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An Approach to Enhance Dissolution Rate of Rilpivirine By Solid Dispersion Technique

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Abstract

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor. The objective of the present investigation is to improve the dissolution rate and solubility of rilpivirine, a poorly water soluble drug by solid dispersion technique using hydrophilic carriers' viz., PEG 8000 and skimmed milk powder (SKM). The approaches described are kneading and solvent evaporation method at two different ratios i.e., 1:1 and 1:3. The prepared solid dispersions were evaluated for % yield, drug content, solubility and *in vitro* drug release as well as interaction studies by FTIR, DSC and powder XRD. The FTIR studies reveals there is no interaction between drug and polymer but the crystallinity was modified to a greater extent justified with DSC and XRD results. One-way ANOVA was used to test the statistical significant difference between rilpivirine and solid dispersions. The DP60 and DE60 values of solid dispersions prepared by kneading and solvent evaporation method are significantly higher ($P<0.05$) when compared to DP60 and DE60 values of pure rilpivirine. The optimised solid dispersions were compressed into tablets. The precompression blend indicated good to fair flowability and compressibility. The formulated tablets were evaluated for various quality control parameters. The tablets passed all the tests. Optimised tablets were subjected to accelerated stability studies for 6 months according to ICH guidelines. The results were found to be satisfactory. Overall the rank order of improvement in dissolution properties of pure rilpivirine was polymer dependent viz., PEG 8000>SKM; method dependent SE > KM > pure drug and ratios in the order 1:3 > 1:1.

Keywords: DSC, FTIR, *In vitro* dissolution, PEG 8000, Rilpivirine, Skimmed milk powder, XRD.

INTRODUCTION

In recent years, the number of poorly soluble drug candidates has increased tremendously; formulation of such poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. Poorly water soluble drug with poor solubility and low dissolution rate is a reason for its poor bioavailability. Limited aqueous solubility of the active pharmaceutical ingredient can result in poor bioavailability, which is a major issue for the pharmaceutical industry [1, 2]. Most useful methods to overcome the inherent difficulties associated with the formulation and development of a poorly water soluble drug is to enhance the solubility of the same. In such case, formulators endeavors toward searching for a way to improve the absorption of a drug by increasing its dissolution rate, the rate limiting step for absorption of many drugs. Among the methods of increasing the dissolution rate, those used most are increasing the surface area by micronization, increasing the wettability of the drug by incorporation of surfactants and using different carriers to diminish electrostatic forces. The solubility of poorly water soluble drugs can be improved by incorporating the drug in a matrix of the hydrophilic carrier(s) obtaining a product called a solid dispersion. In1961 Sekiguchi and Obi [3] developed the method of preparing solid dispersions to reduce the particle size of drugs and subsequently these mixtures were studied in detail [4-7]. Generally solid dispersions of poorly water soluble drugs have revealed remarkably higher availability [8-10] due to the fact that solid dispersions combine the benefits of both a local increase in the solubility and a maximization of the surface area of the drug that comes in contact with the dissolution medium as the carrier dissolves. Traditionally, the carriers used have been water soluble or water miscible polymers such as polyethylene glycols [11], polyvinylpyrrolidone [12] or low molecular weight materials such as sugar[13] Recently other polymers have been reported such as Eudragit® [14], carbomers [15], cellulose derivatives [16], Gelucires® [17] and skimmed milk powder [18-21].

Rilpivirine is non nucleoside reverse transcriptase inhibitor (NNRTI) which is used for the treatment of HIV-1 infections in treatment-naive patients. It is a diarylpyrimidine, a class of molecules that resemble pyrimidine nucleotides found in DNA. Rilpivirine is classified as a BCS class II compound [22]. Although rilpivirine has gained acceptance in the treatment of HIV infection, it is characterized with poor solubility which limits its absorption and dissolution rate which delays onset of action [23]. The chemical structure of rilpivirine is shown in figure 1.

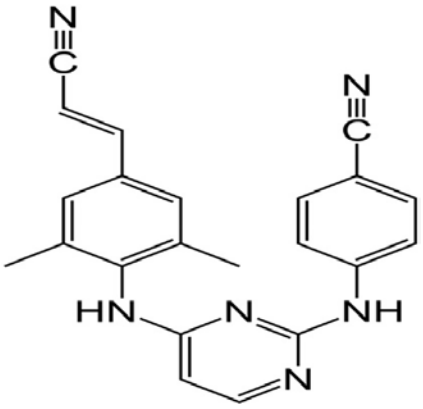

Figure 1: Structure of Rilpivirine

In the present work, solid dispersion systems of rilpivirine were prepared using carriers viz., PEG 8000 and Skimmed milk powder by kneading and solvent evaporation approach at 1:1 and 1:3 w/w ratios. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and Powder X-ray diffraction (XRD) were used to characterize the solid-state properties of rilpivirine and solid dispersions. The aqueous solubility and dissolution behaviour of rilpivirine SDs were evaluated further.

MATERIALS AND METHODS

Materials

Rilpivirine (RPV) was a gift sample from Strides Pharma Ltd., Bangalore, India. PEG 8000 was obtained from Micro Labs Ltd, Bengaluru, India. All other reagents and solvents used were of analytical grade.

Methods

Preparation of solid dispersions: The following dispersion systems of rilpivirine were prepared at 1:1 and 1:3 w/w ratios.

Kneading method (KM): PEG 8000/ skimmed milk powder with rilpivirine at 1:1 and 1:3 w/w ratios were triturated in glass mortar with small volume of dichloromethane. The thick slurry was kneaded for 1h and then dried at 45^0C until dryness. The dried mass was pulverized and sieved through sieve no.120 and stored in a desiccator for further evaluation.

Solvent evaporation method (SE): The aqueous solution of PEG 8000 /skimmed milk powder at 1:1 and 1:3 w/w ratios were dispersed into a solution of rilpivirine dissolved in dichloromethane. The resulting mixture was stirred for 1h and evaporated under vacuum until dry. The dried mass was pulverized and sieved through sieve no.120 and stored in a desiccator for further evaluation.

Detection of solid dispersion systems in solution state

Drug content uniformity: In each case solid dispersion systems equivalent to 50mg of rilpivirine was accurately weighed and transferred to 100ml volumetric flask. 20ml of dried methanol was added and shaked for 30min to extract the rilpivirine. The volume was made up to 100ml with 0.01N HCl. From this 1ml is appropriately diluted with 0.01N HCl, measure the absorbance at 280nm. The drug content was calculated using the calibration curve.

Solubility studies: Excess amount of the rilpivirine were added in a series of 25ml stopper flask containing 0.5-2.5% w/v of PEG 8000 and skimmed milk powder solutions. The solutions were shaken for 48h intermittently in rotary flask shaker to assist the attainment of equilibrium with the undissolved drug particles. Then measured quantities of the filtered drug solution was withdrawn after 48h and appropriately diluted with 0.01N HCl for rilpivirine and were measured using UV spectrophotometer and amount of rilpivirine dissolved were calculated from the calibration curve.

Detection of solid dispersion systems in solid state

Fourier transformation infrared spectroscopy (FTIR): Fourier transform IR spectra were recorded on a Shimadzu FTIR-281-spectrophotometer. The spectra were recorded for rilpivirine, PEG 8000, skimmed milk powder and solid dispersion systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of $5.2Tcm^{-2}$ for 3 min. The scanning range was 450- $4000cm^{-1}$ and the resolution was $1cm^{-1}$.

Differential scanning calorimetry (DSC): DSC measurements were performed on a Shimadzu DSC-50 differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (1mg of rilpivirine or equivalent) were placed in sealed aluminium pans, before heating under nitrogen flow (20ml/min) at a scanning rate of $10^oC\ min^{-1}$, from 25^oC to 300^oC. An aluminium pan was used as reference.

X-Ray diffractometry (XRD): The powder X-ray diffraction patterns of rilpivirine, PEG 8000, skimmed milk powder, and solid dispersion systems were recorded by using Philips X-ray powder diffractometer (model PW 1710) employing Cu-K_α-radiation. The samples were analysed in the 2θ angle range of 5-50^o and the process parameter were set as; scan step time of 1.25s and time of acquisition of 1h.

Dissolution studies: *In vitro* dissolution studies of pure rilpivirine and its solid dispersion systems were carried out in 900ml of 0.01N HCl using a USP XXII type 2 dissolution rate apparatus by the powder dispersed amount method (powder samples were spread over the dissolution medium). Samples equivalent to 50mg of rilpivirine, speed of 50rpm and a temperature of 37^0C were used in each test. A 5ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5ml of fresh dissolution medium to maintain the sink condition. The filtered samples were suitably diluted, if necessary, and assayed for rilpivirine by measuring the absorbance at 280nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0, statistical evaluation by Graph Pad Prism V5.0 and Graph Pad Instant V3.0.

Formulation and evaluation of Rilpivirine tablets:

Fabrication of optimised formulations of rilpivirine solid binary and solid dispersion systems were designed using suitable excipients. Precompression evaluation studies for tablets were performed for the following parameters: Bulk density**,** tapped density, angle of repose, compressibility index, Carr's index and Hausner's Ratio. Postcompression evaluation studies for tablets were performed for the following parameters: Thickness, diameter, hardness test, weight variation, friability test, disintegration time, drug content uniformity and *In vitro* release study.

***In vitro* release study:** *In vitro* drug release studies were carried out for rilpivirine tablets using USP XXII dissolution apparatus type I under standard conditions. The dissolution medium consisted of 900 ml of 0.01N HCl solution at 60rpm and at 37 ± 0.5 °C. The drug release at different time intervals was measured at 280nm using a double beam UV spectrophotometer. The study was conducted in triplicate and data were computed by using dissolution software PCP Disso V3.0.

Stability studies: Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines. All the

selected formulations were subjected to short-term stability testing for 6 months as per ICH norms at a temperature of 400±20C/75%±5%RH and refrigerated at 50±30C. All selected formulations were analysed for the % drug content and *in vitro* dissolution study as mentioned in table 9 and 10.

Table 1: Formula of rilpivirine and its solid dispersion systems prepared with PEG 8000 and skimmed milk powder.

BATCH CODE	Drug	Polymer	Ratio	Method
F1	Rilpivirine	PEG 8000	1:1	KM
F2	Rilpivirine	PEG 8000	1:3	KM
F3	Rilpivirine	PEG 8000	1:1	SE
F4	Rilpivirine	PEG 8000	1:3	SE
F5	Rilpivirine	Skimmed milk powder	1:1	KM
F6	Rilpivirine	Skimmed milk powder	1:3	KM
F7	Rilpivirine	Skimmed milk powder	1:1	SE
F8	Rilpivirine	Skimmed milk powder	1:3	SE

RESULTS

Percentage yield and drug content: The percentage yield and drug content were calculated for solid dispersion systems using standard methods.

Solubility studies: The solubility studies of rilpivirine and its solid dispersion systems were conducted and the results were given in figure 2.

Saturation solubility studies: The saturation solubility studies of rilpivirine and its solid dispersion systems were conducted and the results were given in the figures 3 and 4.

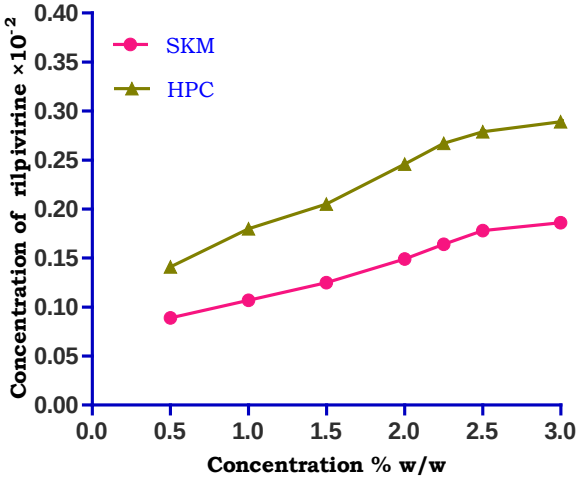

Figure 2: Solubility profile of rilpivirine in PEG 8000 and skimmed milk powder.

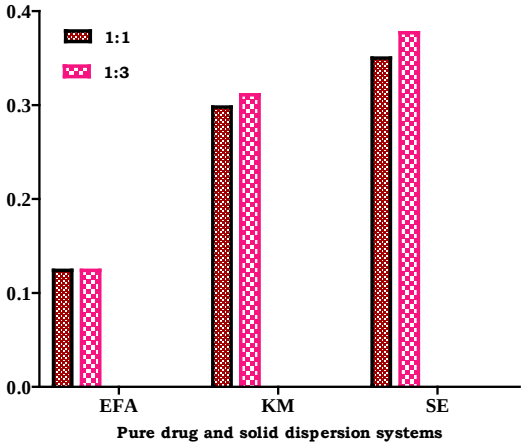

Figure 3: Saturation solubility profile of rilpivirine: PEG 8000 solid dispersion systems.

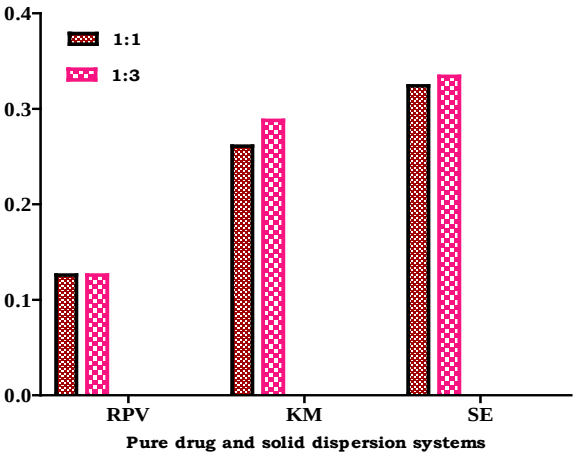

Figure 4: Saturation solubility profile of rilpivirine: skimmed milk powder solid dispersion systems.

FTIR studies: Infrared spectroscopy has been widely used to investigate drug polymer interactions in solid dispersion systems [24]. The FTIR spectrum and spectral data of pure rilpivirine and its solid dispersion systems prepared by both the methods are shown in figure 5 and table 2 respectively.

Table 2: FTIR spectral data of rilpivirine and its solid dispersion systems.

BATCH CODE	N-H stretching	C≡C Stretch	C≡NStretch
RPV	2977.76cm^{-1}	2890.38cm^{-1}	1385.04cm^{-1}
F1	2962.11 cm^{-1}	2851.47 cm^{-1}	1333.68 cm^{-1}
F2	2975.16 cm^{-1}	2897.69 cm^{-1}	1333.34 cm^{-1}
F3	2954.72 cm^{-1}	2848.49 cm^{-1}	1333.35 cm^{-1}
F4	2957.13 cm^{-1}	2892.72 cm^{-1}	1394.01 cm^{-1}
F5	2977.67 cm^{-1}	2857.13 cm^{-1}	1385.07 cm^{-1}
F6	2928.51 cm^{-1}	2861.33 cm^{-1}	1399.11 cm^{-1}
F7	2977.15 cm^{-1}	2857.14 cm^{-1}	1385.64 cm^{-1}
F8	2931.12 cm^{-1}	2871.17 cm^{-1}	1398.23 cm^{-1}

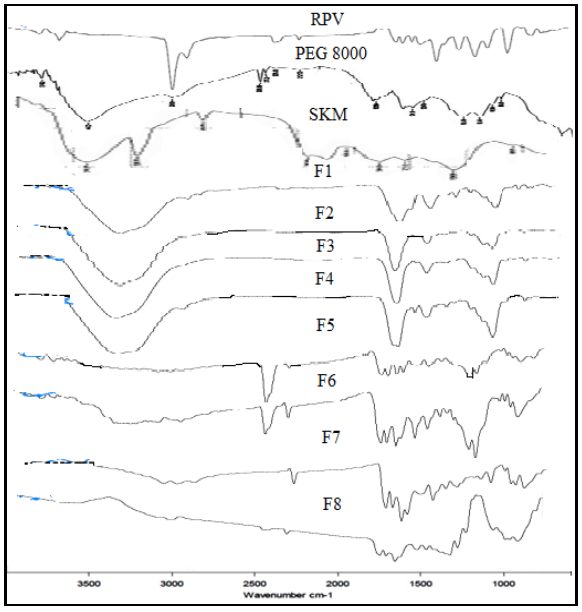

Figure 5: FTIR spectra of rilpivirine, PEG 8000, skimmed milk powder and its solid dispersion systems.

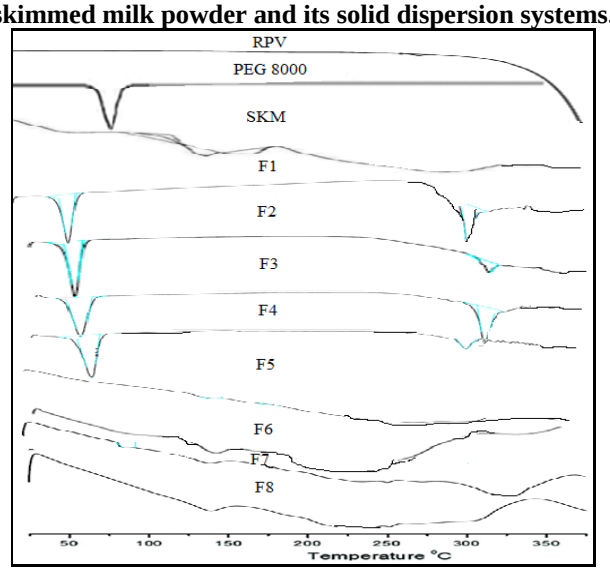

Figure 6: DSC thermograms of rilpivirine, PEG 8000, skimmed milk powder and its solid dispersion systems.

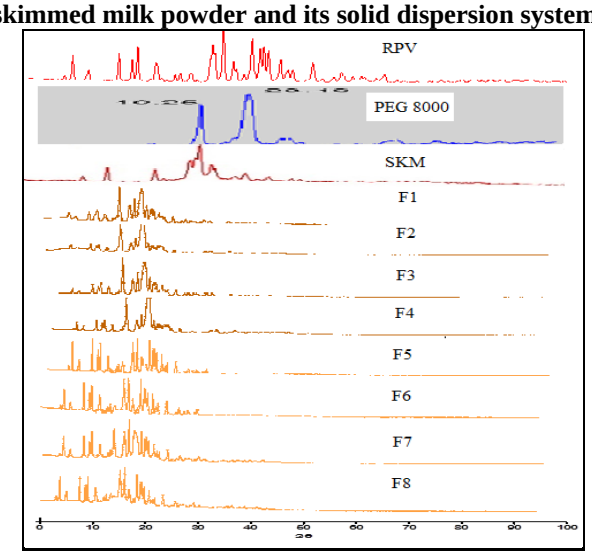

Figure 7: XRD spectra of rilpivirine, PEG 8000, skimmed milk powder and solid dispersion systems.

DSC Studies: DSC thermograms of rilpivirine and its solid dispersion systems were shown in figure 6. The DSC thermogram of rilpivirine exhibited an endothermic peak at 248.49^{o} C, similar to the peak value reported in the literature [23].

XRD studies: The compatibility between pure drug and polymers were studied by XRD. The XRD spectra of rilpivirine, PEG 8000, skimmed milk powder and solid dispersion systems were given in figure 7.

Dissolution studies: In the present investigation, dispersed amount method is used to investigate the various dissolution parameters of rilpivirine and its solid dispersion systems. The dissolution data of rilpivirine and its solid dispersion systems were studied by using dissolution software PCP DISS0 V.3.0**.** DP_{30}, DP_{60}, DE_{30}, DE_{60}, MDT_{30}, MDT_{60}, RDR_{30}, RDR_{60}, T_{50} **,** correlation coefficient (r) of best fit model values were calculated from the dissolution software and are given in table 3 and 4; the dissolution profiles are shown in figure 8 and 9. One-way ANOVA was used to test the statistical significant difference between pure drug and prepared solid dispersion systems. Significant differences in the means of DE_{30}, DE_{60}, DP_{30} and DP_{60} were tested at 95% confidence.

Table 3: Comparative in vitro dissolution data of pure drug, F1, F2, F3 and F4.

Time in Min	Cumulative percent drug release ± SD				
	RPV	F1	F2	F3	F4
DP_{30}	7.0	38.4	41.7	48.0	49.1
DP_{60}	13.4	62.1	66.0	72.9	74.1
DE_{30}	3.41	23.58	24.94	22.72	23.34
DE_{60}	6.42	37.64	39.35	39.78	40.99
MDT_{30}	13.15	12.10	13.24	14.97	15.13
MDT_{60}	29.79	24.99	26.37	26.18	25.36
RDR_{30}	1.0	6.51	7.35	7.50	7.76
RDR_{60}	1.0	5.06	5.51	5.54	5.57
T_{50}	>120	42.9	38.5	31.8	30.8
$K_1 \times 10^2$ $(min)^{-1}R$	0.9955	0.9955	0.9899	0.9909	0.9905
$K_H \times 10^2$ $(mg^{1/3}.min^{-1})R$	0.9970	0.9794	0.9790	0.9976	0.9972

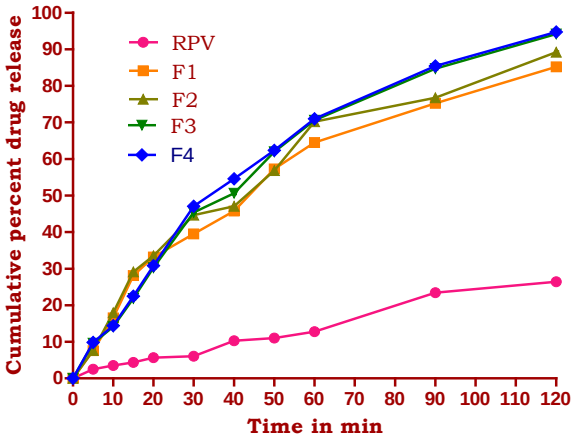

Figure 8: Comparative in vitro dissolution profile of pure drug, F1, F2, F3 and F4 solid dispersion systems.

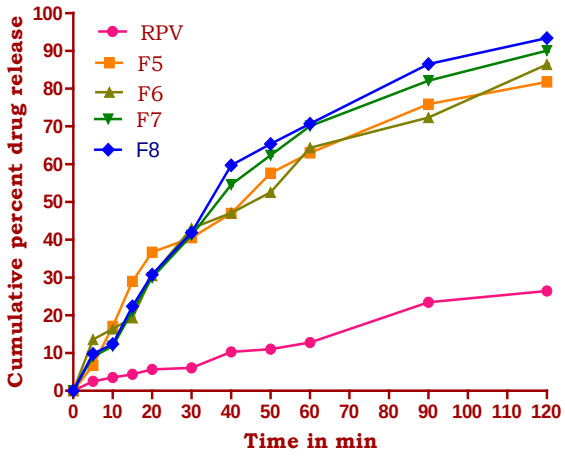

Figure 9: Comparative in vitro dissolution profile of pure drug, F5, F6, F7 and F8 solid dispersion systems.

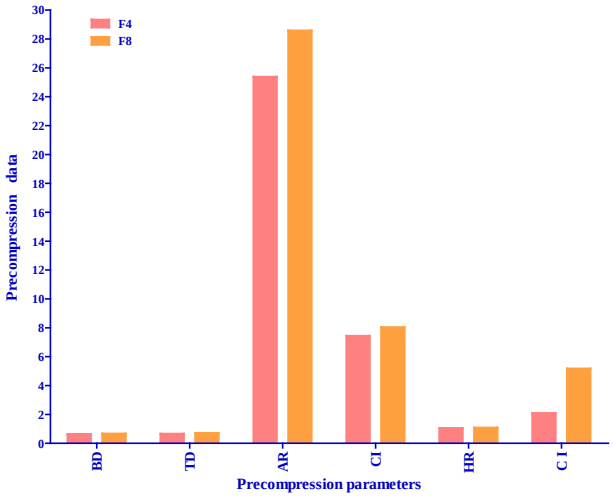

Figure 10: Precompression profiles of tablets.

Table 4: Comparative in vitro dissolution data of pure drug, F5, F6, F7 and F8 solid dispersion systems.

Time in Min	Cumulative percent drug release ± SD				
	RPV	F5	F6	F7	F8
DP_{30}	7.0	37.1	37.8	44.0	48.2
DP_{60}	13.4	60.5	61.7	68.7	73.2
DE_{30}	3.41	24.72	25.21	23.85	22.09
DE_{60}	6.42	37.04	38.42	40.68	41.27
MDT_{30}	13.15	11.69	11.37	12.62	14.18
MDT_{60}	29.79	23.41	23.85	25.17	24.99
RDR_{30}	1.0	6.68	7.08	6.78	6.90
RDR_{60}	1.0	5.09	5.05	5.50	5.55
T_{50}	>120	>120	>120	35.8	31.6
$K_1\times10^2$ $(min)^{-1}R$	0.9955	0.9869	0.9935	0.9986	0.9965
$K_H\times10^2$ $(mg^{1/3}.min^{-1})R$	0.9970	0.9616	0.9831	0.9855	0.9923

Table 5: Formulae of rilpivirine solid dispersion tablets.

Ingredient	F4	F8
SDS equivalent to 25mg	100	100
Lactose (mg)	100	100
Magnesium stearate (mg)	2	2
Talc (mg)	2	2
Galen IQ (mg)	200	200
TOTAL WEIGHT (mg)	400	400

Table 6: Precompression evaluation parameters.

Batches	BATCH SIZE 50 TABLETS					
	Bulk density (gm/cc)	Tapped Density (gm/cc)	Repose Angle	CI	H Ratio	Carr's index
F4	0.6364	0.6499	25°37'	7.43	1.044	2.08
F8	0.6611	0.6971	28°57'	8.03	1.074	5.16

Table 7: Postcompression evaluation data.

Batch Code	Diameter in mm±SD	Thickness in mm±SD	% Drug content	Average Weight	Hardness ±SD (kg/cm^2)	Friability (%)±SD	Disintegration Time in mins ±SD
F4	10.21± 0.005	3.58± 0.005	98.71±0.19	398± 2.91	4.7± 0.13	0.157± 0.0005	16.01± 0.01
F8	10.24± 0.005	3.68± 0.005	98.94±0.58	400± 2.02	4.75± 0.14	0.135± 0.0005	14.16± 0.04

Table 8: Comparative in vitro dissolution data of pure drug, F4 tablet and F8 tablet.

Time in min	Cumulative percent drug release ± SD		
	RPV	F4	F8
DP_{60}	13.4	73.0	69.4
DE_{60}	6.42	41.06	39.76
MDT_{60}	29.79	25.13	26.72
RDR_{60}	1.0	5.54	5.62
T_{50}	>120	31.8	35.2
$K_1 \times 10^2$ $(min)^{-1}R$	0.9955	0.9962	0.9982
$K_H \times 10^2$ $(mg^{1/3}.min^{-1})R$	0.9970	0.9929	0.9893

Table 9: Stability studies data at $40^0 \pm 2^0$C/75%±5%RH

Formulation	F4				F8			
Storage condition	$40^0 \pm 2^0$C/75%±5%RH							
Storage period	Initial	1 M	3M	6M	Initial	1 M	3M	6M
Physical appearance	Good	Good	Good	Good	Good	Good	Good	Good
Moisture content (%)	1.4± 0.16	1.5± 0.48	1.5± 0.19	1.5± 0.02	1.4± 0.12	1.5± 0.34	1.5± 0.17	1.5± 0.34
Drug content (%)	98.69± 0.34	96.90± 0.15	95.65± 0.35	94.18± 0.07	99.11± 0.08	97.25± 0.24	96.41± 0.34	95.62± 0.16
Dissolution (%) at 90 mins	85.44±0.4	83.06± 0.13	82.61± 0.45	81.94± 0.36	86.47± 0.16	84.50± 0.42	83.37± 0.15	82.11± 0.08

Table 10: Stability studies data at $5^0 \pm 3^0$C

Formulation	F4				F8			
Storage condition	$5^0 \pm 3^0$C							
Storage period	Initial	1 M	3M	6M	Initial	1 M	3M	6 M
Physical appearance	Good	Good	Good	Good	Good	Good	Good	Good
Drug content (%)	98.69± 0.34	96.73± 0.3	95.68± 0.08	94.51± 0.2	99.11±0.08	97.51± 0.12	96.36± 0.31	95.58±0.27
Dissolution (%) at 90 mins	85.44± 0.4	83.57± 0.08	82.82± 0.17	81.90± 0.28	86.47± 0.16	84.48± 0.13	83.56± 0.25	82.34±0.08

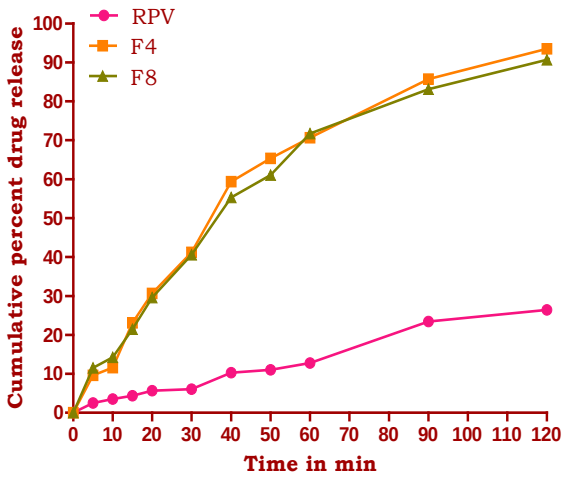

Figure 11: Comparative *in vitro* dissolution profile of pure drug, F4 tablet and F8 tablet.

DISCUSSION

Drug content uniformity: we found a uniform distribution of the drug, which corresponded to a 98-99% recovery rate of the amount that was added to the formulations. Across all experiments, the percentage of drug recovery ranged from 96 ± 0.15% to 98 ± 0.15%.

Solubility studies: The solubility studies of pure rilpivirine were studied and compared with the solid dispersion systems. The solubility of rilpivirine is linear with respect to the ratio of the polymer, type of polymer and is also dependent on method adapted for the preparation of solid dispersion systems. The results suggest in rilpivirine solid dispersion systems that the solubility was in following rank order.

1:3 >1:1; PEG 8000 > Skimmed milk powder>; SE>KM> Pure drug.

These results were indicative of *in vitro* drug release from the solid dispersion systems.

FTIR studies: The FTIR characteristic rilpivirine bands are –NH stretching at 2977.76cm^{-1}, Aryl-CH_3 stretching at 2890.38cm^{-1}, C=O stretching at 1385.04cm^{-1}. Important vibrations detected in the spectrum of PEG 8000 were the

C-H stretching at 2895 cm-1 and the C-O stretching at 1110 cm^{-1}.

In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using PEG 8000 at 1.1 and 1:3 ratios, Aryl-CH_3 stretching of the rilpivirine is shifted towards slightly lower wavelength i.e., 2847.63 cm^{-1} to 2897.69 cm^{-1}. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using PEG 8000 at 1.1 and 1:3 ratios, C=O stretching of the rilpivirine is shifted towards slightly lower to higher wavelength i.e., 1333.34 cm^{-1} to 1394.01 cm^{-1}. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using PEG 8000 at 1.1 and 1:3 ratios , N-H stretching of the rilpivirine is shifted towards slightly lower to higher wavelength i.e., 2957.13 cm^{-1} to 2975.16 cm^{-1} respectively.

In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using skimmed milk powder at 1.1 and 1:3 ratios, Aryl-CH_3 stretching of the rilpivirine are shifted towards slightly lower wavelength i.e., 2857.13 cm^{-1} to 2871.17 cm^{-1}. The spectra of solid dispersion systems prepared with skimmed milk powder by both the methods at 1:1 ratio of drug and polymers, were equivalent to the addition spectrum of pure drug, indicating no interaction. However in the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using skimmed milk powder at 1:3, C=O stretching of the rilpivirine is shifted towards slightly higher wavelength i.e., 1385.07 cm^{-1} and 1399.11 cm^{-1} respectively. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using skimmed milk powder at 1.1 and 1:3 ratios, N-H stretching of the rilpivirine is shifted towards slightly lower wavelength i.e., 2928.51 cm^{-1} to 2977.67 cm^{-1} respectively.

DSC Studies: The DSC thermogram of RPV alone shows an endothermic Tmax of 248.49 ^{0}C, corresponding to the melting point of the crystalline form of RPV. RPV melts with decomposition which starts at about 248.49 ^{0}C. In the DSC thermograms of solid dispersions of RPV with PEG 8000 and skimmed milk powder, the sharp melting point peak of pure RPV at 248.49 ^{0}C was not visible in all the cases. The characteristic features of the RPV peak were lost. This indicated that RPV was molecularly dispersed and no longer present as a crystalline material, but was converted into the amorphous state.

X-Ray diffractometry (XRD): Fig shows the overlaid XRD patterns of pure RPV, PEG 8000, skimmed milk powder and its solid dispersion systems. Rilpivirine showed characteristic diffraction peaks at two theta positions. It is evident that input RPV is in crystalline nature, PEG 8000 and skimmed milk powder are amorphous in nature. The crystallinity of RPV was significantly reduced in the skimmed milk powder systems but to a much greater extent in the PEG 8000 systems, as almost all intense peaks of pure rilpivirine had completely disappeared. The absence of peaks indicated that the drug was uniformly dispersed in the matrix material.

***Dissolution Studies*:** The results of the dissolution rate studies indicated higher dissolution rate of RPV from solid dispersion systems when compared to rilpivirine itself. The DE_{30} and DE_{60} values of the dispersion systems that were prepared by the kneading and solvent evaporation methods were relatively high when compared with the values from the RPV alone. The DE_{30} and DE_{60} values of the rilpivirine – PEG 8000 at 1:3 ratio solvent evaporated were higher than those of the systems prepared at 1:1 ratio by kneading method and systems of skimmed milk powder prepared by both the methods at 1:1 and 1:3 ratios. One-way ANOVA was used to test the statistical significance of difference between pure and prepared solid dispersion systems. Significant differences in the means of DE30 and DE60 were tested at 95% confidence. Overall the rank order of improvement in dissolution properties of rilpivirine solid dispersion systems was as follows:

1:3 >1:1; PEG 8000 > Skimmed milk powder>; SE>KM> Pure drug.

Precompression and post compression evaluation of rilpivirine tablets: The optimized rilpivirine tablets were designed, formulated and evaluated. The results of precompression data were within the permissible limits and possess good flow property, porosity and compressibility index and are suitable for direct compression. The low SD values less than 2 indicate the drug content was uniform in all the fabricated tablets. The average weight and deviation in tablets were found to be within the acceptable range. Formulated tablets passes the weight variation test as per the IP specifications. The thickness, diameter, hardness, friability and disintegration time were within the acceptable range and produce good mechanical strength. The cumulative percent drug release from the tablet prepared with solid dispersion systems using PEG 8000 shows 93.512±0.27% over the period of 120min whereas the other tablet shows 90.642±0.12 release over the period of 120min. Over all dissolution enhancement in the tablet formulated in rank order of F4>F8 for rilpivirine formulation

Stability studies: Stability studies showed no significant changes in drug content and *in vitro* dissolution results after the completion of storage period. There was no significant variation in the drug concentration ($p>0.05$). Thus it indicates that the formulations were stable and can be used satisfactorily.

CONCLUSION

In the dispersion systems of rilpivirine prepared with different hydrophilic carriers showed superior performance in enhancing aqueous solubility and the dissolution of Rilpivirine. FTIR, DSC and XRD studies of the dispersion systems of rilpivirine showed that the crystallinity of rilpivirine was decreased to a greater extent in solid dispersions, which markedly increased the aqueous solubility and dissolution rate of rilpivirine. The main factors contributed for higher solubility and release rate are such as increased wettability and conversion to amorphous state. The dissolution efficiency for all the solid dispersions is greater than 70%. Further higher and significant ($p <0.05$) DE_{30} and DE_{60} values of solid dispersion systems signified that the dispersion technique

effectively enhances the solubility of rilpivirine, which consequently increase its dissolution and bioavailability. Further optimised formulations were prepared as direct compression tablets and evaluated for various parameters. The tablets were found to have desirable physical properties and showed good stability over the period of 6 months at **$40^0 \pm 2^0$C/75%±5%RH** and **$5^0 \pm 3^0$C**. In vitro release studies showed better dissolution profile for tablets prepared with PEG 8000 solid dispersions compared to skimmed milk powder solid dispersions. Overall, our work demonstrated that solid dispersion technique is a feasible approach to enhance dissolution rate of rilpivirine.

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REFERENCES

1. Meredith, P. A., Elliott, H. L., *Clin. Pharmacokinet*. 1992, *22*, 22 – 31
2. Singh, S., Baghe, R. S., Yadav, L., *Int J Pharm Life Sci.* 2011, *2*, 1078-1095.
3. Ankit. M., Manish, Y., Dinesh, C., *Indo Am J Pharm Res.* 2014, *4*, 2855-2866.
4. Sekiguchi, K., Obi, N., *Chem Pharm Bull*. 1961, *9*, 866-872.
5. Chiou, W., Riegelman, A., *J Pharm Sci*. 1971, *60*, 1281-1302.
6. Serajuddin, T. M., *J Pharm Sci*. 1999, *88*, 1058-1066.
7. Leuner, C., Dressman, J., *Eur J Pharm and Biopharm*. 2000, *50*, 47-60.
8. Craig, D. Q. M., *Int J Pharm*. 2002, *231*, 131-144.
9. Fernández, M., Margarit, M. V., Rodriguez, I. C., Cerezo, A., *Int J Pharm*. 1993, *98*, 29-35.
10. Margarit, M. V., Rodriguez. I. C., Cerezo, A., *Int J Pharm*. 1994, 108, 101-107.
11. Cirri, M., Mura, P., Rabasco, A. M., Gines, J. M., Moyano, J. R., Gonzalez., Rodriguez, M. L., *Drug Dev Ind Pharm*. 2004, *30*, 65-74.
12. Law, D., Schmitt, E. A., Marsh, K. C., Everitt, E. A., Wang, W., Fort, J. J., Krill, S. L., Qiu, Y., *J Pharm Sci*. 2004, *93*, 563-570.
13. Marin, M. T., Margarit, M. V., Salcedo, G. E., *II Farmaco*. 2002, *57*, 723-726.
14. Zajc, N., Obreza, A., Bele, M., Srcic, S., *Int J Pharm*. 2005, *291*, 51-58.
15. Pignatello, R., Spadaro, D., Vandelli, M. A., Forni, F., Puglisi, G., *Drug Dev Ind Pharm*. 2004, *30*, 277-288.
16. Ozeki, T., Yuasa, H., Kanata, Y., *J Controlled Release*. 2000, *63*, 287-295.
17. Goracinova, K., Klisarova, Ll., Simov, A., *Drug Dev Ind Pharm*. 1995, *21*, 383-391.
18. Damian, F., Blaton, N., Naesens, L., Balzarini, J., Kinget, R., Augustijns, P., Vanden M. G., *Eur J Pharm Sci*. 2000, *10*,311-322.
19. Purnima, V., Munish, A., Meenakshi, B., *Der Pharmacia Lettre*. 2016, *8(10)*, 55-64.
20. Sonar, P. A., Behera, A. L., Banerjee, S. K., Gaikwad, D. D., Harer, S. L., *J Drug Dev and Ind Pharm*. 2015, *41(1)*, 22-27.
21. Ankush, C., Avtar, C. R., Geeta, A., Virender, K., Foziyah, Z., *Acta Pharmaceutica Sinica B*. 2012, *2(4)*, 421–428.
22. Shivangi, M., Akankasha, M., *Int J Drug Res Tech*. 2015, *5(2)*, 81-102.
23. Reddiah et al., *Int J Pharm Pharm Sci.* 2012, *4(3)*, 595-599.
24. Pavan, K. et al., *Beni Suef Uni J Basic App Sci*. 2015, *4*, 71-9.
25. Rumondor, A. C., Marsac, P. J., Stanford, L. A., Taylor, L. S., *MolPharm*. 2009, *6(5)*, 1492-1505.