ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 4, Issue 37, August: 2016, 07-11

Research Article

STUDY THE EFFECT OF CO SOLVENT ON THE SOLUBILITY OF A SLIGHTLY WATER SOLUBLE DRUG

Minakshi Verma[1*], Sudhir Singh Gangwar[*], Yatindra Kumar[*], Mudit Kumar[*], Ashish Kumar Gupta

* Department of pharmacy, G.S.V.M. Medical College, Kanpur

Department of pharmacy, V.B.S.Purvanchal University, Jaunpur

ABSTRACT

The solubility of a drug depends upon the solvent. Hydrophilic drug are soluble in hydrophilic solvent while hydrophobic drugs are soluble in hydrophobic solvent, sometimes drugs contain both hydrophilic and hydrophobic part and single solvent that in sufficient to improve the solubility of drug is required. Frequently a soluble is more soluble in a mixture of solvents that in a single solvent alone, this phenomenon is known as co solvency and the solvent in combination increase the solubility of the solute is called the co solvents. The aim of present study was to study the effect of co solvents on the solubility of benzoic acid. From the graph it has been seen that the solubility of benzoic acid increases with the increased of concentration of co-solvent. When the straight line was extrapolated to Y axis, the intercept gives the solubility of benzoic acid in water.

Key words: Solubility, poorly soluble drugs, benzoic acid, IPA, co solvents

INTRODUCTION [1-5]

The oral route is the most common and preferred route for drug administration due to its convenience and ease to ingestion [1-3].When drug administered orally in solid dosage form like tablet, capsule; firstly it undergo dissolution in the GI fluids before absorption. For various poorly soluble drugs bioavailability is limited by the dissolution rate. In the development of pharmaceutical dosage form, many difficulties arise due to poor water soluble drugs. Therapeutic efficacy of a drug depends upon the solubility of drug molecules. Solubility can be defined as qualitatively as well as quantitatively. Quantitatively solubility can be defined as the solute concentration in a saturated solution at a particular temperature. Whereas qualitative it can be defined as the spontaneous interaction of two substances to produces a homogenous molecular dispersion [2-6]. Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability[1]. Poorly soluble drugs present a problem in pharmaceutical formulations. Improving dissolution properties is a major obstacle that must be overcome because many new drugs discovered by combinatorial chemistry and high-throughput screening are poorly soluble, making them poor candidates as new drugs. It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability. Various methods to improve the dissolution of poorly soluble drugs have been reported. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption [6-9].

Solid dosage medicaments have to face several barriers and loss at sites in its sequential movement during gastrointestinal absorption takes place. Parenteral administration posses certain advantages if immediate physiological action is needed from a drug which usually can be provided by injecting an aqueous solution [7-10].

Mechanism of Solubility

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature [10-13].

Factors influencing solubility of Drugs [9-12]

- **Solute related**: Nature of solute- Size, Shape and surface area

Physicochemical properties- melting point, heat of fusion, molar volume and pKa

Physical forms- Salt, crystalline state, and polymorphism

- **Solvent related**: Nature of the solvent, i.e., Polarity, pH of the medium, volume of solvent employed.

Corresponding author: Minakshi Verma |E-mail: minakshimpharm@rediffmail.com

- **Environment related**: Temperature and pressure.
- **Formulation related**: Other ingredients.

Importance of Solubility Enhancement includes [12-15]:

Solubility is one of the important parameters to achieve preferred concentration of drug in Systemic circulation for achieving required pharmacological response.

Poorly water soluble drugs frequently require high doses and need high dosage regimens inorder to influence therapeutic plasma concentrations after oral administration.

Low aqueous solubility is the main problem encountered with preparationand development of new chemical entities as well as for generic drugs.

For orally administered drugs solubility is the one of the important rate limiting parameter to reach their desired concentration in complete circulation for pharmacological response.

Water is the solvent of excellent for liquid pharmaceutical formulations. Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility.

Poorly water soluble drugs having slow drug absorption leads to insufficient and gastrointestinal mucosal toxicity and variable bioavailability.

Co-solvency

Organic solvent such as water miscible solvents is used to enhance the aqueous solubility of a water insoluble drug [11]. Water and solvents which are soluble in water form a solution called co-solvent. PEG 300, ethanol, propylene glycol are some of the solvents which are used in preparation of co -solvent mixtures. For example 5-40% concentration of solid binary system comprising polyethylene glycol 6000 has been used to enhance the solubility and dissolution of meloxicam. Many thousand times co-solvency enhances the solubility of poorly soluble compounds compared to the aqueous solubility of the drug. In the design of many different formulations, co-solvency had been highly utilized. The co-solvency mainly used in parenteral dosage forms because of the most surfactants give the irritating effects and many co-solvents show the low toxicity, due to the more ability to make co-solvents to solubilise nonpolar drugs. Low toxic co-solvents used for parenteral dosage forms are glycerine, propylene glycol, polyethylene glycol and ethanol [12]. Co-solvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs[8-10]. Addition of a co-solvent to a formulation improves the solubility of the drug because the co-solvents reduces strong water-water interactions and thereby reduces the ability of water to squeeze out non-polar solutes Co-solvency was often considered at early stages due to its huge solubilization potential [10].

Influence of Solvents [12-14]

In the formulation, water or vegetable oils are normally used as solvents. The solubility of the drug is due to the polarity of the solvent that is dipole movement. In addition, hydrogen bonding between solute and solvent is essential. Therefore, structural features and presence of nonpolar and polar groups in the molecule are important. Syrups and liquid oral solutions are manufactured using water. The simple maxim of like-dissolve-like is the guiding principle.

Table 1: Influencing of solvent on solubility: Intra venous

Solvent	Nature of Solute	Examples of Drug	Dosage forms
Water (Polar)	Polar Substances	Vitamin B1&B2	Elixer
	Strong Electrolytes	Sodium chloride	i.v. infusion
	Weak Electrolytes	Sodium Phenobarbitone	Injection
	Nonelectrolytes	Dextrose	i.v. injection
Oil (nonpolar)	Nonpolar substances	Progeteron	Oil injection

Poorly water soluble drugs are normally dissolved in non-aqueous vehicles such as liquid paraffin, arachis oil and ethyl oleate. In most cases, a mixture of solvents is used for maximum solubility of drugs.

Frequently a solute is more soluble in a mixture of solvents rather than in a single solvent. The solvents, which are used to increase the solubility of a drug in water, are called as co solvents. The phenomenon is known as co solvency. Ethanol, propylene glycol, glycerine, PEG 300, and PEG 400(polyethylene glycols) are

the commonly used co solvents, since these are water miscible. The concept of co solvency is applied in the manufacture of liquid dosage forms such as syrups, elixirs, injections, creams and lotions. In addition, solvents such as benzyl alcohol, dimethyl sulphoxide (DMSO), Dimethyl acetamide (DMA) and Dimethyl formamide (DMF) are used as supplementary solvents.

MATERIALS & METHODS:

Benzoic acid, sodium hydroxide and isopropyl alcohol (IPA) were purchased from Merck Company, Germany. Benzoic acid, sodium hydroxide and IPA were used to carry out this work. All chemicals and reagents used in this study were of analytical grade and obtained from Merck Company, Germany.

METHODS:

50% (v/v) solution of isopropyl alcohol in water was prepared as stock solution. Four clean and dry 250 ml conical flasks were taken. Required amount of stock solution were taken in each flasks to get the followings concentrations and 0, 2, 4 and 6 ml of stock solutions are taken in 1^{st}, 2^{nd} and 3^{rd} and 4^{th} flask respectively. Finally distilled water was added to made up the volume to 50 ml in each.

Table 2: Amount of the IPA and benzoic acid used during the preparation of solution

Sl. No.	**1**	**2**	**3**	**4**
Isopropyl alcohol (%)	0	2	4	6
Purified water (volume made upto)	50 ml			
Benzoic acid	Excess amount			

Excess benzoic acid was added to each flask and shaken in mechanical shaker for 30 min. Titrated against NaOH using Phenopthlein indicators with 10 ml of the filtrate.

RESULTS & DISCUSSION:

Normality of NaOH=NxF=0.05x0.96=0.048 (N)

The filtration involves the reaction-

$C_6H_5COOH+NaOH=C_6H_5COONa+H_2O$

122gm of C_6H_5COOH=1000ml

Table 3: Proportion of IPA used to improve the solubility of benzoic acid

Sl No.	**Volume of water**	**Isopropyl Alcohol (%)**	**Volume of Isopropyl Alcohol (ml)**	**Total Volume (ml)**
1	50	0	0	50
2	48	2	2	
3	46	4	4	
4	44	6	6	

Table 4: Calculation of concentration of the sample

Sl No.	**Volume of filtrate (ml)**	**Volume of NaOH (ml)**	**Strength of the sample (N)**	**Concentration of the sample (g/L)**
1	10	7.8	0.037	4.56
2		8.7	0.041	5.09
3		9.6	0.046	5.62
4		10.4	0.049	6.09

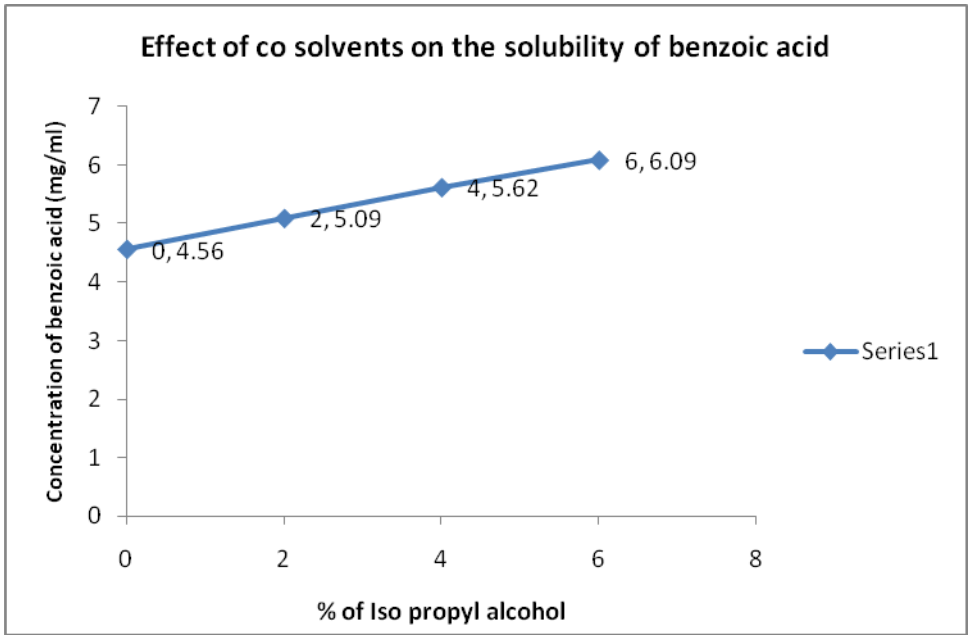

Figure 1: Effect of co solvent (IPA) on the solubility of benzoic acid

From the figure 1 and table 4, it has been seen that the solubility of benzoic acid increases with the increased of concentration of co-solvent. When the straight line was extrapolated to Y axis, the intercept gives the solubility of benzoic acid in water.

REFERENCES:

1. Reddy, T.A., S. Srinivasan, K. Kavitha, R. Kumar and J. Singh, 2013. Review on: better solubility enhancement of poorly water soluble drugs. International Journal of Inventions in Pharmaceutical Sciences. 1(4): 267.

2. Vemula, V.R., V. Lagishetty and S. Lingala, 2010. Solubility enhancement techniques.International Journal of Pharmaceutical Sciences Review and Research, pp: 41-42.

3. Yellela, S.R.K., 2010. Pharmaceutical technologies for enhancing oral bioavailability of poorlysoluble drugs.Journal of Bio-equivalence and Bioavailability, 2(2): 28-36.

4. Chaudhary, A., U. Nagaich, N. Gulati, V.K. Sharma and R.L. Khosa, 2012. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications. A recent review. Journal of Advanced Pharmacy Education and Research, 2(1): 48.

5. Ahmad, Z. and M.N. Khan, 2011. Solubility enhancement of poorly water soluble drugs. International Journal of Pharmacy and Technology, 3(1): 811.

6. Kyung, N., L. Sibeum, H. Sung and S. Jong, 2002. Controlled Release Society 29thAnnual Meeting. International of Pharmaceutical Sciences, July 13-16,2014.

7. Ajit, S., Narang, D. David and Danchen Gao, 2007. Stabledrug encapsulation in micelles and micro emulsions. International Journal of Pharmaceutics, pp: 345.

8. Blagden, N., M. de Mates, P.T. Gavan and P. York, 2007. Crystal engineering of activePharmaceutical ingredients to improve solubility and dissolution rates. Advanced Drug Delivery Reviews, 59(7): 617-630.

9. Patel, J.N., D.M. Rathod, N.A. Patel and M.K. Modasiya, 2012. Techniques to improve the solubility of poorly soluble drugs. International Journal of Life Sciences., 3(2): 1459-1469.

10. Vogt, M., K. Kunath and J.B. Dressman, 2008. Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. European Journal of Pharmaceutics and Biopharmaceutics, 68(2): 283-288.

11. Bibby DC, Davies NM, Tucker IG. Mechanisms by which cyclodextrins modify drug release from

polymeric drug delivery systems. Int J Pharm 2001; 197: 1-11.

12. Brainbanti A, Fisicaro E, Ghiozzi A, Comparic, Bovis G. Host guest interactions between β-cyclodextrin and piroxicam. React Function Polym 1998; 36: 251-255.

13. Patil JS, Kadam DV, Marapur SC, Kamalapur MV. Inclusion complex system; A novel technique to improve the solubility and bioavailability of poorly soluble drug. A Review Int J Pharm Sci Rev Res 2010; 2(2): 29-34

14. Gupta S, Srinivastav S, Vajpai M. Comparative study of solubility enhancement of poorly soluble drug by solid dispersion and inclusion complex. J Pharm Res 2010; 3(4): 692-696.

15. Khan, MA (2013), "Enhancement of solubility of poorly water soluble drugs diclofenac sodium by mixed solvency approach", Int. J. Res. Dev. Pharm. L. Sci., Vol. 2 (2), 368-370.