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Spray Drying: A Approach for Solubility Enhancement of Ritonavir by Solid Dispersion

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ABSTRACT

The aim of present work was to improve the dissolution rate of Ritonavir by preparing micro-particles with certain hydrophilic polymers via spray drying technique. Role of spray drying method was studied for solubility enhancement of poorly aqueous soluble model Ritonavir using solid dispersion approach. All the carriers showed dissolution improvement vis-à-vis pure drug in varying degrees. The solid dispersions were characterized in comparison with pure drug and corresponding Physical mixture (PM). The prepared solid dispersion were evaluated by drug content analysis, saturation solubility, DSC (Differential scanning calorimeter), SEM (Scanning electron microscopy), PXRD (Powder X-ray diffraction), FTIR (Fourier transform infrared spectroscopy).and in vitro drug release. Absence of pure drug peaks in PXRD suggests transformation of crystalline drug into an amorphous form. The transformation of Ritonavir from crystalline to amorphous state by spray drying and the hydrophilic coating of drug particles by the polymers are considered for improvement of Solubility and dissolution of Ritonavir.

Keywords: Spray Drying, Solubility Enhancement, Ritonavir, Solid Dispersion.

INTRODUCTION

Poorly water soluble BCS class II entities, having high permeability, affiliated with obtuse drug absorption which leads to scarce and varying bioavailability. It assumes that the rate of absorption is depends on the drug solubility and dissolution, successive transport on intestinal membrane and liver. Solubility is generally known as amount of a substance dissolves in a given volume of solvent at a specified temperature and pH. Formulation strategies for such class drugs are pointed towards their solubility enhancement. [1] Ritonavir, selected drug in the present studies, is poorly water soluble drug cognized for dissolution or solubility limited absorption. A few endeavors to solubility enhancement of Ritonavir were reported in the literature. [2] The current studies aim towards exploring various water soluble carriers used to solubility enhancement as well dissolution using Spray drying method. [3]

By many estimates up to 40% of NCE discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues affect the delivery of many existing drugs. Solid dispersion technology can be used to improve the *in vitro* and *in vivo* dissolution properties of dissolution dependent poorly water soluble drugs.

The present research work deals with the study of Ritonavir solubility enhancement by using spray drying technique. The usual dose of Ritonavir is 100 mg given twice daily by oral route. But 45% dose excreted

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unchanged in faeces due to its low solubility & this low solubility is the basis to prepare the solid dispersion. Due to this solubility of the Ritonavir get increased & hence the dose of Ritonavir will be reduced. Solubility enhancement may lead to reduction of dose and eventually less side effects of the drug. Former reason results in reduction of cost therapy. Also may lead into dosing frequency increase in patient compliance.

MATERIAL AND METHODS

Materials

Ritonavir was gifted by Lupin research park, Pune, India. Kollidon VA 64, Lutrol F 68 from BASF india, and Hydroxypropyl Methyl cellulose (HPMC 5cps) Colorcon, All other chemicals used were of analytical grade and procured from commercial sources.

Preparation of physical mixtures [4]

Physical mixtures were prepared by mixing of Ritonavir and polymers in mortar and pestle by geometrical dilution method. This mixture is then passed through sieve (335µm). All physical mixtures were prepared by same process as shown in Table 1.

Preparation of SD by spray drying

The Ritonavir and the polymers (Kollidon VA 64, HPMC and Lutrol F68) were weighed accurately in various ratios as shown in Table 1and then dissolved in sufficient quantity of methanol using magnetic stirrer to obtain a clear solution. The solution was spray dried using laboratory-scale spray dryer (LABULTIMA, Diamond Industrial Estate, Mumbai, 400068 India) under the following set of conditions shown in Table 2: Each solid dispersion batch was prepared in triplicates. The dispersions were stored in desiccators under vacuum until used for further study. [5]

Characterization of Drug and Solid Dispersion [6]

Melting point determination

Melting point of Ritonavir was determined by taking a small amount of sample in capillary tube sealed at one end and placed in beaker filled by liquid paraffin in melting point apparatus. The melting point was noted and readings were taken in triplicate. [7]

DSC analysis

Thermal behavior of Ritonavir was recorded by using DSC (Shimadzu 60) by using the DSC parameters (Table 3). The system was calibrated with a high purity sample of Indium. Sample was placed into in aluminum cup and sealed. An empty aluminum cup was used as a reference. [8-9]

Fourier transform infrared spectroscopic study (FTIR)

The IR absorbance spectrum of Ritonavir was traced using IR 200 spectrometer (Thermo Electron Corporation) over a wavelength range of 400 to 4000 cm^{-1}. The sample was directly placed in the sample cell in IR chamber & graph was analyzed for any interaction of drug and polymer in solid dispersion. [10]

Thin layer chromatography (TLC)

TLC was used to check purity & determined the presence of any derivative, impurity or reactant in the sample of Ritonavir. Pure drug and solid dispersion equivalent to 10 mg dissolved in 100 mL of solvent separately. Methanol: acetonitrile (50:50) served as mobile phase. Spots were detected with the help of UV chamber. The R_f (Retention factor) value was calculated.

Powder X-ray diffraction analysis (PXRD)

The powder property of Ritonavir was evaluated by using PXRD. Powder nature of Ritonavir, polymer & optimized prepared SDs were determined using Phillips X-ray diffractometer PW 3710 scanner, IW 1830 generator with scan rate of 1° min^{-1} from at 2θ range from 1 to 40°C. [11]

Scanning electron microscopy (SEM)

The surface morphology of Ritonavir and prepared solid dispersion along with polymer of optimized batch was performed by a scanning electron microscopy using JSM-6390 microscope. [12]

UV spectroscopy

The ultraviolet absorption spectrum of a Ritonavir solution in 0.1N HCl was obtained using SHIMADZU 1700-PC UV visible spectrophotometer and 1 cm quartz cells, over a wavelength range of 200 to 400 nm. The maxima wavelength (λ_{max}) was determined by using UV probe software. [13]

Table 1: Ritonavir solid dispersion formulation

Ritonavir : Polymer ratio (w/w)	Polymers		
	Kollidon VA 64	Lutrol F68	Lutrol F127
1:1	RA1	RH1	RL1
1:2	RA2	RH2	RL2
1:3	RA3	RH3	RL3
1:4	RA4	RH4	RL4
1:5	RA5	RH5	RL5
1:6	RA6	RH6	RL6

Table 2: Optimized process parameters of spray drying

S. No.	Parameter	Optimized value
1	Feed rate	2 mL/min
2	Pressure	0.15 mPa
3	Inlet temperature	70°C
4	Outlet temperature	55°C
5	Aspirator speed	20 mbar
6	Atomization air pressure	2 Kg/cm^2

Table 3: DSC Analysis parameter

Parameter	Value
Weight of sample	3-10 mg
Heating range	50-300°C
Heating rate	10°C/min
Flow of nitrogen gas	20 mL/min

Evaluation of Solid Dispersion [14]

Morphological evaluation

The prepared solid dispersion by spray drying method was subjected for the morphological characterization like color, appearance, flow properties etc. [15]

Drug content uniformity analysis

Prepared solid dispersion batches were subjected for drug content uniformity analysis. Solid dispersion equivalent to 10 mg of Ritonavir was weighed accurately and dissolved in 100 mL of methanol in volumetric flask. The solution was then suitably diluted with methanol and assayed for drug content on UV spectrophotometer. [16]

Saturated solubility analysis

Solubility study was carried out for assessment of solubility enhancement due to preparation of solid dispersion. Excess quantity of drug and prepared solid dispersions were introduced separately in glass vial containing 10 mL of distilled water and vials were shaking for 24 hours continuously at room temperature in laboratory shaker. The resulting solutions were filtered, suitable dilutions were made using distilled water and the drug solubility in the pure from and prepared solid dispersion was calculated by spectrophotometrically. [17]

Wettability study

Wettability study was performed using open capillary tubes. A pure drug & various prepared solid dispersions with different polymers were filled in capillary with their lower capillary ends dipped into aqueous solution of water soluble dye (0.01% w/v eosin in water). The upward migration of the colored front was registered as a function of time and % wettability was calculated for all samples. [18]

***In-vitro* dissolution studies**

In-vitro dissolution studies were performed in triplicate on USP type II apparatus for 2 hours in distilled water at 100 rpm. The temperature was maintained at 37.5 ± 1°C, pure drug and solid dispersions equivalent to 100mg of were taken. The aliquots were taken at the interval of each 10 mins and analyzed for absorbance using UV-spectrophotometer at 247 nm. The results of pure drug and solid dispersions were compared for prediction of dissolution enhancement is achieved. [19]

RESULTS

Melting point determination

The melting point range of Ritonavir sample was found to be 120°C to 123°C, by capillary method which is nearer to the reported melting point range 119 to 123°C.

DSC analysis

The DSC analysis data showed that there was absence of sharp endothermic peak at 125°C in Ritonavir optimized solid dispersion thermogram, base peak, the drug is converted from crystalline form to amorphous form. DSC graph for pure drug showed a sharp endotherm which was indicative of its melting temperature, followed by an exotherm, which signifies that after melting, pure drug decomposes. The DSC thermogram of solid dispersions revealed disappearance of the endothermic peak which demonstrates that drug could be homogeneously dispersed in an amorphous phase and no drug crystallizes out of the solid dispersion. Lower the δH value, more the amorphous product and this was supported with enhancement of dissolution rate.

Fourier transform infrared spectroscopic study (FTIR)

FT-IR analysis of solid dispersion was carried out to observe the possibility of any functional group interactions between the drug and polymer. FT-IR spectra revealed absence of any interaction since, no variations or shifting in the specific absorption bands of functional group was observed.

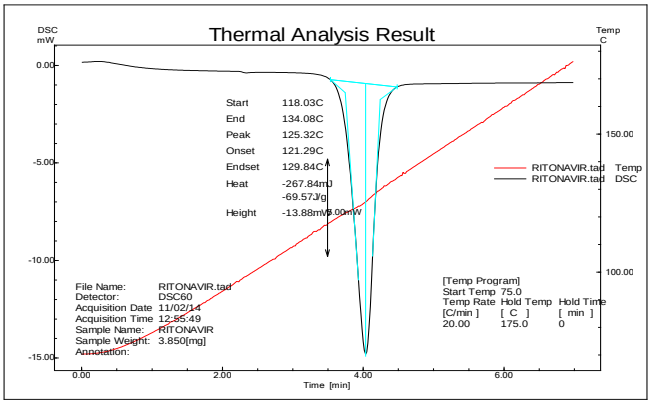

Fig. 1: DSC thermogram of Ritonavir

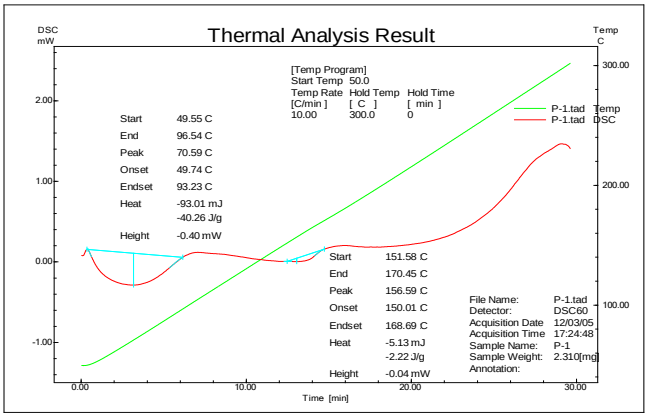

Fig. 2: DSC thermogram of Kollidon VA 64

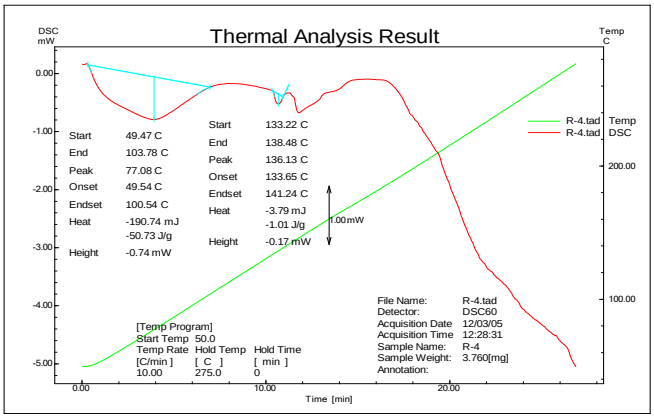

Fig. 3: DSC thermogram of SD

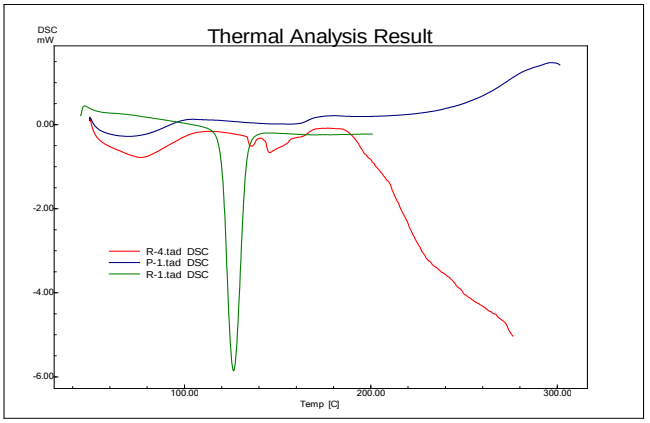

Fig. 4: Overlay DSC thermogram

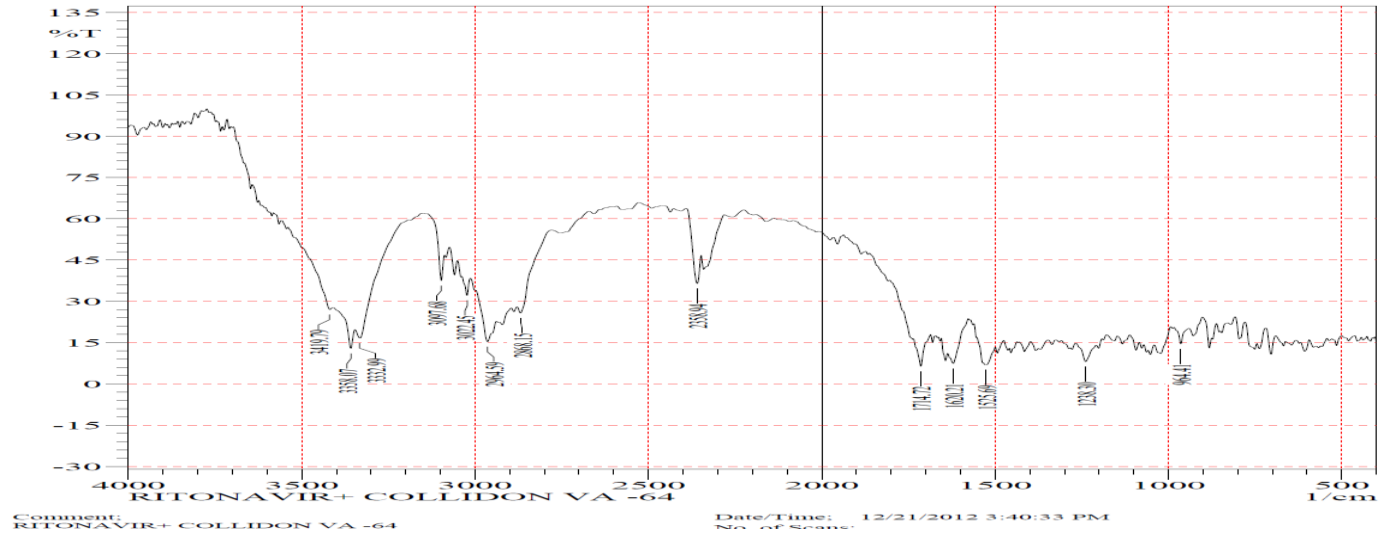

Fig. 5: FT-IR spectra for Ritonavir and Kollidon VA64 (Physical mixture)

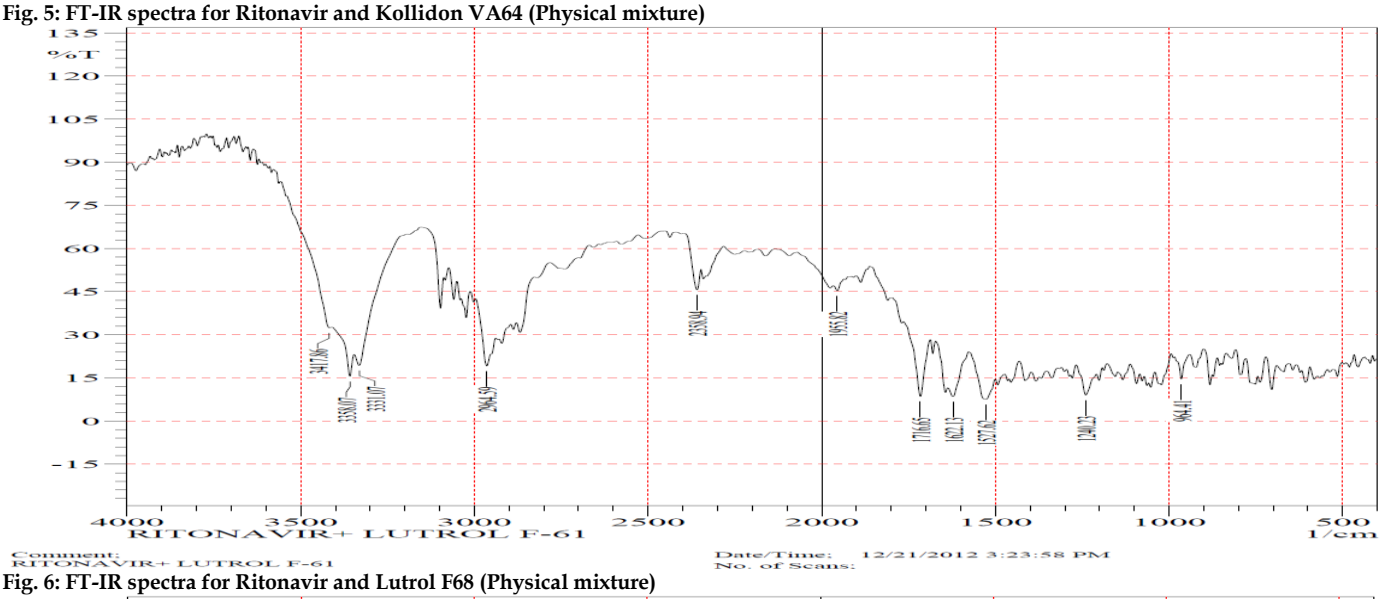

Fig. 6: FT-IR spectra for Ritonavir and Lutrol F68 (Physical mixture)

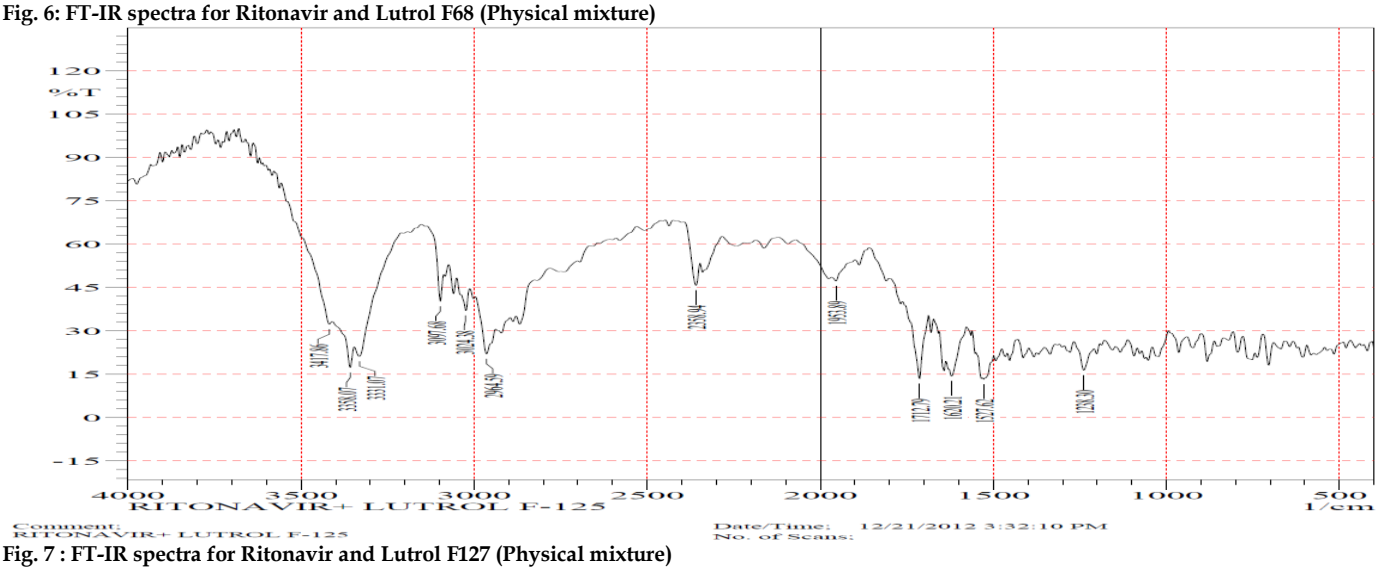

Fig. 7 : FT-IR spectra for Ritonavir and Lutrol F127 (Physical mixture)

Table 4: TLC analysis of Ritonavir solid dispersion

Batch code	R_f value	Batch code	R_f value	Batch code	R_f value
RA1	0.807	RH1	0.813	RL1	0.81
RA2	0.819	RH2	0.806	RL2	0.8125
RA3	0.81	RH3	0.824	RL3	0.817
RA4	0.828	RH4	0.83	RL4	0.829
RA5	0.814	RH5	0.819	RL5	0.8165
RA6	0.805	RH6	0.808	RL6	0.8065

Thin layer chromatography

TLC analysis showed the calculated R_f value for the different solid dispersions for Ritonavir. It was observed that pure drug & SD had similar R_f value which was indicative of absence of chemical alteration of the drug.

Powder X-ray Diffraction (PXRD) Analysis

The crystalline nature of pure drug was again confirmed by powder X-ray diffraction. The sharp peaks revealed in drug PXRD justify that drug was present in crystalline form. But solid dispersion RA4 PXRD doesn't showed any sharp peak in the PXRD analysis represent that there was absence of crystalline structure in Kollidon VA 64 polymer. Also the optimized formulation of spray drying solid dispersion didn't show any sharp peak as given in pure drug alone. Hence it showed that the drugs were converted into amorphous form from crystalline form.

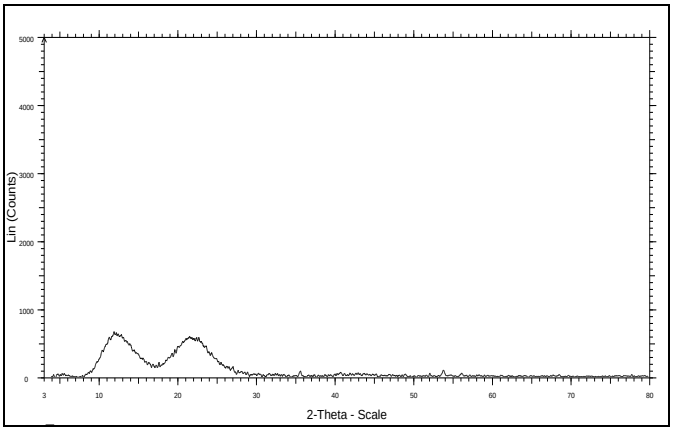

Fig. 8: PXRD of Kollidon VA 64

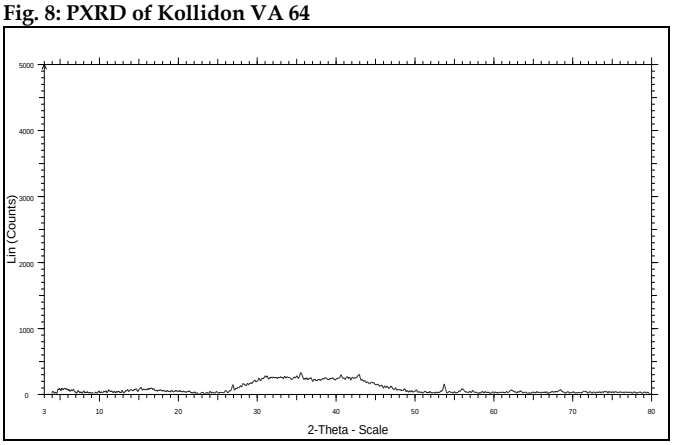

Fig. 9: PXRD of Ritonavir solid dispersion complex

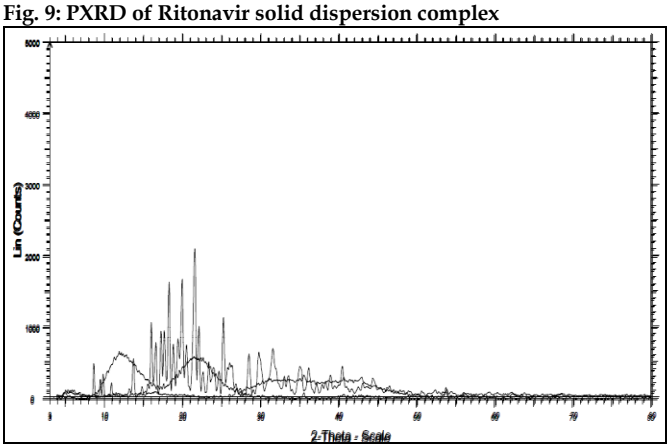

Fig. 10: PXRD of pure Drug, Kollidon VA 64 & RA4 SD overlay

Scanning electron microscopy (SEM)

From the SEM analysis images it was seen that the API Ritonavir were crystalline flakes in nature& the Kollidon VA 64 was in the form of amorphous powder lumps. But after spray drying solid dispersion the microsphere were formed & the drug might be entrapped in the core of polymer which is main phenomenon for solubility enhancement. The polymer coat reduced the surface tension; enhance the wettability, solubility & ultimately dissolution.

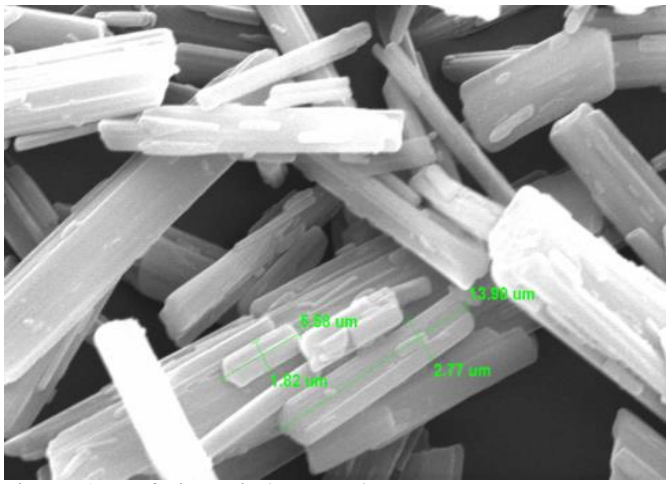

Fig. 11 : SEM of Ritonavir drug powder

Fig. 12: SEM image of Kollidon VA 64

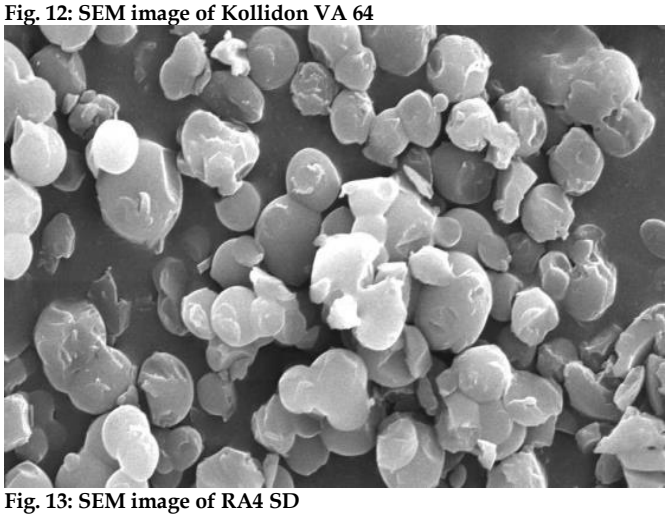

Fig. 13: SEM image of RA4 SD

UV spectral characteristics

UV spectrum of Ritonavir and respective SDs showed the wave length maxima (λ_{max}) and spectrum pattern were remain constant. Hence it can be concluded that the chemical nature of drug remains unchanged.

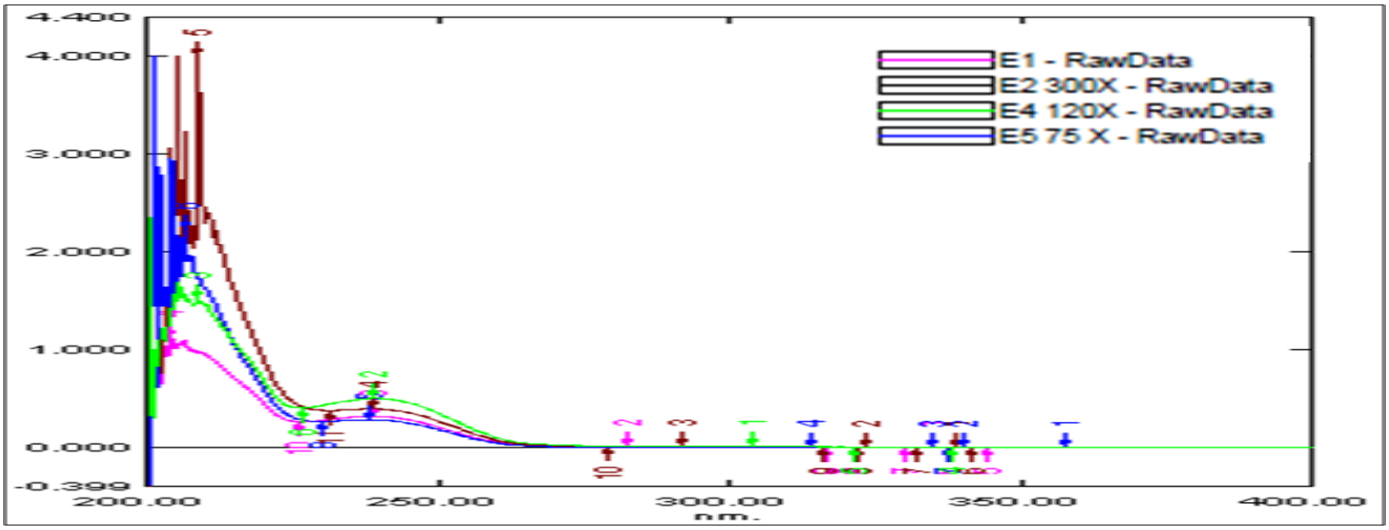

Fig. 14: UV spectrum overlay graph of Ritonavir API & solid dispersions

Table 5: Physical properties of Ritonavir solid dispersions

Method	Polymer	Physical properties of solid dispersions		
		Colour	Appearance	Flow properties
Spray drying method	Kollidon VA64	White	Fluffy powder	Fine powder
	Lutrol F-68	White	Fluffy powder	Fine powder
	Lutrol F-127	White	Fluffy powder	Fine powder

Table 6: Drug content uniformity analysis of Ritonavir solid dispersion

Batch code	% Content	Batch code	% Content	Batch code	% Content
RA1	98.88 ± 1.80	RH1	99.03 ± 1.10	RL1	99.27 ± 1.34
RA2	100.08 ± 1.50	RH2	99.0 ± 2.10	RL2	98.78 ± 1.63
RA3	102.0 ± 1.60	RH3	99.82 ± 1.60	RL3	98.29 ± 1.21
RA4	99.20 ± 1.65	RH4	99.63 ± 1.65	RL4	100.2 ± 1.20
RA5	100.20 ± 1.20	RH5	101.21 ± 1.10	RL5	100.1 ± 1.36
RA6	99.90 ± 1.75	RH6	99.0 ± 0.95	RL6	99.0 ± 2.10

Table 7: Saturated solubility analysis of Ritonavir solid dispersion

Batch code	Solubility (µg/mL)	Batch code	Solubility (µg/mL)	Batch code	Solubility (µg/mL)
RA1	41.805	RH1	35.55	RL1	38.52
RA2	64.96	RH2	53.1	RL2	52.26
RA3	85.375	RH3	71.325	RL3	68.85
RA4	126.76	RH4	91.53	RL4	97.54
RA5	148.92	RH5	97.44	RL5	112.52
RA6	161.59	RH6	102.87	RL6	134.29

EVALUATION OF SOLID DISPERSION

The physical evaluation of prepared solid dispersion showed that all the samples were fine white fluffy powder prepared by spray drying method.

Drug content uniformity analysis

Assay (*i.e.* drug content uniformity) of Ritonavir solid dispersions were determined by the UV analysis. All the readings were carried out in triplicate & calculated as mean ± S.D. It was found that the drug content within range 98%- 102% of drug content.

Saturated solubility analysis

Saturated solubility analysis studies of Ritonavir showed an increased solubility with increase in the concentration of carrier. The solubility result for different carrier in different concentration with Ritonavir. Among the carriers used Kollidon VA 64 showed the promising solubility enhancement. Increase in weight fraction of the hydrophilic polymer resulted in improved saturation solubility. Water was used as dissolution media in the dissolution system to prove aqueous solubility enhancement.

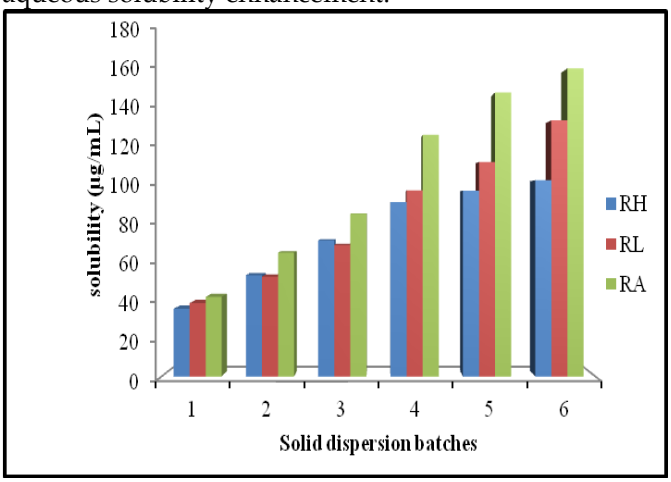

Fig. 15: Saturated solubility analysis of Ritonavir solid dispersion

Wettability study

Table 8: Wettability analysis of Ritonavir solid dispersion

Batch code	% Wetting	Batch code	% Wetting	Batch code	% Wetting
RA1	14	RH1	9	RL1	12
RA2	25	RH2	12	RL2	17
RA3	49	RH3	16	RL3	32
RA4	57	RH4	21	RL4	41
RA5	64	RH5	28	RL5	49
RA6	72	RH6	34	RL6	63

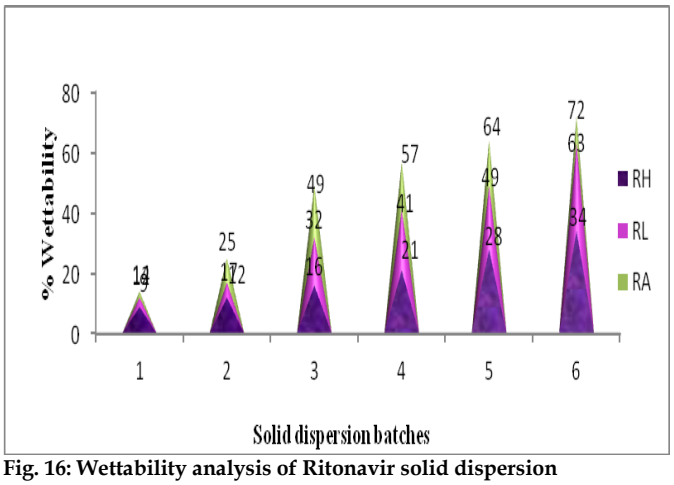

Fig. 16: Wettability analysis of Ritonavir solid dispersion

In vitro dissolution study of Ritonavir Pure drug

Table 9: Percent release of pure Ritonavir

Time (min)	0	10	20	30	40	50	60
Pure drug	0	2.596	4.571	5.653	7.178	7.829	8.812

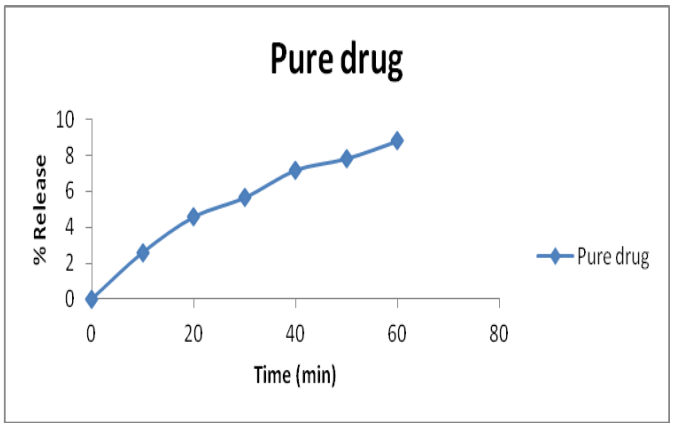

Fig. 17: Percent release of pure Ritonavir

Table 10: Percent release of RA batch SD

Time (min)	RA1	RA2	RA3	RA4	RA5	RA6
0	0.00	0.00	0.00	0.00	0.00	0.00
10	2.12	2.42	2.41	5.86	32.42	25.03
20	17.83	9.68	16.67	38.52	55.41	45.71
30	20.49	17.86	49.76	82.52	72.57	52.95
40	27.99	28.36	64.72	94.92	81.40	60.64
50	30.53	37.45	64.24	97.45	88.21	66.73
60	34.37	50.42	63.61	100.29	89.52	71.21

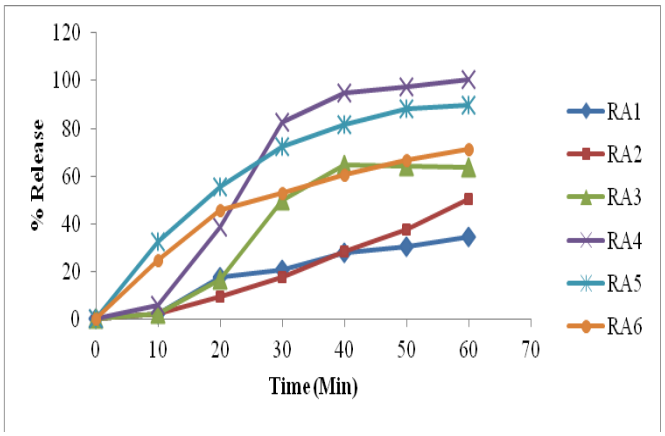

Fig. 18: Percent release of RA batch SD

Table 11: Percent release of RH batch SD.

Time	RH1	RH2	RH3	RH4	RH5	RH6
0	0.00	0.00	0.00	0.00	0.00	0.00
10	7.79	9.31	11.38	20.09	23.59	27.90
20	13.71	14.00	14.32	32.54	38.51	49.43
30	15.76	20.44	20.63	43.81	52.08	66.35
40	21.53	27.31	29.01	51.04	61.41	71.44
50	23.49	31.25	33.93	52.97	67.50	76.35
60	26.44	39.62	43.65	59.01	70.14	78.42

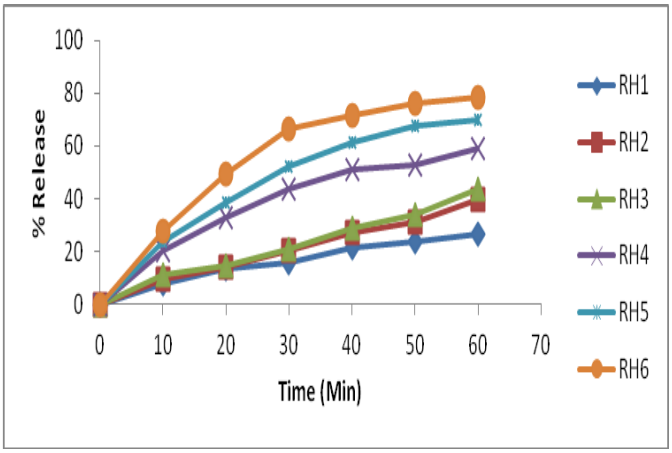

Fig. 19: Percent release of RH batch SD

Table 12: Percent release of RL batch SD

Time (Min)	RL1	RL2	RL3	RL4	RL5	RL6
0	0	0	0	0	0	0
10	3.03	11.46	15.37	22.15	29.14	26.8
20	11.02	18	26.14	34.19	44.92	53.83
30	15.87	24.66	37.17	47.94	60.16	77.18
40	22.32	32.86	46.42	58.07	70.57	97.55
50	26.1	40.97	53.66	62.91	76.3	98.7
60	33.58	51.93	58.07	67.37	81.85	103.41

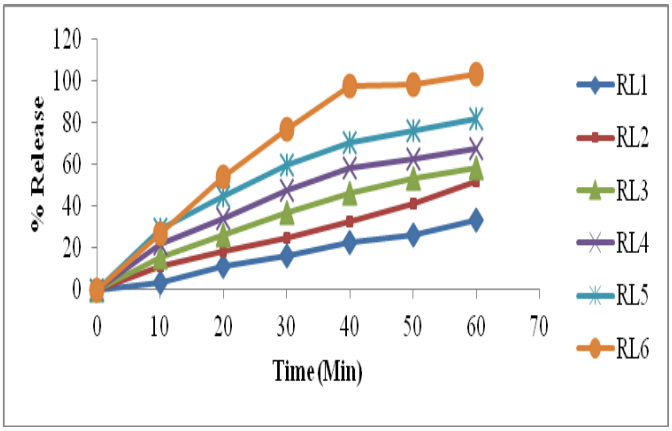

Fig. 20: Percent release of RL batch SD

Pure Ritonavir (100 mg) showed only 7.31 % release after 1 hour (Table 9). The amounts of Ritonavir dissolved in distilled water from different spray dried solid dispersions batches RA, RH & RL were significantly higher when compared to the amount dissolved from pure drug Ritonavir. The pattern observed for prepared solid dispersions using different polymers by spray drying method was found that, an increase in Kollidon VA64, HPMC K4 & Lutrol F68 resulted in a significant increase in the dissolution rate irrespective of increase in the concentration of Ritonavir. It was also noted from dissolution data the

concentration of Kollidon VA 64 increased than optimum concentration then it gave sustained or controlled release effect with solid dispersion formulation. Hence, with the increase in the concentration of Kollidon VA 64 dissolution time was increased.

More solubility enhancement was observed in prepared solid dispersion due to the kollidon VA 64 polymer. Significant improvement in saturation solubility was observed compared to API. This could be attributed to coating of drug particles and formation of polymer coat around the drug particles. Solid dispersion in the ratio of 1:4 for drug: Kollidon VA 64 showed increase in saturation solubility of Ritonavir very effectively. With respect to increase in polymer concentration the solubility enhancement was less in solid dispersion in 1:5 & 1:4 drug : Kollidon VA 64 as compare to Solid dispersion in 1:3 & 1:4 drug: polymer weight ratio. The same behavior was observed with the dissolution study of these two formulations hence solid dispersion of above drugs: Kollidon VA 64 selected as optimized batch.

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