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Research Article

IMPROVING THE SOLUBILITY AND DISSOLUTION OF RITONAVIR BY SOLID DISPERSION

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ABSTRACT
Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Ritonavir were prepared using PEG-4000, PEG-6000 and PEG-8000 to increase its aqueous solubility. Ritonavir SDs was prepared in 1:1, 1:2 and 1:4 ratios of the drug to polymer (by weight) by melting method and solvent evaporation method. The prepared solid dispersion was subjected for solubility, drug content, *In vitro* release and infrared (IR) spectroscopic studies, DSC and stability study. *In vitro* release profiles of all SDs were comparatively evaluated and also studied against pure Ritonavir. Faster dissolution was observed by solid dispersion containing 1:4(P6M4) ratio of drug: PEG-6000. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity.
Keywords: Ritonavir, Solid Dispersion, PEG-4000, PEG-6000, PEG-8000, Melting Method, Solvent Evaporation Method.

INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. Many methods are available to improve dissolution rate and solubility, which includes salt formation, micronization, addition of solvent (co solvency) and surface active agents (Hydrotrophy). Solid dispersions (SDs) are one of those methods, which were most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The concept of solid dispersions was introduced in 1961 by Sekiguchi and Obi[1], in which the drug is dispersed in inert water - soluble carrier at solid state. Several water soluble carriers such as PEG-4000, PEG-6000 and PEG-8000 are used as carriers for SDs[2-5]. Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. Solid dispersions of Ritonavir were formulated to overcome problems like gastric irritation and other side effects that are frequently experienced with antiretroviral agents for the treatment of HIV-infection. Ritonavir is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration[6-7]. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Ritonavir by preparing SDs with various water-soluble polymers such as PEG-4000, PEG-6000 and PEG-8000. The prepared SDs were evaluated for solubility, drug content, *in vitro* dissolution rate studies, IR spectral studies, DSC, stability study.

MATERIALS AND METHODS

Ritonavir was a generous gift from Matrix Labs Limited, Secunderabad, India. PEG-4000, PEG-6000 and PEG-8000 were purchased from SD Fine Chemicals Ltd, Mumbai, India. All reagents were of A.R. grade. Double distilled water was used for all the experiments.

Preparation of Solid Dispersion

Solid dispersion of Ritonavir in PEG-4000, PEG -6000 and PEG -8000 were prepared. Melt method, solvent evaporation and kneading methods are used to prepare solid dispersions. The quantities of each ingredients used are given in Table 1.

Melt Method

Accurately weighed amount of carrier was melted in china dish at 50°C and to this calculated amount of Ritonavir was added and mixed thoroughly at same temperature and the sample was allowed to cool at room temperature. The sample was then scrapped and the dried mass was pulverized and passed through a sieve no 60. Then sample was stored in desiccators for further studies[8].

Solvent Evaporation Method

Accurately weighed amount of Ritonavir and carriers were dissolved in a sufficient amount of methanol. The solvent was then removed by evaporation under reduced pressure at 40°C. The resulting residue was dried and stored overnight in desiccators. After drying the residue was ground in a mortar and then passed through a sieve no 60. The resultant formulations were stored in desiccators for further studies[9].

Evaluation

Solubility Studies

The solubility of Ritonavir and all Ritonavir formulations in 0.1N Hydrochloric acid was carried out and the solubility was determined. Excess amount of Ritonavir (10 mg) and different formulations were added to ten ml of 0.1N Hydrochloric acid in screw capped vials. The vials were shaken for 24 h at 37 ± 0.5°C, the sample were filtered through Whitman filter paper and analyzed for drug content using UV-Spectrophotometer at 246 nm after suitable dilution[8].

FTIR

The IR Spectrum was recorded in the wavelength region of 400-4000^{-1}. The procedure consist of dispersing a sample

(Drug alone or mixture of drug and carriers) in KBr and compressing into disks by applying pressure of 5 ton, in five minutes, in a hydraulic press. The pellets were placed in the light path and the spectrum was recorded.

Differential Scanning Calorimetry

DSC scan of Ritonavir and best formulation were recorded using DSC-60 calorimeter. To study the thermal behavior, all the samples were weighed (8-10 mg) heated at a scanning rate of 20ºC per minute under dry air flow between 25ºC - 250ºC. Aluminum pans and lids were used for all samples.

Drug Content

For the determination of drug contents, formulation (equivalent to 25 mg of Ritonavir) were dissolved in small volume of methanol and the volume was made up to 100 ml with 0.1N Hydrochloric acid solution. The solution was filtered through Whatman filter paper, suitable dilution carried out with 0.1N Hydrochloric acid solution. The concentration of Ritonavir was then determined using UV-Spectrophotometer at a wavelength of 246 nm[10].

***In-vitro* Dissolution Studies**

In-vitro dissolution of Ritonavir and formulations were carried out using USPXXX type-II (Electrolab) dissolution apparatus. The study was carried out in 0.1N Hydrochloric acid solution. The dissolution medium was kept in thermostatically controlled water bath maintained at 37ºC. The basket was rotated at 50 rpm at predetermined time interval; 5 ml of sample were withdrawn and replaced with fresh media to maintain sink condition. The concentration was analyzed using UV-Spectrophotometer at 246 nm[11].

Stability Studies

Stability of a Pharmaceutical preparation can be defined as the capability of a particular formulation in a specific system to remain within its physical, chemical, microbial, therapeutically and toxicological limits throughout its shelf life. The purpose of the stability testing is to provide evidence how the quality of drug products varies with the time under the influence of a variety of environmental factors such as temperature, humidity and light. By enabling the recommended storage conditions; reset periods and shelf life to be established.

Procedure

The selected formulations were subjected to short term stability testing. The formulations were kept in a humidity chamber maintained at room temperature and 40^{+}-2^{0}C RH for three months as per ICH guidelines. The changes in the appearances and drug content were investigated during the period[12].

RESULTS AND DISCUSSION

The poor aqueous solubility and the dissolution rate of a hydrophobic drug is a major problem for the formulation of a solid dosage form. In case of hydrophobic drug, dissolution rate is the rate limiting step in the absorption of the drugs, poor aqueous solubility and the poor dissolution rate intern leads to a poor bioavailability. Among the various approaches to improve the bioavailability of a drug by improving its dissolution rate, formulation of solid dispersion and inclusion complex was one among them. In the present work, Ritonavir solid dispersion were prepared by using PEG-4000,PEG-6000,PEG-8000 in different ratios to improve solubility, dissolution rate there by bioavailability. All formulations were prepared by melt method, solvent evaporation and kneading method .

Table 1: Formulation Containing PEG

Solid dispersion	Formulation Code	Drug-Polymer Ratio	Method
PEG-4000	P4M1	1:1	Melt method
	P4M2	1:2	
	P4M4	1:4	
	P4S1	1:1	Solvent evaporation method
	P4S2	1:2	
	P4S4	1:4	
PEG-6000	P6M1	1:1	Melt method
	P6M2	1:2	
	P6M4	1:4	
	P6S1	1:1	Solvent evaporation method
	P6S2	1:2	
	P6S4	1:4	
PEG-8000	P8M1	1:1	Melt method
	P8M2	1:2	
	P8M4	1:4	
	P8S1	1:1	Solvent evaporation method
	P8S2	1:2	
	P8S4	1:4	

Table 2: Solubility Studies of Pure Drug and PEG Solid Dispersion in 0.1 N Hydrochloric acid

Raito	PEG-4000		PEG-6000		PEG-8000		Pure Drug Solubility In 0.1 N Hydrochloric acid (µg / ml)
	Melt method	Solvent evaporation method	Melt method	Solvent evaporation method	Melt method	Solvent evaporation method	
	Solubility (µg / ml)		Solubility (µg / ml)		Solubility (µg / ml)		
1:1	292	269	323	284	276	230	
1:2	361	323	384	338	323	292	146 µg / ml
1:4	500	430	546	461	369	346	

Table 3: Drug Content Estimation of Ritonavir Solid Dispersions

Solid dispersion	Formulation Code	Method	% Drug content (AM ± SD)
PEG-4000	P4M1	Melt method	86.14 ± 1.31
	P4M2		90.00 ± 1.23
	P4M4		96.92 ± 1.69
	P4S1	Solvent evaporation method	84.28 ± 1.21
	P4S2		86.28 ± 1.01
	P4S4		92.36 ± 1.09
PEG-6000	P6M1	Melt method	98.00 ± 1.94
	P6M2		95.24 ± 1.89
	P6M4		95.56 ± 1.12
	P6S1	Solvent evaporation method	88.52 ± 1.21
	P6S2		97.68 ± 1.70
	P6S4		92.52 ± 2.11
PEG-8000	P8M1	Melt method	93.84 ± 1.10
	P8M2		94.24 ± 1.99
	P8M4		96.80 ± 1.10
	P8S1	Solvent evaporation method	88.12 ± 2.45
	P8S2		90.80 ± 1.23
	P8S4		95.88 ± 2.90

Table 4: **Dissolution Profile of Ritonavir**

Time (minutes)	Abs (nm)	Conc. (µg / ml)	Conc. (mg / 5 ml)	Conc. (mg / 900 m)	Cum amt in 5 ml	Cumulative release	CPR
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15	0.034	2.38	0.011	2.14	0.011	2.11	8.44
30	0.038	2.69	0.013	2.42	0.024	2.46	9.84
45	0.045	3.23	0.016	2.90	0.040	2.94	11.76
60	0.050	3.84	0.019	3.45	0.059	3.50	14.00
90	0.055	4.00	0.020	3.60	0.079	3.67	14.68
120	0.061	4.46	0.022	4.01	0.101	4.11	16.44

Table 5: Dissolution Profile of Ritonavir Solid Dispersion with PEG-4000 Prepared by Solvent Evaporation and Melt Method

Time (minutes)	Cumulative % drug release of PEG-4000 (AM ± SD)					
	P4M1	P4M2	P4M4	P4S1	P4S2	P4S4
0	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
15	29.38 ± 2.12	29.67 ± 2.01	31.05 ± 1.49	21.52 ± 2.80	23.98 ± 2.85	25.66 ± 3.99
30	35.1 ± 1.12	44.75 ± 2.78	39.2 ± 3.07	32.74 ± 1.71	42.52 ± 3.32	44.18 ± 2.34
45	44.57 ± 2.91	58.81 ± 1.25	66.42 ± 5.90	35.72 ± 2.12	50.52 ± 1.12	54.94 ± 2.02
60	52.52 ± 3.15	71.02 ± 4.45	84.13 ± 2.73	40.75 ± 2.89	53.05 ± 1.97	61.69 ± 3.36
90	60.88 ± 5.48	78.73 ± 6.13	89.6 ± 4.85	50.61 ± 3.42	64.37 ± 3.09	69.98 ± 3.38
120	65.48 ± 4.60	87.64 ± 3.50	97.89 ± 2.47	65.46 ± 1.63	71.88 ± 2.3	80.97 ± 3.76

Each value is an average of three determinations; AM = Average mean; SD = Standard deviation

Table 6: Dissolution Profile of Ritonavir Solid Dispersion with PEG-6000 Prepared by Solvent Evaporation and Melt Method

Time (minutes)	Cumulative % drug release of PEG-6000 (AM ± SD)					
	P6M1	P6M2	P6M4	P6S1	P6S2	P6S4
0	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
15	25.12 ± 2.12	26.2 ± 2.12	29.71 ± 1.49	19.17 ± 2.31	24.21 ± 2.64	30.22 ± 1.06
30	36.95 ± 1.12	36.95 ± 2.79	40.68 ± 3.07	33.37 ± 2.26	40.75 ± 1.88	52.84 ± 2.07
45	41.22 ± 2.91	46.43 ± 1.25	64.01 ± 5.90	38.21 ± 1.54	51.03 ± 2.82	66.5 ± 3.08
60	50.64 ± 3.15	59.06 ± 4.45	82.3 ± 2.73	48.46 ± 2.26	59.64 ± 2.94	74.65 ± 2.66
90	55.17 ± 5.48	73.00 ± 6.18	91.64 ± 4.85	55.93 ± 2.02	72.75 ± 2.96	77.84 ± 2.41
120	66.13 ± 4.60	86.66 ± 3.50	100.4 ± 2.44	63.28 ± 1.60	79.94 ± 1.77	86.44 ± 3.66

Each value is an average of three determinations; AM = Average mean; SD = Standard deviation

Table 7: Dissolution Profile of Ritonavir Solid Dispersion with PEG-8000 Prepared by Solvent Evaporation and Melt Method

Time (minutes)	Cumulative % drug release of PEG-8000 (AM ± SD)					
	P8M1	P8M2	P8M4	P8S1	P8S2	P8S4
0	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
15	18.28 ± 1.38	21.76 ± 0.60	28.34 ± 3.01	18.04 ± 0.74	23.9 ± 2.16	29.28 ± 0.87
30	20.73 ± 2.17	24.93 ± 1.16	32.57 ± 2.52	23.06 ± 1.66	27.62 ± 1.01	33.25 ± 1.81
45	24.56 ± 1.04	28.5 ± 1.54	45.13 ± 2.41	26.52 ± 1.17	29.84 ± 0.98	37.88 ± 1.42
60	29.98 ± 2.69	36.93 ± 2.24	53.14 ± 2.70	28.89 ± 1.41	34.37 ± 1.14	45.58 ± 1.83
90	34.18 ± 2.20	41.85 ± 2.38	68.21 ± 2.71	33.7 ± 2.28	41.86 ± 2.04	54.66 ± 2.72
120	37.58 ± 1.54	49.05 ± 1.85	82.57 ± 6.62	36.48 ± 1.87	47.02 ± 2.39	61.92 ± 2.80

Each value is an average of three determinations; AM = Average mean; SD = Standard deviation.

Table 8: T_{30}, T_{60} and T_{90} Values of Ritonavir and its Solid Dispersion with PEG Prepared by Melt and Solvent Evaporation Method (Percentage of Solubility at 30 mts, 60 mts and 90 mts)

Formulation Code	$T_{30(min)}$	$T_{60(min)}$	$T_{90(min)}$
P4M1	15.31	88.69	---
P4M2	15.16	45.91	123.23
P4M4	14.49	40.65	88.12
P4S1	27.48	109.9	---
P4S2	18.76	83.89	---
P4S4	17.53	58.35	---
P6M1	17.91	97.87	---
P6M2	17.17	60.95	---
P6M4	15.14	40.60	88.00
P6S1	15.31	113.7	---
P6S2	15.16	68.54	---
P6S4	14.53	42.18	124.94
P8M1	60.04	191	---
P8M2	47.36	146.7	---
P8M4	15.87	67.74	---
P8S1	62.30	197	---
P8S2	45.24	153	---
P8S4	15.28	116	---
Pure drug	217.6	--	---

Table 9: Data for Effect of Temperature on Drug Content of Ritonavir Formulations (Stability Studies)

Formulation	Days	Relative Humidity	
		Room Temperature	40 ± 2^{0}C / 75 RH
P6M4	0	100	100
	7	99.98	99.95
	14	99.23	99.13
	30	99.10	99.23
	60	99.05	99.14
	90	98.75	99.01

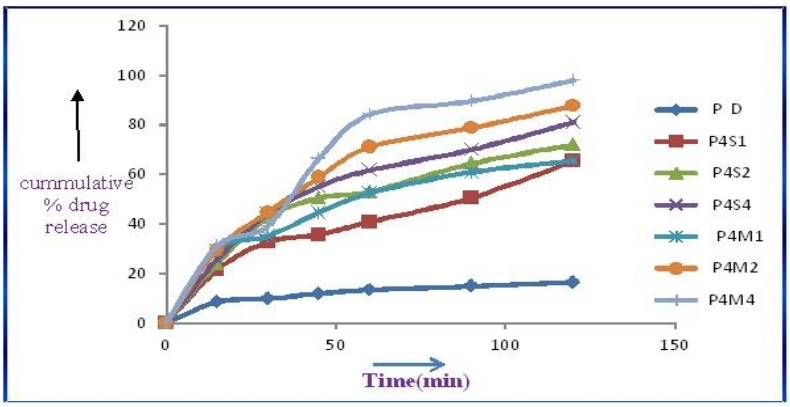

Figure-1: Dissolution profile of Ritonavir solid dispersion with PEG-4000

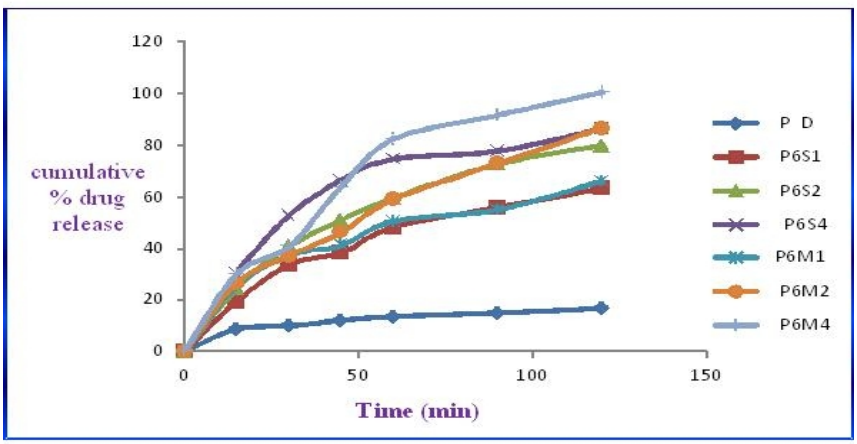

Figure-2: Dissolution profile of Ritonavir solid dispersion with PEG-6000

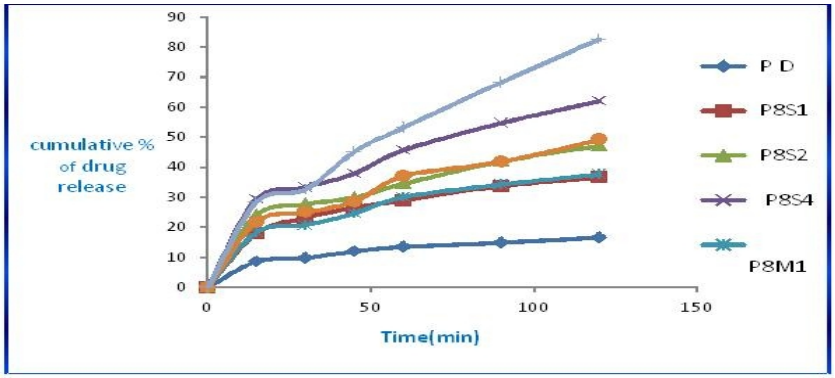

Figure-3: Dissolution profile of Ritonavir solid dispersion with PEG-8000

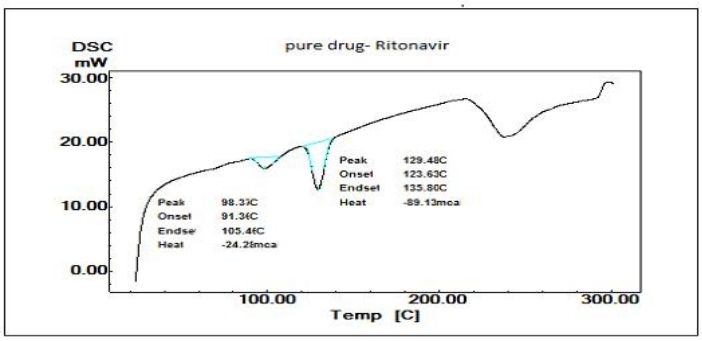

Figure-4: DSC Thermogram of Ritonavir.

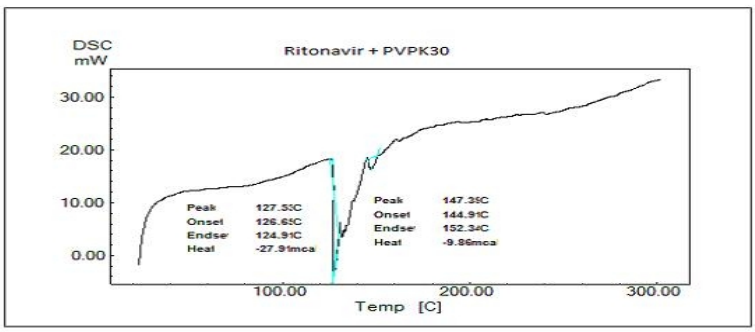

Figure-5: DSC Thermogram of Ritonavir + PEG4000

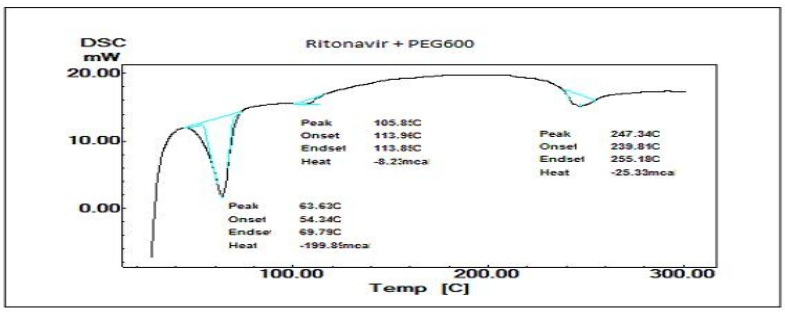

Figure-6: DSC Thermogram of Ritonavir + PEG6000

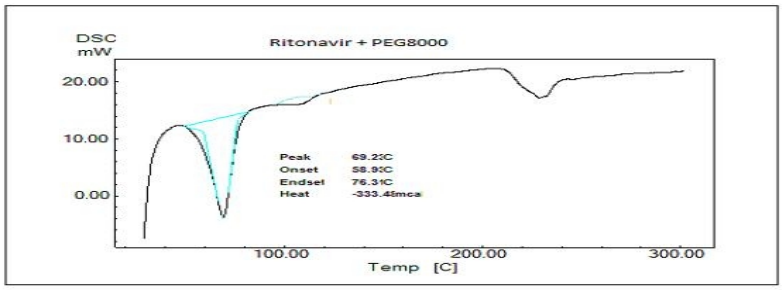

Figure-7: DSC Thermogram of Ritonavir + PEG8000

The solubility studies were carried out for pure drug and prepared formulations in 0.1N Hydrochloric acid. The solubility of Ritonavir in 0.1N Hydrochloric acid at room temperature was 146 µg / ml. The drug solubility against carrier concentration at room temperature indicated a linear relationship between the drug and carrier solution. The solubility of Ritonavir increased with increasing carrier concentrations. The solubility of Ritonavir increased more in PEG-6000 as compared with PEG-4000 and PEG-8000 respectively at room temperature and results were shown in Table 2. Fourier transform infrared spectroscopy (FTIR) has been used to assess the interaction between carrier and drug molecule. From the FTIR spectrum of Ritonavir shows no peaks other than those assigned to Ritonavir which indicate the absence of any well-defined chemical interaction. The differential Scanning Calorimetry thermogram (SEM) of pure drug and best formulation were shown in the Figure 4 to 6 respectively. The differential Scanning calorimetry thermogram of pure drug Ritonavir shows an endothermic peak at 123.63ºC corresponding to its melting point. In the thermogram of formulations the intensity of endothermic peak for P4M4 shows the persistence of endothermic peak of Ritonavir at 113.96C and for P8M4, shows the persistence of endothermic peak of Ritonavir at 121C. This seems to indicate the absence of interaction between drug and carriers. All the prepared formulations were subjected to drug content uniformity studies. The data was given in the Table 3. The drug content in all formulations was in the limit of 84.5 % to 98 %. The results indicate that drug was uniformly dispersed throughout the formulation. In dissolution studies, the formulations prepared by solid dispersion by different methods were studies and shown in Table 4 to 7 and Figure 1 to 3. The dissolution rate of Ritonavir from melt method and solvent evaporation revealed that all the PEG-6000 solid dispersion showed that significantly higher than that of PEG-4000 and PEG-8000. The *in vitro* dissolution of Ritonavir from the solid dispersion with PEG at a ratio of drug carriers as 1:1, 1:2 and 1:4 shows the profile that were distinctive different from each other during the two hour's dissolution period. This suggest the more dissolution rate of Ritonavir from PEG-6000 solid dispersion was due to decreased crystallinity, increased wettability and reduction of drug particle size were consider as a prominent factor. The $T_{30,}$ T_{60} and T_{90}values (% age of drug dissolved at 30, 60 and 90 minutes) were showed in Table 8. In stability studies, the formulations stored at different ambient temperatures did not show significant changes in the % drugs content shown in Table 9. Improvement of dissolution rate of Ritonavir was obtained by solid dispersion.

CONCLUSION

Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with PEG-4000, PEG-6000 and PEG-8000. These solid dispersions were analyzed for the solubility and *In vitro* dissolution profile, solid dispersion of drug with PEG 6000 (1:4) by melting method had shown enhanced solubility with improved dissolution rate. In present study solid dispersion prepared with PEG 6000 shows the presence of amorphous form confirmed by the characterization study.

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