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Effective Estimation of Rilpivirine HCl by Analytical Method in Soild Dispersion and its In-vitro Dissolution Assessment

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ABSTRACT:
Rilpivirine Hydrochloride (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It is indicated for the treatment of HIV-1 infection. The objective of the present investigation is to improve the dissolution rate and solubility of RPV, a poorly water-soluble drug by solid dispersion technique using a water soluble carrier beta-cyclodextrin. Kneading, Microwave Irradiation Methods using beta-cyclodextins as carrier. To evaluate the solubility and invitro drug release of solid dispersions by UV Spectroscopy is the aim for this study. The dispersions were evaluated for various parameters such as solubility study, dissolution study and Fourier transform infrared spectroscopy (FT-IR). Solid Dispersions were prepared with various concentrations of carrier; the prepared solid dispersions were examined for drug release profile. Drug and beta-cyclodextrin showed good result in the ratio 1:3 in Microwave Irradiation Solid Dispersion method.

KEYWORDS: Rilpivirine HCl, Solid Dispersion, Beta-cyclodextrin, Solubility and Dissolution.

I. INTRODUCTION

[1] Solubility is the property of a solute to dissolve in a solvent to form a homogeneous solution. The solute may be a solid, liquid or gaseous substance. The solubility of substance fundamentally depends on the solvent used as well as on temperature and pressure. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include:

(i) Enhancing Solubility and Dissolution Rate of poorly water-soluble drugs.

(ii) Enhancing Permeability of poorly permeable drugs.

Biopharmaceutical classification system (BCS) was introduced by US Food and Drug Administration (FDA) and it classify the drug in to four classes according to permeability and solubility. Solubility impediment are faced in the Class II and Class IV of the system facing dissolution as the rate limiting step for the absorption of drug due to low solubility.

- **To Overcome Poor Solubility:**

I. Chemical Modifications:

1) Salt Formation
2) Co-crystallization
3) Co-solvency
4) Hydrotropy
5) Use of novel solubilizer
6) Nanotechnology

II. Physical Modifications:

1) Particle size reduction

a)Conventional method
b) Micronization
c) Nanosuspension

2) Modification of the crystal habit

a) Polymorphs
b) Pseudo polymorphs
c) Nanosuspension

3) Complexation

a) Physical mixture
b) Kneading method
c) Co-precipitate method

4) Inclusion Complex Formulation Based:

a) Kneading method
b) Lyophilization / Freeze- drying Technique

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c) Microwave irradiation method
5) Solubilization by surfactants
a) Micro emulsions
b) Self micro emulsifying drug delivery system
6) Drug dispersion in carriers
a) Solid solutions
b) Solid dispersions
i. Fusion Process
ii. Solvent Method
iii. Fusion solvent method
iv. Spray drying
v.Lyophilization (Spray Freeze Drying)
vii. Dropping Method
III. pH adjustment
IV. Supercritical fluid process
V. Liquisolid technique
VI. Polymeric alteration

II. MATERIAL AND METHOD

Materials: Rilpivirine was obtained from Mylan laboratory, Hyderabad, India. Beta-cyclodextrin, HCl, Phosphate Buffer were obtained from Merck Specialties Pvt. Methanol was obtained from lab Fine Chem Industries, Mumbai, India.

Preparing Methods for Solid Dispersion:

1. **Kneading Method:**

[2] This method is based on soaking the CDs or suitable polymer with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve.

2. **Microwave Irradiation Method:**

[3]Involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 ^{o}c in the microwave oven.

III. RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES:

Determination of Solubility of Drug in Different Media:

Solubility study of Rilpivirine HCl was carried out in distilled water, 0.1N HCl, 0.01N HCl and phosphate buffer solutions. The results were shown in Table 1.
Absorbance values of drug were higher at distinct λmax (280nm) with 0.1N HCl as solvent. Hence, 0.1N HCl was selected as solvent for further investigation as it is more economical. The λmax is shown in Fig1.

Table 1. Absorbance of Pure Drug Rilpivirine in different Solvent

No	Concentration (µg/ml)	Solvent	Absorbance	λmax (nm)
1	10	Phosphate Buffer pH 2	0.0732	283
2	10	Phosphate Buffer pH 6.8	0.1671	282
3	10	Phosphate Buffer pH 7.4	0.1280	280
4	10	0.01N HCl (Ph 2)	0.1689	280
5	10	0.1N HCl (pH 1.1)	0.1889	280

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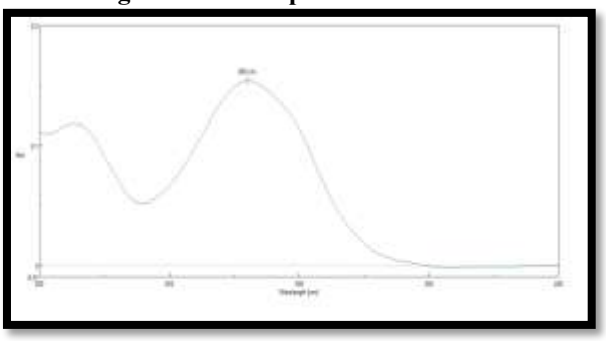
Fig1. λmax of Rilpivirine in 0.1N HCl



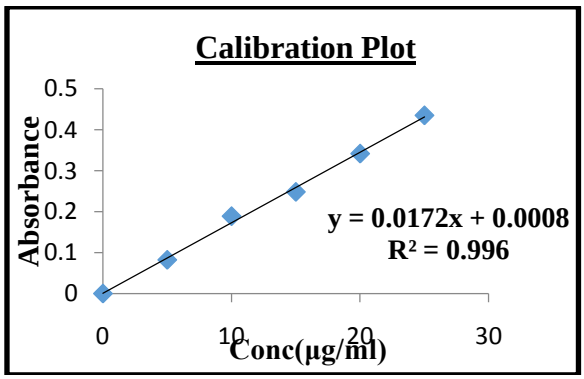
Calibration Plot For Rilpivirine In 0.1N HCl:

10 mg of Rilpivirine HCl was transferred into 10 ml 0.1N HCl in volumetric flask. 1 ml of the Sample was withdrawn from this solution and diluted to 10 ml with 0.1N HCl to form 100 µg /ml (stock solution) then concentration made by withdrawing 0.5, 1, 1.5, 2, 2.5ml from stock solution and diluted to 10 ml ith 0.1N HCl to make solution of concentration 5 ug/ml, 10 ug/ml, 15 ug/ml, 20 ug/ml, 25 ug/ml. Absorbance was taken at λmax of 280 nm using UV visible spectrophotometer and graph was plotted for absorbance versus concentration of Rilpivirine HCl. The results were shown in Table 2 followed by Fig2.

Table 2. Absorbance in 0.1N HCl

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

Fig2. Calibration Curve of Rilpivirine



Determination of Melting Point:

The drug was filled in capillary tube and capillary was placed in the melting point apparatus. The temperature required to melt the drug was noted as 242-246^{0}C. The same procedure was repeated for three times and mean of three readings was calculated.

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Drug-Excipients Compatibility Study:

In the FTIR spectrum of drug, Polymer and Solid dispersion of drug and Polymer all major peaks of drug and polymers are visible in the spectrum. From observation it has been concluded that there is no such major shifting of the peaks of the mixtures in comparison to their individual data. Hence the result of the study reveals a good compatibility between drug and polymer.

Fig3. IR Spectrum of Rilpivirine

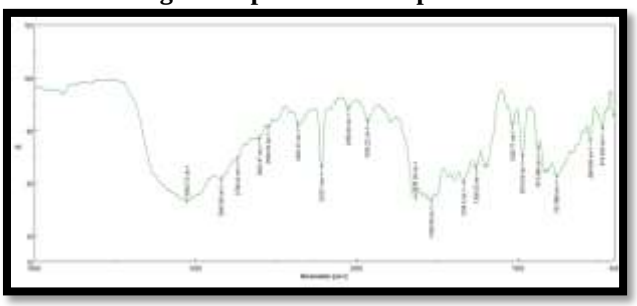

Fig4. IR Spectrum of Beta-cyclodextrin

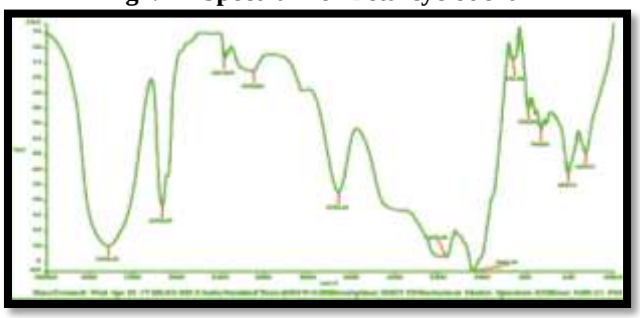

Fig5. IR Spectrum of RPV:Beta-cyclodextrin (1:3)

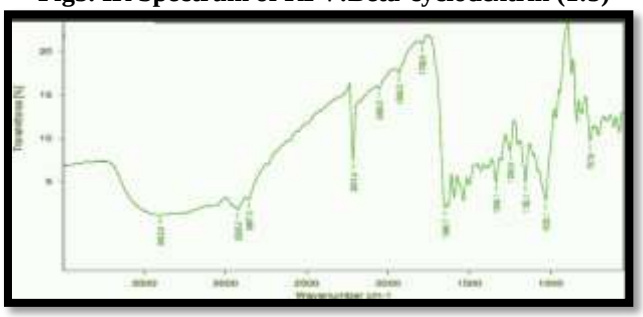

Table3. IR Interpretation

No	PURE DRUG RPV		Beta-cyclodextrin		RPV : Beta-cyclodextrin (1:3)		
	Wavenumber (cm^{-1})	Functional Groups	Wavenumber (cm^{-1})	Functional Groups	Wavenumber (cm^{-1})	Functional Groups	Intensity
1	3053.73	–NH Stretch	3460.00	–OH Stretch	3222.4	–NH & -OH Stretch	Strong, broad
2	2842.56	sp^3 C-H Stretch	2806.34	sp^3 C-H Stretch	2880.17	sp^3 C-H Stretch	Strong
3	2738.42	sp^2 C-H Stretch	2355.93	C=O stretch	2744.21	sp^2 C-H Stretch	Medium

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4	2218.7	C≡N Stretch	1975.45	sp^3 C-H Bend	2217.7	C≡N Stretch	Medium
5	1635.34	C=C stretch	1350.33	sp^3 C-H Bend	1749.62	C=O stretch	Strong
6	1536.99	C=C aromatic stretch	1119.17	C-O stretch	1465.63	sp^3 C-H Bend	Medium
7	1334.5	sp^3 C-H Bend	1001.69	C-O stretch	1348.00	sp^3 C-H Bend	Variable
8	1258.32	C-N Stretch	756.42	C-H Aromatic Bend	1227.61	C-N Stretch	Variable

Preparation of Solid Dispersion:

Solid dispersions of RPV were prepared by Kneading and Microwave Irradiation method. The drug to polymer ratio used is 1:2, 1:3, 1:4 using polymer Beta-cyclodextrin.

Table4. Absorbance of SD in 0.1N HCl at 280nm

No	Method	Conc (µg/ml)	Beta-cyclodextrin		
			1:2	1:3	1:4
1	Kneading	10	0.2947	0.3437	0.3001
		20	0.5077	0.5673	0.5292
2	Microwave Irradiation	10	0.3512	**0.4847**	0.4064
		20	0.6014	**0.7123**	0.5862

Evaluation of SD:

Table5. Evaluation of SD

Sr. No.	Evaluation parameter	Observed	Standards
1	**Bulk Density**	0.49 gm/cm^3	Pass
2	**Tapped Density**	0.62 gm/cm^3	Pass
3	**Carr's Index**	5.5%	Excellent (0-10%)
4	**Hausner's Ratio**	1.05	Excellent (1.00-1.11)
5	**Angle of Repose**	26°	25-30°
6	**Drug Content**	99.01%	97-102%

In-Vitro Drug Release Studies:

From the results obtained from the UV spectroscopy for Solid dispersion (Rilpivirine HCl : Polymer) in the ratio 1:2, 1:3 and 1:4, the Solid dispersion with Beta-cyclodextrinin the ratio 1:3 shows highest drug release compared to other polymer and ratio. Therefore the dissolution study are carried out for **Rilpivirine HCl : Beta-cyclodextrin(1:3)**. The results were shown in Table 6,7,8,9,10 followed by drug relase profile Fig 6,7,8,9,10.

- Medium: 0.5% Polysorbate 20 in 0.01N Hydrochloric acid, pH 2.0.
- Volume: 900 ml.

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- Apparatus: Paddle (USP-II).
- Speed: 75 rpm.
- Temperature: 37.0± 0.5°C.
- Recommended sampling time: 15, 30,45,60,90 and 120 mins.

Concentration (µg/ml)	Absorbance (Abs)
0	0
5	0.2868
10	0.5703
15	0.8823
20	1.1403
25	1..4779

TABLE: 6

Fig6. Calibration Plot

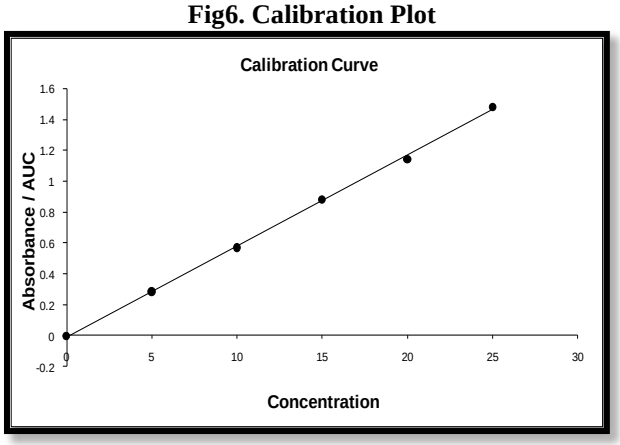

Table7. Drug RPV

Time (mins)	Drug	
	Absorbance (Abs)	% Drug Released
0	0	0
15	0.1956	24.89
30	0.2829	35.21
45	0.3512	43.01
60	0.4733	57
90	0.6014	71.36
120	0.5864	68.79

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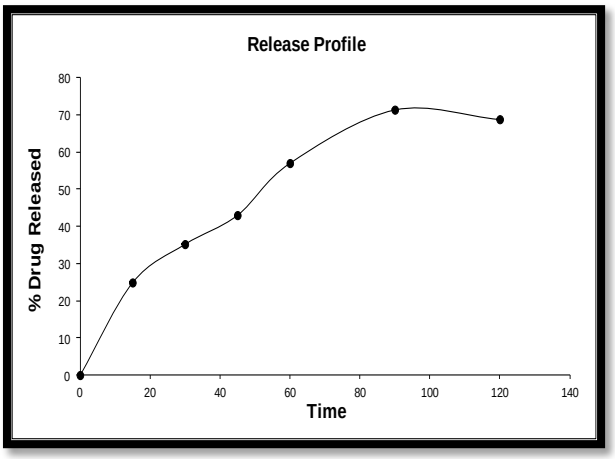

Fig7. Drug Release Profile (RPV)

Table8. RPV: Beta-cyclodextrin (1:2)

Time (mins)	1:2 ratio	
	Absorbance (Abs)	% Drug Released
0	0	0
15	0.2913	36.63
30	0.3306	40.99
45	0.4235	51.68
60	0.5488	65.95
90	0.5987	71.04
120	0.5532	64.95

Fig8. Drug Release Profile RPV:Beta-cyclodextrin(1:2)

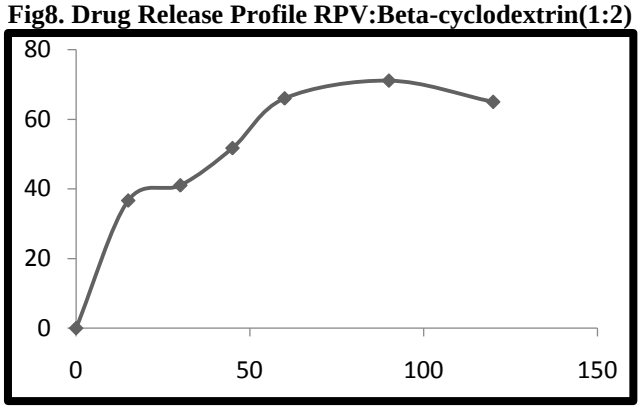

Table9. RPV: Beta-cyclodextrin (1:3)

Time (mins)	1:3 ratio	
	Absorbance (Abs)	% Drug Released
0	0	0

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15	0.3146	39.49
30	0.4306	53.13
45	0.5747	69.82
60	0.6933	83.09
90	0.8314	98.32
120	0.7719	90.29

Fig9. Drug Release Profile RPV:Beta-cyclodextrin(1:3)

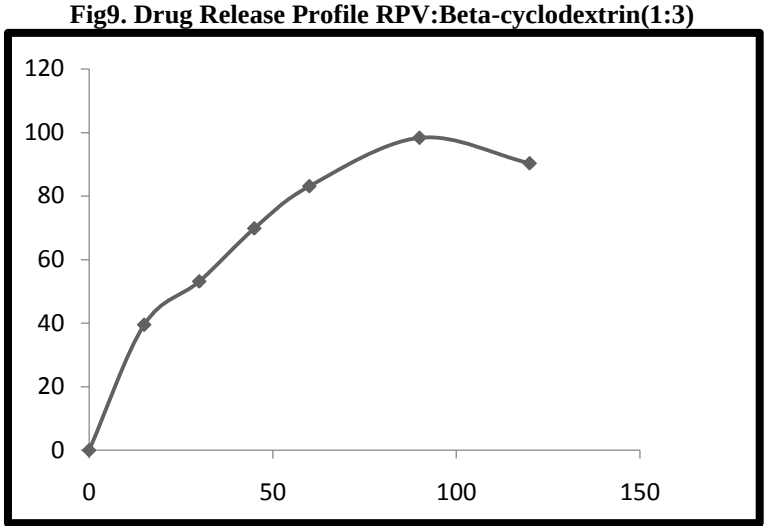

Table10. RPV: Beta-cyclodextrin (1:4)

Time (mins)	1:4 ratio	
	Absorbance (Abs)	% Drug Released
0	0	0
15	0.3119	39.16
30	0.3566	44.15
45	0.4752	57.88
60	0.5699	68.45
90	0.6245	74.07
120	0.5746	67.43

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Fig10. Drug Release Profile RPV:Beta- dextrin (1:4)

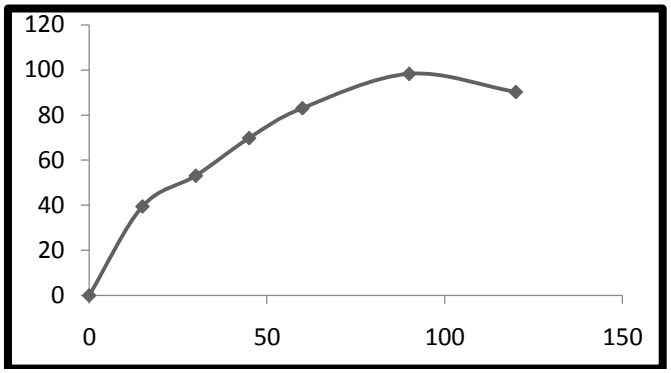
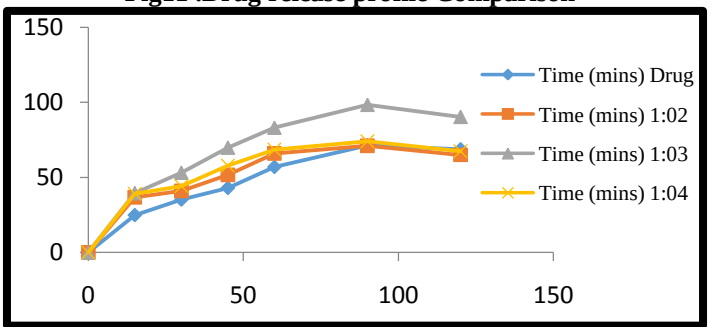


Fig11 .Drug release profile Comparison



IV. SUMMARY AND CONCLUSION

Rilpivirine HCl belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. The Solid Dispersion of RPV-Beta cyclodextrins were characterized with respect to Bulk density, Tapped Density, Carr's index, Hausner's ratio, Angle of Repose and Drug Content**.** Solid dispersions were ready by solvent evaporation, kneading and microwave methodology. The dispersions were evaluated fornumerous in vitro parameters like solubility study, dissolution study, Fourier rework infrared spectrum analysis (FT-IR). Diluents for preparation of varied samples were finalized once finding out the solubility of API in several solvents (methanol, acetonitrile, methylene chloride, water, 0.1N NaOH, 0.1NHCl). The drug was found to be extremely soluble in 0.1N HCl. Detection wavelength was hand-picked once scanning the quality resolution of drug over 200 to 400nm, From the U.V spectrum of Rilpivirine complex it's evident that 280nm. In vitro studies showed higher dissolution profile with beta-cyclodextrin solid dispersions compared to 1:2 and 1:4 within the quantitative relation 1:3 in Microwave method. Thus, microwave technology offers an easy, efficient, solvent-free promising different methodology to arrange solid dispersion of Rilpivirine HCl with vital enhancement of the solubility and dissolution rate.

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CONFLICT OF INTEREST

The authors of the article don't have any conflict of interest.

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