RESEARCH ARTICLE JPAR 2019

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Dissolution rate enhancement and solid state characterization of Ritonavir - PEG 4000 solid dispersions

Anjan Kumar Mahapatra*, P. Narasimha Murthy, Ruchita Kumari Patra, Soudamini Mallik

Dept. of Pharmaceutics, Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India.

Received: 12.09.2019 Revised: 18.09.2019 Accepted: 21.09.2019 Published: 30.09.2019

ABSTRACT: Background: Ritonavir, a biopharmaceutical classification system (BCS) class II drug. **Aim:** The current research work endeavors to provide an account on the application of solid dispersion techniques for solubility and *in vitro* dissolution enhancement of ritonavir with PEG 4000, using physical mixing, solvent evaporation, and melting technique. **Method:** Different drug-to-polymer ratios at 1: 0.5, 1: 1, 1: 1.5, 1: 2 and 1: 2.5 were prepared to investigate the appropriate concentration of polymer required to enhance the solubility of the drug and improve its release kinetics. The phase solubility study of ritonavir was conducted in the presence of various concentrations of PEG 4000. The polymeric dispersions prepared were evaluated for the release of ritonavir over a period of 1 h in 0.1 N HCl using USP type - II dissolution apparatus. Characterization of the solid dispersions was carried out by differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR). **Results:** The Gibb's free energy (ΔG_{tr}^0) values were found negative for carrier at various concentrations, indicating the spontaneous nature of drug solubilization, and it decreased with an increase in its concentration, demonstrating that the reaction more favorable as the concentration of carrier increased. The findings of the work corroborated suggested the suitability of prepared polymeric drug dispersions of ritonavir in enhancing its solubility. **Conclusion:** The *in vitro* release profile and the mathematical models indicated that release of ritonavir can be effectively increased from a formulation containing polymeric dispersion of PEG 4000 at a ratio of 1: 2. The drug and carriers used were found compatible from the interaction studies.

Corresponding author*
Dr. Anjan Kumar Mahapatra
Professor
Royal College of Pharmacy and Health Sciences,
Berhampur-760002, Odisha, India.
Tel: +91- 9437194456
Mail ID: anjanmahapatra@gmail.com

Keywords: Ritonavir, PEG 4000, solid dispersions, characterization, dissolution rate.

INTRODUCTION:

Ritonavir is a large, lipophilic molecule that is practically insoluble in aqueous media and exhibits an exceedingly slow intrinsic dissolution rate. Although it has favorable lipophilicity, *in vitro* permeability studies have shown that ritonavir is a substrate of P-glycoprotein. Thus, the oral absorption of ritonavir could be limited by both dissolution and permeability,

thereby making it a Class IV compound in the Biopharmaceutics Classification System (BCS). Because formulations rarely exert direct influence on local intestinal permeability, the effect of enhanced dissolution rate on oral absorption was explored. More specifically, poly(ethylene glycol) (PEG)-amorphous ritonavir solid dispersions were prepared with different drug loadings [1].

Chemically ritonavir is 1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-methyl-2-{[methyl({[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl})carbamoyl]amino}butanamido]-1,6-diphenyl hexan-2-yl] carbamate [2]. The structure is given under Fig 1.

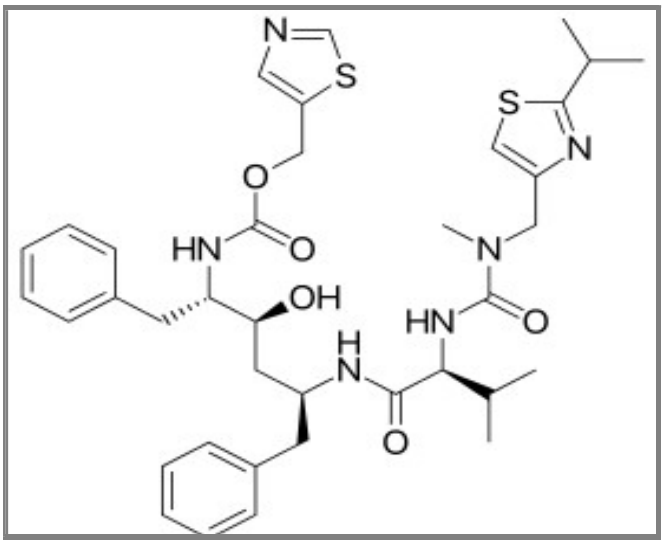

Fig 1. Chemical structure of ritonavir.

The aqueous solubility and permeability of drug (s) through biological membranes are the main physicochemical properties that limit the bioavailability of a new drug molecule. Various methods are proposed to enhance aqueous solubility of poorly soluble drugs that includes: chemical modifications (e.g., pro drugs or salt derivatives), physical modifications (e.g., solid dispersions, size reduction, loading on porous carriers, co crystals), alteration of solvent compositions (e.g., pH adjustment, use of co solvents, addition of surfactants), and use of carrier systems (e.g., cyclodextrins, micelles, liposomes) [3].

Polyethylene glycols (PEGs) with molecular weights of 1,500 to 20,000 are used for the preparation of solid dispersions (SDs). Solubility of PEGs in water is generally good, but decreases with increase in molecular weight. A particular advantage of PEGs for formation SDs is that they also have good solubility in many organic solvents. The melting points of PEGs of interest lies under 65 °C in every case (e.g., the melting ranges of PEG 1000, PEG 4000, PEG 6000, and PEG 20,000 are 30 to 40, 50 to 58, 55 to 63, and 60 to 63 °C respectively) [4,5]. A simple and convenient solubilizing technique is the preparation of solid dispersions.

The rate of oral absorption of poorly soluble or BCS class II drugs is often controlled by their dissolution rate in the gastrointestinal tract. Thus, solubility and dissolution rate are the key determinants of oral bioavailability, which is the concluding point drawn for fate of oral bioavailability [6]. Among the various approaches to improve solubility, the solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous [7]. Solid dispersion technique provides a means of reducing particle size to nearly a molecular level. As the soluble carrier dissolves; the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. In particular, polymers such as Polyethylene glycols and polyvinylpyrrolidone have been extensively used as carriers for dispersions due to their low melting point and their hydrophilic environment [8].

Although most of the drugs have encouraging experimental data obtained *in vitro*, the *in vivo* results have been disappointing. The attributes include: Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration, Drug distribution to other tissues with high drug toxicities (anticancer drugs), Poor solubility of drugs, and Fluctuations in plasma levels owing to unpredictable bioavailability [9,10].

The primary objective of the present study is to investigate solubility and dissolution rate of ritonavir containing solid dispersions in PEG 4000. To this purpose, physical characterizations based on IR spectroscopy and differential scanning calorimetry (DSC) was performed. Solubility analysis and dissolution studies were also carried out.

MATERIALS AND METHODS:

A gift sample of ritonavir was received from Aurobindo Pharmaceuticals (Hyderabad, India) and PEG 4000 was received from Clariant (Germany). Distilled water was used for all dissolution experiments and all the other chemicals used were of analytical grade and procured from authorized dealer.

Analytical Method:

Linear plot for estimation of ritonavir:

A series of standard solutions of ritonavir i.e., 5 to 40 µg/ml were prepared from a stock solution of 50 µg/ml. The drug was dissolved in about 2 to 3 ml of methanol and the volume was made up to get various standard solutions using 0.1 N HCl as solvent. The linear plot was obtained by reading corresponding absorbance values at 245 nm, using UV-Vis spectrophotometer (UV spectrophotometer, Shimadzu 1800).

Preparation of drug-carrier binary mixtures:

The composition of solid dispersion formulations for ritonavir with PEG 4000 are given under Table 1. The SDs of drug with PEG 4000 was prepared at the ratios and techniques mentioned above. The resulting mixtures were sieved through a 60-mesh sieve. The mixtures were stored in a screw-cap vial at room temperature until further studies [11,12].

Table 1. Composition of solid dispersion formulations for ritonavir with PEG 4000.

FC	Polymer used	Drug: polymer ratio	Method
R1	PEG 4000	1:0.5	Physical mixing
R2		1:1	
R3		1:1.5	
R4		1:2	
R5		1:2.5	
R6	PEG 4000	1:0.5	Melt/Fusion
R7		1:1	
R8		1:1.5	
R9		1:2	
R10		1:2.5	
R11	PEG 4000	1:0.5	Solvent evaporation
R12		1:1	
R13		1:1.5	
R14		1:2	
R15		1:2.5	

FC – Formulation code.

Evaluation of drug-carrier binary mixtures:

Drug content study (assay) of the solid dispersions:

All the prepared solid dispersions were assayed for the drug content by using UV - Vis spectroscopy at 245 nm using 0.1 N HCl as solvent system.

Dissolution testing - In vitro drug release studies:

The drug and drug-carrier dissolution studies were performed using 8-station dissolution test apparatus with a paddle stirrer at speed of 50 rpm (LABINDIA Disso 2000 and Electrolab, Mumbai). Dissolution medium consisted of 900 ml of 0.1N HCl maintained at 37± 0.5 °C. At predetermined time intervals an aliquot was withdrawn and replaced with fresh medium. The amount of drug in each aliquot was assayed on a UV-Visible spectrophotometer at 245 nm using 0.1N HCl as blank. All the trials were conducted in triplicate and the average reading was noted.

Fourier Transform Infrared Spectroscopy (FTIR):

The drug-carrier binary mixtures of ritonavir were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 200 cm^{-1} using FTIR spectrophotometer (IR-Affinity-1, Shimadzu, Japan).

Differential Scanning Calorimetry (DSC):

Approximately 2 mg of drug or drug-carrier binary mixture was taken in aluminium pan, sealed with aluminum cap and kept under nitrogen purging (atmosphere). Both the samples were scanned from 40-240 °C with the scanning rate of 10 °C rise/m using DSC (DSC-4000, Perkin Elmer, Singapore).

RESULTS:

The Linear plot for ritonavir is given under Table 2. The dissolution profile of ritonavir is given under Table 3. The dissolution studies of ritonavir - PEG 4000 solid dispersions prepared by physical mixing, melt/fusion and solvent evaporation method are shown under Fig 2, 3 and 4. The IR spectra for pure drug ritonavir and ritonavir with PEG 4000 are given under Fig 5 and 6. The DSC thermograms for pure drug ritonavir and ritonavir with PEG 4000 are given under Fig 7 and 8.

Table 2. Linear plot of ritonavir in 0.1N HCl.

Conc. (µg/ml)	Absorbance
5	0.074±0.003
10	0.129±0.001
15	0.201±0.002
20	0.259±0.004
25	0.315±0.002
30	0.379±0.003
35	0.442±0.001
40	0.503±0.003

The value represents mean ± SD (n=3).

DISCUSSION:

Linear Plot:

Linear plot for ritonavir was constructed by preparing a series of standard solutions from 5 to 40 µg/ml. First the drug was dissolved in about 1ml of methanol and the volume was made up to, to get various standard solutions using 0.1N HCl media. The linear plot was obtained by measuring corresponding absorbance values at 245 nm.

The linear regression equation obtained after regression analysis was used for calculation of drug concentration in further study. The coefficient of determination was found to be more than 0.999.

Drug Content study:

The drug content estimation is the evidence for the presence of required quantity of drug in the formulations. The drug content was studied by taking the solid dispersion powder containing drug equivalent to 50 mg and preparing its 20 and 30 µg/ml solutions. The absorbance value is checked and is compared with the absorbance value of the standard solutions of 20 and 30 µg/ml. The percentage of drug content for all the formulations varied from 91 to 95 %. It indicates that there is uniform distribution of the drug throughout the prepared formulations (SDs).

In vitro dissolution studies of ritonavir:

Ritonavir is practically insoluble in water and has high lipophilicity (log P = 4.24). Thus, the dissolution rate of ritonavir is expected to limit its absorption from the gastrointestinal tract [11].

Table 3. The dissolution profile of pure drug ritonavir.

Time (min)	Drug release (%)
10	10.23±0.25
20	18.34±0.58
30	25.54±1.24
45	34.23±1.45
60	38.83±1.47

The value represents mean ± SD (n=3).

The pure drug showed up to 39 % dissolution over a period of 60 min, but its solid dispersions showed up to dissolution of more than 75 % in 45 min and 90 % over a period of 60 min. Formulation of solid dispersions with PEG 4000, showed improved dissolution rate of the drug compared to physical mixing. More than twofold increase in dissolution rate was observed in case of solid dispersion formulations with increase in carrier concentration from 1:0.5 to 1:2.5 (Drug: Carrier).

This enhancement of dissolution of ritonavir from drug carrier systems can be ascribed to several factors like; lack of crystallinity i.e., amorphization, increased wettability and dispersibility and particle size reduction are considered to be important factors for dissolution rate enhancement. As indicative from dissolution data of physical mixtures, improvement could be attributed to higher wettability and dispersibility. Physical mixing of drug with a hydrophilic carrier results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. Moreover, hydrophilic carrier encircling the hydrophobic drug decreases aggregation and agglomeration of ritonavir particles, allowing a faster dissolution process.

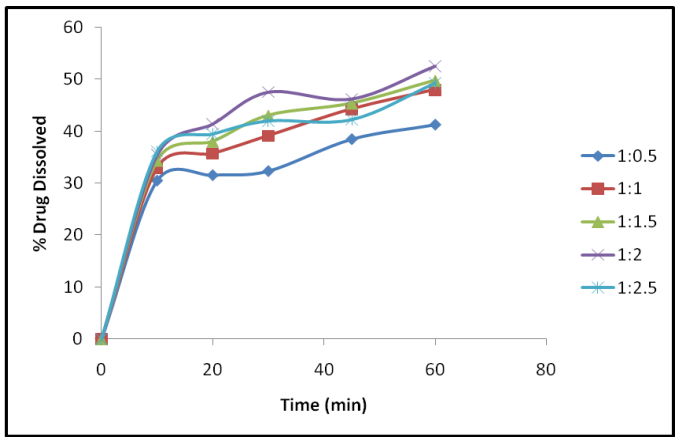

Fig 2. Dissolution studies of ritonavir - PEG 4000 solid dispersions prepared by physical mixing.

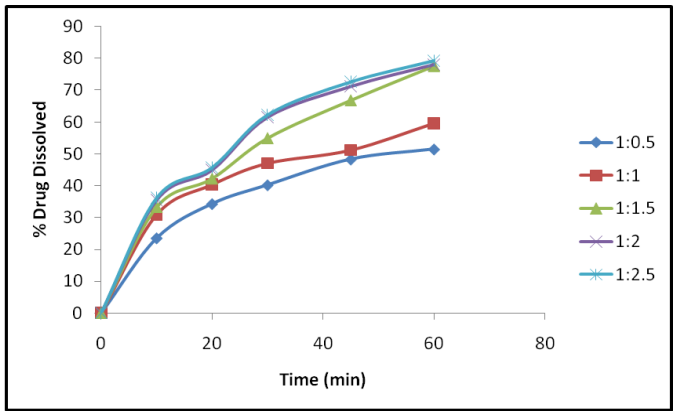

Fig 3. Dissolution studies of ritonavir - PEG 4000 solid dispersions prepared by melt/fusion method.

IR spectroscopic Analysis of Ritonavir:

The IR absorption spectrum of the drug, ritonavir was studied in the range of 4000-400 cm^{-1} using KBr disc method. The major peaks were considered for evaluation of purity. FT-IR spectrum of ritonavir

indicate the presence of a strong N-H stretching peak at 3350 cm^{-1}, aromatic C-H stretching peak around 3092 cm^{-1}, sp^3 C-H stretching at 2928 cm^{-1} (s), 2942 cm^{-1} (As), C=O stretching at 1750 cm^{-1} and CH_2 bending around 720 cm^{-1}. Due to the presence of above-mentioned characteristic peaks, the identity and purity of ritonavir was confirmed [13,14].

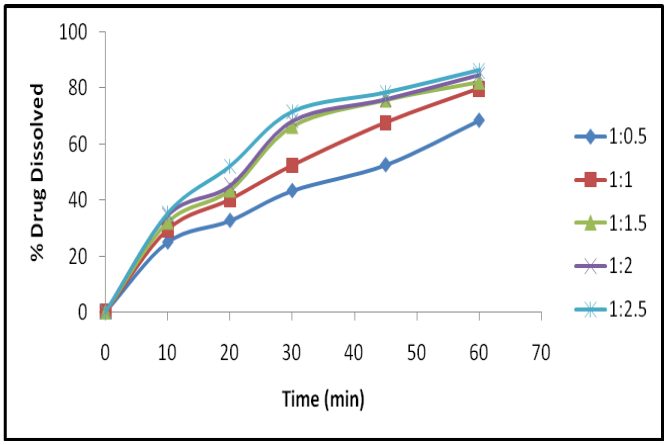

Fig 4. Dissolution studies of ritonavir - PEG 4000 solid dispersions prepared by solvent evaporation method.

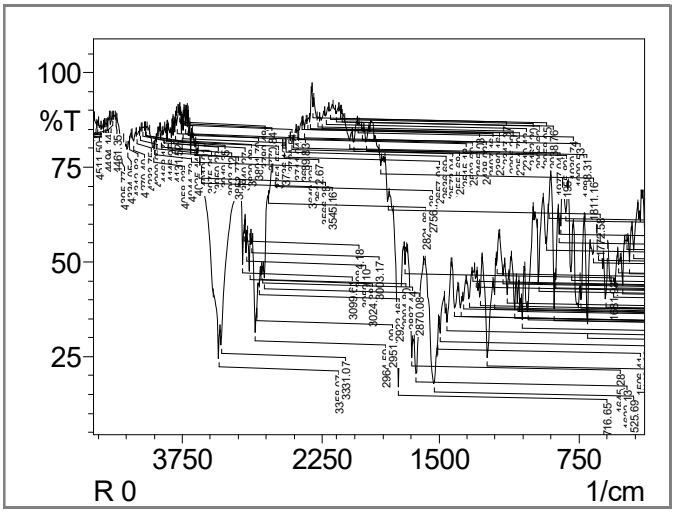

Fig 5. FTIR spectrum of pure drug ritonavir.

DSC Analysis of Ritonavir:

The identity and purity of ritonavir was further confirmed by differential scanning calorimetric method. Its reported melting point was compared with the melting peak of the test sample and found to be 123 °C.

Drug- Excipient Compatibility Study:

FT-IR analysis:

FT-IR spectra of formulations of ritonavir were investigated for any sign of probable interaction. Individual spectrum revealed the presence of characteristic peaks of ritonavir N-H stretching peaks around 3300 cm^{-1}, aromatic C-H stretching peak around 3090 cm^{-1}, sp^3 C-H stretching at 2920 cm^{-1} (s), 2940 cm^{-1} (As), C=O stretching at 1750 cm^{-1} and CH_2 bending around 720 cm^{-1}. Due to the presence of above-mentioned characteristic peaks in the formulations indicates there were no significant interactions in the samples, The IR spectra are shown in Fig 5and 6 [13,14].

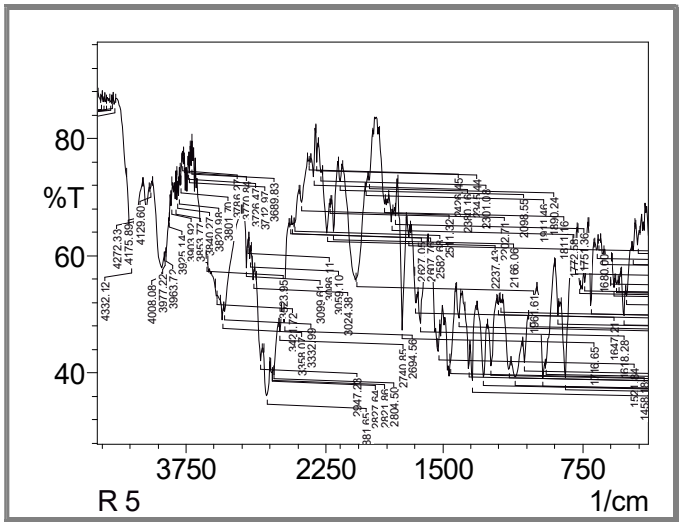

Fig 6. FTIR spectrum of ritonavir with PEG 4000 by melt or fusion method.

DSC analysis:

The interactions between drugs and a distinct mixture (1:1) were then investigated by DSC. Interactions in the sample are derived or deduced from DSC by changes in the thermal events, such as elimination of an endotherm or exotherm peak, or appearance of a new peak. However, some broadening of peaks leading to changes in the area, onset of peak, and changes in peak temperature occur simply due to mixing of the components without indicating any significant interaction. If all thermal features more or less remain the same, compatibility can be expected.

It was observed that there was no significant change in the position and shape of the peak. The endothermic peak for ritonavir was found at 123 ºC. The DSC thermogram of the formulation samples indicate the presence of both drug and excipient endothermic peaks. The respective peaks of the drug and excipients have not undergone any significant change in their shape and position. Therefore, it may be concluded that there are no significant interactions between the drug and excipients The DCS thermograms are shown in Fig 7 and 8.

Results showed that, in general, hydrophilic carrier-based formulations at high carrier levels showed dissolution rates higher than those at low polymer level at different degrees, but not always. Up to a more than

twofold increase in dissolution rate was observed in case of solid dispersions with increase in carrier concentration from 1:0.5 to 1:2.5 (Drug: Carrier).

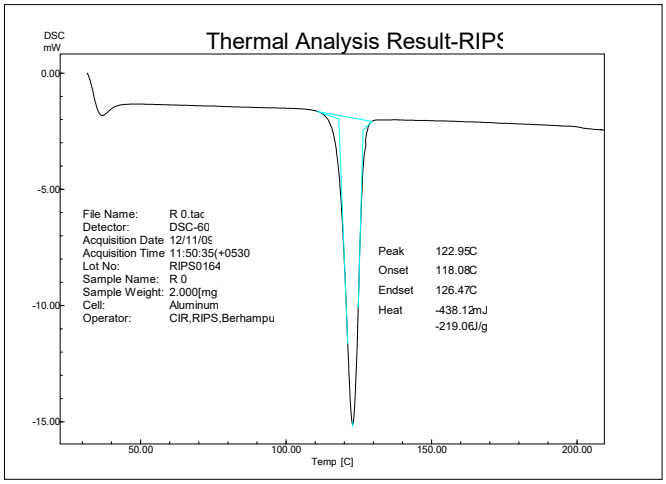

Fig 7. DSC thermogram of ritonavir.

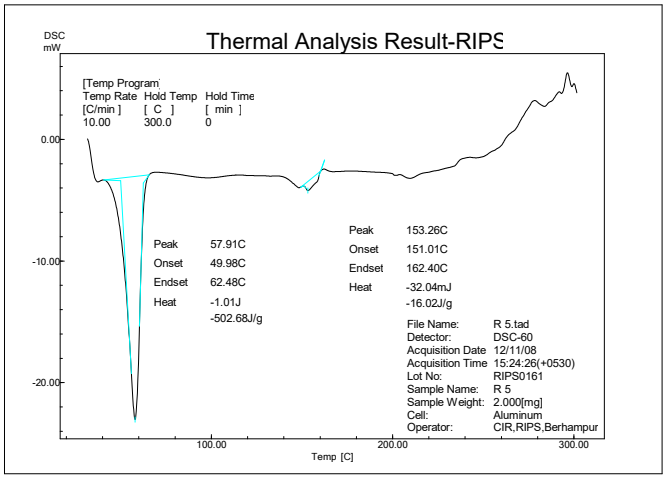

Fig 8. DSC thermogram of ritonavir SD with PEG 4000 by melt/fusion.

FTIR and DSC studies showed that the used carriers are compatible with ritonavir, there is no significant interaction observed between ritonavir and the carriers selected in formulation of SDs as important characteristic peaks are retained in the spectra of SDs. Solid dispersions with PEG 4000 showed a dissolution rate of 70 % in 30 min and 80 % in 60 min.

CONCLUSIONS:

The solubility and dissolution rate of ritonavir can be enhanced by the use of SDs of with PEG 4000. The solubilization effect of PEGs may be contributed due to reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of ritonavir from its SD. From FTIR spectroscopy, it was concluded that there were no well-defined chemical interactions between ritonavir and PEG in SDs, as no important new peaks could be observed. The DSC study reveals no significant interaction between ritonavir and PEG 4000 and there is change in crystallinity of pure ritonavir to amorphous state in their solid dispersions.

ACKNOWLEDGEMENTS:

The authors would like to acknowledge the contributions of Dr. Amit Kumar Panigrahi for providing the samples of drug and excipients. Further, the authors would like to acknowledge Maharajah's College of Pharmacy and Royal College of Pharmacy and Health sciences for providing necessary facilities to carry out the research work.

REFERENCES:

1. Law D, Schmitt EA, Marsh KC, Everitt EA, Wang W, Fort JJ, *et al.* Ritonavir-PEG 8000 amorphous solid dispersions: *in vitro* and *in vivo* evaluations. J Pharm Sci, 2004; 93(3): 563-570.
2. Mahapatra AK, Murthy PN, Sameeraja NH and Palei NN. Dissolution Rate Enhancement of Entacapone and Formulation of its Oro-Dispersible Tablets: Applying Statistical Design. Indian J Pharm Edu Res, 2016; 50(4): 549-562.
3. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersion. Eur J Pharm Biopharm, 2000; 50: 47-60.
4. Liu C, Desai KGH, Liu C. Enhancement of dissolution rate of Valdecoxib using solid dispersions with polyethylene glycol 4000. Drug Dev Ind Pharm, 2005; 31: 1-10.
5. Rane Y, Mashru R, Sankalia M, Sankalia J. Effect of hydrophilic swellable polymers on dissolution enhancement of Carbamazepine solid dispersions using response surface methodology. AAPS PharmSciTech, 2007; 8(2): E1-E11.
6. Shah TJ, Amin AF, Parikh JR, Parikh RH. Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug. AAPS PharmSciTech, 2007; 8(2): E18-E24.
7. Trapani G, Franco M, Latrofa A, Pantaleo MR, Provenzano MR, Sanna E, *et al.* Physicochemical characterization and in vivo properties of Zolpidem in solid dispersions with polyethylene glycol 4000 and 6000. Int J Pharm, 1999; 184(1): 121-130.
8. Karanth H, Shenoy VS, Murthy RR. Industrially feasible alternative approaches in the manufacture of

solid dispersions: A technical report. AAPS PharmSciTech, 2006; 7(4): 87-92.
9. Mura P, Manderioli A, Bramanti G, Ceccarelli L. Properties of solid dispersions of naproxen in various poly ethylene glycols. Drug Dev Ind Pharm, 1996; 22(9,10): 909-916.
10. Dressman JB, Kunath K, Vogt M. Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: Comparison with commercial preparations. Eur J Pharm Biopharm, 2008; 68: 283-288.
11. Tripathy D, Nayak BS, Mohanty B, Mishra B. Solid Dispersion: A Technology for Improving Aqueous Solubility of Drug. J Pharm Adv Res, 2019; 2(7): 577-586.
12. Sharma KS, Sahoo J, Agrawal S, Kumari A. Solid dispersions: A technology for improving bioavailability. J Pharm Adv Res, 2019; 2(4): 512-520.
13. Kemp W. Organic Spectroscopy. London: Palgrave; 1991.
14. Skoog DA, West DM, Holler FJ, Crouch SR. Fundamentals of Analytical Chemistry. 8th ed. Belmont: Thomson Learning; 2004.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Mahapatra AK*, Murthy PN, Patra RK, Mallik S. Dissolution rate enhancement and solid state characterization of Ritonavir - PEG 4000 solid dispersions. J Pharm Adv Res, 2019; 2(9): 550-556.