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Original Article

Preparation, characterization and evaluation of solid dispersions of rilpivirine

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ABSTRACT

Rilpivirine (RPV) is a pharmaceutical drug used for the treatment of HIV infection. The drug is characterized with poor aqueous solubility and dissolution rate leading to low bioavailability of the drug. Hence, there is a need for the improvement of the solubility and dissolution of such drugs. In this exertion, enhancement of the solubility and dissolution of the practically water insoluble drug Rilpivirine was achieved by solid dispersion (SD) preparation using HPC and Poloxamer by kneading method and solvent evaporation method in 1:3 and 3:1 ratios which eventually leads to bioavailability enhancement. The SD's were characterized by Fourier transform infrared spectroscopy and X-ray powder diffraction studies and also evaluated by Powder dissolution studies. It was found that the SD's formed showed the absence of crystalline nature of the drug and its conversion to amorphous state. Overall, the rank order of improvement in dissolution properties of Rilpivirine with different polymers is Poloxamer > HPC, with ratios 1:3 > 3:1 and methods SE > KNE > PM > Pure drug.

Keywords: Rilpivirine, HPC, Poloxamer, Solid dispersion, Dissolution rate.

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INTRODUCTION

The dissolution of a drug from its solid oral dosage forms depends upon its release from the dosage form and its subsequent mixing into physiological fluids. It has been estimated that nearly 35-40% of the drugs suffer from poor aqueous solubility, thereby affecting their absorption from the gastrointestinal tract, which leads to poor oral bioavailability, high intra- and inter-subject variability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development[1]. The development of solid dosage forms for water-insoluble drugs has been a major challenge for pharmaceutical scientists for decades. Various formulation strategies such as micronisation, micellar solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions or dispersions with hydrophilic carriers, self-microemulsifying drug delivery systems, spray drying, nano approaches, pro-drug approaches and salt synthesis[2] have been developed to increase the dissolution rate of water-insoluble drugs. An attractive possibility is employing a simple solid dispersion technique making use of various hydrophilic carriers [3-5]. Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state, and are prepared by the fusion, solvent or solvent- fusion method[3]. This technique enables reducing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poor water-soluble drugs that are cost-effective and significantly reduced in dosage[4,6]. It has been widely demonstrated that a hydrophilic carrier dissolves rapidly, exposing the drug particles to the dissolution medium as fine particles facilitating quick dissolution and absorption. The mechanisms for increased dissolution rate may include reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state[7,8].

One of the world's leading causes of death with a major medical and economic impact on a society is AIDS, caused by the HIV virus. Around 36 million people are infected with human immunodeficiency type-1 (HIV-1) worldwide[9]. Rilpivirine is the most recently approved NNRTI. 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. 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[10,11]. The chemical structure of Rilpivirine is shown in Fig. 1.

The aim of this work was to improve the aqueous solubility and dissolution of Rilpivirine using solid dispersion technique using hydrophilic carriers HPC and Poloxamer. Fourier transform infrared spectroscopy (FTIR) and Powder X-ray diffraction (XRD) were used to characterize the solid-state properties of Rilpivirine, the physical mixture and solid dispersions. The aqueous solubility and dissolution behaviour of Rilpivirine SD's were evaluated further.

MATERIALS AND METHODS

Materials: Rilpivrine (RPV) was a gift from Strides Arc Lab (Bengaluru, India). HPC and Poloxamer were procured from Micro Labs Ltd (Bengaluru, India). Dichloromethane was obtained from S D Fine Chemicals Ltd. All the chemicals used were of analytical reagent grade and used without further purification.

Methods

Preparation of physical mixture: Physical mixtures (PMs) of RPV in the ratio RPV: HPC (3:1) (PM1), RPV: HPC (1:3) (PM2), RPV: Poloxamer (3:1) (PM3) and RPV: Poloxamer (1:3) (PM4) were prepared by blending them for about 10 min and sieved through 500 micron mesh sieve.

Preparation of solid dispersions

Kneading method (KNE): Accurately weighed quantities of Rilpivirine, HPC and Poloxamer at 3:1 and 1:3 weight ratios were triturated in glass mortar with small volume of dichloromethane. The thick slurry was kneaded for 1hr and then dried at 45^0C until dryness. The dried mass was pulverized and sieved through #120 and stored in dessicator until further evaluation.

Solvent evaporation method (SE): Accurately weighed quantities of Rilpivirine, HPC and Poloxamer at 3:1 and 1:3 weight ratios were dissolved in dichloromethane. The resulting mixture was stirred for 1hr and evaporated under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in dessicator until further evaluation.

Detection of solid dispersion systems in solid state

FTIR studies: Fourier transform IR spectra were recorded on a Shimadzu FTIR-281-

spectrophotometer. The spectra were recorded for pure Rilpivirine, HPC, Poloxamer and solid dispersion systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2T Cm^{-2} for 3 min. The scanning range was 450-4000cm^{-1} and the resolution was 1Cm^{-1}.

Powder X-ray diffractometry: The powder X-ray diffraction patterns of pure Rilpivirine, HPC, Poloxamer and solid dispersion systems were recorded by using Philips X-ray powder diffractometer (model PW 3710) employing Cr-radiation. The diffractometer were run at 2.4^0/min in terms of 2θ angle.

Dissolution Studies: *In vitro* dissolution studies of pure Rilpivirine, physical mixture and its solid dispersion systems were carried out in 900 ml of 0.01N HCl using a USPXXI type 2 dissolution rate test apparatus by the powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 20 mg of Rilpivirine, speed of 50 rpm 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 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for Rilpivirine by measuring the absorbance at 280 nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0.

RESULTS AND DISCUSSION

FTIR studies*:* The compatibility between pure drug and polymers were studied by FTIR. The FTIR spectra of Rilpivirine, HPC, Poloxamer and solid dispersion systems were given in Fig 2 & 3. The IR spectrum of RPV is characterized by typical absorption bands at about 2217 cm^{-1} (C≡N), 1652 cm^{-1} (C=O stretch), 1497 cm^{-1} (aromatic νC = C), 1435 cm^{-1} (C–H bending), 1338 cm^{-1}(-CH wagging) and 1199 cm^{-1}(symmetric C–N stretching). Additional absorption bands are observed at 1631 cm^{-1}, 1596 cm^{-1}, 1537 cm^{-1}, 1504 cm^{-1}, 1249 cm^{-1}, 1214 cm^{-1}, 1179 cm^{-1}, 1152 cm^{-1} and 1070 cm^{-1}. There is a reduction of peak intensities is observed in PMs and SDs and all other peaks of RPV were smoothened indicating strong physical interaction of the drug with carrier materials. However, no additional peaks were observed in any of the systems, indicating absence of any chemical interaction between RPV and the carriers.

Powder X-ray diffractometry: Fig 4 & 5 shows the overlaid XRD patterns of pure RPV, HPC, Poloxamer and solid dispersion systems. RPV showed characteristic diffraction peaks at two theta positions. RPV is in crystalline nature, HPC and Poloxamer are amorphous in nature as seen in spectra. Since the Physical mixtures (PMs) of RPV have no additional peaks other than RPV and respective constituents they are compatible. The crystallinity of RPV was reduced to a much greater extent, as almost all intense peaks of pure RPV had completely disappeared. The absence of peaks indicated that the drug was uniformly dispersed in the matrix material. From Fig 4 & 5 it could be concluded that the drug might have transferred to the amorphous state, as no peaks were visible.

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. The *in vitro* drug dissolution was studied by using standard procedure and conditions. The dissolution data, dissolution profiles and model fitting data and profiles were given in Table 1-4 and Fig 6-7.

The dissolution data obtained were subjected to model fitting and the model which fits the observed dissolution data was evaluated by correlation coefficient (r) between the variables involved. The `r' values in various models for all complexes are studied along with $T_{50,}$ RDR_{30}, RDR_{60}, DE_{30}, DE_{60}, DP_{30}, DP_{60}, MDT_{30} and MDT_{60} values were calculated from the dissolution software.

The results of the dissolution rate studies indicated higher dissolution rate of Rilpivirine from solid dispersion systems when compared to Rilpivirine itself and the corresponding physical mixtures. The slight increase in dissolution rate and efficiency values recorded for the physical mixture may be explained on the basis of the solubility of the drug in polymer solutions. Since the hydrophilic polymers dissolve more rapidly in the dissolution medium than the drug alone, it can be assumed that, in early stages of the dissolution process, the polymer molecule will operate locally on the hydrodynamic layer surrounding the particles of the drug.

The $T_{50,}$ RDR_{30}, RDR_{60}, DE_{30}, DE_{60}, DP_{30}, DP_{60}, MDT_{30}, MDT_{30} values of the binary systems that were prepared by the kneading and solvent evaporation methods were relatively high when compared with the values from the physical mixtures and Rilpivirine alone. Overall the rank order of improvement in dissolution properties of Rilpivirine with different polymers is Poloxamer > HPC, with ratios 1:3 > 3:1 and methods SE > KNE > PM > Pure drug.

The dissolution data was model fitted using dissolution software and the best fit model was found to be Hixon crowel and the release was follows first order kinetics.

One-way ANOVA was used to test the statistical significant difference between pure and prepared solid dispersion systems. Significant differences in the means of DP_{30}, DP_{60}, DE_{30} and DE_{60} were tested at 95% confidence. The DP_{30}, DP_{60} DE_{30} and DE_{60} values of solid dispersion systems prepared by kneading and solvent evaporation method are significantly higher ($P<0.05$) when compared to DP_{30}, DP_{60}, DE_{30} and DE_{60}values of pure Rilpivirine, physical mixture.

CONCLUSIONS

In the solid dispersion systems of Rilpivirine prepared with different hydrophilic carriers showed superior performance in enhancing aqueous solubility and the dissolution of Rilpivirine. FTIR 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%. Thus, the study provided a way to enhance solubility and understand the release mechanism.

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Table 1: dissolution parameter data of rpv, rpv: hpc physical mixtures and its solid dispersion systems.

Batches	DP_{30}	DP_{60}	DE_{30}	DE_{60}	MDT_{30}	MDT_{60}	RDR_{30}	RDR_{60}	T_{50}
RPV	7.0	13.4	3.41	6.42	13.15	29.79	1.0	1.0	>120
PM 3:1	8.7	16.7	4.64	8.84	13.00	32.35	1.35	1.50	228
PM 1:3	10.8	20.5	5.64	11.56	16.39	30.49	2.05	1.84	181.7
KM 3:1	32.1	53.9	16.36	31.39	14.15	27.79	5.10	4.59	53.8
KM 1:3	37.4	60.8	21.86	35.82	13.02	25.82	6.36	4.93	44.4
SE 3:1	37.6	61.0	22.37	38.71	11.77	23.94	6.68	5.05	44.1
SE 1:3	38.3	65.4	24.54	38.76	13.81	26.11	6.83	5.38	41.6

Table 2: Model fitting values of RPV, RPV: HPC physical mixtures and its solid dispersion systems.

Batches	$K_1 \times 10^2 (min)^{-1}$		$K_H \times 10^2 (mg^{1/3}.min^{-1})$	
	R	K	R	K
Pure RPV	0.9955	-0.0024	0.9970	-0.0008
PM 3:1	0.9945	-0.0035	0.9926	-0.0035
PM 1:3	0.9947	-0.0043	0.9925	-0.0014
KM 3:1	0.9921	-0.0144	0.9721	-0.0039
KM 1:3	0.9790	-0.0251	0.9959	-0.0057
SE 3:1	0.9965	-0.0154	0.9896	-0.0041
SE 1:3	0.9484	-0.0295	0.9936	-0.0062

TABLE 3: DISSOLUTION PARAMETER DATA OF RPV, RPV: POLOXAMER PHYSICAL MIXTURES AND ITS SOLID DISPERSION SYSTEMS.

Batches	DP_{30}	DP_{60}	DE_{30}	DE_{60}	MDT_{30}	MDT_{60}	RDR_{30}	RDR_{60}	T_{50}
RPV	7.0	13.4	3.41	6.42	13.15	29.79	1.0	1.0	>120
PM 3:1	10.0	19.0	5.21	10.31	15.18	31.33	1.74	1.69	197.7
PM 1:3	12.2	22.9	6.09	12.70	15.84	28.88	2.13	1.92	159.8
KM 3:1	35.0	57.8	22.39	35.90	12.40	24.70	6.29	4.79	48.2
KM 1:3	43.3	71.8	25.30	42.55	13.06	26.73	7.38	6.02	35.9
SE 3:1	37.0	60.4	21.82	35.33	12.63	54.22	6.21	4.86	44.9
SE 1:3	46.1	75.3	25.85	44.65	13.05	25.12	7.54	6.03	33.3

TABLE 4: MODEL FITTING VALUES OF RPV, RPV: POLOXAMER PHYSICAL MIXTURES AND ITS SOLID DISPERSION SYSTEMS.

Batches	$K_1 \times 10^2 (min)^{-1}$		$K_H \times 10^2 (mg^{1/3}.min^{-1})$	
	R	K	R	K
Pure RPV	0.9955	-0.0024	0.9970	-0.0008
PM 3:1	0.9942	-0.0030	0.9928	-0.0010
PM 1:3	0.9906	-0.0038	0.9876	-0.0012
KM 3:1	0.9943	-0.0129	0.9836	-0.0036
KM 1:3	0.9951	-0.0156	0.9880	-0.0042
SE 3:1	0.9877	-0.0157	0.9624	-0.0042
SE 1:3	0.9958	-0.0199	0.9961	-0.0050

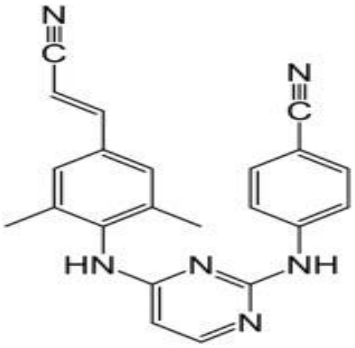

Fig 1: Chemical structure of Rilpivirine

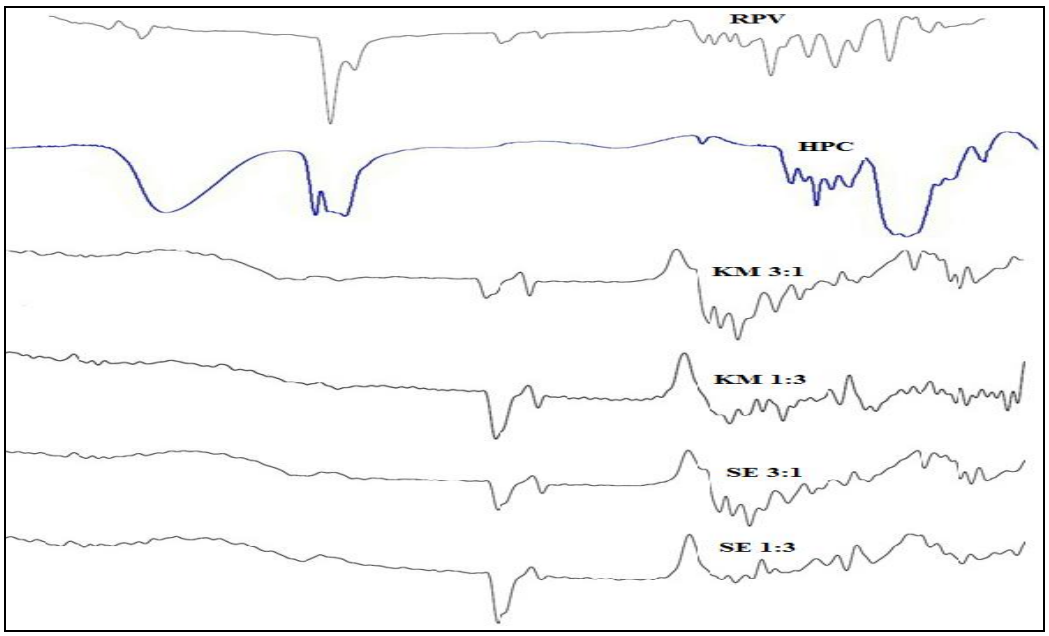

Fig 2: FTIR spectra of Rilpivirine, HPC and their solid dispersion systems.

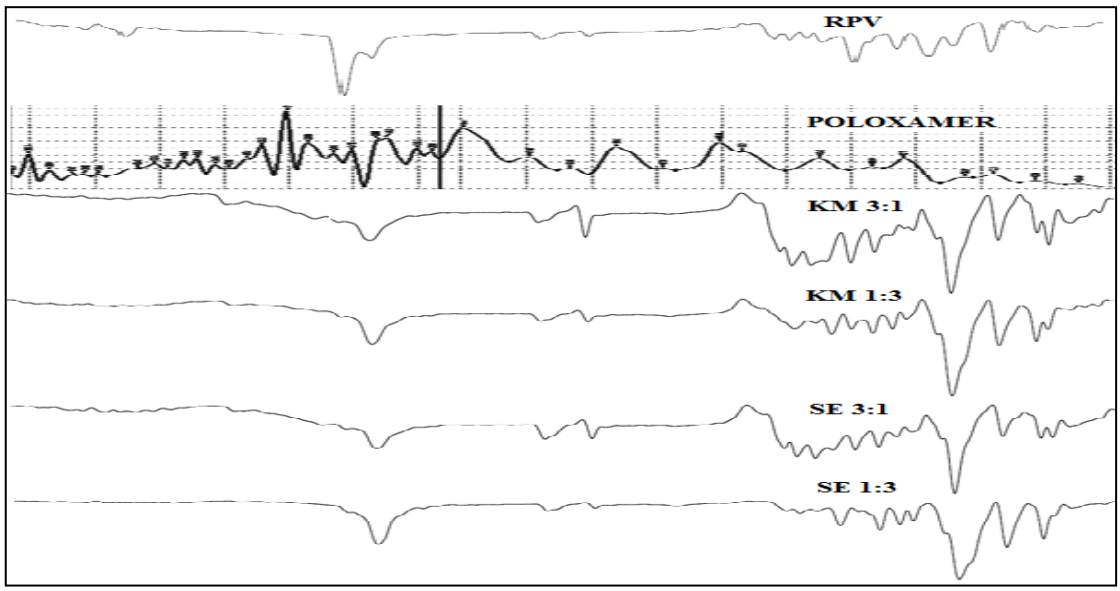

Fig 3: FTIR spectra of Rilpivirine, Poloxamer and their solid dispersion systems.

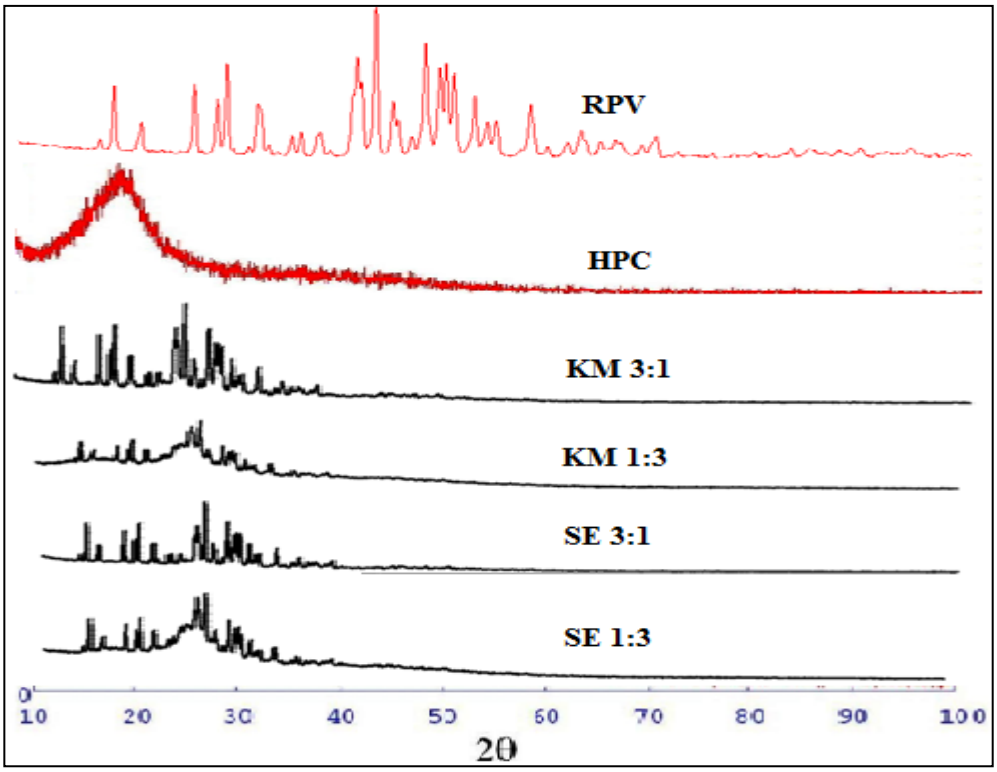

Fig 4: XRD patterns of Rilpivirine, HPC and their solid dispersion systems.

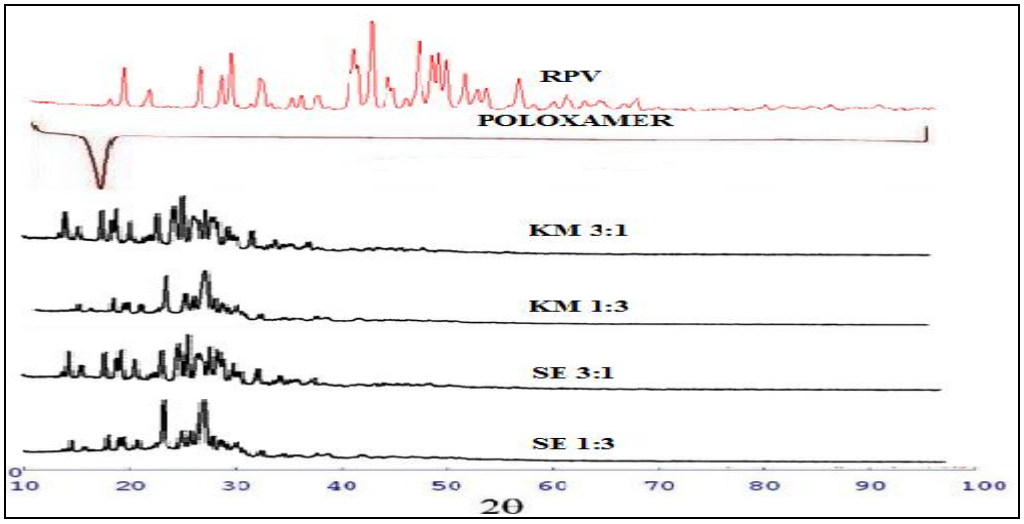

Fig 5: XRD patterns of Rilpivirine, Poloxamer and their solid dispersion systems.

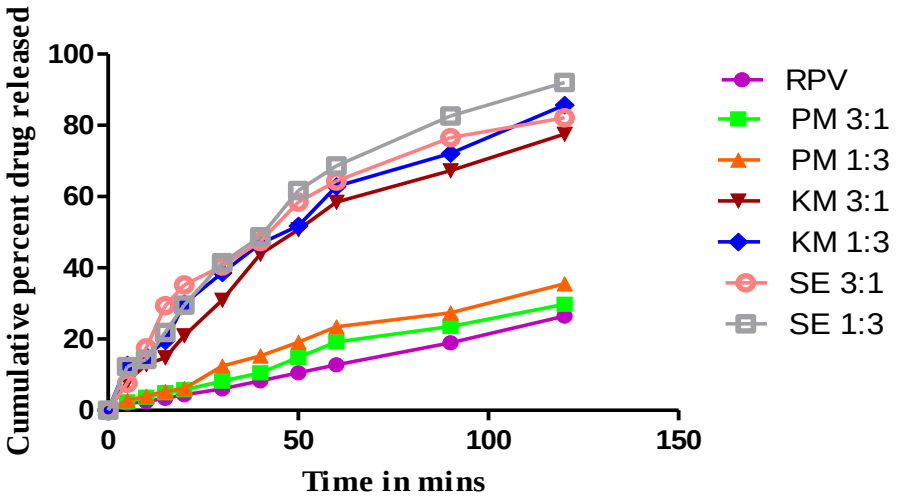

Fig 6: Comparative dissolution profiles of Rilpivirine solid dispersion systems using HPC at 3:1 & 1:3 ratio by PM, KM & SE method.

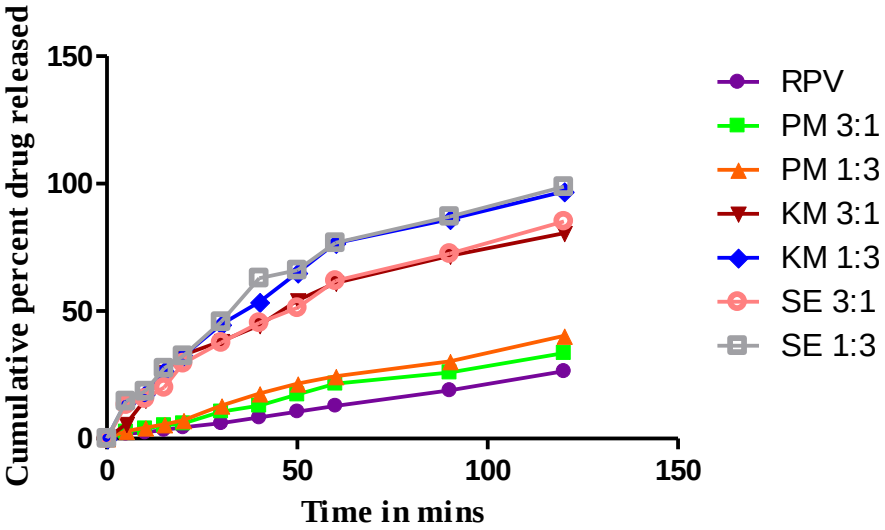

Fig 7: Comparative dissolution profiles of Rilpivirine solid dispersion systems using Poloxamer at 3:1 & 1:3 ratio by PM, KM & SE method.

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