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ENHANCING THE SOLUBILITY OF RITONAVIR SOLID DISPERSION USING SPRAY DRYING TECHNIQUE

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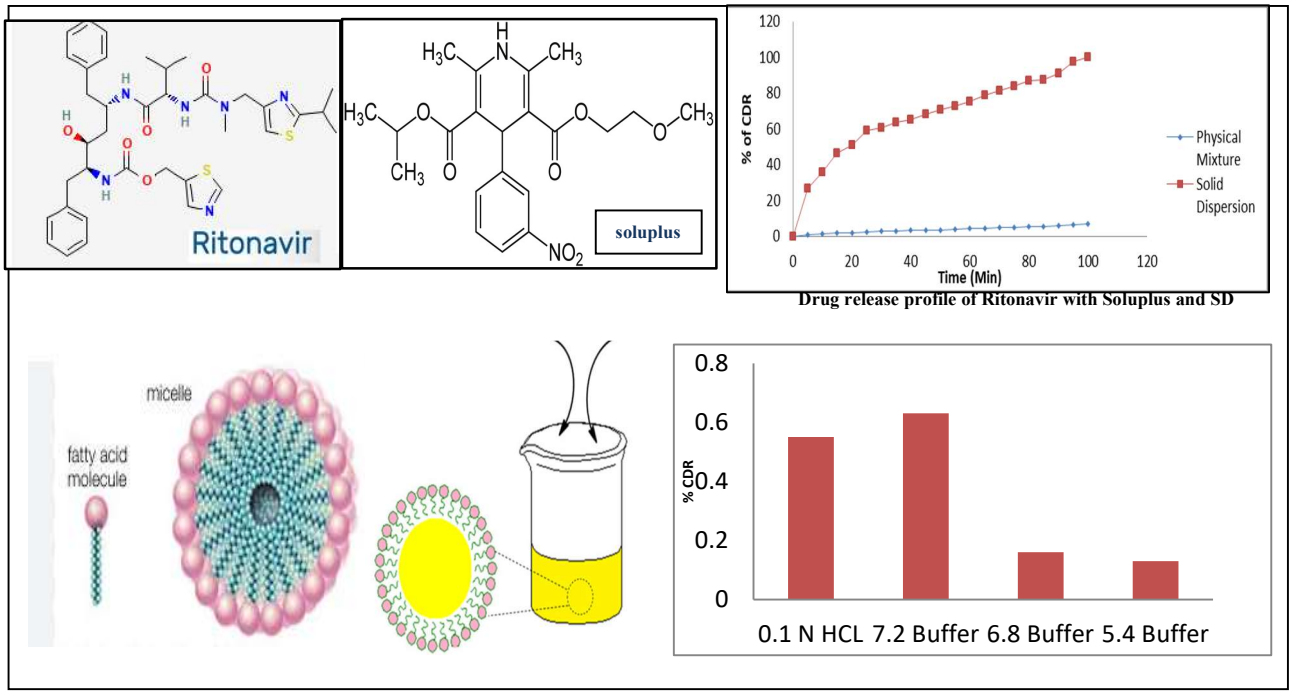
ABSTRACT

The Proposed investigation was focus on Improvement in the solubility of Ritonavir (BCS-II, anti-HIV drug). Addition of soluplus as polymer which is compatible with active ingredient to increase its solubility will be the main objective of research work. The solid dispersion was prepared by the spray drying technique using Drug and polymer in 1:3 ratios. The prepared solid dispersions of Ritonavir were characterized by XRD, DSC thermogram, % Entrapment Efficiency. In the present research work, a spray drying technique was successfully developed for the preparation of Solid Dispersion of ritonavir exhibiting improved solubility thereby increase rate of dissolution and oral bioavailability. The final batch of solid dispersion of Ritonavir with Soluplus shows the higher solubility in 0.1 N HCL, pH 7.2 buffer compare with pH 6.8 buffer and pH 5.4 buffer. The developed technique could be successfully applied for solubility enhancement of other BCS-II drugs also.

Keywords: Ritonavir, Soluplus, Spray Drying Technique, Differential Scanning colorimetry, Entrapment Efficiency

Graphical Abstract



Drug release profile of Ritonavir with Soluplus and SD

INTRODUCTION

Most of the pharmaceutical drugs show solubility limited bioavailability despite of good physiological activity which undesirably affects the formulation development as well as probable therapeutic effect. In a solid dispersion, the API and polymer may interact with number of mechanism including hydrogen bonds **[1]**. Solid dispersion is defined as the dispersion of one or more active ingredients in inert excipients, where the active ingredients could exist in finely crystalline, Solubilized or amorphous state **[2]**. Spray drying technology is defined as a unit operation in which a liquid stream is constantly divided into very fine droplets into a glass compartment, where they come in contact with hot gas and dried into fine particles[3]. spray drying is one of the most common techniques used to prepare solid dispersions due to the possibility of continuous manufacturing, ease of scalability, good uniformity of molecular dispersion and cost-effectiveness in large scale production with high recoveries (more than 95%) **[4]**. Ritonavir is a poorly water soluble drug and used for treatment of HIV **[5]**. Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its

predetermined specifications and quality characteristics **[6]**. Reasons for process validation of new product are change in site of manufacturing, change in batch size, and change in equipment, change in the critical control parameters, and change in vendor of API, change in specification on input material **[7]**. HPLC provides not only useful quantitative information on drug loss but also insights into the number of degradation products formed and their corresponding quantities. The chromatography was evaluated with a good resolution of all the peaks **[8]**. A significant portion of newly developed pharmaceutical molecules suffer from poor solubility and low bioavailability. They belong to the biopharmaceutical classification system- class II. Hence, developing an efficient, economical and reliable method for enhancing the solubility and bioavailability of poorly water-soluble drugs is need of the hour **[17]**.

MATERIAL AND METHODS

Material

Ritonavir was obtained from Glenmark pharmaceutical, sinnar and the Polymer soluplus was obtained from BASF (Thane). The solvent ethanol, Acetonitrile and Methanol purchased through S.D. fine chemicals. Spray dryer (Labultima LU 222 Advanced), HPLC (water 600 controller), FT-IR Spectrophotometer (Bruker, Alpha), Dissolution Apparatus (Electro lab, TDT-08L), Water heater cum shaker bath (Classic Scientific), pH Meter (Hanna instrument, HI2211), Digital weighing Balance (Shimadzu, AUX220) are used from respective mentioned model sources.

Preparation of Solid Dispersion by Spray Drying Technique [10, 11]

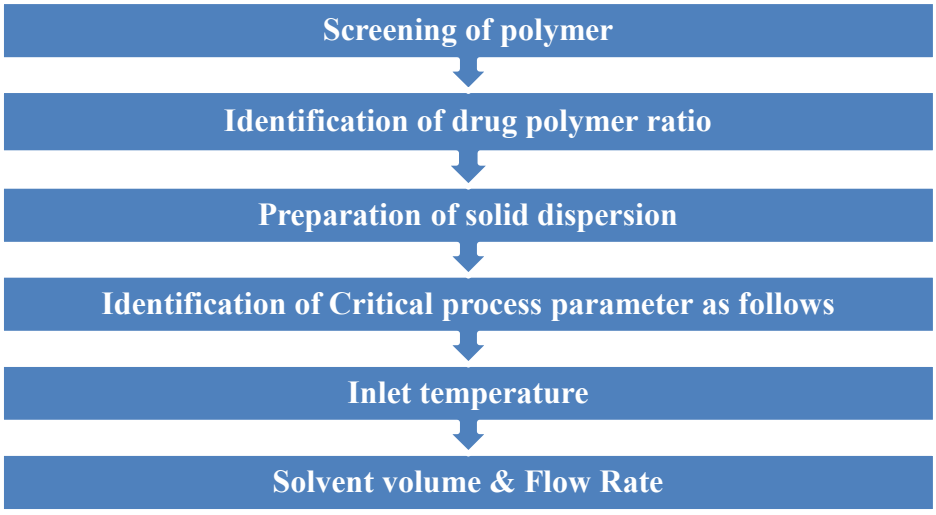


Figure 1: Steps for preparation of solid dispersion

The solid dispersion was prepared by using the spray drying technique (Labultima LU 222 Advanced) by Drug and polymer as 1:3 ratios. The weighed amount of Ritonavir and polymer dissolved in 20 ml ethanol solvent, the mixture stirred on magnetic stirrer at 510 rpm. Then the mixture spray through the spray dryer by setting critical process parameter shown in **Table 1**.

Critical process parameter

Table 1: Critical process parameter of spray drying technique

Inlet temperature	**45^{0}c**
Outlet temperature	**40^{0}c**
Feed flow rate	**1 ml/min**
Solvent volume	**20 ml**
Ratio	**1:3**
% Yield	**15.14%**

Solubility study [12]

The prepared Solid dispersion of Ritonavir was add in 10 ml of different solvent like 0.1N HCL, 7.2 buffer, 6.8 buffer and 5.4 buffer then the mixture kept in water heater cum shaker bath at temperature 37^{0}C for 48 hrs. The solution was removed and diluted up to 4 ml methanol injected in HPLC for further analysis with same HPLC variables.

Preparation of physical mixture [13]

In vitro dissolution studies were carried out using USP apparatus with 900 ml of 0.1 N HCl as dissolution media, maintained at temperature 37±0.5^{0}C at100 rpm for 60 min. The 5 ml sample were withdrawn at 5, 10, 15, 20, 25, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and replaced by 5 ml of fresh 0.1 N HCL dissolution media. The collected sample injected in HPLC for further analysis.

Evaluation of final solid dispersion and physical mixture

Morphological evaluation [18, 19]

The prepared solid dispersion by was subjected for the morphological characterization like color, appearance, flow properties etc.

Practical Yield [14]

Percentage practical yield was calculated to know about percent yield by adopted method which helps in selection of appropriate ratio for preparation of solid dispersions.

Equation 1: Percentage Practical yield calculation

$$\text{Practical yield \%} = \frac{\text{Actual weight of solid dispersion}}{\text{Theoretical weight (Drug + carrier)}} \times 100$$

Drug content determination

Drug content was calculated by dissolving SDs equivalent to 20 mg SD in 20ml 0.1N HCl and filtered the solution, suitably diluting with up to 4ml Methanol (the 1ml filtrate dilute with 3 ml methanol) and solution directly injected in HPLC.

Equation 2: Drug content determination

$$\text{Drug content (\%)} = \frac{\text{Amount of drug in SD}}{\text{Amount of Solid dispersion}} \times 100$$

Dissolution Studies:

The dissolution profile of physical mixture (PM) and Solid dispersion were studied up to Time point 5min to 100min with respect to % drug release hence the difference evaluated namely physical mixture (PM) and Solid Dispersion (SD). In vitro dissolution studies for Solid dispersion and Physical Mixture were carried out using USP apparatus method in 900 ml of 0.1 N HCl dissolution media, maintained at temperature 37±0.5^{0}C at100 rpm for 60 min. The 5 ml sample were withdrawn at 5, 10, 15, 20, 25, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and replaced by 5 ml of fresh 0.1 N HCL dissolution media. The collected samples then injected in HPLC for further quantitative determination.

% Entrapment Efficiency

Prepared SDs adds in 6.8 buffers in test tubes the mixture kept in water heater cum shaker bath at 37^0 for 48 hrs **[15, 16]**. Then the solution filtered, suitably dilution with Methanol and phosphate buffer and the solution injected in HPLC.

Equation 3: % Entrapment Efficiency

$$\%EE = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Differential scanning Calorimetry

Differential scanning Calorimetry has been widely used calorimetric tool to study the solid state interaction of drug and Soluplus polymer. Modulated temperature DSC equipped with an intercooler (DSC Q20 V24.11 build 124) to calibrate the temperature and enthalpy scale. The heat flow range 0.5-4.5 w/g over a temperature range is 40-390^{0}C.

X-ray diffraction

In this investigation, samples of pure sample of ritonavir solid dispersion were analyzed using XRD equipment ASCII Dump (XRD) instrument. The samples 50 mg were quickly placed into the section used for sample

analysis. The produced diffraction pattern of each sample was read and examined. The method reported earlier was followed in this study **[20]**.

RESULTS AND DISCUSSION

Whenever Ritonavir drug solution analyzed by HPLC it shows sharp peak at retention time 2.1 min. shown in **Figure 2**.

From calibration curves of Ritonavir **(Table 2, Figure 3)**, it was concluded that when graph of AUCVs. Concentration is plotted the graph shows that Ritonavir shows linearity in 75-175 ppm concentration and shows linearity when AUC was taken at 240 nm.

Solubility study: The final batch of Ritonavir-Soluplus solid dispersion shows the higher solubility in 0.1 N HCl, pH 7.2 buffer compare with pH 6.8 buffers and pH 5.4 buffers with different solubilizers Poloxamer 407, Poloxamer 188 and Kollidon VA 64 **(Table 3, Figure 4)**.

Practical yield

The practical yield of solid dispersion was found to be 14.5 %w/w. The drug content of Ritonavir SD prepared using Soluplus (1:3 ratio) in 20 ml ethanol at 45^0C and 1 ml/min flow rate. The final batch of solid dispersion of Ritonavir with Soluplus shows the higher solubility in 0.1 N HCL, pH 7.2 buffer, pH 6.8 buffer and pH 5.4 buffer compare with Poloxamer 407, Poloxamer 188 and Kollidon VA 64 (Solubility study).

% Entrapment Efficiency:

The entrapment efficiency of Ritonavir in 6.8 buffers was found to be 48%. And it was found to be satisfactory.

Dissolution Studies

Physical mixture and Solid dispersion

The dissolution studies of physical mixture was carried out and release profile data was analyzed at different time intervals as shown in below **Table 4**.

The physical mixture of Ritonavir with Soluplus (1:3 ratios) shows sharp endothermic peak at 125.79^0C indicating unchanged form of drug whereas polymer Soluplus transition peaks at 326.68 ^{0}C and 358.86^0C.

In DSC thermogram of SD **(Figure 6, 7)** the Ritonavir not shown sharp peak indicating its entrapment polymer.

X- Ray diffraction

Ritonavir and Physical Mixture

From graphical analysis it was found that given sample of drug was amorphous in nature because peaks pattern appeared random in nature and as physical mixture contains drug and excipients it shows variations in the XRD graph. Because drug is amorphous & excipients are in crystalline form. X-RD analysis was carried out on Peak Data ASCII Dump (XRD) instrument with scan range 10.000-80.000, scan speed 5. 000 degree/min, sampling pitch preset time 0.0200 (deg), 0.24 sec **(Figure 8)**.

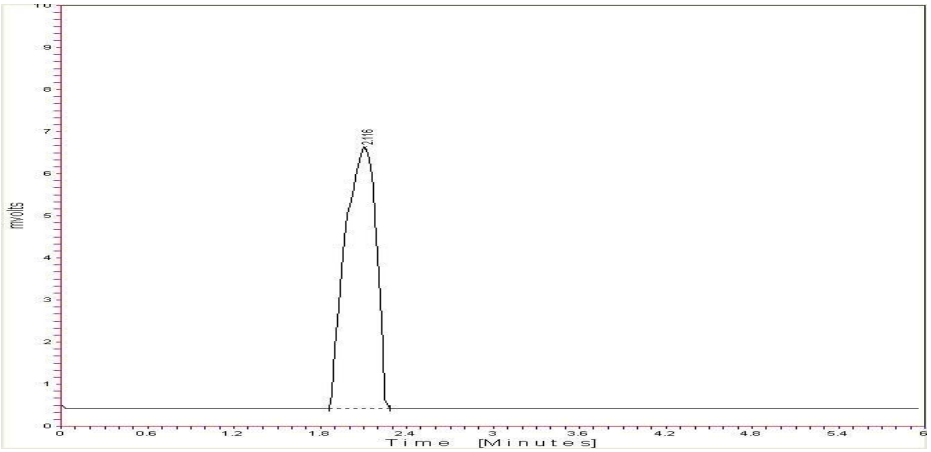


Figure 2: HPLC chromatogram of Ritonavir in methanol

Table 2: AUC of different Ritonavir solutions

S. No.	Concentration µg/ml	AUC
1	75	61400.51
2	100	75163.42
3	125	98019.00
4	150	134213.2
5	175	146207.7

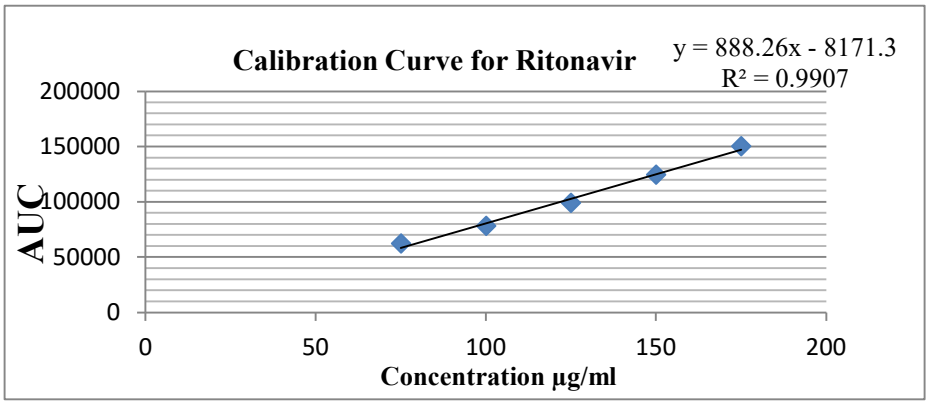


Figure 3: Calibration curve of Ritonavir

Table 3: Solubility of Optimized Batch

Solubility Media	Solubility (µg/ml)
0.1 N HCL	0.53
Buffer 7.2	0.60
Buffer 6.8	0.18
Buffer 5.4	0.16

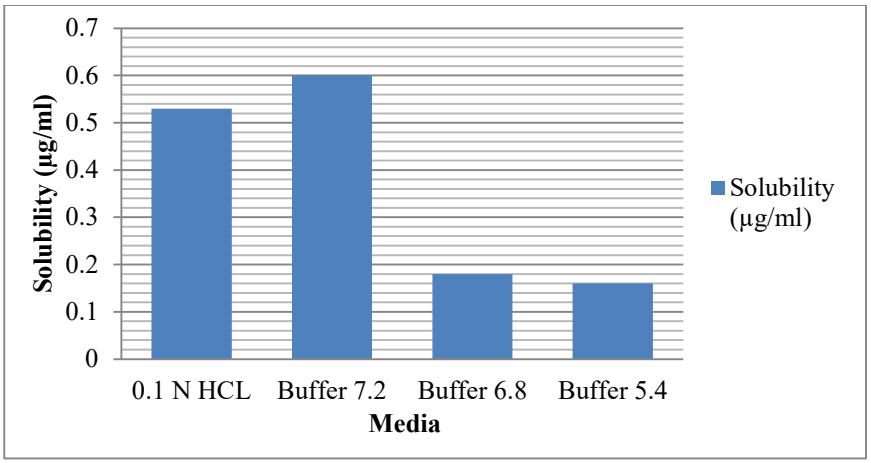


Figure 3: Solubility of prepared Ritonavir SDs

Table 4: Dissolution studies of physical mixture and solid dispersion

Time (Min)	% of Drug Release (PM)	% of Drug Release (SD)
5	0.81	22.5
10	1.32	34
15	1.69	42.5
20	2.11	50.2
25	2.24	57.25
30	2.98	59.75
35	3.13	61.25
40	3.33	64.22
45	3.40	63.15
50	3.44	71.5
55	3.90	72.45
60	4.11	71.3
65	4.24	78.56
70	4.38	80.28
75	4.78	82.22
80	5.00	86.81
85	5.48	87.20
90	6.11	90.94
95	6.24	97.56
100	7.2	99.20

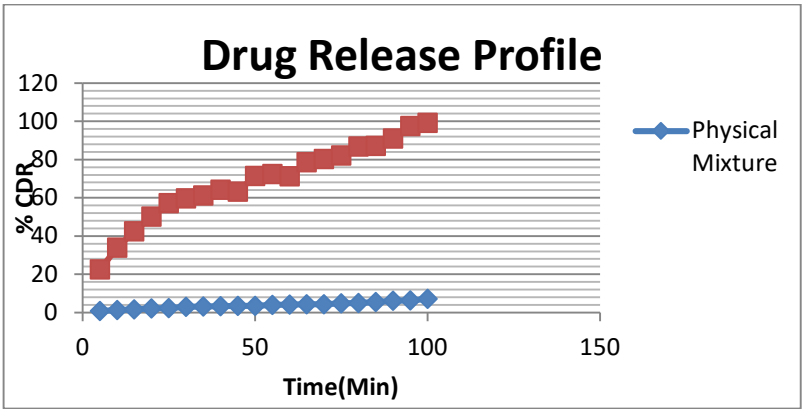


Figure 4: Drug release profile of Ritonavir and Physical mixture with Soluplus and SD

Differential scanning Calorimetry a) Physical Mixture

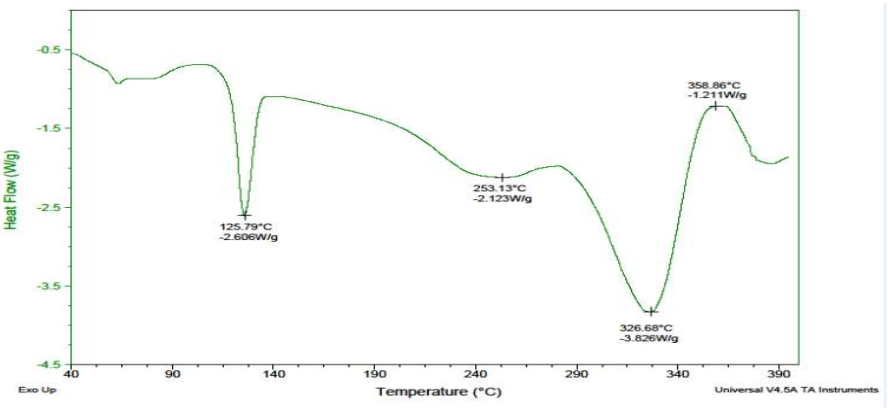


Figure 6: DSC thermogram of physical mixture

b) Solid dispersion

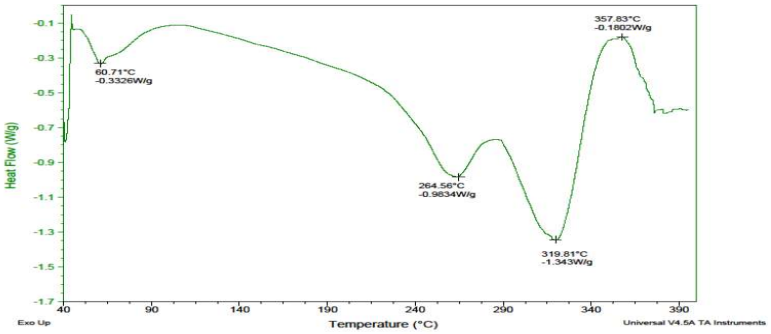


Figure 7: thermogram of Solid dispersion

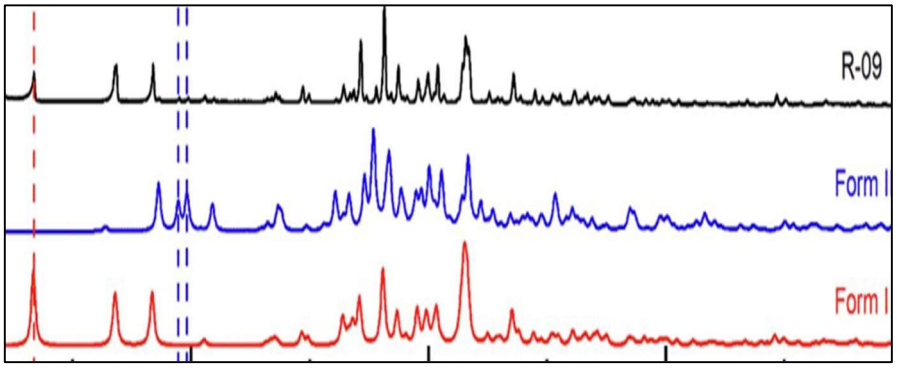


Figure 8: X-ray diffraction spectra of Ritonavir, solid Dispersion and Physical Mixture

CONCLUSION

Ritonavir a poorly soluble drug was encapsulated into Spray dried solid dispersion with soluplus polymer which has been used as solubility enhancers. From present study it was concluded that Solid dispersion in the ratio of 1:3 for drug: soluplus showed very effective increase in saturation solubility of Ritonavir. More solubility enhancement was observed in prepared solid dispersion due to the soluplus polymer.

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