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FORMULATION DEVELOPMENT AND DISSOLUTION RATE ENHANCEMENT OF RILPIVIRINE BY SOLID DISPERSION SYSTEMS

Bharati Arali[1]*, Anand Kumar Y.[2], Mallikarjuna Setty C.[3]

[1*]Department of Pharmaceutics, East West College of Pharmacy, Bengaluru, Karnataka, India.
[2]Department of Pharmaceutics, V.L.College of Pharmacy, Raichur, Karnataka, India.
[3]Department of Pharmaceutics, Oxford College of Pharmacy, Bengaluru, Karnataka, India.

***Corresponding Author: Bharati Arali**

Department of Pharmaceutics, East West College of Pharmacy, Bengaluru, Karnataka, India.

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ABSTRACT

The aim of this study was to enhance the dissolution rate of rilpivirine (RPV) using solid dispersion systems. A comparison between kneading and solvent evaporation method was also investigated. Solid dispersions of rilpivirine were prepared using poloxamer 407 and HPC at 1:1 and 1:3 w/w ratios. Dissolution tests were conducted and evaluated on the basis of cumulative percentage drug release and dissolution efficiency. Physicochemical characterizations of the solid dispersions were carried out using Fourier transform infrared spectroscopy, differential scanning calorimetry and powder X‑ray diffraction. Dissolution was remarkably improved in both systems compared to pure rilpivirine (P<0.05). Physicochemical characterization results suggested that rilpivirine existed in the amorphous form in the entire solid dispersion systems providing evidence of improvement in dissolution. Formulations of rilpivirine solid dispersion systems prepared using poloxamer 407 by solvent evaporation method showed best dissolution profile and 1:3 were identified as an optimum drug‑polymer weight ratio. 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 $40^0\pm2^0$C/75%±5%RH and $5^0\pm3^0$C. Thus the present study demonstrated that poloxamer 407 as carrier and solvent evaporation technique is a highly effective strategy for enhancing the bioavailability of poorly water soluble rilpivirine.

KEYWORDS: Solid dispersion, rilpivirine, dissolution enhancement, poloxamer 407, HPC.

INTRODUCTION

Rilpivirine, 4-{[4-({4-[(E)-2-cyanovinyl]-2, 6-dimethylphenyl} amino) pyrimidin-2-yl] amino} benzonitrile is a pharmaceutical drug used for the treatment of HIV infection. It is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with higher potency, longer half-life and reduced side-effect profile compared with older NNRTIs, such as efavirenz.[1,2] 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.[3,4] The chemical structure of rilpivirine is shown in Fig. 1. According to the Biopharmaceutical Classification System (BCS), most of the drugs exhibiting insolubility belong to BCS class II. This class includes drugs having low water solubility with high membrane permeability. For this reason dissolution will be the rate-limiting step in drug absorption from the oral solid dosage forms of this class.[5] Current statistics report that about 40% of new chemical entities (NCEs) are known to belong to the biopharmaceutics classification systems (BCS) class II type of molecules with poor solubility and high permeability properties.[6,7] Rilpivirine is classified as a BCS class II compound.[8] Different solubility and dissolution enhancement techniques are applied such as inclusion complexation[9], drug micronization in to amorphous form[10], prodrug formation[11] and solid dispersion.[12-15] Among these methods, solid dispersion technique is most frequently used.

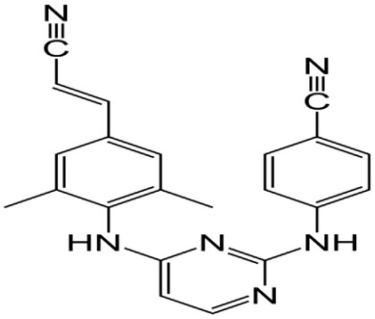

Figure 1: Structure of Rilpivirine.

The aim of this work was to improve the aqueous solubility and dissolution of rilpivirine (RPV) by solid dispersion techniques such as kneading and solvent evaporation methods using hydrophilic carriers' viz., poloxamer 407 and HPC 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. Poloxamer 407 and HPC were 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): Poloxamer 407/ HPC 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 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.

Table 1: Formula of rilpivirine and its solid dispersion systems prepared with Poloxamer 407 and HPC.

BATCH CODE	Drug	Polymer	Ratio	Method
F1	Rilpivirine	Poloxamer 407	1:1	KM
F2	Rilpivirine	Poloxamer 407	1:3	KM
F3	Rilpivirine	Poloxamer 407	1:1	SE
F4	Rilpivirine	Poloxamer 407	1:3	SE
F5	Rilpivirine	HPC	1:1	KM
F6	Rilpivirine	HPC	1:3	KM
F7	Rilpivirine	HPC	1:1	SE
F8	Rilpivirine	HPC	1:3	SE

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 Poloxamer 407 and HPC 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 measuredusingUVspectrophotometer 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, Poloxamer 407, HPC 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, Poloxamer, HPC, 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.

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 Fig. 2.

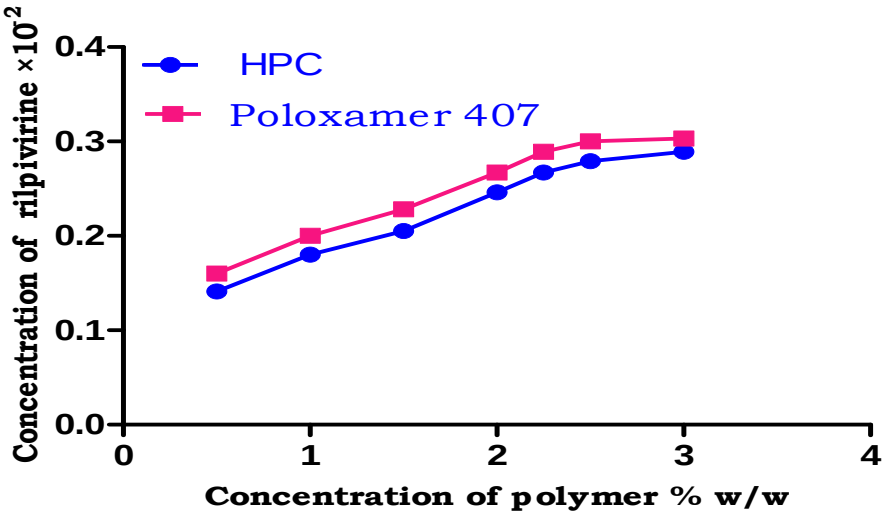

Figure 2: Solubility profile of rilpivirine in Poloxamer 407 and HPC.

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

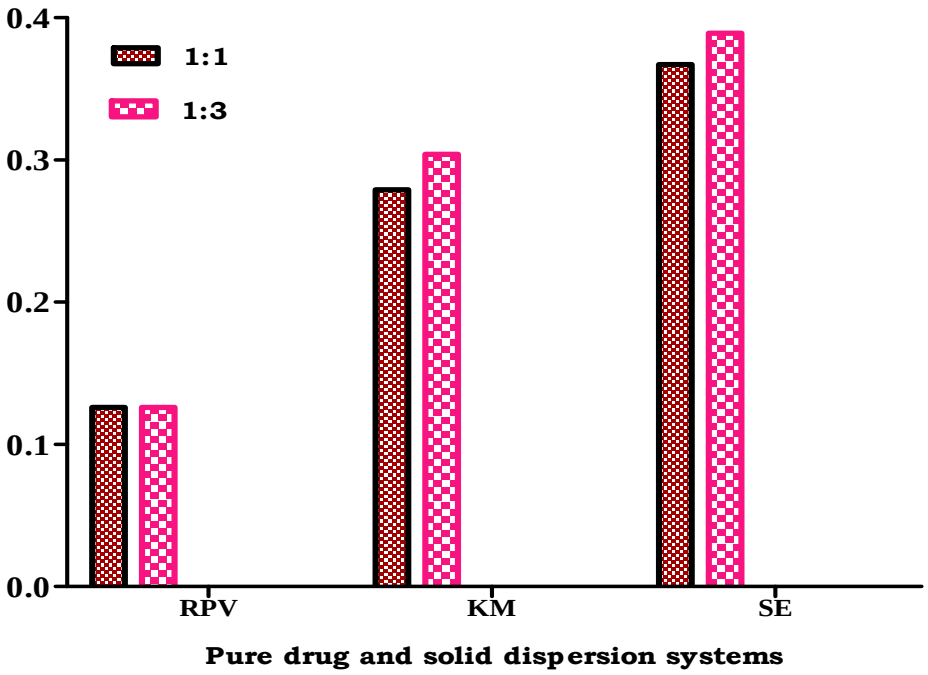

Figure 3: Saturation solubility profile of rilpivirine: Poloxamer 407 solid dispersion systems.

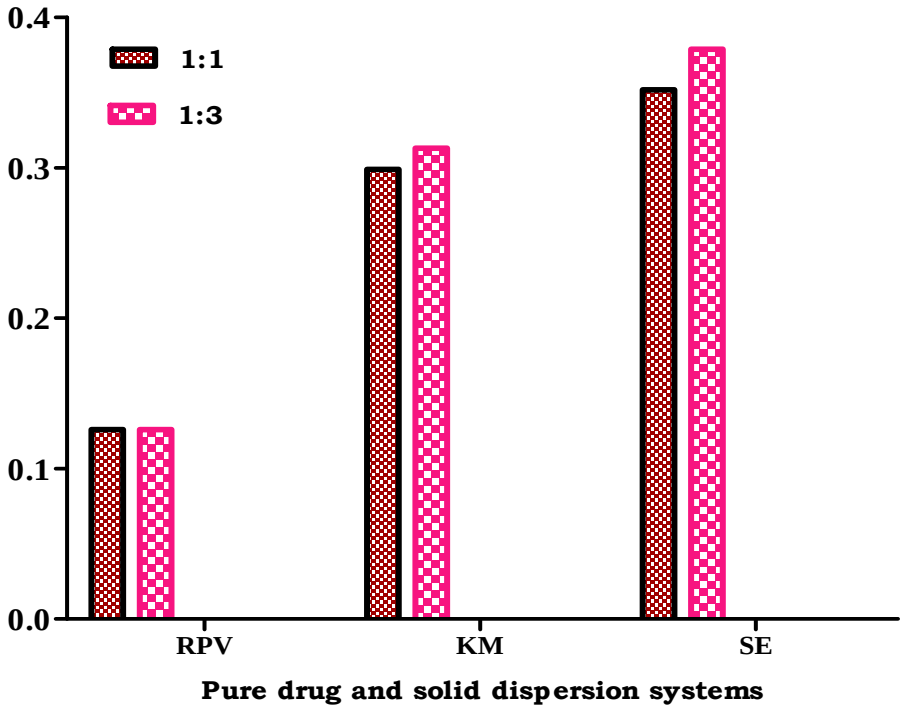

Figure 4: Saturation solubility profile of rilpivirine: HPC solid dispersion systems.

FTIR studies: Infrared spectroscopy has been widely used to investigate drug polymer interactions in solid dispersion systems.[16] The FTIR spectrum and spectral data of pure rilpivirine and its solid dispersion systems prepared by both the methods are shown in Fig. 5 and table 2 respectively**.**

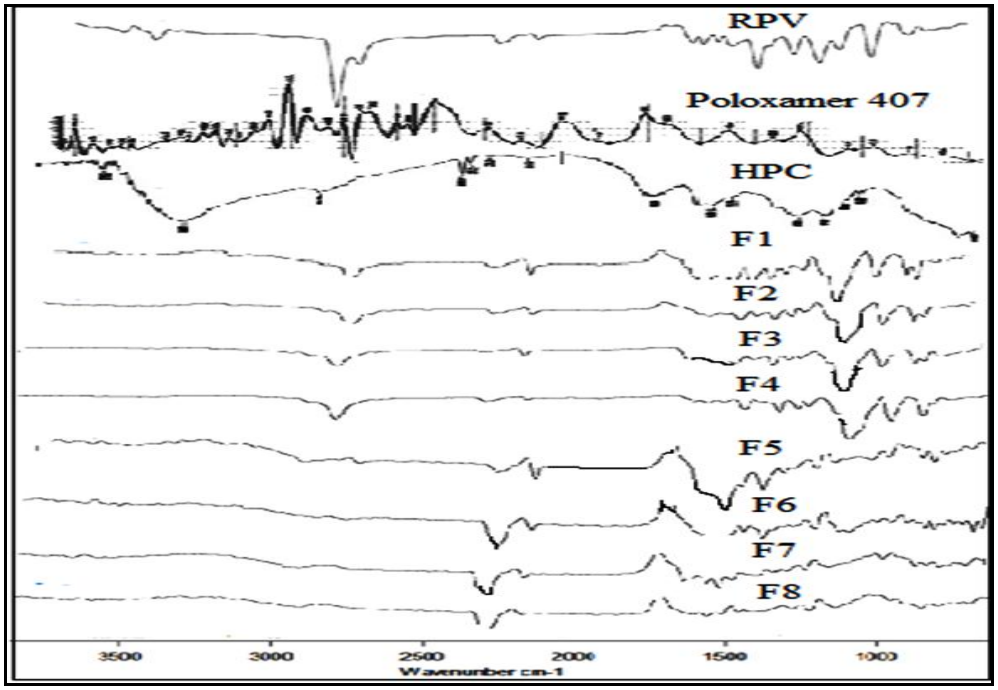

Figure 5: FTIR spectra of F5, F6, F7 and F8.

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

BATCH CODE	N-H stretching	C≡C Stretch	C≡N Stretch
RPV	2977.76cm^{-1}	2890.38cm^{-1}	1385.04cm^{-1}
F1	2970.08 cm^{-1}	2875.89 cm^{-1}	1337.30 cm^{-1}
F2	2970.34 cm^{-1}	2876.27 cm^{-1}	1340.82 cm^{-1}
F3	2974.51 cm^{-1}	2880.12 cm^{-1}	1337.86 cm^{-1}
F4	2979.13 cm^{-1}	2880.01 cm^{-1}	1341.33 cm^{-1}
F5	2917.06 cm^{-1}	2843.39 cm^{-1}	1334.90 cm^{-1}
F6	2975.60 cm^{-1}	2874.74 cm^{-1}	1377.67 cm^{-1}
F7	2991.24 cm^{-1}	2779.97 cm^{-1}	1334.95 cm^{-1}
F8	2993.08 cm^{-1}	2869.52 cm^{-1}	1383.81 cm^{-1}

***DSC Studies*:** DSC thermograms of rilpivirine and its solid dispersion systems were shown in Fig. 6. The DSC thermogram of rilpivirine exhibited an endothermic peak at 248.49^{o} C, similar to the peak value reported in the literature.[17]

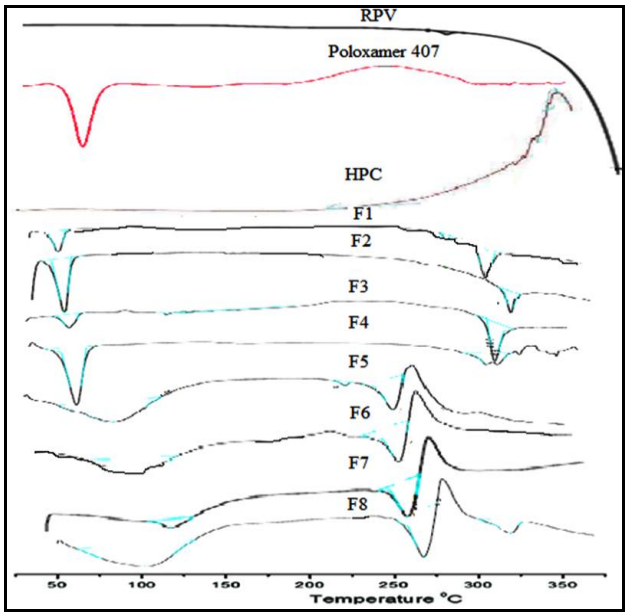

Figure 6: DSC thermograms of rilpivirine, poloxamer 407, HPC and its solid dispersion systems.

XRD studies: The compatibility between pure drug and polymers were studied by XRD. The XRD spectra of rilpivirine, poloxamer 407, HPC and solid dispersion systems were given in Fig. 7.

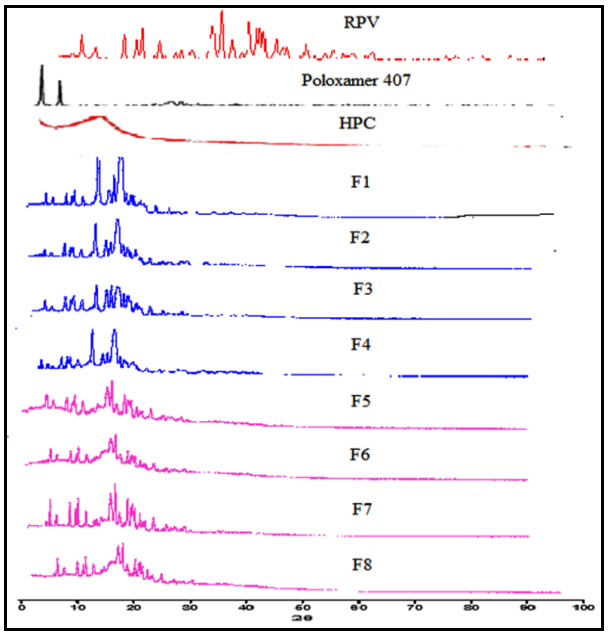

Figure 7: XRD spectra of rilpivirine, poloxamer 407, HPC and solid dispersion systems.

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 Fig. 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 rilpivirine, F1, F2, F3 and F4.

Time in Min	Cumulative percent drug release ± SD				
	RPV	**F1**	**F2**	**F3**	**F4**
DP_{30}	7.0	46.0	52.4	48.3	58.4
DP_{60}	13.4	70.8	77.4	73.3	82.7
DE_{30}	3.41	24.28	25.11	23.07	26.66
DE_{60}	6.42	41.48	42.60	40.79	45.58
MDT_{30}	13.15	14.64	14.20	15.44	14.53
MDT_{60}	29.79	25.43	25.86	25.38	24.20
RDR_{30}	1.0	7.81	8.05	7.83	8.52
RDR_{60}	1.0	5.65	5.96	5.54	5.99
T_{50}	>120	33.7	28.0	31.5	23.7
$K_1 \times 10^2$ $(min)^{-1}$ R	0.9955	0.9909	0.9953	0.9927	0.9492
$K_H \times 10^2$ $(mg^{1/3}.min^{-1})$ R	0.9970	0.9880	0.9931	0.9965	0.9912

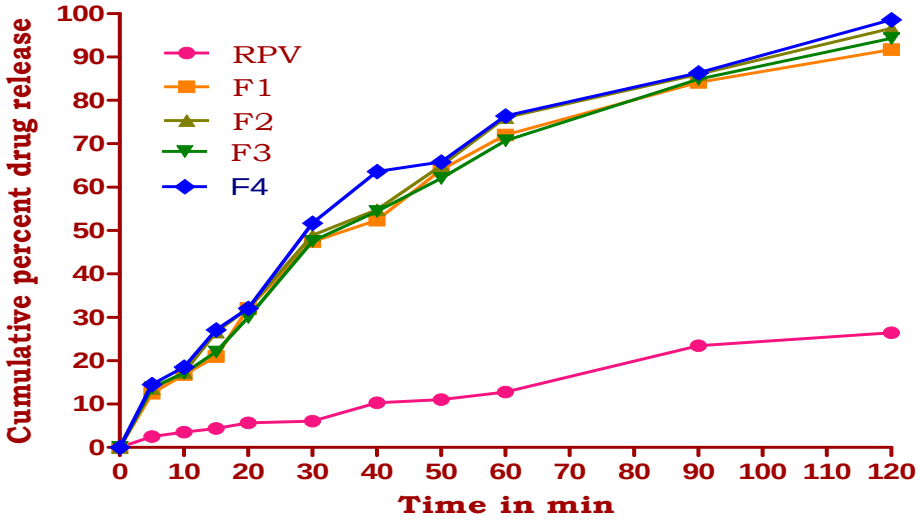

Figure 8: Comparative in vitro dissolution profile of pure drug, F1, F2, F3 and F4 solid dispersion systems.

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	36.7	37.2	42.4	45.0
DP_{60}	13.4	60.0	60.5	66.9	69.8
DE_{30}	3.41	23.98	22.48	24.37	22.42
DE_{60}	6.42	37.92	36.32	41.05	39.37
MDT_{30}	13.15	12.05	13.91	14.53	13.71
MDT_{60}	29.79	23.28	25.0	24.78	25.89
RDR_{30}	1.0	6.60	6.90	6.60	6.79
RDR_{60}	1.0	4.83	4.89	5.24	5.43
T_{50}	>120	45.9	44.6	37.7	34.8
$K_1 \times 10^2$ $(min)^{-1}$ R	0.9955	0.9870	0.9943	0.9982	0.9974
$K_H \times 10^2$ $(mg^{1/3}.min^{-1})$ R	0.9970	0.9633	0.9850	0.9857	0.9940

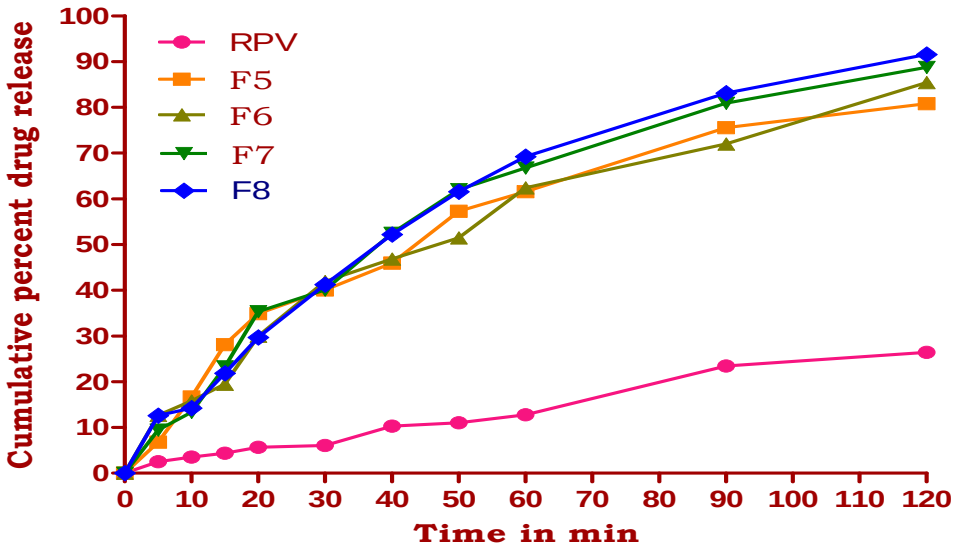

Figure 9: Comparative in vitro dissolution data of pure drug, F5, F6, F7 and F8 solid dispersion systems.

Table 5: Formulae of solid dispersion tablets.

Ingredient	F4	F8
SBS equivalent to 25mg	---	---
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	0.5892	0.6305	28°80'	6.19	1.063	6.55
F8	0.5944	0.6388	24°62'	7.12	1.031	6.95

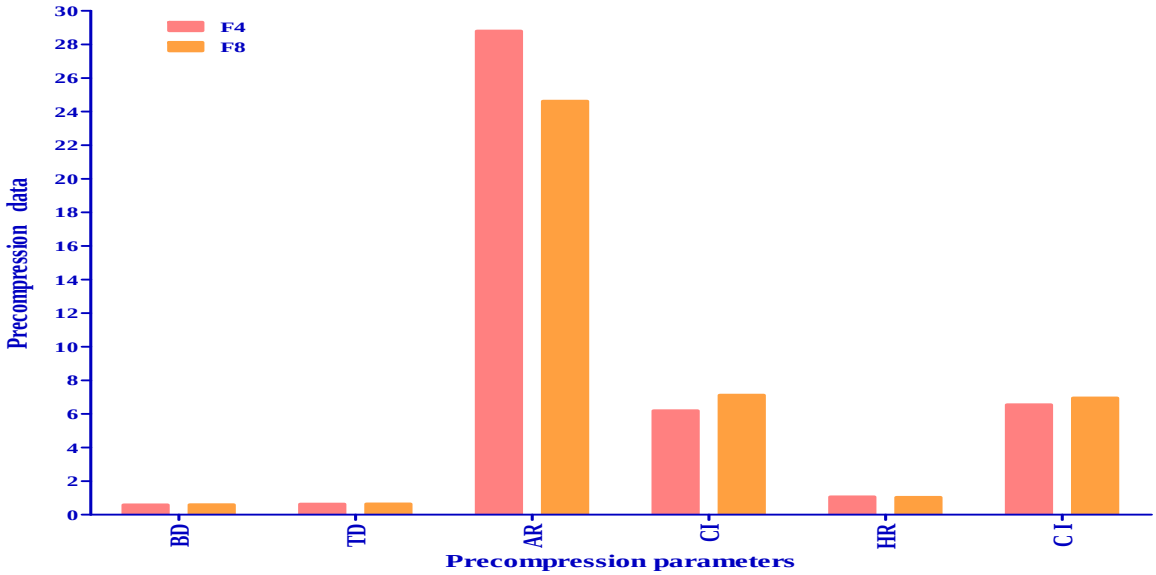

Figure 10: Precompression profiles of tablets.

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	10.13±0.005	3.71±0.005	99.11±0.41	399.±1.79	4.81±0.11	0.099±0.0005	12.68±0.03
F8	10.11±0.005	3.53±0.005	98.83±0.51	402±1.52	3.9±0.10	0.164±0.0005	17.25±0.02

Table 8: Comparative in vitro dissolution data of rilpivirine, F4 and F8 tablets.

Time in min	Cumulative percent drug release ± SD		
	RPV	F4	F8
DP_{60}	13.4	81.70	77.7
DE_{60}	6.42	47.47	47.71
MDT_{60}	29.79	22.36	22.24
RDR_{60}	1.0	5.94	5.93
T_{50}	>120	24.9	27.7
$K_1 \times 10^2$ $(min)^{-1}$ R	0.9955	0.9792	0.9992
$K_H \times 10^2$ $(mg^{1/3}.min^{-1})$ R	0.9970	0.9911	0.9827

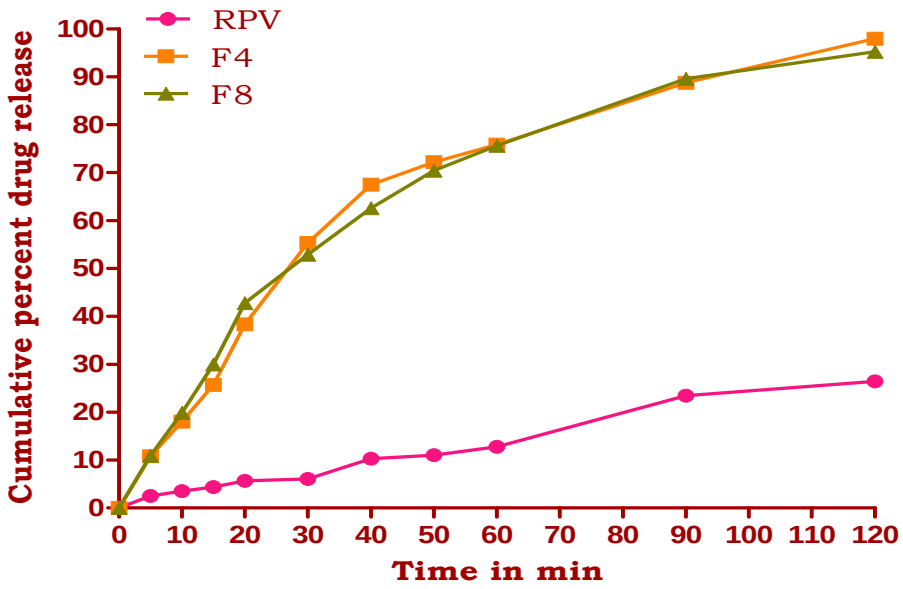

Figure 11: Comparative *in vitro* dissolution data of pure drug, F4 and F8 tablets.

Table 9.

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	6 M
Physical appearance	Good	Good	Good	Good	Good	Good	Good	Good
Moisture content (%)	1.5± 0.08	1.6± 0.2	1.6± 0.07	1.6± 0.9	1.5± 0.01	1.6± 0.25	1.6± 0.43	1.6± 0.63
Drug content (%)	98.40± 0.37	96.07± 0.42	95.29± 0.49	94.19± 0.07	98.66± 0.05	96.83± 0.27	95.17± 0.18	94.73± 0.11
Dissolution (%) at 90 mins	86.35± 0.37	84.62± 0.3	83.37± 0.14	82.21± 0.07	83.12± 0.49	81.38± 0.12	80.66± 0.31	79.31± 0.28

Table 10.

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 (%)	98.40± 0.37	96.18± 0.08	95.38± 0.42	94.27± 0.36	98.66± 0.05	96.74± 0.15	95.28± 0.41	94.08±0. 23
Dissolution (%) at 90 mins	86.35± 0.37	84.71± 0.1	83.49± 0.3	82.08± 0.2	83.12± 0.49	81.12± 0.42	80.55± 0.19	79.67±0. 34

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; Poloxamer 407> HPC>; 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}. IR spectrum of poloxamer 407 is characterized by principal absorption peaks at 2893.02 cm^{-1} (C-H stretch aliphatic), 1355.86 cm^{-1} (in-plane O-H bend) and 1124.42 cm^{-1} (C-O stretch). The FTIR absorbance of the hydroxypropyl cellulose is related by the stretching vibrations of the –OH groups located at 3600– 3100 cm^{-1}, with a maximum at 3419 cm^{-1}, by the stretching

vibrations ν(C-O-C) groups located at 1049 cm^{-1} and the bands corresponding to aliphatic groups located at 2873 cm^{-1}.

In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using Poloxamer 407 at 1.1 and 1:3 ratios, Aryl-CH_3 stretching of the rilpivirine is shifted towards slightly lower wavelength i.e., 2875.89 cm^{-1} to 2880.12 cm^{-1}. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using Poloxamer 407 at 1.1 and 1:3 ratios, C=O stretching of the rilpivirine is shifted towards slightly lower wavelength i.e., 1337.30 cm^{-1} to 1341.33 cm^{-1}. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using Poloxamer 407 at 1.1 and 1:3 ratios , N-H stretching of the rilpivirine is shifted towards slightly lower to higher wavelength i.e., 2970.08 cm^{-1} to 2979.13 cm^{-1} respectively.

In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using HPC at 1.1 and 1:3 ratios, Aryl-CH_3 stretching of the rilpivirine is shifted towards slightly lower wavelength i.e., 2779.97 cm^{-1} to 2874.74 cm^{-1}. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using HPC at 1.1 and 1:3 ratios, C=O stretching of the rilpivirine is shifted towards slightly lower wavelength i.e., 1334.90 cm^{-1} to 1383.81 cm^{-1}. In the spectra of solid dispersion systems prepared by kneading and solvent evaporation methods using HPC at 1.1 and 1:3 ratios , N-H stretching of the rilpivirine is shifted towards slightly lower to higher wavelength i.e., 2917.06 cm^{-1} to 2993.08 cm^{-1} respectively.

DSC Studies: The DSC thermograms of RPV alone show 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 poloxamer 407 and HPC, 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, poloxamer 407, HPC and its solid dispersion systems. Rilpivirine showed characteristic diffraction peaks at two theta positions. It is evident that input RPV is in crystalline nature, poloxamer 407 and HPC are amorphous in nature. The crystallinity of RPV was significantly reduced in the HPC systems but to a much greater extent in the poloxamer 407 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 – poloxamer 407 at 1:3 ratio solvent evaporated were higher than those of the systems prepared at 1:1 ratio by kneading method and systems of HPC 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; Poloxamer 407> HPC>; 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 pass 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 poloxamer 407 shows 97.930±0.36% over the period of 120min whereas the other tablet shows 95.235±0.01 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

From the above studies, it can be concluded that solubility enhancement is a major aspect in drug development. The solubility and dissolution rate of rilpivirine was enhanced by solid dispersion prepared by kneading and solvent evaporation method using poloxamer 407 and HPC as carrier at 1:1 and 1:3 ratios showed improved solubility and dissolution rate. FTIR, DSC and PXRD studies confirmed amorphization of the drug. Results of FTIR concluded that there was no

interaction between drug and polymers. The dissolution efficiency for all the solid dispersions is greater than 70%. 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 poloxamer solid dispersions compared to HPC solid dispersions. We may hence conclude that solid dispersions of rilpivirine using poloxamer 407 at 1:3 ratios by solvent evaporation method showed improved aqueous solubility and dissolution rate.

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