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Research Article

Bioavailability Enhancement of Ritonavir by Solid Dispersion Technique

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Abstract

Ritonavir is an antiretroviral agent used in the treatment of HIV-infection. It is a BCS class IV drug having poor aqueous solubility leading to poor bioavailability. Bioavailability is the amount of drug that enters the systemic circulation. The bioavailability is affected by various factors like solubility, dissolution and stability. In order to improve bioavailability, many techniques like solid dispersions, nanoparticles, liposomes, encapsulation methods were present. The main aim of this study is to improve the bioavailability of ritonavir with the help of Polyvinyl Pyrrolidone (PVP) K-30 by using solid dispersion technique. Different formulations were made with varied concentrations of polymer. Characterization of solid dispersion was done by phase solubility, drug content, Fourier transformed infrared spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC) and *in-vitro* dissolution studies. From phase solubility studies that apparent solubility constant was found to be $42.227M^{-1}$. The drug content of the binary system of ritonavir and PVP was found to be ranging from 99.17% to 103.06%. %. FT-IR studies revealed that there was no drastic change in the wave number indicating polymer compatibility with drug. *In-vitro* dissolution studies proved that there was an increase in drug release of ritonavir with incremental ratios of polymer and F5 formulation has shown almost 95% of drug release.

Keywords: Bioavailability, Solid dispersion, Polyvinyl pyrrolidine, Solvent evaporation, Dissolution.

INTRODUCTION:

The term solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state. A drug is formulated in the form of solid dispersions to enhance its bioavailability, thereby resulting in an increased therapeutic efficacy. The bioavailability of a drug depends on various properties like solubility, dissolution and stability. Drug dissolution in the gastrointestinal fluid is very important for the increased absorption of orally administered drugs. Hence to improve the bioavailability of poorly water-soluble drugs solid dispersions are formulated using a variety of polymer matrix.[1]

Ritonavir is an antiretroviral agent used in the treatment of HIV-infection. Ritonavir is a poorly aqueous soluble drug resulting in decreased dissolution rate and hence lower rates of oral bioavailability. [2] Therefore, solid dispersion technique is one of the most promising approach to enhance the dissolution rate of ritonavir, thereby increasing its oral bioavailability.

The solid dispersion technique is having several advantages such as reduction in the particle size increases the surface area which leads to increase in dissolution rates thereby increasing the bioavailability.[3] The another added advantage is that the particles of solid dispersions have high porosity which aids in bioavailability enhancement.[4]

In this study Ritonavir solid dispersion was prepared by solvent evaporation method using PVP K-30 as a carrier. PVP is an ideal carrier for increasing the bioavailability of drugs. Ethanol was used as a solvent.

MATERIALS AND METHODS

Ritonavir was a gift sample from hetero labs PVT Ltd, polyvinyl pyrrolidone K-30 (Loba chemicals), ethanol.

Phase solubility studies:

Phase solubility studies were carried out to determine the suitable concentration of the carrier for Ritonavir drug. Different concentrations of carrier solutions were prepared by dissolving Polyvinylpyrrolidone in distilled water. Excess of drug was added to each carrier solution and shaken in rotary shaker for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 238nm after dilution. [5,6]

Physical mixture:

Physical mixture was prepared in order to optimize the drug – carrier ratio. Physical mixture was prepared by miring Ritonavir and PVP in 1:1 molar ratio in a mortar and

triturated for five minutes and then passed through sieve No.60. [7]

Solvent Evaporation Method:

Solid dispersion was prepared by taking drug and carrier in different concentrations like 1:1, 1:2, 1: 3, 1:4, and 1:5 respectively. Both the drug and carrier are separately dissolved in ethanol solution. Two solutions were mixed and evaporated. The obtained solid mass was scrapped and further dried at room temperature.[8] using this method the thermal decomposition of drug and polymer can be prevented as evaporation of organic solvents takes place at relatively lower temperatures. [9]

Table 1: Formulation table

S. No	COMPOSITION	RATIO	CODE
1	Ritonavir + PVP K30	1:1	F1
2	Ritonavir + PVP K30	1:2	F2
3	Ritonavir + PVP K30	1:3	F3
4	Ritonavir + PVP K30	1:4	F4
5	Ritonavir + PVP K30	1:5	F5

Drug content estimation:

100mg of dispersion was accurately weighed and transferred to a 100ml volumetric flask containing ethanol. From the above solution, 1ml was taken in 10ml volumetric flask and volume is adjusted upto the mark with same solvent. The absorbance of the solution was measured at 246nm using appropriate blank. The drug content of Ritonavir was calculated using calibration curve. [10]

Fourier Transform Infrared (FTIR) Spectroscopy:

Fourier transform IR spectra were recorded on FT-IR-4100 type A. The solid dispersion was dispersed in dry potassium bromide, ground well in mortar and pestle. Potassium bromide disc was prepared at a pressure of 1000 psig. The disc was placed in FT-IR sample holder. The scanning range is 500 – 4000 cm^{-1} using resolution of 1 cm^{-1}. [11]

Differential scanning calorimetry (DSC):

The samples were analyzed by DSC using a Mettler Toledo SR system. The samples were placed in the pierced aluminum container. The studies were performed under static air atmosphere in the temperature range of 20°C to 200°C at a heating rate of 10° C/min. The peak temperatures were determined after calibration with standard. [12]

***Invitro* dissolution studies:**

In dissolution of solid dispersion was studied using USP dissolution apparatus type II. 900ml of 0.1N HCl was used as dissolution medium at 50 rpm. The temperature of 37±0.5°C was maintained throughout the experiment. Samples were withdrawn at time intervals of 5, 10, 15, 30, 45, and 60 minutes by means of syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium. The collected samples were analyzed for drug release by measuring the absorbance at 235nm. The percentage of drug release was calculated from the obtained absorbance values. [13]

RESULTS AND DISCUSSION

Phase Solubility Studies:

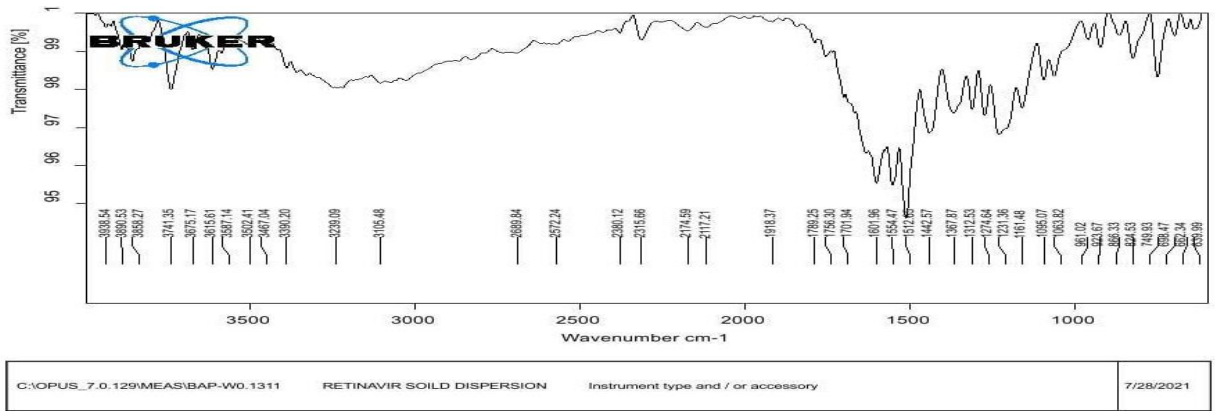
The phase solubility diagrams of ritonavir: PVP was obtained by plotting the changes in guest solubility as a function of PVP concentration. The solubility curves were carried out as per Higuchi and Connorsand AL type of curve was obtained, which suggests that water-soluble complex, was formed in solution. The slope values obtained were less than 1, which indicates that inclusion complex in the molar ratio of 1:1 between the guest and the host molecule were obtained irrespective of the pH. The phase solubility profile indicated that the solubility of ritonavir was significantly increased in the presence of PVP and Apparent stability constant (K_C) was found to be 42.227M^{-1}

Drug Content Estimation:

UV spectrophotometry was used to determine the drug content of the binary system of the ritonavir and PVP. The ratios of drug and PVP were (1:1), (1:2), (1:3), (1:4) and (1:5). drug polymer ratio would therefore remain as same in formulation in the final solution to calculate the drug content. The Drug content in all the system was found to be 49.56 % w/w to 52.5% w/w (99.17 % to 105.01%) for F1 formulation. Followed by 33.11% w/w to 33.82% w/w (99.34% to 102.55%) for F2 formulation. For F3 formulation it was found to be 24.89% w/w to 25.75% w/w (99.76% to 103.01%). In F4 formulation the %w/w was found to be 19.95 to 20.61 (99.76% to 103.06%) and finally in F5 formulation it was 16.61% w/w to 17.03% w/w (99.69% to 102.22%).

FTIR:

IR spectra of pure drug and solid dispersion of ritonavir with incremental ratios of PVP was prepared. As clearly seen from the spectra the characteristic peaks of ritonavir are at 3480, 2964, 1716, 1622 and 1522 cm^{-1} were modified significantly as a result of solid dispersions.

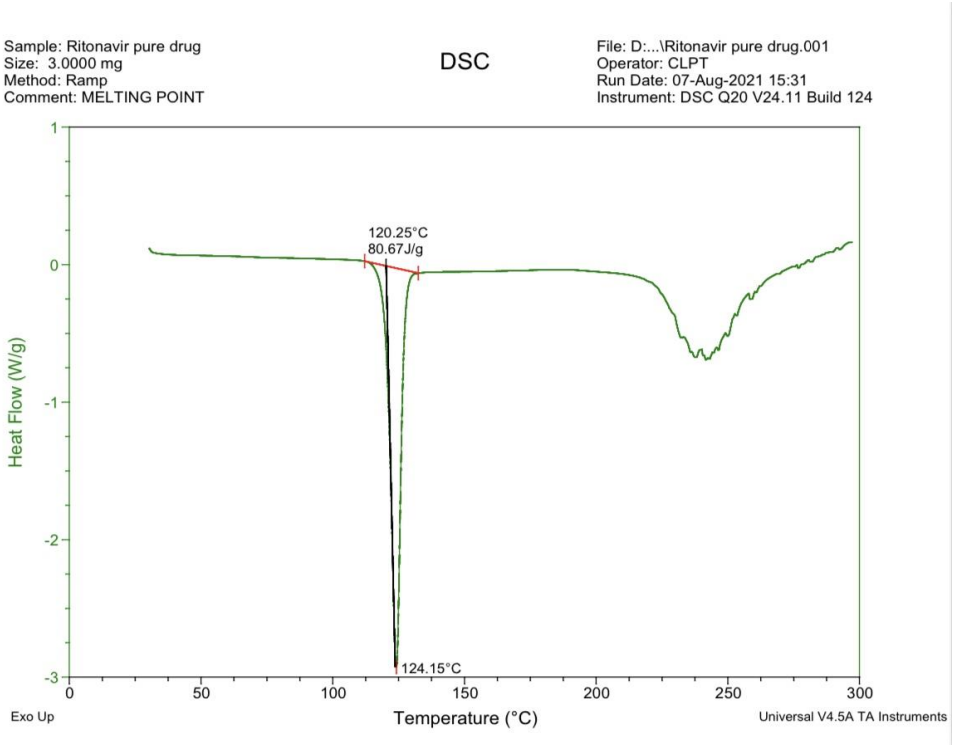


(a)

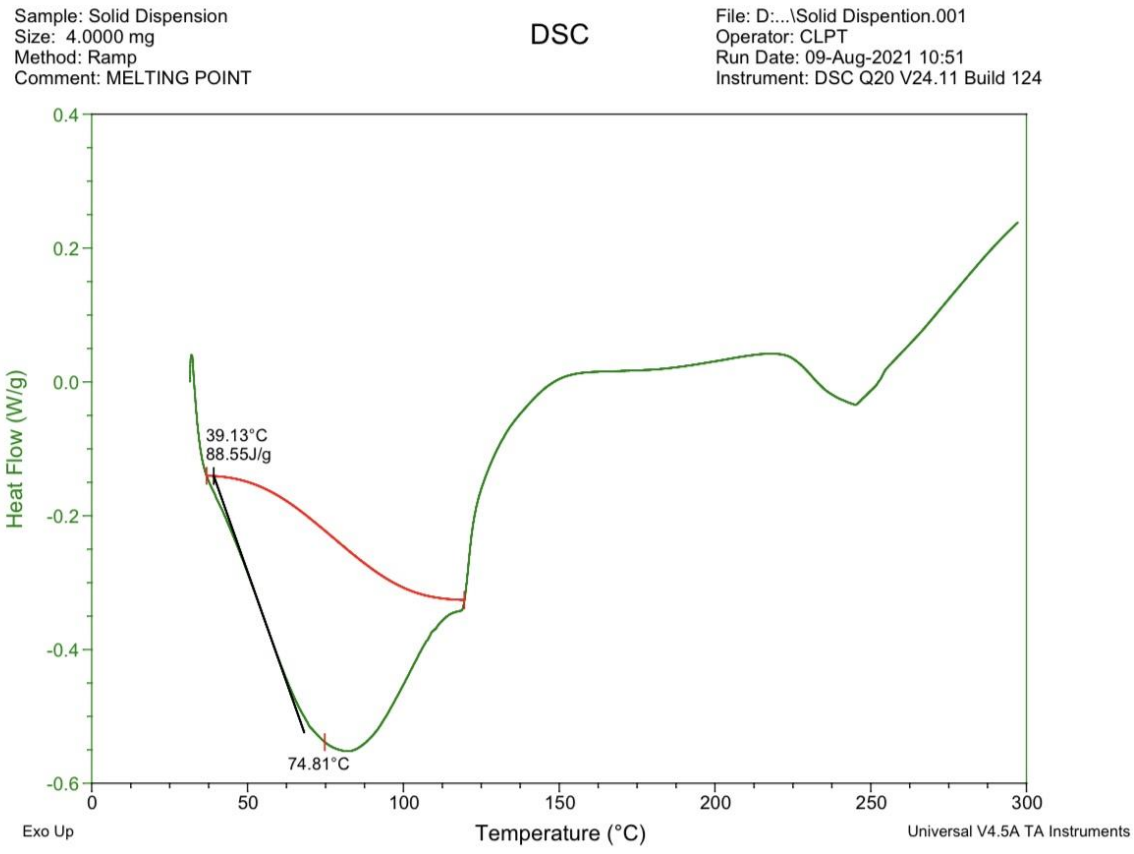
Figure 1: (a) FTIR for solid dispersion of ritonavir

4.4 Differential scanning calorimetry (DSC)

The thermogram of pure ritonavir shows a sharp endothermic point at 124.15°C, indicating that it is in the crystalline form. Solid dispersion of ritonavir has shown a peak at 78.14 °C indicating that the crystalline form of ritonavir is converted to amorphous form.



(a)



(b)

Figure 2: (a)DSC for pure Ritonavir (b) DSC for solid dispersion of ritonavir

***In-vitro* dissolution studies:**

The results of *invitro*dissolution studies have shown a clear evidence of increase in the drug release where, the pure API has shown a drug release of less than 35% and solid dispersion has shown a drug release in incremental order as polymer ratio increases. Out of all formulations formulated F5 is said to have higher drug release content with almost of 94.04%.

TABLE 2: Percentage drug release of API and solid dispersions

S. No	Time in min	Percentage Drug Release					
		API	F1	F2	F3	F4	F5
1	5	7.3488±0.77	18.09±1.92	22.37±1.46	24.51±1.62	26.27±1.53	31.11±1.20
2	10	15.6279±2.94	27.20±0.91	37.53±2.05	43.06±3.60	55.86±1.10	60.27±0.88
3	15	20.5116±4.58	37.72±1.92	48.60±1.89	59.95±4.39	71.48±2.90	73.20±1.28
4	20	24.5581±3.17	54.41±0.79	60.00±3.31	72.23±3.03	79.44±3.58	81.34±1.72
5	30	28.1860±2.76	66.74±1.12	70.13±1.96	80.27±0.98	83.81±1.67	88.04±1.08
6	45	31.0232±3.35	69.72±1.25	74.51±1.49	81.72±0.74	88.65±1.16	92.88±0.57
7	60	31.5813±3.50	70.09±1.08	74.79±1.56	82.23±0.80	89.20±1.02	94.04±0.56

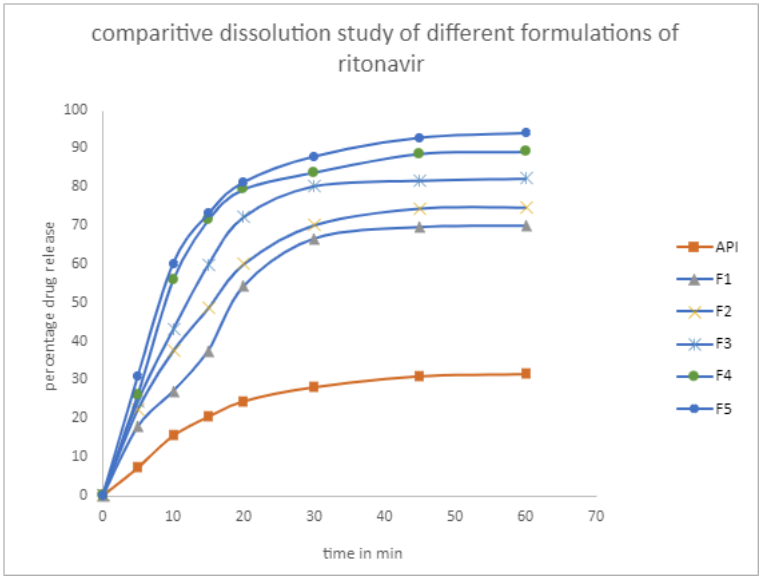


FIGURE 3: comparative dissolution study of different formulations of ritonavir

5.0 CONCLUSION:

From the phase solubility studies ,it is clear that the solid dispersion of ritonavir with PVP K30 in molar ratio of 1:1 will improve the solubility ,and therefore dissolution rate will increase.The FTIR spectra of solid dispersions showed characteristic peaks of ritonavir indicates formation of solid dispersions and compatibility problems.The DSC thermogram of ritonavir showed sharp endothermic peak at124.14^{o}C and solid dispersion of ritonavir showed a peak at 78.14^{o}C,indicates amorphous form. The dissolution profiles indicate improved dissolution rate of solid dispersions of drug compared to the pure drug. Ritonavir is a BCS class IV drug with pure aqueous solubility and bioavailability was found to be 30%.Various formulations of solid dispersions were prepared by solvent evaporation method using PVP K30 as a carrier. Among all the formulations, F5 formulation of solid dispersion showed improved dissolution rate compared to pure drug therefore solid dispersion will improve the bioavailability of drug. The attempt to improve bioavailability of ritonavir by solid dispersion technique results in enhanced bioavailability

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CONFLICT OF INTEREST:

Conflict of interest was found to be none.

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