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Research Article

SOLUBILIZATION OF MEFANAMIC ACID

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Abstract

Solubility of mefanamic acid in various solvents like water, phosphate buffer pH 7.4, ethanol, propylene glycol, ethylene glycol, polyethyleneglycol-400, glycerin, and 10% surfactant solutions (Tween-80, SLS and Brij-35) and solvent–co solvent mixtures were determined. Solubility of mefanamic acid is low in water (0.2 mg/ml), but increased drastically when semi-polar solvents were added. Among the solvents used, ethanol and PEG-400 were found to enhance the solubility significantly (> 11 mg/ml). The solubility of mefanamic acid was reduced drastically upon addition of water to PEG-400 and ethanol, which may be due to increase in polarity of the system. The optimum concentration of PEG-400 was found to be 80% and solubility is more than 5.7 mg/ml. The surfactants marginally improved the solubility. Solid dispersions of drug with urea, mannitol and polyvinyl pyrolidine (1:1, 1:2) as carriers showed a negligible improvement of aqueous solubility; indicated that the carriers did not yield high energy forms of the drug. The solubility of drug was found to be increased with increase in concentration of buffer (pH 1.2 to 11), on account of ionization (pK_a = 4.32) at higher pH. Simplex method was also used for optimization to get an optimum blend of solvent mixture (ternary system). The ternary mixtures containing propylene glycol– PEG 400–ethanol (30:30:40, 30:40:30, 40:40:20) and ethanol–PEG 400–water (40:50:10) systems were found to be optimum to formulate solution dosage forms. Higher solubility of drug in propylene glycol– PEG 400–ethanol system indicated that hydrophobic interactions are more predominant than hydrogen bonding.

Key words: Solubility, Mefanamic acid, Co solvency, Micellar solubilization, pH modification, Solid dispersion, Simplex method.

Introduction

Liquid pharmaceuticals have been in demand, though drugs are being used mostly in the form of tablets and capsules. The very old, the very young and many otherwise not normal patients are incapable of swallowing tablets and capsules. They must be provided with liquid oral dosage forms. The most frequently encountered difficulty in the preparation of solutions is the insolubility of the drug. The solubility phenomenon is one of the least understood of all the physicochemical properties particularly with reference to pharmaceutical solutions. Therefore, solubility knowledge is important to the pharmacist as it permits in choosing the best solvent medium for a drug or a combination of drugs.

NSAIDs exhibit analgesic, anti-inflammatory, antipyretic, and platelet inhibitory properties. Mefenamic acid (MA) is a NSAID of the enolic acid class, which shows preferential inhibition of cyclo-oxygenase-2 and inhibits the prostaglandin synthesis[1]. It belongs to biopharmaceutical classification system class II low solubility-high permeability drug with approximately 90% bioavailability. The present work is aimed towards enhancing the solubility by using different techniques such as co solvency, micellar solubilization, pH modification.

Weak electrolytes and nonpolar molecules have poor water solubility, which it can be improved by altering polarity of the solvent system. This can be achieved by addition of another solvent. Co solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute i.e., solvent blending. Most co solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions[4]. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting water's self-association, co solvents reduce water's ability to squeeze out non-polar, hydrophobic compounds.

Micellar solubilization is used as an efficient tool for solubilization of hydrophobic drugs in aqueous environments. Reversible interaction with the micelles (of a surfactant in water) to form a thermodynamically stable isotropic solution with reduced thermodynamic activity. The surfactant molecules aggregate and form

micelles at particular concentration critical micelle concentration (cmc), with formation of hydrophobic interior core and hydrophilic external environment. The concentration of water decreases from the surface towards the core of the micelle, with a completely hydrophobic core. Consequently, the drug distribute itself in a micelle on basis of its polarity which means that non-polar molecules in the micellar core. Depending on the polarity drug get distributed along the surfactant molecules in certain intermediate positions[3].

Materials and Methods

Mefenamic acid was a gift sample from Wan bury Ltd., Iragavaram, A.P. Poly ethylene glycol 400 (PEG 400), propylene glycol, glycerin, ethanol, ethylene glycol, urea, mannitol, cetrimide, sodium acetate, sodium benzoate, sodium salicylate, sodium lauryl sulphate, Tween 80 was purchased from S.D. Fine- Chem. Ltd., Mumbai. All other reagents used were of analytical grade. Double distilled water was prepared using all glass distillation apparatus.

Solubility determination:

The solubility of mefanamic acid was determined in individual solvents as well as mixed solvents. About 10 ml of the solvent blend was introduced into the 50 ml volumetric flask containing excess mefanamic acid. The flasks were agitated in a cryostat constant temperature reciprocating shaker bath (Kemi-Instruments, Kerala, India) at room temperature (25 ± 1°C) for at least 24 hr in order to obtain equilibrium. Preliminary studies showed that this period was sufficient to ensure saturation at 25° C. After 24 hr of equilibrium, aliquots were withdrawn, filtered (0.22 mm pore size), diluted, and analyzed at 333 nm on Shimadzu UV/Vis spectrophotometer (UV-1700PC, Shimadzu, Japan). All solubility experiments were conducted in triplicate.

Co solvency (Ternary mixtures) – Simplex method[6]

Procedure:

Initially, three readings (1, 2, and 3) are required for constructing a triangle. The composition of the solvents must be preferably at low levels, so that higher solubility can be expected in subsequent steps. The lowest solubility is obtained at any of these three points. It is necessary to move away from the lowest solubility point obtained. Therefore, its mirror image is plotted across the line joining the two points, the mirror image is obtained. The procedure and calculations are as reported in the literature.

Micellar solubilization

Different concentrations of (0.3, 0.6, 0.9, 1.2, 1.5% w/v) of surfactants (sodiumlaurylsulphate, tween 80 and cetrimide) were used. An excess amount of mefanamic acid was added to the surfactant solution, taken in 50 ml volumetric flasks. The flasks were shaken for 24 h.At equilibrium samples were withdrawn and properly diluted through filter of pore size 0.22 mm and finally analyzed for concentration of mefanamic acid spectrophotometrically at 333 nm.

pH modification

The method of solubility determination remained the same. A pH-solubility profile of mefenamic acid was obtained in the buffers of pH range 1.2 to 11 by determining the solubility. The pH of the saturated drug solution, measured on a pH meter, was taken as the final pH in each case. Samples were analyzed spectrophotometrically at 333 nm.

Solid dispersions:

Solid dispersions of mefanamic acid were prepared by using three methods like melting method, solvent evaporation and kneading method by using carriers (mannitol, urea and PVP).

Results and Discussion

Solubility in Pure Solvents

The solubility data of mefanamic acid in water and in other solvents at 25°C are recorded in **Table 1**. The solubility of mefanamic acid in water is low (0.2088 mg/ml). Solubility of mefanamic acid was found to be particularly high in ethanol and PEG 400. In general, alcohols are better solvents than water. Mefanamic acid was found to have maximum solubility in ethanol and high solubility next to ethanol is PEG 400 is probably because of extensive hydrophobic interactions with the solvent, because PEG 400 has a long nonpolar part compared with other solvents.

Table 1. Solubility of mefanamic acid in various solvents at 25 ^{o}C.

Solvent / vehicle	Solubility (mg/ml)	Fold increase
Water	0.2088	1
Ethanol	14.7846	70.81
Propylene glycol	0.2188	1.05
Glycerin	0.1564	0.75
Brij-35 (10%)	0.1467	0.70
Buffer 7.4	0.0252	0.12
S.L.S (10%)	0.3138	1.5
Tween-80	0.3712	1.78
Polyethylene glycol 400	11.5086	55.12
Ethylene glycol	0.2197	1.05

Solubility by Micellar Solubilization

Surfactants, viz., cationic, anionic and nonionic, were studied for improvement of solubility of mefanamic acid. Nonionic surfactants were more tolerable and compatible with biological system. All surfactants improved the aqueous solubility of mefanamic acid. The solubility data of mefanamic acid in surfactant solutions (0.3 – 1.5% w/v) are given in the **Table 2.** Rank order of solubility improvement is as follows cetrimide > SLS > Tween 80. This order is in accordance with the electrostatic interactions between the drug and the surfactants. **Table 2** summarizes amount of drug (mg) solubilized in gm of surfactant and corresponding distribution coefficient. It is clearly evident that higher the solubilization efficiency, higher the distribution coefficient. This suggests that more amount of drug is being partitioned in micellar core. The more non polar the solute, the more likely it is to be incorporated in the core of the micelle. The relationship between the drug solubility in a micellar solution and surfactant concentration is described by the following equation[7].

$$S_{total} = S_w + k\,(C_{surf} - \mathrm{CMC}) \qquad (1)$$

where C_{surf} is the concentration of micellar surfactant (i.e., the total surfactant concentration minus the critical micellar concentration) and k is the molar solubilization capacity, the number of moles of solute that can be solubilized by one mole of micellar surfactant. If the critical micellar concentration (CMC) is much lower than C_{surf}, equation can be approximated by the following equation;

$$S_{total} = S_w + k\,C_{surf} \qquad (2)$$

Cetrimide, being a cationic surfactant, showed a marginal increase in solubility with increase in concentration. The increased solubility in presence of cetrimide (+ve) and the mefanamic acid (-ve, due to –COOH group) acquired. These two molecules interact electro staticall. Probably, the drug molecules can attach with micelles of cetrimide at the exterior (outside) of structure. In this case micellar solubilization can be presumed. Therefore the effect is combined. Sodium lauryl sulphate, an anionic surfactant, showed a linear increase in solubility with increasing concentration, but the solubility is lower than its solubility in water. This data suggests that locus of solubilization of mefanamic acid is different from what is postulated for nonionic series of surfactants. Alkhamis *et al* have demonstrated that site of solubilization for anionic solubilizers are out side palisade region of micelles, which results in reduced solubility of mefanamic acid.

Table 2: Solubility and distribution coefficient of mefanamic acid in surfactant solution

Surfactant	Concentration range (% w/v)	Molar solubilization capacity (k) (mg/g of surfactant)	Distribution coefficient (K_m)
Cetrimide	0.3 - 1.5	0.1877	19.3105
Sodium lauryl sulphate	0.3 - 1.5	0.0612	2.4571
Tween 80	0.3 - 1.5	0.0345	1.8913

pH modification

The solubility of mefanamic acid in buffers at different pH values ranging from1.2 to 11 was determined at 25 and 37 °C, mimicking the conditions of pH and temperature in the GI tract. The aqueous solubility of mefanamic acid is pH dependent because the pK_a of mefanamic acid is 4.32. Comparison of the solubilities of mefanamic acid in the buffers at two different temperatures is shown in Figure 2. Due to their low solubility in water, it is often difficult to determine. The solubility of most of the acidic drugs in aqueous solutions was very low in acidic medium. Significant increase in solubility was obtained at and above pH 6.0.

Solubility by co solvency

Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs. The mixed-solvent systems in the present study include ethanol-water, polyethylene glycol 400-water based on the solubility reported earlier. The solubility profiles of mefanamic acid in various binary mixtures are shown in

the **Figure 3**. According to the results obtained in the binary mixtures (solubilization capacities values) are given in the **Table 3,** the co solvents can be arranged with their solubilizing power in the following rank: ethanol > propylene glycol > PEG 400. It can also be noted that the maximum solubilizing effect was observed with ethanol, whereas ethylene glycol exhibited the minimum effect. However the effect was dependant on both the concentration and the type of co solvent used. It can be generally observed that the solubility of mefanamic acid increases by increasing the cosolvent concentration. Further, the effect is much significant at higher cosolvent concentrations. This finding is in accordance with previous reports on indomethacin and etodolac solubility in some selected co solvents[7]. The co solvents were reported to decrease the dielectric constant of water, the effect increasing with cosolvent concentration[8]. The solubility results obtained in the present study are in accordance with the dielectric constant concept, which states that when the polarity of the solvent is decreased, it becomes a more favorable medium for the dissolution of nonpolar or relatively non polar drugs[9].

The exponential dependence of the solubility of non-polar solutes on cosolvent concentration in a semiaqueous solution is described by the following equation.

$$\log [S_{mix}] = \log [S] + \phi [V_{cs}]$$

$$\phi = \log [S_{mix}/S] / [V_{cs}]$$

where $[S_{mix}]$ is the total apparent drug solubility in solvent mixture, $[S]$ is the intrinsic drug solubility in water, $[V_{cs}]$ is the cosolvent concentration, ϕ is the co solvent solubilization power.

Table 3: Solubilization capacities of different co solvents for mefanamic acid

Solubilizer	Concentration range	ϕ value
Ethanol	10 -100%	- 4.0422
PEG-400	10 -100%	- 2.0908

Simplex method (Ternary mixtures)

The solubility of mefanamic acid in ternary mixtures was determined by simplex method in three solvent blends (ethanol-PEG-water, ethanol-PG-water, PG-PEG-ethanol systems). The solvent blend ratios were chosen

at lower levels based on the solubility determinations obtained in binary mixtures[10]. Simplex method was also used to get an optimum solvent mixture (ternary solvent system). The ternary mixtures containing PG-PEG-ethanol and ethanol-PEG-water were found to be optimum to formulate solution dosage forms. Higher solubility of mefanamic acid obtained in the PG-PEG-ethanol system.

Although mefanamic acid aqueous solubility is less, attempts were successful to enhance its solubility using a series of pure solvents and mixed solvent systems. The aqueous solubility of mefanamic acid could be enhanced significantly by the use of ethanol as the second solvent. In general ethanol, polyethylene glycol 400 mixtures are found to be good solvents for mefanamic acid. The commonly used doses of mefanamic acid and the minimum solubility of the mefanamic acid required for a 20 ml, 10 ml, 5 ml, and 2 ml doses are given (**Table 4**).

Table 4: Ratios of solvent systems required for drug solubility (250 mg) on volume basis

Volume of system required	System	
	Ethanol-PEG-water	**PG-PEG-ethanol**
20 ml	40:50:10	30:30:40, 30:40:30 and 40:40:20
10 ml	--	30:30:40, 30:40:30 and 40:40:20
5 ml	--	30:30:40, 30:40:30 and 40:40:20
2 ml	--	30:40:30

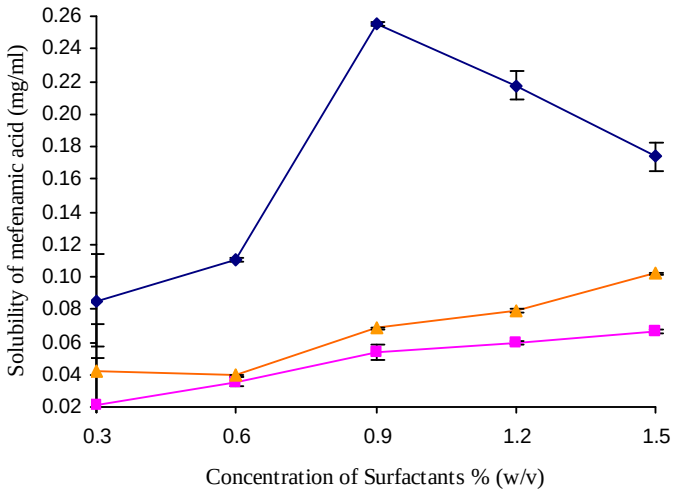

Figure 1: Solubility of mefanamic acid in surfactant solutions. Cetrimide (♦), SLS (■), and Tween 80 (▲) at 25 °C

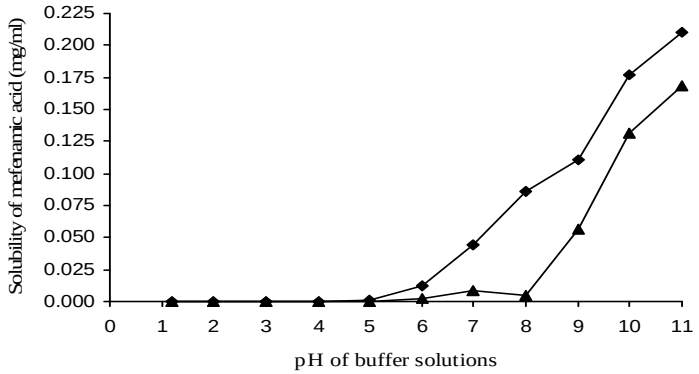

Figure 2: Comparison of solubility of mefanamic acid in buffers at different temperatures

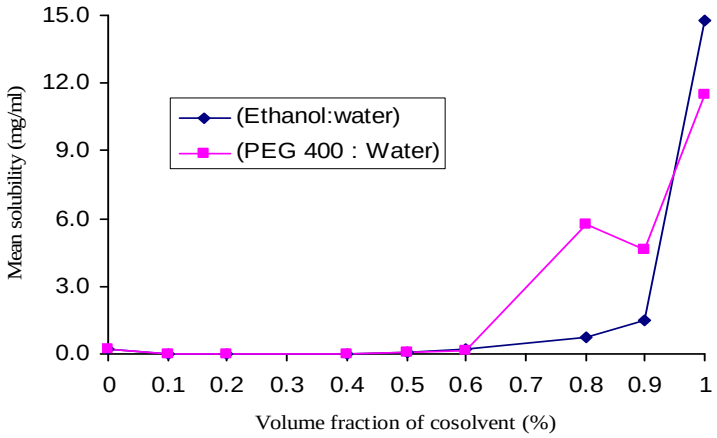

Figure 3: Comparison of solubility of mefanamic acid in water-co solvent mixtures

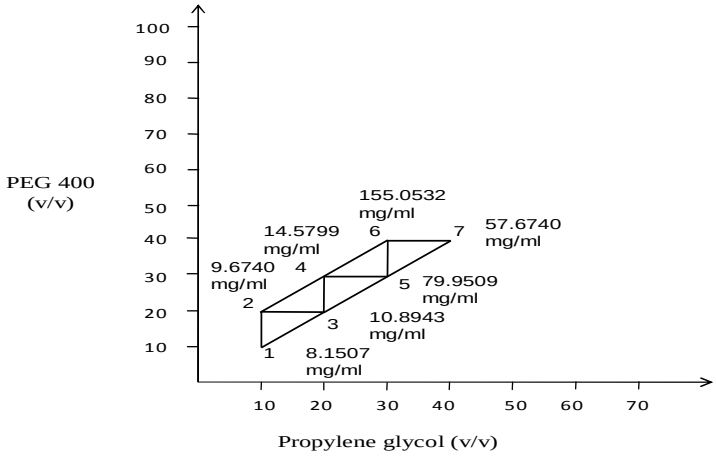

Figure 4: Solubility studies of mefanamic acid in PG-PEG-ethanol blend by using simplex method.

Conclusion

Different approaches were used for the enhancement of solubility of mefanamic acid including co solvency, micellization, pH modification, and solid dispersions. The order of the co solvents based on their solubilizing power (ϕ) are Ethanol > PG > glycerin > PEG 400 > EG. Solid dispersions of mefanamic acid were prepared with an attempt to increase its solubility in water. Solid dispersion technique does not improve the solubility of mefanamic acid. Simplex method was also used to get an optimum solvent mixture (ternary solvent system). The ternary mixtures containing PG-PEG-ethanol and ethanol-PEG-water were found to be optimum to formulate solution dosage forms. Higher solubility of mefanamic acid obtained in the PG-PEG-ethanol system.

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