

SOLUBILITY ENHANCEMENT OF RITONAVIR BY HOT MELT EXTRUSION

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ABSTRACT

Objective: The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. The aim of the present study was to prepare and characterize solid solution of water insoluble anti-HIV drug (Ritonavir).

Methods: There are various techniques such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, the addition of surfactants, and others are used by which the dissolution and bioavailability of sparingly soluble drugs can be improved. Among the various approaches, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of the poorly soluble drug. Solid Solution were prepared by Hot Melt Extrusion technique at 1:1.5, 1:2 (Ritonavir: Soluplus) and 1:1.5:0.5 (Ritonavir: Soluplus: Leutrol F68/leutrol 127/TPGS) ratios respectively. Solid Solution was evaluated for Saturation solubility, dissolution rate, XRD, FTIR, DSC and SEM.

Results: Among all prepared Solid solution systems, the systems which contain 1:2 ratios of Ritonavir and Soluplus, has shown 13 fold increases in solubility than pure Ritonavir. DSC, XRD and SEM results shown to change from crystalline to amorphous form for all ratios of Ritonavir.

Conclusion: From the above results, it was concluded that the improved drug dissolution could be achieved by formulating Ritonavir as a solid solution with the polymers such as Soluplus. The low hygroscopicity and low glass transition temperature of Soluplus make it particularly suitable for hot melt extrusion.

Keywords: Solid solutions, Hot melt extrusion, Bioavailability, Soluplus

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INTRODUCTION

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. The poor solubility and low dissolution rate of drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability [1-4]. Ritonavir is a protease inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Ritonavir is having poor solubility and low dissolution rate in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Among various techniques like micronization, solid dispersion (SD), solubilization, salt formation, complexation, selected SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drug because it is simple, economical and advantageous [5]. HME is the process of embedding drug in a polymeric carrier. Specifically, HME dosage forms are complex mixtures of API, functional excipients, and processing aids which are blended using industry-standard equipment [6]. The mixture is processed at elevated temperature and pressure, which disperses the drug in the matrix at a molecular level through the formation of a solid solution [7-9]. Hot-melt extrusion (Solid dispersion technology) can be used to improve the rate of dissolution of poorly soluble drugs [10]. Soluplus is a hydrophilic polymer have been used as a carrier for increasing the dissolution of a poorly water soluble Ritonavir. Soluplus is amphiphilic polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer having 70 °C as glass transition temperature and because of low glass transition temperature is suitable for hot melt extrusion process of Ritonavir. Leutrol F 68, Leutrol 127 and TPGS are used as solubilizer as well as a plasticizer. Thus, the aim of present investigation was to improve the dissolution rate of poorly water-soluble Ritonavir by preparing its solid solution by hot melt extrusion.

MATERIALS AND METHODS

Materials

Ritonavir was supplied by Lupin pharmaceutical ltd. Pune. Soluplus, Leutrol F 68, Leutrol 127 and TPGS were provided by BASF, Mumbai. All other chemicals used were of analytical grade.

Method for preparation

Prior to melt extrusion, Ritonavir was mixed with Soluplus, Leutrol F 68, Leutrol 127, TPGS with different concentration ranges. This premixed powder was added into melting zone of 16 mm twin screw extruder. As components and concentration of batch changes the processing parameter (processing temperature, feed rate, torque, speed rate) changes. Then the molten material was extruded in compression zone and came through the cylindrical die with 2 mm diameter opening. The melt left the die plate as pale yellow, transparent, semisolid stands which were cooled through a conveyer belt with a pelletizer [11-13].

Characterization of solid dispersion

Drug content

Solid solution equivalent to 39 mg of Ritonavir were weighed accurately and dissolved in a suitable quantity of 0.1N HCl. The drug content was determined at 246 nm by UV-spectrophotometer (Shimadzu).

Saturation solubility

Saturation solubility of physical mixture and a solid solution prepared by hot melt method were determined by equilibrating excess physical mixture and solid solution in different media distilled water, 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4. The suspension was stirred for 48 h by magnetic stirrer at 120 rpm at the temperature of 37.5±0.5 °C. The solution was centrifuged at 7000 rpm for 10 min supernatant was filtered through 0.45 membrane filter, appropriately diluted and analyzed for Ritonavir spectrophotometrically at 246 nm.

In vitro drug release study

The dissolution studies were performed using USP XXIV type II (paddle type) dissolution test apparatus (VEEGD, India). The samples equivalent to 100 mg Ritonavir were placed in dissolution vessel containing 900 ml 0.1N HCl maintained at 37±0.5 °C and

stirred at 50rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no.41, the concentration of Ritonavir was determined spectrophotometrically at 246 nm [14-16].

Fourier-transform Infrared spectroscopy (FTIR)

Fourier-transform infrared (FTIR) spectra of Ritonavir solid solution extrudes obtained using IR spectrophotometer (Shimadzu, FTIR-8400S, and Japan). The samples were scanned over the wave number range from 4000 to 400 cm^{-1} .

Scanning electron microscopy (SEM)

Microscopic observations of Ritonavir solid solution extrudes performed using a scanning electron microscope (SEM, JEOL JSM-6360 A, Tokyo, Japan) at an acceleration voltage of 5kV [17]. Samples were sputtered (JEOL JFC-1600 Auto fine coater, Tokyo, Japan) with gold-palladium and then observed at different magnifications.

Differential scanning calorimetry (DSC)

The DSC patterns were recorded by a heat flow method. Solid solution sample of Ritonavir (6-10 mg) was heated in crimped aluminum pans with a pierced lid at a scanning rate of 5 $^{\circ}\text{C}/\text{min}$ in an atmosphere of nitrogen gas purge (20 ml/min) using the range of 0-300 $^{\circ}\text{C}$. The DSC was calibrated for a baseline using empty pans, and for temperature and enthalpy using indium.

X-ray powder diffraction (XRPD)

The XRPD patterns of solid solution samples of Ritonavir were recorded for 2θ between 4 $^{\circ}$ to 50 $^{\circ}$ at 0.1 $^{\circ}$ intervals and a scanning

rate of 6 s^{-1} using a BRUKER D8 Advance (BRUKER AXS UK) diffractometer equipped with copper tube operating at 40 kV and 40 mA. This analysis was performed at the University of Pune.

RESULTS AND DISCUSSION

Drug content

The percentage drug content in various Ritonavir solid solution ranged from 97.54 \pm 1.6 and 99.67 \pm 1.2. This indicated that Ritonavir was uniformly distributed in all of this prepared solid solution as shown in table 1.

Table: 1 Drug content study

Batch name	Drug content (%)
Ritonavir+Soluplus (1:1.5)	98.23
Ritonavir+Soluplus (1:2)	99.67
Ritonavir+Soluplus+Leutrol F 68	98.02
Ritonavir+Soluplus+Leutrol 127	97.54
Ritonavir+Soluplus+TPGS	99.17

Saturation solubility

Saturation solubility of pure Ritonavir was found to be 50 $\mu\text{g}/\text{ml}$, 97.1 $\mu\text{g}/\text{ml}$, 11.51 $\mu\text{g}/\text{ml}$, 31.5 $\mu\text{g}/\text{ml}$ in distilled water, 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 at room temperature as mention in table 2. A significant improvement in the saturation solubility was observed with a solid solution.

Table 2: Saturation solubility of solid solution

Batch name	Solubility of solid solution in different media ($\mu\text{g}/\text{ml}$)			
	Water	0.1 N HCl	Phosphate buffer (pH 6.8)	Phosphate buffer (pH 7.4)
Ritonavir	50	97.1	11.5	31.5
Ritonavir+Soluplus(1:1.5)	343.57	566.42	84.71	126.84
Ritonavir+Soluplus(1:2)	362.14	602.85	147.8	255.26
Ritonavir+Soluplus+Leutrol F 68	317.88	447.14	109.47	137.89
Ritonavir+Soluplus+Leutrol 127	289.28	413.57	88.42	113.15
Ritonavir+Soluplus+TPGS	332.85	499.28	80.92	123.17

The increase in weight fraction of the hydrophilic polymer resulted in improved saturation solubility. The solid solution with Soluplus in 1:2 Ritonavir-Soluplus ratio showed high saturation solubility which was significantly high as compared to pure drug and other solid solution. There was 7 to 13 fold increase in a solid solution of Ritonavir in distilled water, 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4. The results showed that the carrier Soluplus was able to enhance the solubility of Ritonavir.

In vitro drug release study

Dissolution testing of 100 mg crystalline Ritonavir showed 27.36% release of drug in 2 h in 0.1 N HCl due to low solubility. In comparison, the solid solution of Soluplus and Ritonavir showed near about complete drug release and enhances 4 fold drug releases as compared with crystalline Ritonavir. The results are shown in the following fig. 1 (fig. 1).

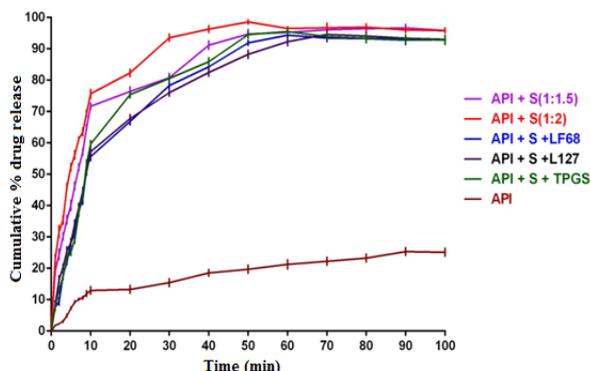


Fig. 1: In vitro drug release of solid solutions batches and Ritonavir

It was cleared from the graph, as the concentration of Soluplus increases, there was a significant increase in the rate of release of Ritonavir solid solution. As Soluplus concentration enhance the rate of release ultimately Ritonavir dissolution.

Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra revealed the formation of hydrogen bond which might be attributing enhanced dissolution of the drug.

The FTIR spectra of crystalline Ritonavir show a characteristic peak at 3358.60 cm^{-1} (N-H stretching). In comparison, spectra of the hot melt extrude solid solution show a significant change at 3358.60 cm^{-1} , related to weakening or removal of the N-H stretching. The significant disappearance of N-H stretching in hot melt extruder solid solution of Ritonavir is strong evidence of H-bonding between the drug and polymer via the secondary amine group of Ritonavir. This may attribute to the possible interaction between the N-H group of Ritonavir and C=O group of Soluplus leading to the formation of the amide group. All other peaks of Ritonavir such as 1738 cm^{-1} are remain constant hence, the improved dissolution of Ritonavir further supported this fact.

Scanning electron microscopy (SEM)

SEM photomicrograph of the solid solution indicated the smooth uniform surface due to the homogeneous molecular dispersion of the drug in the polymer.

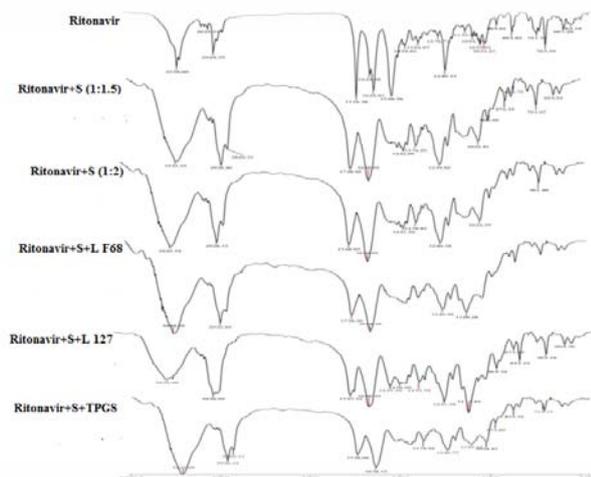


Fig. 2: FTIR spectra of solid solution batches and Ritonavir

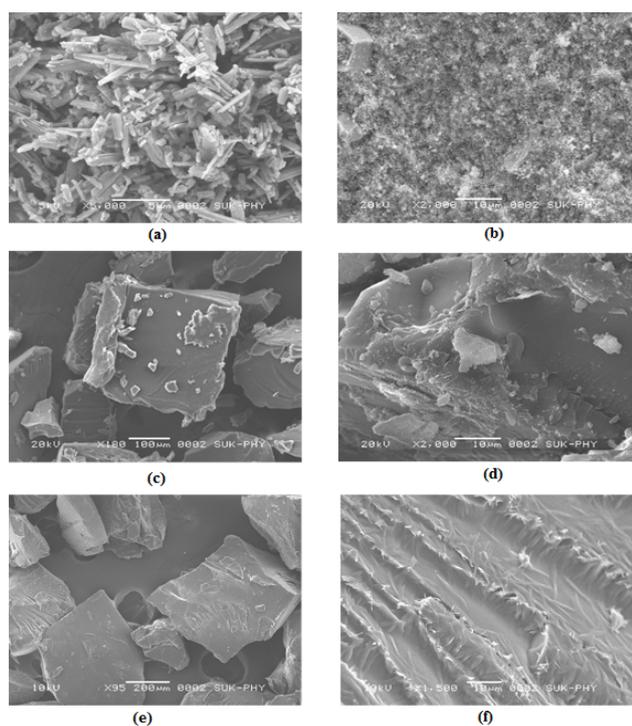


Fig. 3: SEM photograph of, (a) pure Ritonavir, (b) Ritonavir-Soluplus (1:1.5), (c) Ritonavir-Soluplus (1:2), (d) Ritonavir-Soluplus-Leutrol F 68, (e) Ritonavir-Soluplus-Leutrol 127, (f) Ritonavir-Soluplus-TPGS

SEM photograph of pure Ritonavir (a) appeared like needle-shaped, rectangular crystalline structure. Whereas from SEM photograph of the solid solution is shown in b, c, d, e, f respectively gives an idea about change in surface morphology and change in the crystalline structure of drug in amorphous form. This suggests that the drug was diffused in polymer and has been distributed uniformly in the carrier mass.

Differential scanning calorimetry (DSC)

Thermal analysis of Ritonavir by differential scanning calorimetry showed a characteristic sharp endothermic peak at 125.55°C indicating the melting point of the drug. The DSC thermogram of the solid solution shows absence of characteristic melting endotherm of Ritonavir in all batches. As single glass transition of solid solution

in case of Ritonavir-Soluplus (1:2) solid solution indicating the perfect miscibility of Ritonavir and Soluplus.

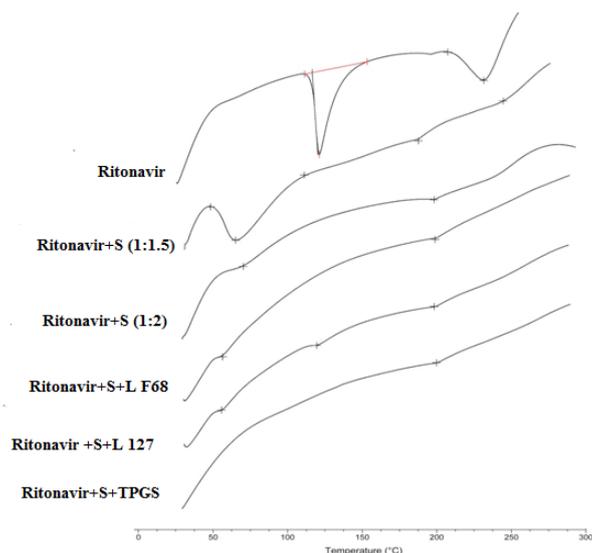


Fig. 4: DSC of Ritonavir and solid solution batches

As single glass transition temperature is characteristic of the thermoplastic system, the DSC thermogram shows complete amorphization of Ritonavir.

X-ray powder diffraction (XRPD)

XRPD was used to determine the crystallinity of the hot melt extrudes of a solid solution. The X-ray diffractograms of the solid solution were compared with those of crystalline drug.

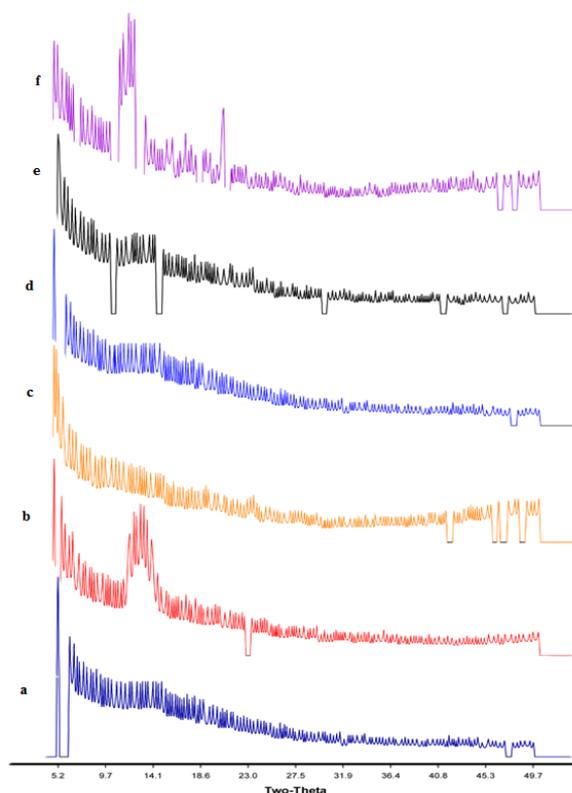


Fig. 5: XRD of, (f) pure Ritonavir, (e) Ritonavir-Soluplus (1:1.5), (d) Ritonavir-Soluplus (1:2), (c) Ritonavir-Soluplus-L F 68, (b) Ritonavir-Soluplus-L 127, (a) Ritonavir-Soluplus-TPGS

From above fig. it is observed that t semi rigid peaks were absent from the diffract grams of the hot melt extrude of a solid solution. Hence, the absence of peaks of crystallinity of pure Ritonavir indicated complete amorphization of Ritonavir in solid solution. Thus, amorphization of Ritonavir due to processing with Soluplus was the reason for the dissolution enhancement.

CONCLUSION

To enhance, the dissolution rate of Ritonavir with hydrophilic polymers such as Soluplus, Leutrol F 68, Leutrol 127 and TPGS, Solid solution were prepared by hot melt extrusion. The solid solution obtained by Hot melt method with Ritonavir: Soluplus ratio of 1:2 showed 7-13 fold increase in saturation solubility of the drug in different media such as distilled water, 0.1 N HCl, phosphate buffer pH 6.8 and 7.4. *In vitro* drug release of a solid solution of Ritonavir-Soluplus (1:2) in 0.1 N HCl showed highest drug release as compared to other batches. From the above results, it was concluded that the improved drug dissolution could be achieved by formulating Ritonavir as a solid solution with the polymers such as Soluplus. The low hygroscopicity and low glass transition temperature of Soluplus make it particularly suitable for hot melt extrusion, and the addition of a plasticizer is not required in case of Soluplus because of low glass transition temperature.

CONFLICT OF INTERESTS

Declared none

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