3], it has been demonstrated[7] that nimesulide administered intramuscularly is superior to other routes of administration when fast onset of action is required with high plasma concentrations. Moreover, parenteral route is an alternative mode of administration in unconscious or uncooperative state of the patient[8].

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MATERIALS AND METHODS

Nimesulide was obtained as a gift from Panacea Biotec. Ltd., Lalru, Punjab. All other solvents used were of analytical grade. Analytical grade acetonitrile was refluxed over phosphorus pentoxide and distilled. Phosphate buffer (0.1 M) prepared by mixing requisite amounts of 0.2 M sodium dihydrogen phosphate and 0.2 M disodium hydrogen phosphate was used throughout.

For determination of solubility of nimesulide, excess of drug was placed in contact with 5 ml of solvent/solvent-co-solvent mixture in stoppered glass tubes. The tubes were maintained at 30° and were shaken occasionally on a vortex mixer. A time period of 24 h was found sufficient for the

attainment of equilibrium. The saturated solution was filtered and analyzed for drug concentration. An ultraviolet absorption spectrophotometric method[9], using 50% acetonitrile as solvent, was used for the estimation of nimesulide. Calibration plot (absorbance versus concentration of drug) was obtained by preparing standard solutions of drug in the concentration range 10-50 μg/ml and determining absorption spectra in the range 250-450 nm. Absorption maxima were obtained at 300 nm when 50% acetonitrile in water was used and 402 nm when 50% acetonitrile in phosphate buffer of pH 7.4 was used as solvent. Extinction coefficients obtained from slopes of absorbance versus concentration of drug plots were 0.025 $cm^2/\mu g$ at 300 nm and 0.050 $cm^2/\mu g$ at 402 nm. For determination of solubility, saturated solution of drug was diluted with acetonitrile in such a way that the final acetonitrile concentration was 50% in each case and the final drug concentration was in the limits of linearity of the proposed method (10-50 μg/ml). Absorbance of diluted solutions was determined at 300/402 nm and the drug concentration was calculated using Beer Lambert law.

RESULTS AND DISCUSSION

Solubility of nimesulide in various solvents is given in Table 1. It is seen that the solubility is very low in aqueous solvents. Addition of salt (0.15 M NaCl) to water increased solubility by a small amount. This may be due to the fact that the increase in ionic strength of solvent decreases the activity coefficient and hence solubility increases. Further solubility increased when phosphate buffer of pH 7.4 was used as solvent. Since drug is a weak acid, increase of pH increases the ionization and hence the solubility of the drug. Solubility increased significantly in the presence of non-ionic surfactant, polyoxyethylene (20) sorbitan monooleate (Tween 80) (10%). Since the concentration of surfactant used is much higher than the critical micellar concentration, it appears that the drug has predominantly hydrophobic character and is solubilized into the surfactant micelles.

Solubility was found to increase appreciably when semi-polar solvents such as ethyl alcohol or propylene glycol were used as solvents. Small non-polar hydrocarbon region in these solvents does not interact strongly with water and hence reduce the ability of the aqueous system to squeeze out non-polar solutes[10]. Enhancement of solubility of a number of drugs in the presence of these co-solvents has been reported in the literature[10-12]. Solubility increased drastically (>70 mg/ml) when polyethylene glycols (PEG 300 and PEG 400) were used as solvents. Polyethylene glycols with a large non-polar part and many hydroxyl groups is again a solvent

TABLE 1: SOLUBILITY OF NIMESULIDE IN DIFFERENT SOLVENTS.

Solvent	Solubility (mg/ml)
Water	0.0137
Sodium chloride (0.15 M)	0.0173
Phosphate buffer (0.1 M, pH 7.4)	0.1052
Tween 80 (10%)	2.6496
Ethyl alcohol	5.4144
Propylene glycol	5.8656
PEG 300	71.488
PEG 400	73.600

PEG = Polyethylene Glycol, Tween 80= polyoxyethylene (20) sorbitan monooleate. Reported solubility values are at 30°.

of intermediate character. In pharmacy, the most commonly used measure of polarity is the octanol-water partition coefficient (log P). Octanol-water partition coefficient (log P) of nimesulide, calculated using software MOLCONN-Z[13], was 1.80. This value when compared with the log P values of the solvents employed, calculated using the same software, showed that nimesulide should be considered as semi-polar and hence the solubility of drug in semi-polar solvents is high. Solubility was found to be slightly higher in PEG 400 than in PEG 300.

Solubility of nimesulide in mixtures of PEG with various co-solvents; water, buffer, alcohol, propylene glycol and non-ionic surfactants polyoxyethylene (4) lauryl ether (Brij 30) and polyoxyethylene (20) sorbitan monooleate (Tween 80) is given in Table 2. In general, solubility increased steeply on increasing the concentration of PEG in the solvent mixture. When water, buffer and Brij 30 were used as co-solvents, the solubility was highest in 100% PEG. In the case of alcohol, propylene glycol and non-ionic surfactant, Tween 80, however, mixtures containing 90% PEG and 10% co-solvent had highest solubility. It may be mentioned that PEG has a much lower dielectric constant (12.4) as compared to alcohol (24.3) and propylene glycol (32.0). Since nimesulide has semi-polar nature, it appears that the addition of a small amount of polar co-solvent to a relatively non-polar solvent PEG helps in matching the polarity of solute and solvent and thus increasing the solubility.

Quantification of the effect of co-solvent on the

TABLE 2: SOLUBILITY OF NIMESULIDE IN VARIOUS SOLVENT - CO-SOLVENT MIXTURES.

PEG (%)	Co-solvent (%)	Solubility (mg/ml)					
		PEG-Water	PEG-Buffer	PEG-Alcohol	PEG-Tween 80	PEG-Brij 30	PEG-PG
0	100	0.0137	0.1052	5.414	-	-	-
20	80	0.0357	0.5197	8.614	-	-	-
40	60	0.1540	1.8880	17.318	-	-	-
60	40	1.0137	7.7376	27.648	-	-	-
80	20	10.562	16.864	50.272	66.784	59.072	48.640
90	10	35.664	42.960	74.722	75.600	70.848	72.960
100	0	71.488	71.488	71.488	71.488	71.488	71.488

Percentage is expressed as volume/volume. Alcohol refers to ethyl alcohol and buffer used is 0.1 M phosphate buffer of pH 7.4. Tween 80 = polyoxyethylene (20) sorbitan monooleate, Brij 30 = Polyoxyethylene (4) lauryl ether, PG = Propylene glycol.

solubility of drug in a solvent may be obtained by Setschenow equation[14], $\log S/S_a = k f_a$, where S and S_a are the solubility of solute in the absence and presence of co-solvent, k is called the salting coefficient and f_a is the volume fraction of the co-solvent. The sign and magnitude of k is a measure of the effect of co-solvent on the solubility of solute. Since up to a mole fraction of 0.10 for some of the co-solvents, abnormal solubility behaviour was observed, k values were obtained from the log S/S_a versus f_a plots for various systems at f_a values higher than 0.10 (Table 3). Positive sign shows that beyond 10% co-solvent concentration, the solubility decreases in the presence of co-solvents in all cases. The decrease being maximum when water was used as co-solvent and minimum when non-ionic surfactant tween 80 was used as co-solvent. Thus magnitude of k values give a quantitative comparison of various systems.

TABLE 3: SALTING COEFFICIENT (K) FOR VARIOUS SOLVENT - CO-SOLVENT MIXTURES

System	k Value
PEG-Water	3.924
PEG-Buffer	2.771
PEG-Alcohol	1.196
PEG-PG	0.836
PEG-Brij 30	0.415
PEG-Tween 80	0.150

PEG = Polyethylene glycol, Buffer = 0.1 M Phosphate buffer, PG = Propylene glycol, Tween 80 = polyoxyethylene (20) sorbitan monooleate, Brij 30 = Polyoxyethylene (4) lauryl ether. k values were obtained from log S/S_a versus f_a plots at f_a values higher than 0.10 (Setschenow equation).

To suggest a suitable solvent for parenteral formulations, solubility of nimesulide was determined in a series of binary and ternary solvent mixtures. The solubility was found to decrease sharply with decrease in the concentration of PEG in the solvent mixture. In order to inject a 100 mg dose of nimesulide in a convenient 2 ml volume, the solubility of drug should be greater than 50 mg/ml. As such fifteen different solvent mixtures were prepared and solubility of nimesulide in each mixture was determined at 30°. The results are given in Table 4. It is seen that the PEG concentration in the solvent mixture for parenteral formulation can be varied from 80 to 100%. PEG is a relatively non-toxic solvent. Combinations of PEG and ethyl alcohol are common co-solvent vehicles that are considered safe for use in the preparation of parenteral solutions[15-17]. All the drug solutions prepared in solvent mixtures were slightly acidic with pH around 6.5. Solutions containing alcohol were less viscous than other solutions.

Although solubility of drug was high in 100% PEG, it was not recommended as solvent for parenteral formulations. This is because the solutions prepared in 100% PEG are highly viscous and viscosity may pose a problem in dissolution rate of drug from tissues. However, there is a need to explore the use of 100% PEG in controlled release parenteral formulations. Further, if we also take into account

TABLE 4: SOLUBILITY OF NIMESULIDE IN VARIOUS BINARY AND TERNARY SOLVENT MIXTURES.

Composition of solvent mixture	Solubility (mg/ml)
PEG 300 (100%)	71.49
PEG 400 (100%)	73.60
PEG 300 (90%) + EtOH (10%)	74.72
PEG 300 (80%) + EtOH (20%)	50.27
PEG 300 (90%) + PG (10%)	72.96
PEG 300 (80%) + PG (20%)	48.64
PEG 300 (90%) + Tween 80 (10%)	75.60
PEG 300 (80%) + Tween 80 (20%)	66.78
PEG 300 (90%) + Brij 30(10%)	70.85
PEG 300 (80%) + Brij 30 (20%)	59.07
PEG 300 (80%) + PG (10%) + EtOH (10%)	54.78
PEG 300 (90%) + Tween 80 (8%) + BA (2%)	66.30
PEG 300 (90%) + Tween 80(5%) + EtOH(5%)	69.34
PEG 300 (80%) + Tween 80 (10%) + EtOH(10%)	58.59
PEG 300 (80%) + Brij 30 (10%) + EtOH (10%)	54.78

PEG = Polyethylene glycol, PB = 0.1 M Phosphate buffer, PG = Propylene glycol, EtOH=Ethyl alcohol, Tween 80= polyoxyethylene (20) sorbitan monooleate, BA = Benzyl alcohol, Brij 30= Polyoxyethylene (4) lauryl ether.

the change in solubility of drug due to temperature fluctuations in the developed formulation, the solubility of the drug should be much higher than 50 mg/ml. It is, therefore, recommended that a solvent containing 90% PEG and 10% cosolvent (alcohol, propylene glycol, Tween 80 and Brij 30) with solubility greater than 65 mg/ml can be used as a solvent in the parenteral formulations of nimesulide. Alternatively, 2% benzyl alcohol can be added as an anaesthetic agent, since intramuscular injections sometimes cause irritation and pain. Effect of benzyl alcohol on the solubility of nimesulide has also been studied. It is seen that the addition of benzyl alcohol resulted in a small decrease in solubility but the values were greater than 65 mg/ml. This is shown in Table 4 for 90% PEG + 8% Tween 80 + 2% benzyl alcohol system.

REFERENCES

1. Singla, A.K., Chawla, M. and Singh, A., **J. Pharm. Pharmacol.**, 2000, 52, 467.
2. Lipsky, P.E., **Amer. J. Med.**, 1999, 106, 51.
3. Bernareggi, A., **Clin. Pharmacokinet.**, 1998, 35, 247.
4. Kapoor, A., Majumdar, D.K. and Yadav, M.R., **Indian J. Chem.**, 1998, 37, 572.
5. Vavia, P.R. and Adhage, N.A., **Drug Develop. Ind. Pharm.**, 1999, 25, 543.
6. Piel, G., Pirotte, B., Delneuville, I., Neven, P., Llabres, G., Delarge, J. and Delattre, L., **J. Pharm. Sci.**, 1997, 86, 475.
7. Gupta, S.K., Bhardwaj, P., Tyagi, S., Sengupta, S. and Velpandian, T., **Pharmacol. Res.**, 1999, 39, 137.
8. Gupta, S.K., Velpandian, T., Mathur, P. and Sengupta, S., **Pharmacology**, 1998, 56, 137.
9. Chandran, S. Saggar, S., Priya, K.P. and Saha, R.N., **Drug Develop. Ind. Pharm.**, 2000, 26, 229.
10. Ran, Y., Zhao, L., Xu, Q. and Yalkowsky, H., **AAPS Pharm. Sci. Tech.**, 2001, 2.
11. Yalkowsky, S.H. and Roseman, T.J., In; Yalkowsky, S.H., Eds., Techniques of Solubilization of Drugs, Vol. 12, Marcel Dekker Inc., New York, 1981, 91.
12. Zhao, L., Li, P. and Yalkowsky, S.H., **J. Pharm. Sci.**, 1999, 88, 967.
13. MOLCONN-Z, Version 3.5, Daylight Chemical Information Systems Inc., Cambridge, UK.
14. Florence, A.T. and Attwood, D., In; Physicochemical Principals of Pharmacy, 3rd Edn., Macmillan Press Ltd., London, 1998, 162.
15. Krishna, G., Hodnick, W.F., Lang, W., Lin, X., Karra, S., Mao, J. and Almassian, B., **AAPS Pharm. Sci. Tech.**, 2001, 2.
16. Powell, M., Nguyen, T. and Baloian, L., **PDA J. Pharm. Sci. Technol.**, 1998, 52, 238.
17. Mottu, F., Laurent, A., Rufenacht, D. and Doelker, E., **PDA J. Pharm. Sci. Technol.**, 2000, 54, 456.