



## INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

### Enhancement of bioavailability of rifapentine by solid dispersion technique

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#### Abstract

This work describes a solid dispersion technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug, rifapentine. The solid dispersion with polyethylene glycol (PEG) 4000 and Mannitol have been prepared by different methods in different ratios and found that solvent evaporation (CS<sub>4</sub>) shows the better enhancement of solubility in comparison to the kneading and physical mixture method.

**Key- Words:** Rifapentine, Solid dispersion (SD), Dissolution rate

#### Introduction

Rifapentine is an antibiotic in the rifampycin family of drugs that treats pulmonary tuberculosis (TB), it is poorly soluble in water. These drugs are derived from a fungus called *Amycolatopsis mediterranei* which originated from a pine forest outside of Nice, France. The drug's brand name is Prifkin, and it is marketed by Sanofi-Aventis. It was approved by the Food and Drug Administration in June 1998. Rifapentine has a potential advantage over rifampicin because its long half-life (13 hours compared with 3 hours) could allow for less frequent dosing. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the efficacy *in vivo*. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability.

Solubilization of poorly aqueous soluble drug forms an important activity in formulation process. For many formulation scientists in the big pharma companies, it became clear in the early 1990s that they had to learn and invest much more into solubilizing/enhancing technologies like complexation of drug candidates with cyclodextrins, microemulsion (SMEDDS formulations), nanosuspension or solid dispersion formulation technologies having the potential to enhance bioavailability. This study seeks to investigate kneading method, physical mixture, and solvent evaporation as a method for the preparation of these binary systems as well as their solid state characterization by employing analytical tools such as Fourier Transform infrared (FTIR) and Scanning electron microscopy (SEM).<sup>1-3</sup>

#### Material and Methods<sup>4-8</sup>

##### Materials

The Rifapentine was a gift from Lupin Pharmaceuticals, India. PEG 4000 and Mannitol were purchased from C.D.H. Reagent, India. All other chemicals and reagents used were of analytical grade.

##### Methods

The Preparation of drug- PEG 4000 & mannitol solid dispersion were prepared by different Techniques which are described below: (Table 1)

##### Physical Mixture (PM)

Physical mixture were prepared by simple blending in a glass mortar of accurately weighed quantities of drug(s) and carrier(s) for about one hour in ratio of 1:1

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and passed through sieve no.85 and stored in dessicator over fused calcium chloride.

#### **Kneading Method (KN)**

A mixture of polymer 4000 & Mannitol and Rifapentine were weighed accurately in specified quantity. The mixture was wetted with water: methanol (50% v/v) and kneaded thoroughly for 45 min in glass mortar. Further, the products was dried at 40 OC for 48 hr, passed through sieve No.85 and stored in a desiccator over fused calcium chloride.

#### **Solvent-Evaporation method (SE)**

The Accurately weighed amount of Drug and PEG 4000 and Mannitol were dissolved in methanol to get a clear solution. The resulting solution was stirred at ambient temperature until complete evaporation of the solvent occurred. The resulting preparation were kept in desiccators for the least 48 hr and then grounded in a glass mortar for size reduction and passed through sieve no.85 and stored in desiccators over fused calcium chloride.

#### **Characterization of solid dispersion (SD)**

##### **Drug Content Analysis**

The Solid Dispersion containing an equivalent amount of 20 mg of Rifapentine was added to a volumetric flask (25 ml) containing 0.1N HCl, the flask was shaken for 15 min and final volume was made up using 0.1N HCl .The sample was filtered and assayed for rifapentine spectrophotometrically (Simaduz 1800) at 480 nm.

##### **In Vitro dissolution**

A LABINDIA Disso 2000 (Mumbai) dissolution test apparatus type I (Basket) at rotation speed of 100 rpm was used for the study. Dissolution of the drug and samples was carried out on an equivalent of 450 mg of the Rifapentine As per USP XXVI, 0.1 N HCL was used as dissolution media. The volume and temperature of the dissolution media were 900 ml and  $37 \pm 0.2$  OC, respectively. After fixed time intervals, 5 ml of samples were withdrawn and sink condition was maintained. These samples were assayed through ultraviolet absorbance measurement at 480 nm using UV-Visible Spectrophotometer (Shimadzu UV-1700, Japan) by an analytically validated method ( $r^2 = 0.9995$ ). To increase the reliability of the observations, the dissolution studies were performed in triplicate (Table 2, 3, 4)

#### **Results and Conclusion**

All SDs were found to be fine and free flowing prepared by kneading method and solvent evaporation method as compare to physical mixture method with low standard deviation values in percent drug content ensured uniformity of drug content in each batch, all the dispersions contained  $96 \pm 4\%$  of the drug. Figure 1 shows the in vitro dissolution profiles of rifapentine

from SDs containing various ratios of drug to Mannitol in which max % drug release was obtained in batch CS<sub>4</sub> ( $96.84 \pm 0.22$ ). Figure 2 shows the in vitro dissolution profiles of rifapentine from SDs containing various ratios of drug to PEG 4000 in which max % drug release was obtained in batch ES<sub>4</sub> ( $97.04 \pm 0.22$ ). In contrast, the dissolution rate of rifapentine from all Mannitol and PEG 4000 SDs was significantly higher than that of rifapentine alone. Physical mixture of PEG also improves the dissolution profile of rifapentine due to its hydrophilic nature but not such an extent as by kneading method and solvent evaporation method. The improvement of dissolution may be due to reducing particle size of rifapentine and hence improving drug wettability and significantly improved dissolution. In the solid dispersion state because of kneading of rifapentine with the polymers, it was converted into amorphous form or change in crystal form may changes the different physicochemical properties. The solid dispersion with polyethylene glycol and Mannitol have been prepared by different methods in different ratios and found that solvent evaporation (CS<sub>4</sub>) shows the better enhancement of solubility in comparison to the kneading and physical mixing method.

#### **Acknowledgments**

We would like to thanks Lokesh Tyagi, Kashif Hussain, Amandeep Singh and Pankaj Nainwal for their Cooperation in this work.

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**Table 1: Formulation code of Solid Dispersion for different method of preparation**

| S./No. | Name of the Method                  | Drug: Polymer ratio | Solid dispersion (SD) |                 |
|--------|-------------------------------------|---------------------|-----------------------|-----------------|
|        |                                     |                     | PEG 4000              | Mannitol        |
| 1.     | Physical mixture<br>Kneading method | 1.1                 | E                     | C               |
|        |                                     | 1.1                 | EK <sub>1</sub>       | CK <sub>1</sub> |
|        |                                     | 1.2                 | EK <sub>2</sub>       | CK <sub>2</sub> |
|        |                                     | 1.3                 | EK <sub>3</sub>       | CK <sub>3</sub> |
|        |                                     | 1.4                 | EK <sub>4</sub>       | CK <sub>4</sub> |
| 2.     | Solvent Evaporation method          | 1.1                 | ES <sub>1</sub>       | CS <sub>1</sub> |
|        |                                     | 1.2                 | ES <sub>2</sub>       | CS <sub>2</sub> |
|        |                                     | 1.3                 | ES <sub>3</sub>       | CS <sub>3</sub> |
|        |                                     | 1.4                 | ES <sub>4</sub>       | CS <sub>4</sub> |
|        |                                     | 1.5                 | ES <sub>5</sub>       | CS <sub>5</sub> |

**Table 2: Drug Content and Invitro release of prepared solid dispersions of Rifapentine by physical mixture**

| S./No. | PEG 4000           |                      | Mannitol           |                      |
|--------|--------------------|----------------------|--------------------|----------------------|
|        | % Drug Content±S.D | % vitro drug release | % Drug Content±S.D | % vitro drug release |
| 1.     | 65±0.15            | 62±1.10              | 70±0.05            | 67.09±1.14           |

**Table 3: Drug Content and In-vitro release of prepared solid dispersions of Rifapentine & PEG 4000 by kneading and solvent evaporation method**

| S./No. | Kneading method |                    |                      | Solvent Evaporation method |                    |                      |
|--------|-----------------|--------------------|----------------------|----------------------------|--------------------|----------------------|
|        | Batch code      | % Drug Content±S.D | % vitro drug release | Batch code                 | % Drug Content±S.D | % vitro drug release |
| 1.     | EK1             | 95.5±0.21          | 82.23±1.35           | ES1                        | 93.0±0.21          | 84.1±0.21            |
| 2.     | EK2             | 94.48±0.20         | 88.16±0.74           | ES2                        | 90.71±0.02         | 87.54±0.11           |
| 3.     | EK3             | 95.0±0.19          | 90.03±1.08           | ES3                        | 89.94±0.21         | 93.54±1.11           |
| 4.     | EK4             | 93.3±0.14          | 92.00±1.23           | ES4                        | 96.3±0.23          | 96.84±0.22           |
| 5.     | EK5             | 96.4±0.11          | 94.52±0.81           | ES5                        | 95.1±0.14          | 94.54±0.33           |

**Table 4: Drug Content and Invitro release of prepared solid dispersions of Rifapentine & Mannitol by kneading and solvent evaporation method**

| S./No. | Kneading method |                    |                      | Solvent Evaporation method |                    |                      |
|--------|-----------------|--------------------|----------------------|----------------------------|--------------------|----------------------|
|        | Batch code      | % Drug Content±S.D | % vitro drug release | Batch code                 | % Drug Content±S.D | % vitro drug release |
| 1.     | CK1             | 95.11±0.34         | 83.22±0.88           | CS1                        | 96.3±0.11          | 85.22±0.20           |
| 2.     | CK2             | 96.40±0.21         | 87.12±1.04           | CS2                        | 93.73±0.82         | 89.24±0.01           |
| 3.     | CK3             | 94.5±0.29          | 90.21±0.98           | CS3                        | 93.04±0.11         | 94.44±1.18           |
| 4.     | CK4             | 96.8±0.34          | 94.10±1.03           | CS4                        | 96.4±0.33          | 97.04±0.22           |
| 5.     | CK5             | 96.4±0.15          | 96.12±0.71           | CS5                        | 95.3±0.04          | 93.50±0.30           |

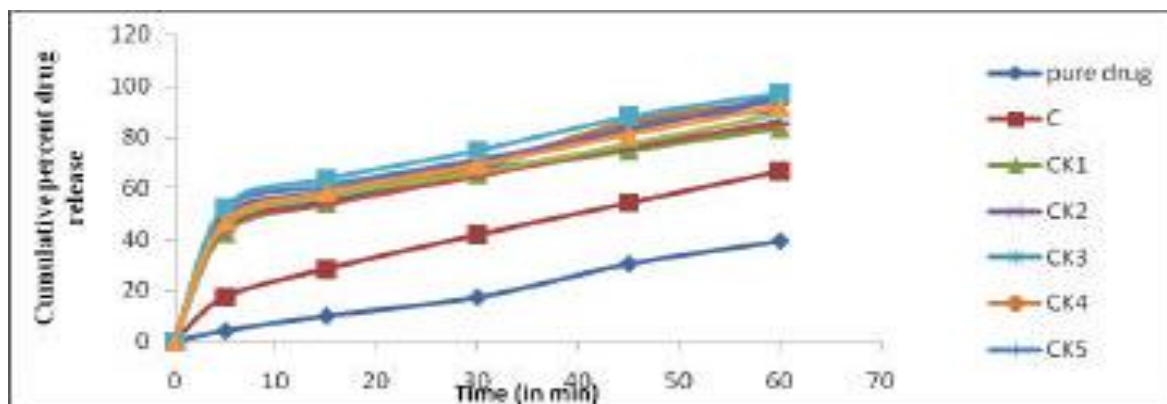


Fig. 1: Dissolution profiles of Rifapentine and mixtures of Rifapentine and Mannitol in 0.1N HCl at 37±0.5°C

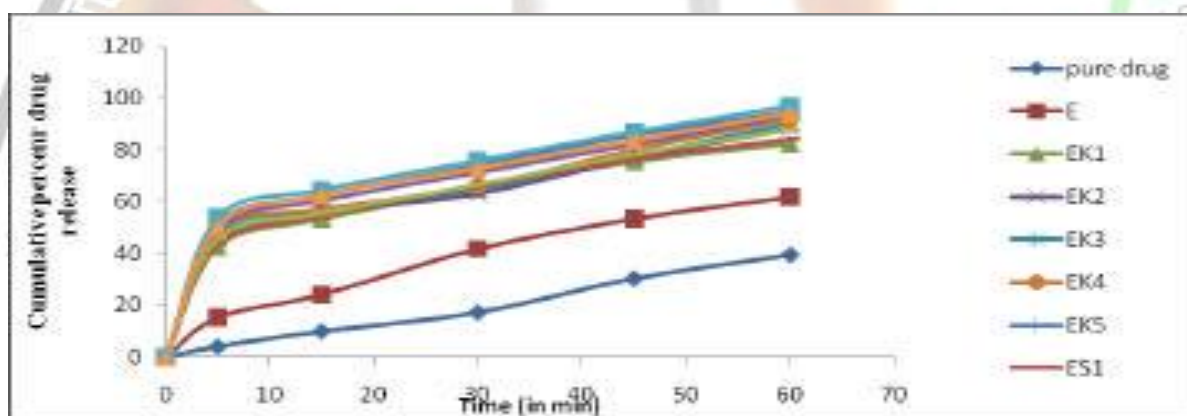


Fig. 2: Dissolution profiles of Rifapentine and mixtures of Rifapentine and PEG 4000 in 0.1N HCl at 37±0.5°C



Fig. 3: IR-Spectra of Rifapentine