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Comparative study of solubility enhancement of rifapentine by solid dispersion and inclusion complex

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Abstract

Solubility enhancement of poorly aqueous soluble drugs is an important aspect of formulation development. The objective of the study was to compare the aqueous solubility and dissolution characteristics of rifapentine enhanced by solid dispersion and inclusion complex technique. The inclusion complex with Hydroxypropyl-ß-cyclodextrin (HPß-CD) and ß-cyclodextrin (ß-CD) have been prepared by different methods in different ratios and found that the kneading method (AK1) shows the better enhancement of solubility in comparison to the solvent evaporation and physical mixing method. 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_4) shows the better enhancement of solubility in comparison to the kneading and physical mixture method. As both methodologies are compared, it was observed that, inclusion complex method was found to be the best because it caused significant improvement in dissolution profile (99.23±0.25). The drug content (99.5±0.13) and % inclusion yield (99.6%) was also highest with the kneading method (AK_1). The characterization (FTIR and SEM) of the complexes shows that the drug shows amorphous form in the complexes. Amorphous form has higher dissolution efficiency than the crystalline drug. Infrared (IR) Spectroscopy and Scanning electron microscopy were performed to identify any physicochemical interaction between the drug and the carrier and its effect on dissolution behavior.

Key-Words: Rifapentine, solid dispersion (SD), inclusion complex (IC)

Introduction

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.

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The formation of inclusion complexes of a drug with nontoxic agent is a promising approach used to improve the dissolution properties of the drugs. Cyclodextrins (CDs) have been recognized as useful pharmaceutical excipients. Due to their exhaustive studies, intensive basic research and industrial production, they can be used widely in pharmaceutical industry. The most common natural CDs are a-cyclodextrin, ß-cyclodextrin and l-cyclodextrin, which are formed by six, seven, and eight glucose units respectively with hydrophilic outer surface and hydrophobic cavity 13 Inclusion complex improve . stability, solubility, dissolution rate and bioavailability. Objective of present study was to provide a comparison of formulation techniques of for solid dispersion and inclusion complex by hydrophilic substance and complexing agent respectively. Furthermore, 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). 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 rifampcin because its long half-life (13 hours compared with 3 hours) could allow for less frequent dosing.

Material and methods

Materials

The Rifapentine was a gift from Lupin Pharmaceuticals, India and ß-CDs, HPß-CD was a gift from Merck Chemicals. 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-CD solid binary systems and 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 quantites of drug(s) and carrier(s) for about one hour in ratio of 1:1 and passed
through sieve no.85 and stored in dessicator over fused calcium chloride.

Kneading Method (KN)

A mixture of cyclodextrin (ß-CD & HPß-CD) / 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 0C 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 cyclodextrin (HPß-CD & ß-CD)/ 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 ± 0.2 0C, 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 (r2 = 0.9995). To increase the reliability of the observations, the dissolution studies were performed in triplicate (Table 2, 3, 4)

Characterization of inclusion complex

Fourier Transform Infra red spectroscopy (FTIR)

FTIR spectra of prepared formulation were recorded on Shimadzu FTIR-8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm-1 at spectral resolution of 2 cm-2 and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.(Fig 3-5)

Scanning electron microscopy

The surface morphology of the raw materials and of the optimized binary systems was examined by means of Phillips 1500, scanning electron microscope. The powders were previously fixed on a brass stub using double sided adhesive tape and then were made electrically conductive by coating in vacuums, with a thin layer of gold (approximately 300 Å), for 30s and at 30 W. The pictures were taken at an excitation voltage of 15 Kv and a magnification of 750 or 5000X. SEM studies were carried out at Birbal Sahni Institute of Paleobotany, Lucknow.(Fig 6)

Drug content

Accurately weighed quantities of inclusion complex were suspended in 0.1N HCl, to extract the drug from inclusion complex. It was then shaken in mechanical shaker. After 24 hours, the filtrate was analyzed spectrophotometrically at 480 nm for drug content against 0.1N HCl as blank.

In vitro dissolution

The experiments were conducted according to the following procedure: 900 milliliters of 0.1N HCl, maintained at 37±0.5°C was used as a dissolution medium. The stirring speed of the paddle was at 50 rpm. After the required amount of each sample had been placed into the dissolution medium, an aliquot portion of the solution was withdrawn at appropriate time intervals to be analyzed by spectrophotometer for the amount of the dissolved drug. Each point on the dissolution profiles represented the average of three determinations.(Table 5,6,7)

Results and Discussion

All SDs and inclusion complexs (ICs) 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±4% of the drug. IR spectra (figs.3-5) of pure rifapentine, HPß-CD and its ICs were not found to be identical, thus indicates interaction between rifapentine and carriers in the prepared ICs. This means that the extent of complexation was less in the complexes made by physical mixing. While complexes made by kneading method showed better complexation, as their spectra were significantly different from the spectra of pure drug and HPß-CD. Disappearance in the intensity of peak sharpness for kneaded and solvent evaporation initiate that complexation was practically complete. Figure 6 shows SEM images of the pure components and inclusion complex. HPß-CD existed in irregular shape mixture of smooth-surfaced particles with few smaller particles (10-30 µm). In the case of Inclusion Complex 1:1 by kneading method the particles presented a surface morphology more irregular and smaller to that of pure HPß-CD and physical mixture. These micrographs demonstrate the homogeneity of inclusion complex; it is impossible to distinguish the presence of rifapentine particle among the HPß-CD particles. The novel arrangements between rifapentine and HPß-CD might be responsible for the enhanced drug dissolution rate found for inclusion complex, in comparison to pure rifapentine. 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_4 (96.84±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_4 (97.04±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. Figure 7 shows the in vitro dissolution profiles of rifapentine from ICs containing various ratios of drug to HPß-CD in which max % drug release was obtained in batch AS_3 (91.50±1.33). Figure 8 shows the in vitro dissolution profiles of rifapentine from ICs containing various ratios of drug to ß-CD in which max % drug release was obtained in batch EK_1 (95.5±0.21).In the case of the physical mixtures, the small rise in solubility when compared to, pure rifapentine is due to the rapid formation of inclusion complexes in the dissolution medium or to the wetting effect of HPß-CD. Incidentally, HPß-CD has surfactant-like properties owing to the hydrophilicity of its exterior surface which can lower the interfacial tension between poorly soluble drugs and the dissolution medium, resulting in higher solubility.

The Inclusion complex with cyclodextrin have been prepared by different methods in different ratios and found that the kneading method (AK_1) shows the better enhancement of solubility in comparison to the solvent evaporation and physical mixing method. The solid dispersion with polyethylene glycol and Mannitol have been prepared by different methods in different ratios and found that solvent evaporation (CS_4) shows the better enhancement of solubility in comparison to the kneading and physical mixing method. As both methodologies are compared, it is observed that, Inclusion complex method was found to be the best because it caused significant improvement in dissolution profile. The drug content and % inclusion yield was also highest with the kneaded method (AK_1).

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

Name of the Method	Drug: Polymer ratio	Solid dispersion (SD)		Inclusion complex(IC)	
		PEG 4000	Mannitol	HP-ß-CD	ß-CD
Physical mixture	1.1	E	C	A	B
Kneading method	1.1	EK_1	CK_1	AK_1	BK_1
	1.2	EK_2	CK_2	AK_2	BK_2
	1.3	EK_3	CK_3	AK_3	BK_3
	1.4	EK_4	CK_4		
	1.5	EK_5	CK_5		
Solvent Evaporation method	1.1	ES_1	CS_1	AS_1	BS_1
	1.2	ES_2	CS_2	AS_2	BS_2
	1.3	ES_3	CS_3	AS_3	BS_3
	1.4	ES_4	CS_4		
	1.5	ES_5	CS_5		

Table 3: Drug Content and Invitro 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

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

PEG 4000		Mannitol	
%Drug Content±S.D	%vitro drug release	% Drug content±S.D	%vitro drug release
65±0.15	62±1.10	70±0.05	67.09±1.14

Table 6: Drug Content and Invitro release of prepared Inclusion complex of Rifapentine & HP-ß-CD by kneading and solvent evaporation method

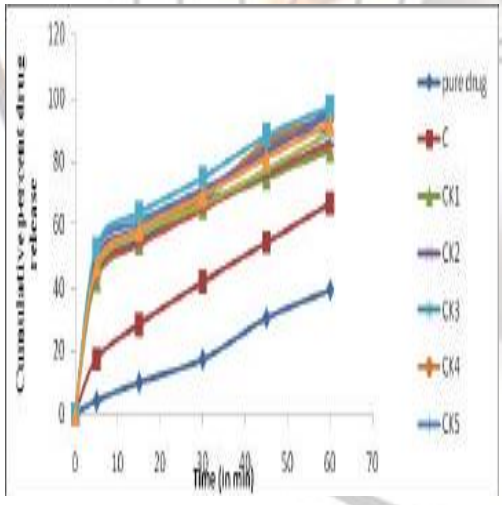
S.No.	Kneading method			Solvent Evaporation method		
	Batch code	%Drug Content±S.D	%vitro drug release	Batch code	% Drug content±S.D	%vitro drug release
1	AK1	99.5±0.13	99.23±0.25	AS1	98.68±0.13	97.22±0.77
2	AK2	98.98±0.20	96.11±1.14	AS2	97.78±0.62	94.50±1.15
3	AK3	98.08±0.12	93.99±1.01	AS3	96.92±0.21	91.50±1.33

Table 7: Drug Content and Invitro release of prepared Inclusion complex of Rifapentine & ß-CD 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	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

Table 5: Drug Content and Invitro release of prepared Inclusion complex of Rifapentine by physical mixture

HP-ß-CD		ß-CD	
%Drug Content±S.D	%vitro drug release	% Drug content±S.D	%vitro drug release
98.1±0.25	69.32±1.55	95.99±0.15	64.32±1.4



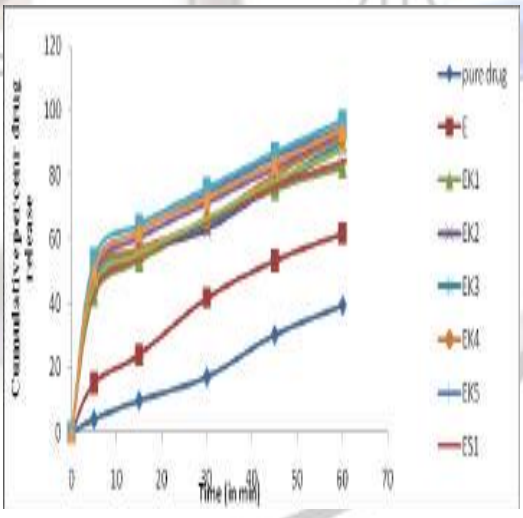


Figure 1: Dissolution profiles of Rifapentine and mixtures of Rifapentine and Mannitol in 0.1N HCl at 37±0.5°C

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

Fig. 3: IR-Spectra of Rifapentine

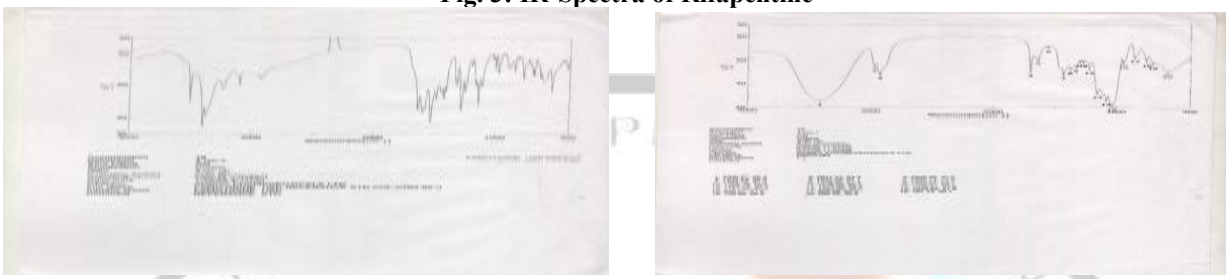
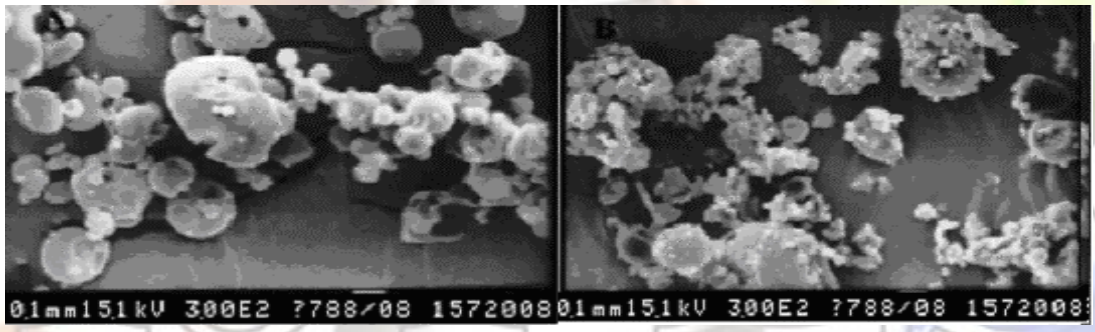


Fig 4: IR-Spectra of Formulation AK1

Fig 5: IR-Spectra of HP-BetaCyclodextrin

Fig 6: Scanning electron micrograph of HP-ßCD (A), HP-ßCD: RIF physical mixture (B), RIF: HP-ß-CD kneading (C)



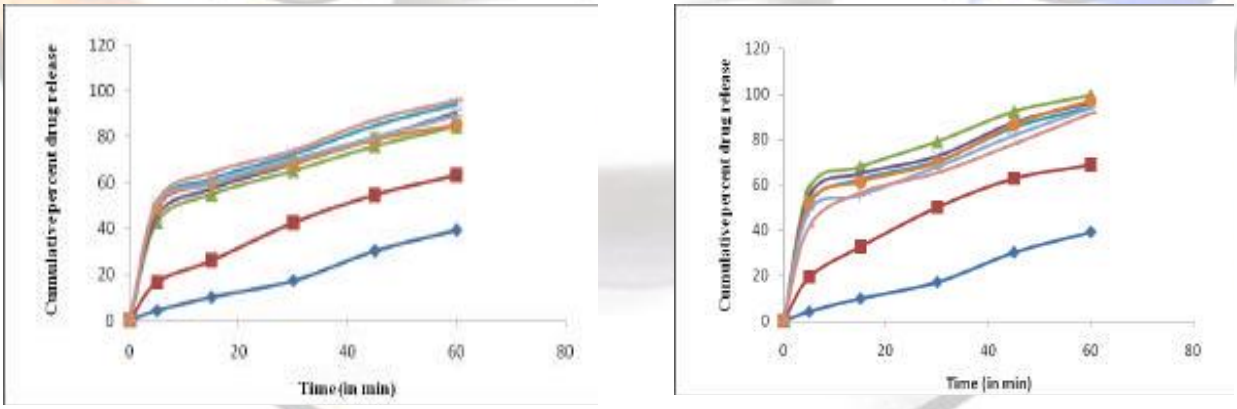


Fig. 7: Dissolution profiles of Rifapentine and mixtures of Rifapentine and ß-cyclodextrin in 0.1N HCl at 37±0.5°C

Fig. 8: Dissolution profiles of Rifapentine and mixtures of Rifapentine and HPß-cyclodextrin in 0.1N HCl at 37±0.5°C