Original Article

Solubility Enhancement of Rifabutin by Co-solvency Approach

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Abstract

Rifabutin is wide spectrum antimicrobial agent, effective in the treatment of infection caused by M. tuberculosis, M. avium and M. Leprae and also used in the treatment of multidrug resistant TB. Rifabutin is very poorly water soluble drug (0.19mg/ml) with high permeability. For enhancement of solubility of a hydrophobic drug has a significant role in the development of a liquid dosages form. The main purpose of this study was to improve the solubility of Rifabutin by co solvency method. Different blends were prepared by usinf different solvents and surfactants in different proportions have been used to enhance the solubility of Rifabutin like water, phosphate buffer, ethanol, propylene glycol and PEG 400, Tween 80 and Brij 35. In thisit was found that the blend 90% PEG and 10% co solvents (ethanol and propylene glycol) give highest solubility and among the surfactant systems, Tween 80 had shown enhanced solubility of Rifabutin. Solubility of rifabutin was determined by preparing saturated solutions of rifabutin in pure solvents and in mixture of co solvents with or without surfactants. It observed that the blend of 90% PEG and 10% ethanol and propylene glycol had shown the better improvement of solubility when compared with the other solvents and co solvents as it caused a noteworthy enhancement in solubility of Rifabutin that was 1.6803 mg/ml.The above observations lead to propose that the addition of small amount of polar solvent enhances the solubility of drug.Thus, the study generated an important array of data to compare the effect of these cosolvents on the aqueous solubility of rifabutin.

Keywords: Co solvency, rifabutin, solubility enhancement, surfactants.

1. INTRODUCTION

Solubility is defined as the highest portion of a drug molecule that will be totally dissolved in a given solvent at a fixed temperature and pressure. Solubility of the drug is a crucial characteristic in order to get the effective concentration of drug in the blood circulation for their pharmacological response. At present time about 40% of newly discovered drug molecules are poorly water soluble or highly lipophilic in nature. The poor solubility of a drug is a very complicated issue for drug delivery. Most of the pharmaceutical companies are trying to increase the solubility of poorly water soluble drugs. A drug with low solubility having problem in their bioavailability and also affect their pharmacological action and amount of drug used. 1

Oral absorption of a drug, enough bioavailability and all pharmacokinetic profile of a drug molecule into the body is a crucial challenge in the oral dosages form development of newly found drug molecule. Bioavailability of a drug, absorption of a drug and the solubility of a drug ultimately affects the pharmacological effectiveness of drug molecule. So in simple words we can say that the therapeutic effectiveness of drug molecule depends upon its solubility.2 Thus solubility of a drug molecule is considered as a most important factor to obtain the desired amount of drug in the blood circulation so that the drug can give its pharmacological effect. Around one-fourth of the newly discovered drugs listed in the united state pharmacopoeia are comes into the category of poorly water-soluble drugs. The oral delivery of the new drugs can be affected by the solubility issues and also the delivery of many existing drugs. Poorly water soluble drugs cause many difficulties in the formulation development, such as limited choices of delivery of drug and a very complex dissolution testing with inadequate correlation to the in vivoabsorption. Due to the poor solubility drug cant reached into the systemic circulation and cause problem in attaining expected in vivo/in vitro correlations. However, various leading pharmaceutical companies have been able to triumph over technical hitches with very slightly aqueous soluble drugs, those with aqueous solubility of less than 0.1 mg/mL present some unique challenges. These drugs are particularly good candidates for advanced solubilisation technologies developed by

companies specializing in drug delivery. Solubilisation of poorly aqueous soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. There are various solubility enhancement techniques which are used to improve the solubility of such drugs.3

Cosolvency, pH adjustment, surfactant addition, and complexation are the most commonly encountered pharmaceutical approaches for solubilising drug candidates with low aqueous solubility. Among them, use of cosolvent (i.e., cosolvency) is one of the most popular approaches for improving the solubility of poorly aqueous soluble drugs in pharmaceutical liquid formulations [5]. Cosolvents are the mixtures of miscible solvents often used to water which can dramatically change the solubility of poorly aqueous soluble drugs [6].

Non-polar molecules and weak electrolyte have poor aqueous solubility. Generally the solubility profile of such drugs can be improved by the addition of a water miscible solvent in which the drug is easily soluble. This process of solubilization is known as co solvency and the combination of solvents used to increase the solubility of the solute molecule are called as co solvents.4The mechanism of co solvency for enhancement of drug solubility is not clearly understood. It has been proposed that the co solvent system work by decreasing the interfacial tension between the predominantly aqueous solution and the hydrophobic solute. Ethanol, Sorbitol, glycerine, propylene glycol and several numbers of the Polyethylene glycol polymer series represent the limited number of co solvent that are both useful and generally acceptable in the formulation of aqueous liquids.7

2. MATERIALS AND METHODS

2.1. Drugs and chemicals

Rifabutin was obtained from Lupin Pharmaceuticals Mumbai as a gift sample. PEG and SLS were obtained from Merck Ltd. And other co solvents were obtained from Sun-BioDiagonists, Dehradun.

2.2. Methods

Preformulation Study of Drug

Preformulation studies are developed for the preparation of a stable and therapeutically effective and safe dosage form. The preformulation studies included identification of drug, solubility analysis, partition coefficient etc

Identification test

Rifabutin was identified based on its melting range and the physical examination. The melting range of the drug was determined by melting point apparatus.

FTIR spectroscopy

FTIR study of drug sample and identification studies was performed by potassium bromide (KBr) dispersion method (Shimadzu). The drug sample was dried in vacuum for 12 hours. After proper drying 5 mg of drug sample was taken out and mixed with 100 mg of potassium bromide then compressed with a hydrostatic force to converts the samples into pellets. The scanning range was 400 to 4000 cm-1 and the resolution was 4 cm-1.

Preparation of calibration curve

10 mg of rifabutin was dissolved in a sufficient quantity of methanol to prepare stock solution of 1000 µg/ml and then a second stock solution was prepared from the stock solution one. For this purpose 1 ml solution was taken out from the first stock solution and then volume was make up with methanol up to 10 ml. Working standard dilutions of 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 and 14 µg/ml were prepared from the second stock solution and volume was made off with methanol. Filtered the aliquots and then analyzed at 275 nm.

Partition coefficient

Partition coefficient of rifabutin was determined by shake flask method using n-octanol as oil phase and water as aqueous phase. 10 ml of water and 10 ml of n octanol were placed in a separating funnel and then 10 mg of rifabutin was added into it. For about one hour, the separating funnel was vigorously shaken. The drug was spilt into two pahses for complete distribution. After that the oil and water phase were collected individually and the drug concentration in each phase were analysed spectrophotometrically at 275nm after appropriated dilutions. The partition coefficient of rifabutin was calculated by using the following formula:-

Partition coefficient of rifabutin = amount of drug in oil phase / amount of drug in water phase

Determination of solubility of rifabutin

Solubility of rifabutin was determined by preparing saturated solutions of rifabutin in pure solvents and in mixture contains 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100% various co solvents. Distilled water and co solvents were mixed volumetrically at different ratios in a well stoppered glass flask. Excess amount of drug was directly added into the pure solvents and co solvents mixed solvents. The flasks were shaken at room temperature using a shaker at 50 rpm for 24 hours to obtain the equilibrium. After 24 hours the samples were withdrawn and analyzed spectrophotometically at 275 nm. Solubility of rifabutin in each sample was calculated in mg/ml.

3. RESULTS AND DISCUSSION

Identification tests

Procured rifabutin was identified based on their physical examination and melting point.(Table 1)

Table 1-Physical Properties of Rifabutin

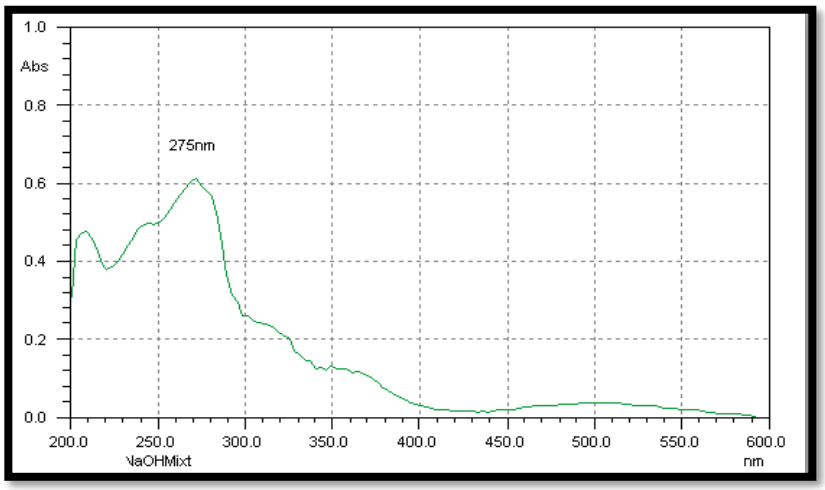
S.No.	Test	Specification	Observation	Inference
1	State	Solid crystalline	Solid crystalline	Complies
2	Colour	Red violet	Red violet	Complies
3	Odour	None	None	Complies
4	Melting range	169º-171º C	168-171º C	Complies

It was observed that the obtained value of rifabutin's melting point was found to be close to the reported value of melting point of rifabutin. This result proved that the received drug sample of rifabutin meet the reported properties. Any impurity, if present, will cause variation in the melting point of a given drug substance.

Determination of UV absorption maxima of rifabutin

An Absorption maxima of rifabutin was determined by UV spectrophotometric method and it was found at 275nm.(Figure 1)

Figure 1 Absorption Maxima of Rifabutin



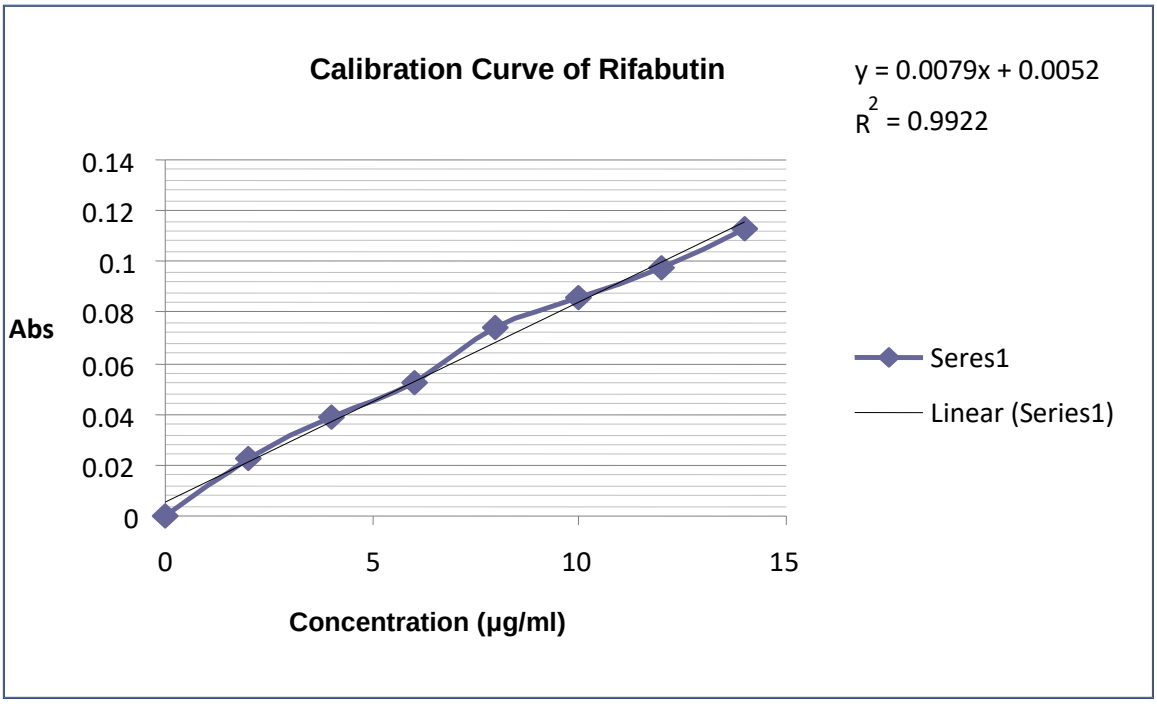
Calibration curve of rifabutin

Calibration curve of rifabutin was prepared in Methanol at 275 nm in the concentration range of 2-14 µg/mL.(Table 2 and Figure 2)

Table 2 UV absorption Data of Rifabutin

S.No.	**Conc. (µg/ml)**	**Absorbance at 275nm**
1.	2	0.035±0.0007
2.	3	0.039±0.0010
3.	4	0.048±0.0020
4.	6	0.059±0.0015
5.	8	0.078±0.0035
6.	10	0.097±0.0048
7.	12	0.102±0.0087
8.	14	0.126±0.0074

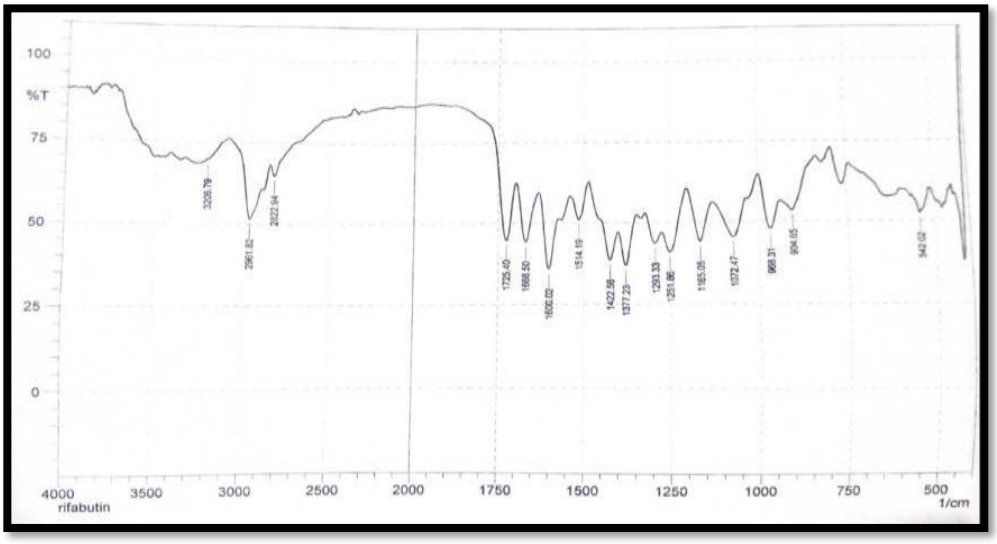
Figure 2 Calibration Curve of Rifabutin



FTIR Spectroscopy

The FTIR spectrum of rifabutin is shown in figure 3and it shows various peaks corresponding to different bonds present in the structure of rifabutin. The presence of OH group is confirmed by a weak absorption band at 3461.0 cm-1. Aromatic structure in the drug is confirmed by the characteristic absorption bands at 2961.1 cm-1 and at 1601.2 cm-1 due to C–H stretch and C-C stretching respectively. Conjugated system with ester functional group is depicted by prominent C=O stretch at 1671.2 cm-1. The spectrum illustrates amine stretch at 1064.9 cm-1. Characteristic peaks at 1727.3 cm-1 and 1747 cm-1 correspond to the C=O and N-H stretching of secondary amine.

Figure 3 FTIR Spectra of Rifabutin



Solubility profile of rifabutin in pure solvents

The solubility profile of rifabutin in various solvents was listed in table number 3. The solvents used for this study were water, phosphate buffer, ethanol, propylene glycol and PEG 400 and the solubility studies were carried out at room temperature. After determining the solubility profile of rifabutin it was found that the drug rifabutin had very poor solubility in water. The reason of poor solubility of rifabutin in water of its non polar nature, due to this it can not break down the lattice structure of water and remain insoluble. When the solubility study was carried out in different solvents then it was observed that the rifabutin is freely soluble in PEG 400 as compare to other solvents used in the study. For further study of solubilization, the dielectric constants (ε) of different solvents were obtained from the literature survey and listed in table 3. This table indicates that if the polarity of solvents get increases then the solubility of rifabutin get decreases. Thus, we can consider the solvent's polarity as an important factor which governing the solubility of drug. If we observe the solubility of rifabutin in glycols such as in PEG-400 and PG then it was found that the solubility of rifabutin increases highly. This occurs due to the hydrophobic interactions between drug and solvent, so hydrophobic interaction was also considered as an important factor for the solubility of the drugs in glycols. Rifabutin had highest solubility in PEG 400 due to the extensive hydrophobic interactions. The solubility profile of rifabutin in different solvents was shown in table 3.

Table 3 Solubility profile of rifabutin in pure solvents

Solvents	Di electric constant	Solubility(mg/ml)
Water	78.36	0.18
Phosphate buffer	79	0.51
Ethanol	24.55	19
PG	32.00	8.35
PEG 400	12.40	13.12

Solubility of rifabutin in mixtures of solvents

From the above results of solubility profile of rifabutin in different pure solvents, it was cleared that the solubility of rifabutin in propylene glycol and in PEG 400 is not very high, so for further improvement in the solubility profile of rifabutin the combined solvency approach was used, in which different solvent systems were created for solubility enhancement. In this study it was proved that PEG 400 is best solvent then others. So the solubility behavior of rifabutin was determined in mixture of solvent and co solvents with the use of surfactants like tween 80 and brij 35. PEG 400 was considered as the essential solvent. The solubility blend composition data were listed in table 4

Table 4 Solubility of rifabutin in mixtures of solvents

S.No.	Solvent blend	Solubility(mg/ml)
1	20%PEG400+80%Water	1.27
2	40%PEG400+60%Water	6.78
3	60%PEG400+40%Water	12.56
4	80%PEG400+20%Water	19.87
5	70%PEG400+10%Water+10% Tween 80	26.57
6	70%PEG 400+10%Water+10% Brij 35	19.76
7	50%PEG 400+20%Water+30%PG	24.89
8	90%PEG 400+10% Ethanol and PG	31.56

Addition of co-solvents for solubility enhancement of poorly water soluble drugs is very effective and simple approach. A tiny non polar hydrocarbon part is present in the structure of co solvent due to the presence of this part the water system does not squeeze out the nonpolar solute molecules. The cosolvents are easily miscible in water so they are most widely and most commonly used for the solubilization of drug in the field of pharmaceutics. There are three commonly used cosolvents in the

pharmaceutical field, PEG 400, PG, and ethanol. Surfactants are also used with co solvents to increase the solubility of drugs. In the present study two surfactants were used with co solvents these were tween 80 and brij 35 for enhancing the aqueous solubility of rifabutin. The co solvents were further divided into two categories stronger solvents and weaker solvents. Stronger solvents were those in which the drug shown higher solubility when they used alone and the others were considered as weaker solvent. All of the mentioned cosolvents miscible with water and formed a homogenous mixture. The solubility of rifabutin was increased with increasing the amount of PEG. Among the co-solvents, ethanol showed better co-solvency compared to propylene glycol. A mixture of 90% PEG, 10% ethanol and propylene glycol show highest solubility. Tween 80 surfactant system had shown enhanced solubility of rifabutin. 10% solution of tween-80 also increases the solubility of rifabutin and that indicating the micellar type of solubilisation. So tween 80 is better than brij 35. The above observations propose that the addition of small amount of polar solvent enhances the solubility of rifabutin. Though rifabutin is nonpolar aromatic compound, the oxygen functional groups had definite role to play in hydrogen bonding. The combined effect of hydrophobic forces and hydrogen bonding made to believe that rifabutin molecules accommodate themselves in the interior surface of the spherical micelle.

4. CONCLUSION

The present study evaluated and compared aqueous solubility enhancement of rifabutin using different cosolvents and surfactants. The study may also generate an array of data for solubilisation of rifabutin using various pharmaceutically accepted cosolvents which will be useful in formulation design and development of liquid dosage forms containing rifabutin.

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REFERENCES

1. James K., Solubility and related properties, 2nd edition, vol 28, Marcel Dekker Inc Newyork, 2 , 355 – 395, 2010.
2. http://www.chem.lsu.edu/lucid/tutorials/tutorials.html, 2016.
3. Nayaz, A., Thakur, R.S. and Koushik, Y., Formulation and evaluation of solubility enhanced ciprofloxacin. International Journal of Pharmaceutical Sciences and Nanotechnology, 6(3), 2131-2136, 2013.
4. Sultana, S., Halder, S., Kabir, A.L. and Rouf, A.S.S., Effect of solubility enhancers on the release of carbamazepine from hydrophilic polymer based matrix tablet. Dhaka University Journal of pharmaceutical sciences, 13(2), 167-173 , 2015.
5. United State Pharmacopoeia and National Formulary (USP 29 NF-24), Rockville, MD: United State Pharmacopoeia Convention; 2, 3392 – 3394, 2007.
6. Kansara, H, Panola, R. and Mishra, A, Techniques used to enhance bioavailability of BCS class II drugs: a review. International journal of drug development and research, 7(1), 82-93, 2015.
7. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharmaceutical research , 12:413-420,1995.
8. V.Rajesh Babu, S.H.Areefulla, V.Mallikarjun, Solubility and dissolution enhancement: An overview, J Pharm Res, 3(1), 141-145,2010.
9. Thorat Yogesh, Gonjari Inderjeet, Hoshmani Avinash, A review on solubility enhancement techniques, International Journal of Pharmaceutical Sciences and Research, 2(10), 2501-2513, 2011.
10. R. K. Maheshwari, Potentiation of solvent character by mixed-solvency concept :A novel concept of solubilisation, Journal of pharmaceutical research ,3(2),411-413,2010.
11. Crabol Yoan, A overview of rifabutin-Where we stand, Journal of Antimicrobial Chemotherapy, 71(1), 1759-1771, 2016.
12. Horne J David, Experience with rifabutin replacing rifampin in the treatment of tuberculosis, Int J Tubers Lung Diseases, 15(11), 1485-1488,2011.
13. J. T. Rubino and S. H. Yalkowsky, “Co-solvency and deviations from log-linear solubilization,” Pharmaceutical Research, vol. 4, no. 3, pp. 231–236, 1987.
14. A. Das, A. K. Nayak, B. Mohatny, and S. Panda, “Solubility and dissolution enhancement of etoricoxib by solid dispersion technique using sugars,” ISRN Pharmaceutics, vol. 2011, Article ID 819765, 8 pages, 2011.