RESEARCH ARTICLE

Formulation for Enhancement of Rate of *In Vitro* Drug Release Profiles of Poorly Soluble Rilpivirine Hydrochloride by Spray Drying Technique

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Abstract

Aim: The aim of the present research work was to enhance the rate of in vitro drug release profiles of poorly soluble Rilpivirine Hydrocloride (RH) by Spray drying technique. Rilpivirine is a non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type-1 (HIV-1). **Method:** RH is belongs to BCS class-II. It is insoluble in water and practically insoluble across the pH range of 1 – 7.5. One of the major concerns with the formulation of RH is its poor solubility, which results into poor bioavailability after oral administration. Spray drying technique has been proven to be an efficient technique for conversion of poorly soluble crystalline form into highly soluble amorphous form and make it useful for formulating lab scale batches to commercial batches. Hence, Spray drying technique was chosen for reducing the % of crystallinity / or converting crystalline form into highly soluble amorphous form by spray drying technique. The organic dispersion comprising RH, hydrophilic carriers like Soluplus / Kollidon VA64 / Kolliphor SLS / Kolliphor P407 / Kollidon 30 at different ratios along with finer grade of microcrystalline cellulose (Avicel PH 105) was subjected to spray drying using Buchi spray dryer. **Results & Discussion:** The dissolution profiles of formulated product (RT2 & RT3) in FDA recommended dissolution media was compared against the dissolution profiles of corresponding innovator product. The rate of in vitro drug release was at faster and complete from test product as compared to Innovator product profiles i.e., EUDRANT™ 25 mg tablets. From the characterization of spray dried powder RSD8 by DSC and XRD concluded that % crystallinity of RH was reduced significantly. **Conclusion:** The obtained results suggested that Spray drying technique might be an efficacious approach in enhancing the therapeutic potential of Rilpivirine Hydrochloride.

Key words: Amorphous form, hydrophilic carriers, rate of drug release, rilpivirine hydrochloride, spray drying

INTRODUCTION

The oral route of administration is the most preferred and widely acceptable route of delivery due to ease of ingestion for many drugs. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility.[1,2] Rilpivirine is a non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus Type 1 (HIV-1). It is used in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infections.[3]

Poorly water soluble drug with poor solubility and low dissolution rate is a reason for its poor bioavailability. The solubility of such drugs can be improved by incorporating the drug in a matrix of the hydrophilic carrier(s) obtaining a product called a solid dispersion. Limited aqueous solubility of the active pharmaceutical ingredient can result in poor bioavailability, which is a major issue for the pharmaceutical industry.[4,5]

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Poor solubility and bioavailability of an existing or newly synthesized drug always pose a challenge in the development of efficient pharmaceutical formulation. Numerous technologies can be used to improve the solubility and among them amorphous solid dispersion based spray drying technology can be successfully useful for the development of a product from lab scale to commercial scale with a wide range of powder characteristics.[6]

Spray drying is an efficient technology for solid dispersion manufacturing since it allows extreme rapid solvent evaporation leading to the fast transformation of a drug-carrier solution to solid drug carrier particles. Solvent evaporation kinetics certainly contribute to formation of amorphous solid dispersions, but also other factors like the interplay between the drug, carrier, and solvent, the solution state of the drug, formulation parameters (e.g., feed concentration or solvent type) and process parameters (e.g., drying gas flow rate or solution spray rate) will influence the final physical structure of the obtained solid dispersion particles.[7]

The biologically active molecule can maintain its structure and activity because of mild preparation process. Hence, this technology is suitable for the preparation of thermosensitive and sparingly soluble drugs. The use of amorphous solid dispersions is an interesting strategy to increase the bioavailability of poorly soluble drugs by improving their rate and extent of dissolution.[8,9]

Spray drying is a particle processing technology that transforms a liquid feedstock into a powder product by the first spraying the feedstock to create droplets, and then evaporating the feedstock liquid through the use of a heated drying medium, typically air. The liquid feedstock can take the form of a solution, suspension, or emulsion, and must be easily pumpable and capable of droplet formation.[10]
The aim of the present study was to improve the rate of drug release profiles as compared to that of dissolution profiles of corresponding Innovator product. In general, the resulting spray dried powder will be fluffy and doesn't have acceptable flow properties to be filled into capsules/ compressed into tablet dosage forms. To improve the flow properties of spray dried powder, finer grade of microcrystalline, Avicel PH 105 was added to the organic dispersion of drug substance and hydrophilic polymer and the dispersion was subjected to spray drying using lab scale model Buchi spray dryer. In the present work, it was attempted to formulate tablet dosage form by compressing the spray dried powder along with flow aid and lubricant, followed by evaluating the *in vitro* dissolution profiles and compared against the corresponding Innovator product, i.e., EUDRANT™ 25 mg tablets in FDA recommended dissolution media.[11]

The obtained results suggested that spray drying might be an efficacious approach in enhancing the rate of drug release and thereby improving the therapeutic potential.

MATERIALS

EUDRANT™ (rilpivirine) tablets 25 mg were obtained from Manufactured by: Janssen-Cilag SpA, Latina, Italy. Rilpivirine hydrochloride (RH) (with d_{90} of 132.2 µ) drug substance was gifted by Hetero Drugs Ltd, Hyderabad, India. Kolliphor P 407, Kollidon VA64, Soluplus and Kolliphor SLS were generous gift samples of Signet Chemicals, Mumbai. Microcrystalline cellulose (Avicel PH 105 and Avicel PH 102) was gift sample of Hetero Labs Ltd (being procured from FMC Biopolymer, U.S). Aerosil 200 Pharma was gifted by Evonik, Mumbai. Magnesium stearate was gifted by Peter Greven, Germany. All other chemicals and suitable buffer salts used were of the analytical grade being procured from SD Fine Chemicals, Mumbai, India.

METHODS

Analytical method

Standardization of RH by UV-visible spectrophotometry

i. Preparation of standard stock solution: The standard stock solution of rilpivirine was prepared by transferring 10 mg of working standard (eq.to Rilpivirine) into 50 ml of volumetric flask, to which 25 ml of methanol was added and shaken well and the volume was made up to the mark with 0.01N HCl
ii. Preparation of solutions of analytical concentration range: The working standard solution of Rilpivirine was prepared by transferring 10 mL stock solution into 25 ml of volumetric flask and made up to the mark with 0.01N HCl (concentration 80 µg/ml). Appropriate aliquots were pipette out from the working standard solution into a series of 50 ml volumetric flasks. The volume was made up to the mark with 0.01N HCl to obtain solutions of concentration range, ranging from 0.8 to 8.0 µg/mL of Rilpivirine and absorbance was measured at 280 nm.

Solubility studies of RH[12]

Solubility of RH was determined by adding an excess amount of RH to volumetric flask of 100 ml of 0.1N HCl/0.01N HCl (pH eq.to 2.0)/pH 4.5 acetate buffer/pH 6.8 Phosphate buffer/ pH 7.5 Phosphate buffer/purified water and then samples were shaken for the 48 h at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper. Filtered solutions were analyzed for RH by UV/visible spectrophotometer at λ_{max} of 280 nm.

Formulation of RH solid dispersions by spray drying technique

Numerous technologies can be used to improve the solubility and among them spray drying is one of the techniques and can

be successfully useful for the development of product from lab scale to commercial scale with a wide range of powder characteristics.[6] The spray drying of organic solution/ dispersion comprising poorly soluble drug substance, hydrophilic polymer and with additive results into particle size reduction, leading to increase in surface area, is a very promising tool to increase dissolution rate and, in turn, the bioavailability of poorly water-soluble compounds.

Considering the weight of the Innovator product (average weight = 115 mg), it was planned to target the test product weight of NMT 150 mg (Table 1).

Manufacturing procedure

1. Hydrophilic polymer like Soluplus/Kollidon VA64/ Kolliphor SLS/Kolliphor P407/Kollidon 30 was dissolved in solvent mixtures of dichloromethane and methanol (1:1), a clear solution was formed
2. RH was added slowly to the above polymer solution under continuous stirring and stirred well until to get a homogenous dispersion
3. Microcrystalline cellulose, grade Avicel PH105 was dispersed in the above dispersion. The above dispersion was subjected to spray drying using BUCHI spray dryer (inlet air temperature 60-70°C, aspiration 90-100%; nozzle tip: 0.4 mm; nitrogen gas cylinder).

The particle size of microcrystalline cellulose was selected such that when mixed into the homogenous dispersion of active drug substance and hydrophilic polymer should not block/clog the atomizer, should be easily atomizable. The density of the resulting spray dried powder will be increased with the addition of microcrystalline cellulose, it also helps in improvement of flow properties of resulting spray dried mixture, may also function to increase the properties compressibility, disintegration and dissolution of the resulting spray dried powder of RH.[13]

The majority of the spray dried powder was collected in the drying chamber cylinder with aspiration below 90% and it was found to be coarser powder as compared to spray dried powder, which was collected in Extraction cyclone cylinder where aspiration above 90-100%. The parameters are depicted in Table 2.

The resulting spray dried powder evaluated for physical appearance and then determined for drug substance solubility.

The physical appearance and powder nature of resulting spray dried powder is presented in the Table 3.

Among the 15 formulations, the resulting spray dried powder in RSD7-RSD9 can be compressed into tablets along with diluent, glidant, and lubricant. These 3 batches were compressed into tablets (along with some other raw materials

Table 1: Quantitative composition of rilpivirine hydrochloride by spray drying technique

Ingredients	RSD1	RSD2	RSD3	RSD4	RSD5	RSD6	RSD7	RSD8	RSD9	RSD10	RSD11	RSD12	RSD13	RSD14	RSD15
	1:2:1	1:2.5:1	1:2.5:1.5	1:2:1	1:2.5:1	1:2.5:1.5	1:2:1	1:2.5:1	1:2.5:1.5	1:2:1	1:2.5:1	1:2.5:1.5	1:2:1	1:2.5:1	1:2.5:1.5
Mg/unit															
RH	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5
Soluplus	55.0	68.75	68.75	-	-	-	-	-	-	-	-	-	-	-	-
Kollidon VA64	-	-		55.0	68.75	68.75	-	-	-	-	-	-	-	-	-
Kolliphor SLS	-	-	-	-			55.0	68.75	68.75	-	-	-	-	-	-
Kolliphor P407	-	-	-	-	-	-	-	-	-	55.0	68.75	68.75	-	-	-
Kollidon 30	-	-	-	-	-	-	-	-	-	-	-	-	55.0	68.75	68.75
Avicel PH 105	27.5	27.5	41.25	27.5	27.5	41.25	27.5	27.5	41.25	27.5	27.5	41.25	27.5	27.5	41.25
Methanol	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Dichloromethane	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total quantity of spray dried powder	110.0	123.75	137.5	110.0	123.75	137.5	110.0	123.75	137.5	110.0	123.75	137.5	110.0	123.75	137.5

RH: Rilpivirine hydrocloride

Table 2: Parameters during spray drying

Atomizer parameters	
Nozzle tip	0.4 mm
Nozzle diameter	1.0 mm
Cap diameter	1.2 mm
Spray drying parameters	
Inlet temperature	55-65°C
Pump rate for spraying dispersion	27.5-35%
Nitrogen gas pressure	30-40 mmHg

Table 3: Observations at the end of spray drying process

Spray drying formulation	Observation and remarks
RSD1-RSD3	Off-white to slightly yellowish, waxy and sticky in nature. Not suitable for compression into tablets and hence not evaluated further
RSD4-RSD6	Off-white, sticky in nature, very poor flow properties. Not suitable for compression into tablets and hence not evaluated further
RSD7	Off-white, porous and fluffy powder, very poor flow properties. Can be compressed into tablets by adding flow aids and lubricant
RSD8	White, very porous and fluffy powder, very poor flow properties. Can be compressed into tablets by adding flow aids and lubricant
RSD9	White powder. Flow properties were found to be superior to RSD7 and RSD8. Can be compressed into tablets by adding flow aids and lubricant
RSD10-RSD12	Off-white, waxy and sticky in nature. Not suitable for compression into tablets and hence not evaluated further
RSD13-RSD15	Off-white to yellowish, sticky in nature. Not suitable for compression into tablets and hence not evaluated further

like diluent, flow aids and lubricant, etc.), and were evaluated compression parameters and dissolution profiles in Table 4.

Manufacturing procedure

Step-1: The spray dried powder (#40 mesh passed) (RSD7, RSD8, and RSD9), Microcrystalline cellulose and Colloidal silicon dioxide were sifted together through # 40 mesh and mixed well in a poly bag for 10 min.

Step-2: Magnesium stearate was sifted through #60 mesh, added to the blend of step-1 and manually mixed in a poly bag for 5 min.

Step-3: The above lubricated blend was compressed into Rilpivirine Tablets 25 mg using Cadmach compression machine with 7.10 mm, standard concave round shape punches, upper punch embossed with "RT" and lower punch embossed with "25" at hardness range of 5-8 kp.

EVALUATION OF RILPIVIRINE FORMULATIONS

Assay of spray dried powder and core tablets[14]

Weight equivalent to 20 units of spray dried powder were taken in a mortar and mixed well (ensure no lumps) and from this weight equivalent to 50.0 mg of rilpivirine was transferred to 100 ml of volumetric flask and the volume was made up to the mark with mixture of methanol and 0.01N HCl (40:60 parts) and subjected to sonication for 30 min. From this 1 ml of solution was taken in a 100 ml volumetric flask and was made up to the mark with a mixture of methanol and 0.01N HCl (40:60 parts) and absorbance was measured at λ_{max} 280 nm against blank.

20 No's of core tablet were taken in a mortar and crushed into fine powder and from this weight equivalent to 50.0 mg of rilpivirine was transferred to 100 ml of volumetric flask and the volume was made up to mark with mixture of Methanol and 0.01N HCl (40:60 parts) and subjected to sonication for 30 min. From this 1 ml of solution was taken in a 100 ml volumetric flask and was made up to the mark with mixture of methanol and 0.01N HCl (40:60 parts) and absorbance was measured at λ_{max} 280 nm against blank.

In vitro drug release studies[11]

Preparation of dissolution medium[14]

Accurately weighed and transferred about 5 g of Tween 20 into beaker containing 1000 mL of 0.01N HCl solution and mixed well and pH of 2.0±0.05 was verified (If necessary, adjust the pH of the solution to 2.0±0.05 with 1N HCl or 1N NaOH).

Dissolution parameters

The *in vitro* drug release profiles for test product (RT1-RT3) and its corresponding innovator product was evaluated in FDA recommended dissolution media and conditions. The conditions and parameters of dissolution testing are presented in Table 5.

The samples were withdrawn at specified time intervals, and the obtained samples were analyzed for drug release by using UV/visible spectrophotometer at λ_{max} 280 nm. The cumulative percentage release was calculated.

Table 4: Composition of rilpivirine tablets 25 mg

Ingredients	Function	Qty (mg/unit)		
		RT1	RT2	RT3
Spray dried powder RSD7	-	110.00	x	X
Spray dried powder RSD8		x	123.75	X
Spray dried powder RSD9		x	x	137.50
Extra granular materials				
Microcrystalline cellulose, USNF (Avicel PH 102)	Diluent	34.75	21.00	7.25
Colloidal silicon dioxide, USNF (Aerosil® 200)	Glidant	3.0	3.0	3.0
Magnesium stearate, USNF	Lubricant	2.25	2.25	2.25
Total weight of tablet		150.00	150.00	150.00

Table 5: *In-vitro* dissolution conditions

Instrument	Electro lab - USP Type 2 (Paddle) Dissolution test apparatus
Dissolution medium	0.50% Tween - 20 in 0.01N HCl (pH of 2.0)
Apparatus	USP Type 2 (Paddle)
Temperature	37±0.5°C
RPM	75
Volume of medium	900 ml
Sampling intervals	5, 10, 15, 30,45, 60 and 75 min
Sample volume	10 ml withdrawn and replaced with 10 ml of dissolution medium

Characterization

Based on the spray drying process feasibility, weight of spray dried powder and *in vitro* drug release profiles, the spray dried powder RSD8 was being selected for characterization of polymorphic form by powder X-ray diffraction (p-XRD) and differential scanning calorimetry (DSC).

p-XRD[15,16]

A Bruker D8 diffractometer was used to perform p-XRD of all samples. A Cu K-α 1 tube was the source, set at 40 KV and 50 mA. A scan from 2° to 60° 2θ was carried out at a rate of 0.01220° 2θ/s. The diffractometer was calibrated using powdered α-alumina. The spray dried powder samples were ground before analysis.

DSC[15,16]

DSC studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminum plate, sealed with aluminum lids and heated at a constant rate of 5°C/min, over a temperature range of 0-250°C.

RESULTS AND DISCUSSION

Determination of λ_{max} and calibration curve of RH

An UV-visible spectrophotometric method was used for the estimation of RH. The standard concentration was scanned over a range of 400-200 nm which resulted into a peak at 280 nm. The 280 nm was taken as absorption maxima for RH. The absorbance of active ingredient was determined at concentration range of 0.8-8 µg/ml solutions at λ_{max} 280 nm against blank.

The selected analytical method obeyed Beer's law in the concentration range of 0-20 µg/ml and is suitable for the estimation of rilpivirine from different solutions. The obtained standard graph was linear, with a regression coefficient of 0.99.

Solubility studies of RH

The solubility RH was determined in different media covering pH range of 1-7.5. The results are tabulated in Table 6.

Among the different pH medias, comparatively the drug substance is highly soluble in 0.01N HCl (pH 2.0).

Formulation of RH by spray drying process

Based on the process feasibility and suitability of resulting spray dried powder for compression into tablets, the spray dried powder RSD7-RSD9 can be compressed into tablets along with diluent, glidant and lubricant.

Assay of the spray dried powder

The spray dried powder RSD7 and RSD8 was fluffy in nature, whereas spray dried powder RSD9 was found to be having satisfactory flow properties. The assay of spray dried powder was analyzed and the results are tabulated in Table 7.

Table 6: Solubility of RH

Media	Solubility (mg/ml)*
0.1 N HCl	0.019±0.003
0.01N HCl (pH 2.0)	0.022±0.002
pH 4.5 acetate buffer	0.0001
pH 6.8 phosphate buffer	0.000
Purified water	0.019±0.004
pH 7.5 phosphate buffer	0.0001

*Range, *n*=3, RH: Rilpivirine hydrochloride

Table 7: Assay of spray dried powder

Formulation	% Assay*
RSD7	93.2±0.9
RSD8	95.1±1.1
RSD9	96.4±0.6

*Mean±SD, *n*=3, SD: Standard deviation

Table 8: Compression parameters of rilpivirine tablets 25 mg

Parameters	RT1	RT2	RT3
Tablet weight	148-158 mg	146-158 mg	147-157 mg
Hardness	5.5-7 kp	5.5-7 kp	5.5-7 kp
Disintegration time	5-6 minutes	4-5 minutes	4-5 minutes

Compression

The spray dried powder along with Avicel PH 102, Aerosil® 200 Pharma and Magnesisum stearate was compressed into tablets. The compression parameters of test product are presented in Table 8.

Assay of core tablets

Assay of core coated tablets is presented in Table 9.

The assay of test products was found to be in the range of 96.6-99.2%

In vitro dissolution studies

The test product tablets and innovator product were evaluated for dissolution profiles in FDA recommended dissolution media. The results presented in Table 10.

Graphical representation for comparative dissolution profiles is presented in Figure 1.

Based on the *in vitro* drug release profiles, it was clearly evident that the rate of drug from RT1 was on lower side, while the rate of drug release from RT2 was found to be slightly on higher side and at faster rate, higher side from RT3 as comapated to the *in vitro* drug release profiles of innovator product.

Table 9: Assay of rilpivirine tablets 25 mg

B. No	% Assay
RT1	96.6±1.2
RT2	97.4±1.4
RT3	99.2±0.9

Table 10: *In vitro* dissolution profiles in 0.01 N HCl with 0.05% tween 20

Time (minutes)	Eudrant® 25 mg tablets	Rilpivirine tablets 25 mg		
		RT1	RT2	RT3
Cumulative % drug release*				
0	0	0	0	0
5	39.3±3.4	34.2±12.8	45.2±12.2	50.1±8.6
10	64.4±2.7	54.8±11.0	67.8±10.2	72.4±6.6
15	75.1±1.9	66.2±7.6	80.2±8.4	86.6±4.2
30	85.4±1.6	75.4±6.6	87.4±6.3	92.4±3.1
45	90.4±1.4	82.3±3.1	91.4±4.1	96.0±2.8
60	94.4±1.5	86.6±1.8	94.6±2.0	97.2±1.2
75	97.6±0.8	90.3±1.1	97.9±1.7	99.4±0.6

*Mean±SD, *n*=3, SD: Standard deviation

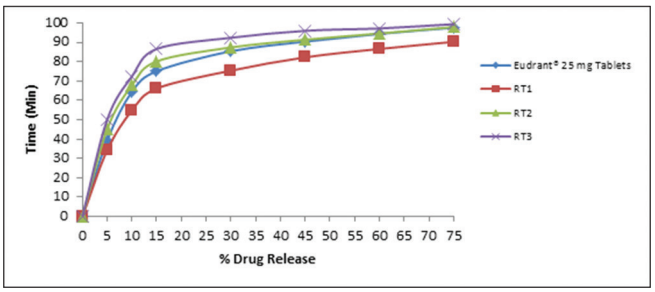

Figure 1: Comparative *in vitro* dissolution profile of innovator product and rilpivirine tablets 25 mg (RT1-RT3)

Characterization

Based on the spray drying process feasibility, weight of spray dried powder and *in vitro* dissolution profiles, spray dried powder RSD8 was selected for characterization of polymorphic form within solid dispersion by p-XRD and DSC.

X-ray diffractogram (p-XRD)

The diffractogram of RH and spray dried powder is presented in the Figure 2.

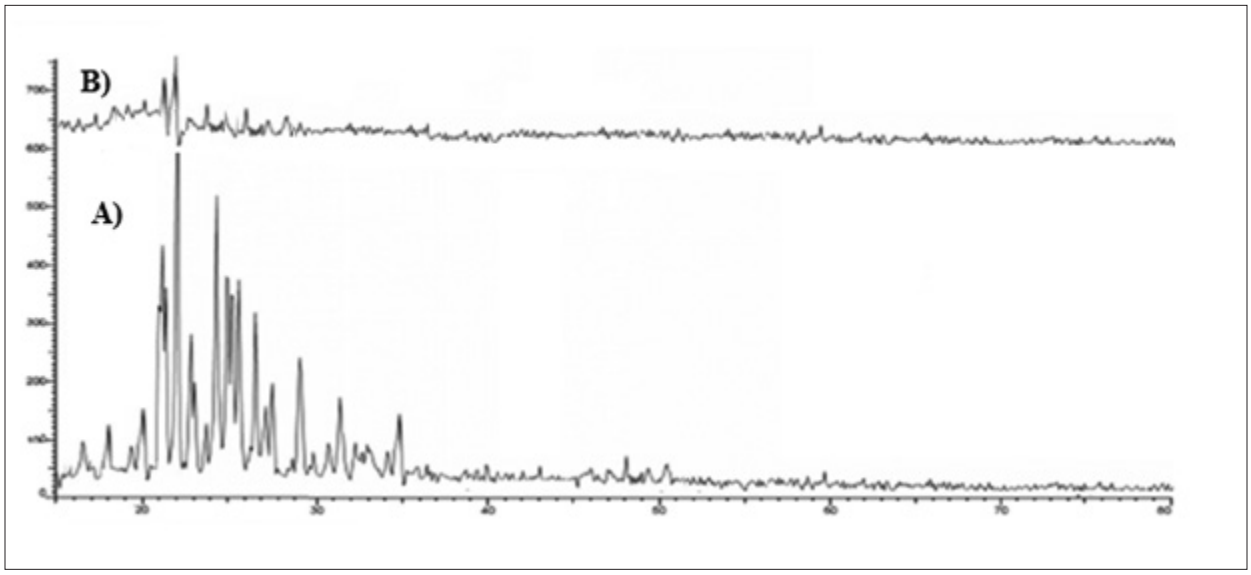

Figure 2: X-ray diffractogram (a) Rilpivirine hydrochloride; (b) Spray dried powder RSD8

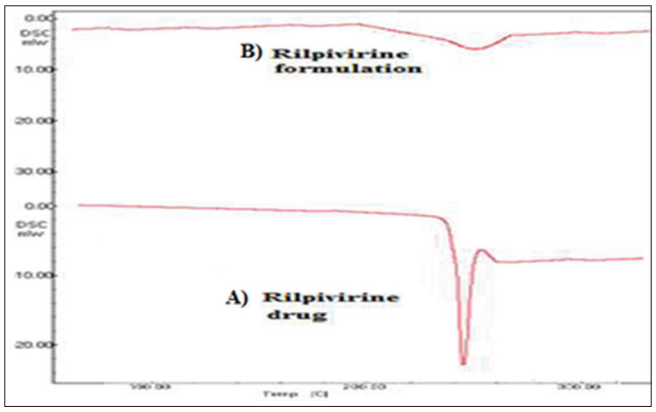

Figure 3: Differential scanning calorimetry thermogram (a) Rilpivirine hydrochloride; (b) Spray dried powder RSD8

The diffractogram of RH shows so many numbers of peaks, it indicates that the drug substance is in crystalline form.

The diffractogram of spray dried powder RSD8 shows a very few less intensive peaks. It indicates that the % of crystallinity has been reduced significantly, the drug substance was converted into an amorphous form almost/or % of crystallinity was reduced significantly.

DSC

The DSC thermograms of Plain RH and spray dried powder RSD8 is shown in Figure 3.

The DSC thermogram of RH shows sharp endothermic peak due to melting point (242°C), indicating that the drug is crystalline in nature.

The absence of endothermic peak in the spray dried powder RSD8 indicating that the polymorphic form of the drug was converted from crystalline into an amorphous form/or % of crystallinity was almost absent or very less.

CONCLUSION

In the present research work aimed at enhance the rate of *in vitro* drug release profiles as compared to the markated corresponding Innovator product in U.S market. Spray drying technique has been proven to be an efficient technique for enhancement of the rate of *in vitro*/and *in vivo* drug release profiles, thereby bioavailability of poorly soluble drug substances. In this current research work, solid dispersions of poorly soluble RH drug substance with different hydrophilic polymers such as Soluplus, Kollidon VA64, Kolliphor SLS, Kolliphor P407, and Kollidon 30 along with finer grade of microcrystalline cellulose were formulated by spray drying techniques. Based on the process feasibility and flow properties of spray dried powder it was noticed that with increasing the quantity of avicel PH105 there was a high chances of gun blocking, but it will improves the flow properties. Among the resulting spray dried powders, only spray dried powder RSD7-RSD9 were suitable for compression into tables along with diluent like Avicel PH102, glidant like aerosil 200 Pharma and lubricant like magnesium stearate. The core tablets were evaluated for dissolution profiles in FDA recommended dissolution media and compared against the markated innovator product in U.S, i.e., Eudrant™ 25 mg tablets. Based on the *in vitro* drug release profiles and weight of the respective spray dried powder, the spray dried powder RSD8 was being selected for characterization of the polymorphic form of drug substance by DSC and p-XRD. The obtained results suggested that solid dispersion by spray drying technique might be an efficacious approach for enhancing the therapeutic potential of RH.

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