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AN APPROACH TO ENHANCE THE SOLUBILITY OF RILPIVIRINE HYDROCHLORIDE USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The aim of the current research was to enhance the solubility and dissolution characteristics of poorly water soluble drug rilpivirine by solid dispersion technique. The study includes solubility enhancement of rilpivirine by using several water soluble carriers such as PEG 6000, PEG 4000, polyvinyl alcohol in different ratios (1:2, 1:3, 1:4) and with different techniques such as solvent evaporation technique, Fusion method and microwave irradiation method.

The solid dispersions were evaluated for various in vitro parameters such as dissolution study and Fourier transform infrared spectroscopy (FT-IR). The FTIR spectral analysis showed that there was no drug interaction with formulations additives of the tablet as there is no variation and shift in bands observed which justified that there is no interaction between drug and polymer. Solubility and dissolution rate of rilpivirine was found to be significantly higher in microwave-assisted solid dispersions. Solid dispersion of rilpivirine: PEG 6000 (1:3) exhibits fastest dissolution among all solid dispersions and thus it was selected for formulation. The solid dispersion of rilpivirine: PEG 6000 (1:3) was taken and formulated into tablets using direct compression method. The results indicated that formulated tablets of solid dispersions by microwave method gives better dissolution profiles. Microwave technology offers a simple, efficient, solvent-free promising alternative method to prepare solid dispersion with significant enhancement of solubility and dissolution rate.

KEYWORDS: Rilpivirine, PEG 6000, solid dispersion, dissolution.

INTRODUCTION

The two major challenges in pharmaceutical drug development include enhancement of solubility of sparingly water-soluble drugs and enhancing penetrations of poorly permeable drugs. Low aqueous solubility creates lots of hindrances in formulation development and clinical trials due to poor dissolution rate of drug and also in order to achieve the required plasma concentrations and stability of formulations. Various approaches including physical, chemical and other modification have been attempted to improve the solubility and bioavailability of the drugs.[1-4] Among them, solid dispersion is promising technologies to improve dissolution which is defined as the dispersion of active ingredient in an inert carrier in solid state. It is simple, scalable, convenient method and prepared using numerous processes.[5-6]

The present study deals with solid dispersion formulation of rilpivirine using various carriers such as PEG 6000, PEG 4000, polyvinyl alcohol in different ratios (1:2,1:3,1:4) and by different techniques such as solvent evaporation technique, Fusion method and microwave irradiation method.[7-9]

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) works by blocking an enzyme HIV reverse transcriptase. This prevents HIV from replicating and lowers the amount of HIV in the blood. It is an example of Biopharmaceutical Classification System (BCS) class II compound. It has low aqueous solubility leading to poor dissolution and insufficient oral bioavailability.[10-13]

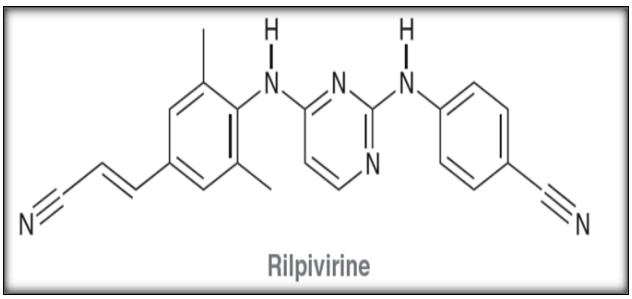

Fig 1. Structure of Rilpivirine.

MATERIALS AND METHODS

Rilpivirine was obtained from Emcure pharmaceuticals, Pune India. PEG 6000, PEG 3000, Polyvinyl Alcohol were obtained from Research lab Pvt. Ltd. Mumbai, India.

PREFORMULATION STUDIES

Determination of melting point

The drug was filled in capillary tube and capillary was placed in the melting point apparatus. The temperature required to melt the drug was noted and the same procedure was repeated for three times.

Drug-excipients compatibility studies

The infrared absorption spectrum of rilpivirine was obtained by finely grounding and dispersing the drug in finely powdered potassium bromide (KBr) and the spectrum of rilpivirine was recorded in the region of 4000 to 400 cm^{-1}. Similarly the drug and polymer were mixed physically in different ratio and were scanned by FTIR.

Determination of solubility of drug in different media

Solubility study of rilpivirine was carried out in distilled water, 0.1N HCl and phosphate buffer solutions pH 6.8. An excess of drug was dissolved in 20 ml in each media in conical flask and was kept at mechanical shaker for 8 hrs followed by filtration of solution. The solutions were then filtered, suitably diluted and absorbances were recorded at predetermined absorption maxima in triplicate.

Standard calibration curve of rilpivirine in 0.1 N HCl

100 mg of rilpivirine was transferred into 100 ml of 0.1 N HCl in volumetric flask. 10 ml of the sample was withdrawn from this solution and diluted to 100 ml with 0.1 N HCl to form 100 µg/ml (stock solution) then concentrations were made by withdrawing 5, 10,15 ,20, 25 ml from stock solution and diluted to 10 ml with 0.1 N HCl to make solution of concentration 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml and 25 µg/ml. Absorbance were taken at λmax of 280 nm using Jasco uv/visible double beam spectrophotometer and graph was plotted for absorbance versus concentration for rilpivirine.

Preparation of rilpivirine solid dispersion (SD):

Solid dispersions of rilpivirine were prepared by fusion method, solvent evaporation method and microwave method.

Fusion method

Rilpivirine SD was prepared using the carriers PEG 6000 and PEG 3000 in ratios of 1:2, 1:3 and 1:4, respectively by fusion (melt) process.

Accurately weighed quantities of polymers were taken in a china dish and kept it on a hot plate and allowed to melt at 50 to 60°C with continuous stirring. In order to achieve homogeneity the mixture was heated to obtain homogeneous melt. The known amount of rilpivirine was added by continuous stirring into the polymers. The melt was transferred to petridish and cooled at room temperature. The dried SD was pulverised and sieved through sieve number 60. The product were held in amber bottles sealed with rubber corks and placed in desiccators.

Solvent evaporation method

Rilpivirine SD's were formulated using carriers PEG 6000 and PEG 3000 in varying ratios of 1:2, 1:3 and 1:4 for the solvent evaporation process. Rilpivirine and carriers were accurately measured and dissolved in appropriate quantity of ethanol in flask. The solution was kept for evaporation at room temperature. A solid residue was produce and the solid mass was compressed, pulverized, and sieved for further use by sieve no.44. The prepared solid dispersion was then filled, sealed and placed in a desiccator in glass bottles for further use.

Microwave irradiation method

In this process, the drug is kept in the microwave for 7 minutes at 360 W along with the polymer. After every 30sec, proper mixing of the mixture was carried out. Only one beaker at a time was put inside the microwave oven (LG solo intellowave technology). The beaker was removed from the oven after 7 minutes and the sample was cooled at room temperature. The product was sieved via sieve no. 44 and stored in desiccators.

In-vitro dissolution study of rilpivirine solid dispersion

In vitro dissolution studies of pure rilpivirine and its solid dispersion systems were carried out in 900 ml of Media using a USP type 2 Dissolution rate apparatus. Samples equivalent to 25 mg of rilpivirine, speed of 75rpm and a temperature of 37^0C were used in each test. These conditions were kept constant for all dissolution studies. A 10ml aliquot was withdrawn at different time intervals, filtered it and replaced with 10ml of fresh dissolution medium to maintain the sink condition. The drug release study was carried out in 0.1 N HCl. The filtered samples were suitably diluted and measured at 280 nm and the results were computed.

Formulation of solid dispersion tablets

On the basis of in-vitro dissolution studies and solubility studies of all solid dispersion one best solid dispersion was selected. This optimized solid dispersion was compressed into the tablet form and was evaluated for various parameters like thickness, hardness, weight variation, friability, in vitro disintegration test and in vitro dissolution testing.

Evaluation of solid dispersion formulated tablets

Thickness: Thickness of the tablets was measured by varnier calipers. From all the batches three tablets were selected randomly and the diameter of tablets thickness is determined in mm.

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of solid dispersion formulated tablets was determined using hardness tester. Three tablets were randomly picked from each batch and analyzed for hardness. It is expressed in kg/cm^2.

Weight variation: Twenty tablets were selected from each batch at random and weight was determined. The tablets were weighed individually and each weight was compared with an average weight. The % variation in the weight is determined.

Friability test: The friability of six tablets was determined by using Roche friabilator. Friability can be determined by the following equation.

% Friability = Wt $_{initial}$ – Wt $_{final}$ X 100/ Wt $_{initial}$

In-vitro disintegration test: The tablet disintegration was carried out by placing one tablet in each tube (6 tablets) of the basket and the assembly was suspended in a beaker containing 0.1 N HCl and operated without the disc for 120 minutes by maintaining temperature at 37 ± 2°C. The experiment was carried out in triplicate.

RESULTS AND DISCUSSIONS

Preformulation studies

Determination of melting point

The reported melting point of rilpivirine was 248 °C and the observed melting point was found to be 242-246°C which is nearby to reported value.

Fourier Transform Infrared (FT-IR) spectroscopy for drug-excipients compatibility

FTIR spectrum of pure drug, Solid dispersion and polymer PEG 6000 are shown in figures [2-5]. All major peaks of drug and polymers are visible in the spectrum. From the spectrum observation it has been observed that there is no such major shifting of the peaks of the mixtures were observed in comparison to their individual data. The interpretation of IR spectrum is given in Table 1. Thus the study reveals a good compatibility between drug and polymer.

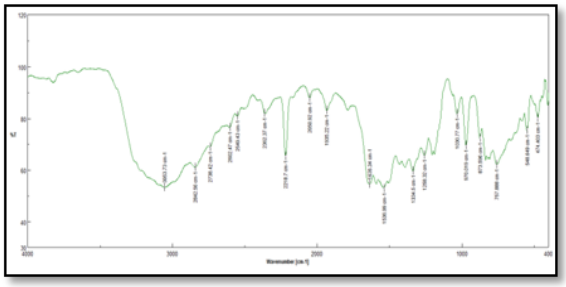

Fig. 2: IR Spectrum of Rilpivirine

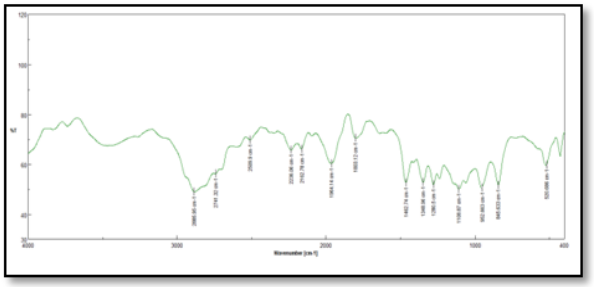

Fig. 3: IR Spectrum of PEG 6000

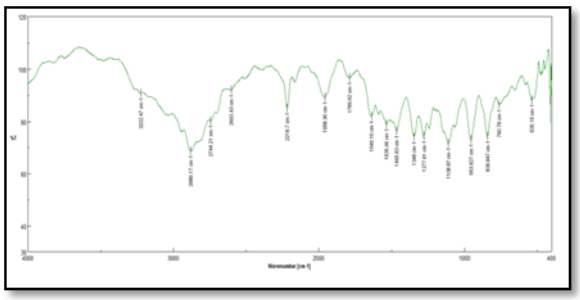

Fig. 4: IR Spectrum of RPV:PEG 6000 (1:3)

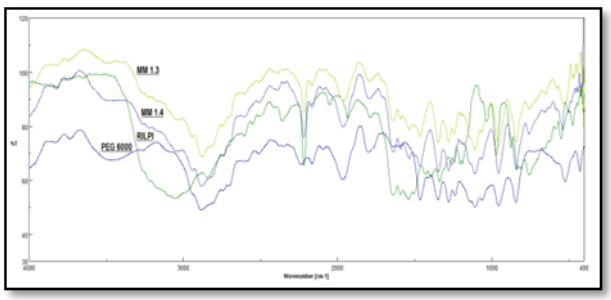

Fig.5: IR Overlay spectrum

Table 1: IR study of drug and polymer in different ratio.

Sr. No	DRUG rilpivirine		PEG 6000		RPV : PEG 6000 (1:3)	
	Wavenumber (cm^{-1})	Functional Groups	Wavenumber (cm^{-1})	Functional Groups	Wavenumber (cm^{-1})	Functional Groups
1	3053.73	–NH Stretch	3446.65	–OH Stretch	3222.4	–NH & -OH Stretch
2	2842.56	sp^3 C-H Stretch	2855.95	sp^3 C-H Stretch	2880.17	sp^{3}C-H stretch
3	2738.42	sp^2 C-H Stretch	1803.12	C=O stretch	2218.7	C≡N Stretch
4	2218.7	C≡N Stretch	1462.74	sp^3 C-H Bend	1789.62	C=O stretch
5	1635.34	C=C stretch	1348.96	sp^3 C-H Bend	1640.16	C=C stretch

Determination of solubility of drug in different media

Solubility study of rilpivirine HCl was carried out in distilled water, 0.1N HCl and phosphate buffer solutions. The results are shown in Table 2. Absorbance values of drug were higher with 0.1N HCl at 280nm. Hence, 0.1N HCl was selected as solvent for further investigation.

Table 2: Absorbance of Pure Drug Rilpivirine in different Solvent.

Sr. No	Concentration (µg/ml)	Solvent	Absorbance
1	10	Phosphate Buffer pH 2	0.0732
2	10	Phosphate Buffer pH 6.8	0.1671
3	10	Phosphate Buffer pH 7.4	0.1280
4	10	0.01N HCl	0.1689
5	10	0.1N HCl	0.1889

Calibration study of rilpivirine in 0.1N HCl

10 mg of Rilpivirine was transferred into 10 ml 0.1N HCl in volumetric flask. 1 ml of the sample was withdrawn from this solution and diluted to 10 ml with 0.1N HCl to form 100 µg /ml (stock solution) then concentration made by withdrawing 0.5, 1, 1.5, 2, 2.5ml from stock solution and diluted to 10 ml with 0.1N HCl to make solution of concentration 5 ug/ml, 10 ug/ml, 15 ug/ml, 20 ug/ml, 25 ug/ml. Absorbance was taken at λmax of 280 nm using UV visible spectrophotometer and graph was plotted for absorbance versus concentration of rilpivirine. The results are shown in Table 3 and the calibration curve plot is shown in Fig 3.

Table 3: Absorbance in 0.1N HCl

Sr. No	Concentration (µg/ml)	Absorbance at 280nm
1	5	0.0823
2	10	0.1889
3	15	0.2482
4	20	0.3417
5	25	0.4351

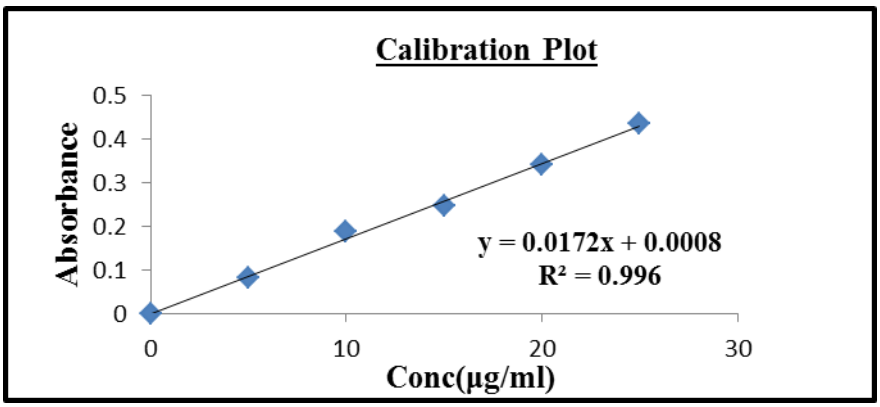

Fig. 3: Calibration Curve of Rilpivirine.

Preparation of Solid Dispersion

Solid dispersions of rilpivirine were prepared by solvent evaporation method, fusion and microwave irradiation method. The drug to polymer ratio used was 1:2, 1:3, 1:4 using Polymer PEG 6000, PEG 4000 and PVA. Rilpivirine solid dispersion drug: polymer ratio (1:3) in PEG 6000 by microwave irradiation method showed maximum absorbance. Thus this ratio was selected for tablet formulation. The results were shown in Table 4.

Table 4: Absorbance of Solid Dispersion in 0.1NHCl at 280nm.

Sr. No	Method	Conc (µg/ml)	PEG 6000			PEG 4000			PVA		
			1:2	1:3	1:4	1:2	1:3	1:4	1:2	1:3	1:4
1	Solvent Evaporation	10	0.205	0.265	0.278	0.213	0.273	0.220	0.294	0.343	0.300
		20	0.392	0.483	0.509	0.400	0.462	0.357	0.507	0.567	0.529
2	Fusion	10	0.213	0.268	0.172	0.200	0.263	0.163	0.214	0.234	0.163
		20	0.402	0.476	0.323	0.395	0.491	0.332	0.352	0.419	0.371
3	Microwave Irradiation	10	0.229	0.651	0.452	0.215	0.407	0.258	0.351	0.484	0.406
		20	0.436	1.017	0.631	0.412	0.643	0.477	0.601	0.712	0.586

In-vitro drug release studies of all the solid dispersion prepared from microwave method

In solid dispersion method the amount of carrier needed to achieve the desired improvement in dissolution characteristics of the drug is a major factor. In-vitro release profile of all the solid dispersion prepared from microwave method in different ratios was examined in 0.1 N HCl with all drug: carrier ratios and its influence on dissolution characteristics of the rilpivirine was carefully studied. Rilpivirine solid dispersion in (1:3) drug: polymer ratio in PEG 6000 by microwave irradiation method showed maximum drug release of 98.776 % in 0.1 N HCl as compared to plain drug. The results of the dissolution study are shown in Table 5 and % drug release was shown in Fig. no 6.

Table 5: In-vitro drug release study of rilpivirine solid dispersions by microwave method.

Time (mins)	Plain Drug	1:2	1:3	1:4
	% Drug Released	% Drug Released	% Drug Released	% Drug Released
0	0.000	0.000	0.000	0.000
15	20.750	22.088	25.766	24.111
30	40.457	41.682	70.081	43.840
45	68.052	67.446	71.496	69.786
60	84.610	84.839	95.606	87.034
90	84.463	78.977	85.199	84.959

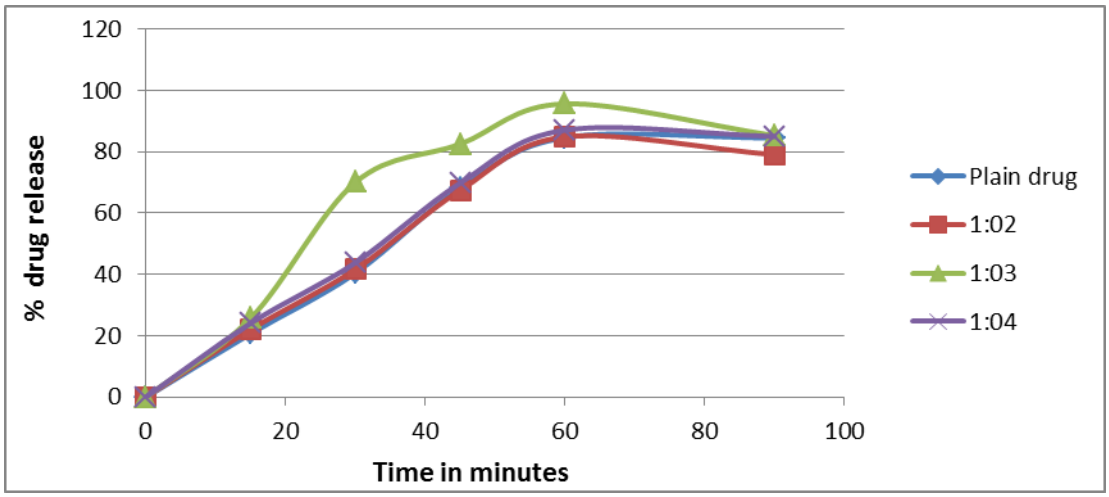

Fig.6: Percent cumulative drug release of rilpivirine in different ratios.

Formulation and evaluation of tablets

On the basis of in-vitro dissolution studies and solubility studies of all solid dispersion one best solid dispersion was selected. This optimized solid dispersion was compressed into the tablet form and was evaluated for various parameters like thickness, hardness, weight variation, friability, in vitro disintegration test and in vitro dissolution testing. The in-vitro release studies of optimized tablet formulation is shown in Table 6 and in-vitro drug release study of rilpivirine solid dispersions tablet is shown in Table 7. The formulated tablets were found satisfactory with respect to physical parameters such as thickness, hardness, friability and drug content. The tablets also complied with test for uniformity of weight and disintegration time. The dissolution studies from formulated tablets exhibited almost expected dissolution behavior as that previously obtained from their binary systems, with best dissolution enhancement by rilpivirine: PEG 6000(1:3) ratio.

Table 6: Evaluations Parameters of Solid Dispersion Formulated Tablets.

Sr. no	Tests	Specification (Solid dispersion tablet)
1	Thickness (mm)	4
2	Hardness (kg/cm^2)	5.33
3	Weight variation (mg)	208.21mg - 41.98
4	Friability (%w/w)	0.18
5	Disintegration time (min)	13.25
6	Drug content (%)	100.1

Table 7: In-vitro drug release study of rilpivirine solid dispersions tablet.

Time (mins)	Plain Drug	Solid dispersion tablet (1:3)
	% Drug Released	% Drug Released
0	0.000	0.000
15	20.750	29.273
30	40.457	50.608
45	68.052	81.560
60	84.610	99.163
90	84.463	92.393

CONCLUSION

The solid dispersion was prepared by Rilpivirine: PEG 6000 in 1:2, 1:3, 1: 4 ratio by microwave irradiation method. The solubility of rilpivirine was found to be more in PEG 6000 in 0.1N HCl. The dissolution rate of rilpivirine from all solid dispersion was significantly higher than that of pure drug. IR studies indicated that no chemical interaction between drug and polymer takes place during preparation of solid dispersion of rilpivirine. The solid dispersion showed that the highest dissolution was observed with PEG 6000 in ratio 1:3 as compared to other ratios. Thus solid dispersion with PEG 6000 in ratio 1:3 was selected for tablet formulation and was compressed into immediate release tablets. The formulated tablets were found satisfactory with respect to physical parameters such as thickness, hardness, friability and drug content. The dissolution studies from formulated tablets exhibited almost expected dissolution behaviour. The tablets also complied with test for uniformity of weight and disintegration time.

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