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# Solid Dispersion and Inclusion Complex for Solubility Enhancement of Rifabutine: A Comparative Study

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ABSTRACT

Improvement in the solubility of a hydrophobic drug has a significant role in formulation development. The target of this study was the use of solid dispersion and inclusion complex method to enhance and to compare the watery solubility and dissolution qualities of Rifabutin. Various strategies in various proportions have been used in the preparation of the consideration complex with ß-cyclodextrin (ß-CD) and Hydroxypropyl-ß-cyclodextrin (HPß-CD) and found that the better-improved solubility has been seen in kneading technique (AK1) in comparison to the physical mixture method and solvent evaporation method. Various techniques were applied in the preparation of the solid dispersion of Mannitol and polyethene glycol (PEG) 4000. They observed that solvent evaporation (CS4) had shown the better improvement of solubility when compared with the physical mixture method and kneading method. As the two methodologies were analysed, it was observed that the inclusion complex technique was far better as it caused a noteworthy enhancement in dissolution profile (99.23±0.25). The drug content was calculated (99.15±0.14) and % inclusion yield was calculated (99.5 %), which was found to be maximum with the kneading technique (AK1). The characterization FTIR and SEM of the complexes shows that the drug had an amorphous structure. The amorphous structure of a drug has higher dissolution potential than the crystalline structure of the drug. The IR Spectroscopy and Scanning electron microscopy (SEM) were done to check their impact on dissolution behaviour and any if there was any physicochemical interaction between the carrier and the drug.

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## INTRODUCTION

For active therapeutic substance, aqueous solubility is an essential property as it administers — dissolution, absorption, and along with these lines the adequacy in vivo. Drug's therapeutic effectiveness relies on the solubility and bioavailability of drug particles. For pharmacological action to appear, the solubility of the drug is a considerable parameter to get a desirable amount of drug in the systemic circulation. Only 8 per cent to 10 per cent of new drug entities have high permeability and solubility as well. (Yalkowsky and Valvani, 1980; Ministry of Health and Family Welfare, 1996) In formulation

process solubilisation of hydrophobic drug plays a significant role In the mid-1990s it turned out to be clear by formulation researchers in the enormous pharma organisations that they must learn and put substantially more efforts in solubilising or enhancing technologies like cyclodextrins and drug complexing, nanosuspension, microemulsion (SMEDDS details), or formulation of solid dispersion as these technologies can improve bioavailability. (James, 1986; Modi and Tayade, 2006)

To enhance the dissolution properties of the drugs, the formulation of the inclusion complexes of a drug with a nontoxic agent is a unique methodology. Thorough investigations, serious essential research and industrial production, Cyclodextrins (CDs) have been perceived as useful pharmaceutical excipients. Hence, they can be utilised broadly in the pharmaceutical industry. (Patel *et al.*, 2010; Nagasamy *et al.*, 2017) The l -cyclodextrin, a -cyclodextrin and ß -cyclodextrin, are the most common natural CDs which are formed by six, seven, and eight glucose units respectively along with hydrophobic cavity and hydrophilic external area. Inclusion complex improves bioavailability, solubility rate, dissolution profile and stability. (Moriwaki *et al.*, 2008; Serajuddin, 1999; Jain and Yalkowsky, 2007)

The goal of the present examination was to give a correlation between techniques for the formulation of inclusion complexes and solid dispersions by hydrophilic substance and complexing agent, respectively. Besides, examination tried to investigate physical mixture, solvent evaporation and kneading method, as a technique for the formulation of these binary systems, as their solid-state portrayal by utilising analytical instruments, for example, SEM (Scanning electron microscopy) and FTIR (Fourier Transform infrared). (Emara *et al.*, 2002; Inamdar *et al.*, 2008) Rifabutine is an antibiotic of rifampicin group which is used to treat pneumonic TB (tuberculosis), but this was not effectively water-soluble. The drugs were obtained from a fungus named Amycolatopsis mediterranei which began from a pine woodland outside of Nice, France. Sanofi-Aventis marketed the medication's image, and its name is Prifkin. In the year 1998 June, the Food and Drug Administration endorsed it. Rifabutin has merit over rifampicin that Rifabutine's long half-life, which is 13 hours contrasted and 3 hours, could be taken into less frequent dosing. (Lo and Law, 1996; Betageri, 1995)

## MATERIALS AND METHODS

### Materials

Lupin Pharmaceuticals, India gifted the Rifabutine and ß-CDs, HPß-CD. Mannitol and PEG 4000 were purchased from Sun Biochemicals. All analytical grade, other chemicals and reagents were used.

### Methods

Different Techniques were used in the formulation of drug- mannitol & PEG 4000 solid dispersion and drug-CD stable binary systems.

### PM (Physical Mixture)

To prepare physical mixture precisely weighed quantities of carriers and drugs were mixed in a glass mortar in a ratio of 1:1 for almost one hour and then sieved by sieve no.85 and kept in a desiccator containing fused Cacl2. (Yadav *et al.*, 2009)

### KNM (Kneading Method)

A specified quantity of a mixture of cyclodextrin (ß-CD & HPß-CD) / polymer 4000, Rifabutine & Mannitol were weighed. By adding water: methanol (50% v/v) the mixture was thoroughly kneaded in glass mortar for about 45-50 min. After that, the products were dried at 35 0C for around 48 hours, and then sieved by sieve No.85 and kept in a desiccator over fused Cacl2. (Tayade and Modi, 2007)

### SEPM (Solvent-Evaporation method)

The properly weighed amount of cyclodextrin (HPß-CD & ß-CD)/ PEG 4000, Mannitol & Drug dissolved in methanol, and hence obtained a clear solution. At controlled temperature, the resulting solution was stirred until the solvent evaporated completely. For around 48 hr the resulting preparation was kept in desiccators and after that blended in a mortar (made up of glass) for reducing its size and then sieved by sieve no.85 and kept in desiccators over fused Cacl2. (Breitenbach, 2002)

### Characterization of SD (Solid Dispersion)

### Drug Content Analysis

In a 25 ml volumetric flask containing 0.1N HCl, the Solid Dispersion containing 20 mg of Rifabutine was added. The flask was shaken continuously for 18-20 minutes, and then by utilising 0.1N HCl, the final volume was made up. The sample obtained was filtered and eventually assayed for Rifabutine at 478 nm spectrophotometrically. (Moriwaki *et al.*, 2008; Emara *et al.*, 2002; Inamdar *et al.*, 2008)

### In vitro dissolution

Dissolution test assembly [Campbell Electronics, Mumbai, India] type I Basket, the revolution speed of 100 rpm was utilised for this study work. According to USP XXVI dissolution of the sample, the drug was carried out on an equivalent of 450 mg of the Rifabutine, 900ml volume of 0.1 N HCL at 37 $\pm$ 0.2 0C was utilised as dissolution media. Individually 5 ml of

samples were withdrawn after fixed time intervals, in the maintained sink condition. These samples were examined by using UV absorbance estimation at 478 nm utilising UV-Vis Spectrophotometer (UV 2203 Double beam spectrophotometer, Systronics) by a logically approved strategy (r2 = 0.9995). Dissolution studies were performed in triplicate.

**Inclusion Complex Characterization**

**FTIR (Fourier Transform Infrared spectroscopy)**

Shimadzu FTIR-8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan) was used to record FTIR spectra of the prepared formulation. KBr pellet technique was used, and the background spectrum was gathered in indistinguishable circumstance. (Rawat and Jain, 2004; Singh *et al.*, 2017) Every spectrum was obtained from each average scans gathered in the region of around 400 – 4000 $cm^{-1}$ at a spectral resolution of 2 $cm^{-2}$ and proportion against the background interferogram. Programming provided by Shimadzu was utilised to analyse the Spectra. (Jain and Yalkowsky, 2007; Lachman *et al.*, 1986)

**Scanning electron microscopy**

By means for Phillips 1500, SEM the surface morphological characteristics of crude materials and the enhanced binary systems were analysed. Previously with the help of twofold sided sticky tape, the powders were fixed on a metal stub and were covered in vacuums with a meagre gold layer (around 300 Å), for 29s and at 29 W, to make it electrically conductive. The photos were captured at a magnification of 750 or 5000X and an excitation voltage of 15 Kv. At Birbal Sahni Institute of Paleobotany, Lucknow, SEM considers were completed.

**Drug content**

To extract the drug from the inclusion complex, the inclusion complex was weighed precisely and suspended in 0.1N HCl, and then were shaken in a mechanical shaker. The filtrate was investigated after 24 hours, at 478 nm spectrophotometrically against 0.1N HCl as blank for sedate drug content.

**In vitro dissolution**

For dissolution test 900 mL of 0.1N HCl, was utilised as a dissolution medium at 37±0.5°C. The blending pace of paddle was adjusted at 50 rpm. Then the necessary measure of every sample had been sent into the dissolution medium, At suitable time intervals, an aliquot segment of the solution was withdrawn and analysed for the measure of the dissolved drug by using a spectrophotometer. Each point on the dissolution profiles represented the average of three conclusions.

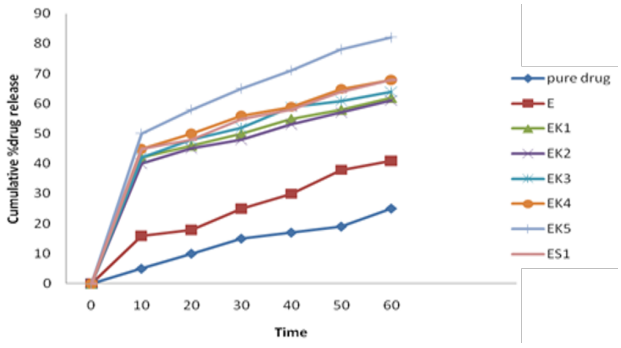


**Figure 1: Dissolution profiles of Rifabutine and mixture of Rifabutine and PEG 4000 in 0.1N HCl at 37±0.5°C**

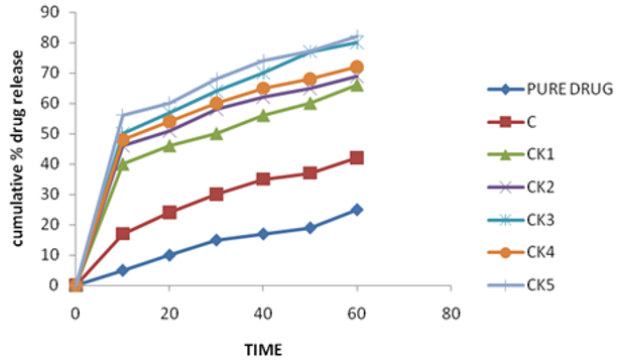


**Figure 2: Dissolution profiles of Rifabutine and mixture of Rifabutine and Mannitol in 0.1N HCl at 37±0.5°C**

**Figure 3: Infrared-Spectra of Rifabutine**

**Figure 4: Infrared -Spectra of Formulation AK1**

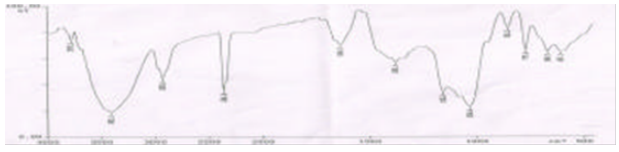

**Figure 5: Infrared Spectra of HP-Beta Cyclodextrin**

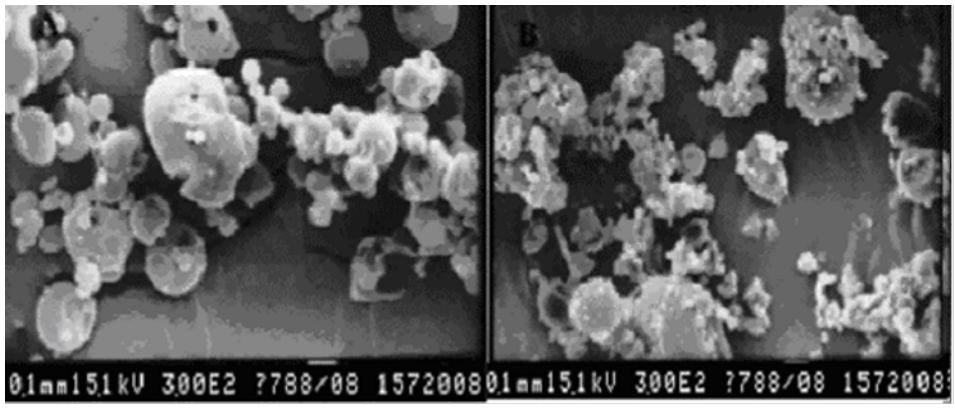


**Figure 6: SEM of HP-ßCD (A), RIF: HP-ß-CD kneading (C), HP-ßCD:RIF physical mixture (B)**

**Table 1: Formulation code for a different method of preparation of Inclusion Complex and Solid Dispersion**

| Method name | The ratio of Drug:Polymer | SD (Solid Dispersion) PEG 4000 | SD (Solid Dispersion) Mannitol | IC (Inclusion Complex) HP-ß-CD | IC (Inclusion Complex) ß-CD |
|---|---|---|---|---|---|
| PM (Physical Mixture) | 1:1 | E | C | A | B |
| KNM (Kneading Method) | 1:1 | EK1 | CK1 | AK1 | BK1 |
| | 1:2 | EK2 | CK2 | AK2 | BK2 |
| | 1:3 | EK3 | CK3 | AK3 | BK3 |
| | 1:4 | EK4 | CK4 | | |
| | 1:5 | EK5 | CK5 | | |
| SEPM (Solvent Evaporation Method) | 1:1 | ES1 | CS1 | AS1 | BS1 |
| | 1:2 | ES2 | CS2 | AS2 | BS2 |
| | 1:3 | ES3 | CS3 | AS3 | BS3 |
| | 1:4 | ES4 | CS4 | | |
| | 1:5 | ES5 | ES5 | | |

**Table 2: Drug Content and Invitro release of solid dispersions of Rifabutine prepared by PM (Physical Mixture)**

| PEG 4000 | | Mannitol | |
|---|---|---|---|
| %Drug Content ± SD | In vitro drug release% | %Drug Content ± SD | In vitro drug release% |
| 65±0.15 | 62±1.10 | 70±0.05 | 67.09±1.14 |

**Table 3: Drug Content and In vitro release of SDs of Rifabutine & PEG 4000 prepared by solvent evaporation and kneading method**

| S.NO | Kneading method | | | Solvent Evaporation method | | |
|---|---|---|---|---|---|---|
| | Batch code | % Drug Content ±SD | In-Vitro drug release % | Batch code | % Drug Content ±SD | In-Vitro drug release % |
| 1 | EK1 | 95.2±0.21 | 81.13±1.35 | ES1 | 92.0±0.21 | 83.1±0.21 |
| 2 | EK2 | 92.48±0.20 | 86.16±0.74 | ES2 | 90.11±0.02 | 87.14±0.11 |
| 3 | EK3 | 95.20±0.19 | 91.23±1.08 | ES3 | 89.84±0.21 | 93.44±1.11 |
| 4 | EK4 | 91.43±0.14 | 92.20±1.23 | ES4 | 97.3±0.23 | 97.03±0.23 |
| 5 | EK5 | 96.2±0.11 | 95.12±0.81 | ES5 | 95.1±0.14 | 94.54±0.33 |

**Table 4: Drug Content and Invitrorelease of SDs of Mannitol & Rifabutine prepared by solvent evaporation and kneading method**

| S.NO | Kneading method | | | Solvent Evaporation method | | |
|---|---|---|---|---|---|---|
| | Batch code | % Drug Content ±S.D | In-Vitro drug release % | Batch code | % Drug Content ±SD | In-Vitro drug release % |
| 1 | CK1 | 95.15±0.34 | 83.22±0.84 | CS1 | 94.3±0.11 | 86.22±0.20 |
| 2 | CK2 | 96.20±0.21 | 87.00±1.04 | CS2 | 92.73±0.82 | 88.24±0.01 |
| 3 | CK3 | 92.5±0.29 | 90.21±0.98 | CS3 | 92.04±0.11 | 93.44±1.18 |
| 4 | CK4 | 96.81±0.34 | 93.10±1.03 | CS4 | 95.4±0.33 | 96.83±0.23 |
| 5 | CK5 | 96.42±0.15 | 96.15±0.71 | CS5 | 94.3±0.04 | 92.50±0.30 |

**Table 5: Drug Content and In vitro release of ICs of Rifabutine prepared by physical mixture**

| HP-ß-CD | | ß-CD | |
|---|---|---|---|
| %Drug Content ± SD | In vitro drug release% | %Drug Content ± SD | In vitro drug release% |
| 98.1±0.25 | 69.32±1.55 | 95.99±0.15 | 64.32±1.4 |

**Table 6: Drug Content & In vitro release of ICs of Rifabutine & HP-ß-CD prepared by SEPM (solvent evaporation and kneading method)**

| S.NC | Kneading method | | | Solvent Evaporation method | | |
|---|---|---|---|---|---|---|
| | Batch code | % Drug Content ±S.D | In-Vitro drug release % | Batch code | % Drug Content ±S.D | In-Vitro drug release % |
| 1 | AK1 | 99.15±0.13 | 99.23±0.25 | AS1 | 98.48±0.13 | 97.45±0.77 |
| 2 | AK2 | 97.98±0.20 | 96.11±1.14 | AS2 | 97.18±0.62 | 94.10±1.15 |
| 3 | AK3 | 97.28±0.12 | 93.99±1.01 | AS3 | 96.11±0.21 | 91.50<br>91.50±1.33 |

**Table 7: Drug Content and Invitro release of ICs of ß-CD & Rifabutine prepared by solvent evaporation and kneading method**

| S.NO | Batch code | % Drug Content ±S.D | In-Vitro drug release % | Batch code | % Drug Content ±S.D | In-Vitro drug release % |
|---|---|---|---|---|---|---|
| 1 | BK1 | 95.22±0.30 | 84.29±0.99 | BS1 | 94.2±0.12 | 85.12±0.75 |
| 2 | BK2 | 98.33±0.10 | 90.66±1.94 | BS2 | 96.73±0.12 | 89.33±1.05 |
| 3 | BK3 | 97.77±0.14 | 95.23±1.48 | BS3 | 97.84±0.11 | 95.22±1.23 |

## RESULTS AND DISCUSSION

All the solid dispersions and inclusion complexes prepared by solvent evaporation method and kneading method (Table 1) were found in a free-flowing and fine state when compared to physical mixture method which has low standard deviation values in drug percentage content (Table 2) ensure the uniformity of drug content in each batch, 96±5% of the drug was contained in all the dispersions. IR spectra (Figures 3, 4 and 5) of pure Rifabutine, HPß-CD and its inclusion complex's were found identical, which shows interaction b/n Rifabutine & carriers in the prepared inclusion complexes. This depicts that complexes prepared by physical mixing have less complexation. On the other hand, better complexation was shown by the complexes prepared by the kneading method, because their spectra were significantly different from the HPß-CD and pure drug spectra. Intensity disappearance in the sharpness of peak for both solvent evaporation and kneaded indicates the completion of complexation. SEM images of the inclusion complex HPß-CD & pure components found in irregular shape mixture of smooth-surfaced particles with few smaller particles (10-30 $\mu$m) are shown in Figure 6. When compared with

 

pure HPß-CD and physical mixture, the IC 1:1 prepared by kneading method presented smaller and irregular surface morphology. These micrographs demonstrate the homogeneity of IC; the presence of Rifabutine particles with the HPß-CD particles was impossible to distinguish.

In comparison to pure Rifabutine, the inclusion complex had shown improved drug dissolution rate,

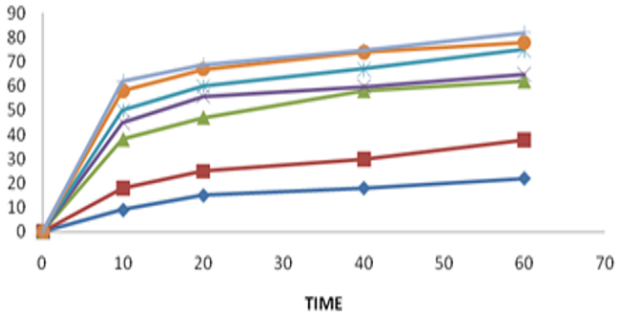


**Figure 7: Dissolution profiles of the mixture of Rifabutine and ß-cyclodextrin and Rifabutine in 0.1N HCl at 37±0.5°C**

which might be due to the novel arrangements between Rifabutine and HPß-CD. Figure 1 depicts the in vitro dissolution profiles of Rifabutine from solid dispersions containing various drug ratios to PEG 4000 in which batch $ES_4$ had obtained max % drug release (97.03±0.23). Figure 2 depicts the in vitro dissolution profiles of Rifabutine from solid dispersions containing various drug ratios to Mannitol, and batch $CS_4$ has obtained max % drug release (96.83±0.23). Instead of Rifabutine alone, the rate of dissolution of Rifabutine from all PEG 4000 (Table 3) and Mannitol (Table 4) SDs was significantly higher. A physical mixture of Polyethylene glycol also showed improved dissolution profile of Rifabutine because of its hydrophilic nature but not to that extent as by solvent evaporation method and kneading method (Table 5).

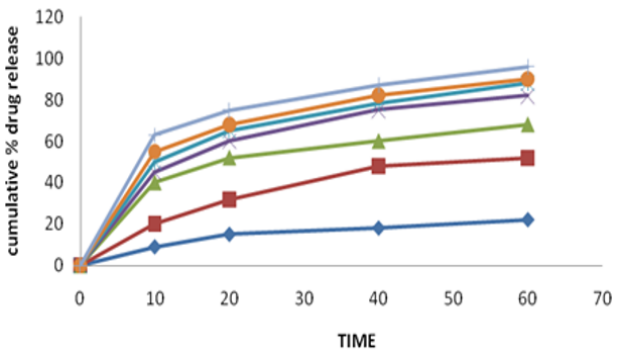


**Figure 8: Dissolution profiles of the mixture of Rifabutine and HPß-cyclodextrin and Rifabutine in 0.1N HCl at 37±0.5°C**

The enhancement in dissolution could be occurred due to reduced size of particles of Rifabutine and hence lead to the improvement in drug wettability and eventually the significant improvement in dissolution. Rifabutine kneaded with the polymers in solid dispersion state due to which it was turned into an amorphous form or may be changed crystal form might change the different physicochemical properties. Figure 7 depicts the in vitro dissolution profiles of Rifabutine from inclusion complexes containing different ratios of drug to HPß-CD (Table 6), in which batch $AS_1$ had shown max % drug release (97.45±0.77). The in vitro dissolution profiles of Rifabutine from ICs containing different ratios of drug to ß-CD (Table 7) has shown in Figure 8, in which batch $EK_5$ had obtained max % drug release (95.12±0.81). In case of the physical mixtures, the little enhancement insolubility in comparison to pure Rifabutine is because of the wetting effect of HPß-CD or due to the rapidly formed ICs in the dissolution medium. Incidentally, due to the hydrophilicity of the exterior surface of HPß-CD, it has surfactant-like properties which can reduce the interfacial tension between the dissolution medium and poorly soluble drugs, hence resulting in higher solubility.

## CONCLUSIONS

Different methods in different ratios have been used to prepare Inclusion complex with cyclodextrin. It was concluded that the $AK_1$, i.e. kneading method, has shown the better enhancement in solubility when compared with physical mixing method & the solvent evaporation. Similarly, different methods in different ratios have been used to prepare the solid dispersion with Mannitol and polyethene glycol and observed that there was a better enhancement of solubility by using solvent evaporation ($CS_4$) method in comparison to the physical mixing and kneading method. When both the methodologies were compared, a significant improvement in dissolution profile was observed in Inclusion complex method. Hence, the ICM (Inclusion complex method) was found to be considerable. The kneaded method ($AK_1$) had shown the highest drug content and % inclusion yield.

### Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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