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Enhancement of Dissolution Rate of Ritonavir: A Comparative Study Using Various Carriers and Techniques

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Abstract: *Aim of study*: The aim of present work is to study the release of Ritonavir from solid dispersions with different grades of PEGs and cyclodextrins using various techniques like physical mixing, solvent evaporation, melting technique and kneading. *Material and methods*: Different drug-to-polymer ratios were prepared to investigate the appropriate concentration of polymer required to enhance the solubility of the drug and improve its release kinetics. The physicochemical properties of dispersions were evaluated by using Fourier transform infrared spectroscopy (FTIR), the study of FTIR could not show significant interaction between Ritonavir and the polymers incorporated i.e., PEGs and cyclodextrins. The Polymeric dispersions prepared were evaluated for the release of ritonavir over a period of 1 hour in 0.1N HCl using USP type II dissolution apparatus. The *in vitro* drug release study revealed that the dispersion techniques have increased the dissolution rate. *Conclusions*: It concluded that the various grades of PEGs (PEG 4000, PEG 6000, PEG 8000, PEG 20000), beta cyclodextrins and hydroxyl propyl beta cycldextrins were used in preparation of polymer dispersions for improving the dissolution and physical stability by various techniques. The *in vitro* release profile and the mathematical models indicate that release of Ritonavir can be effectively increased from a formulation containing polymeric dispersion of PEG grade 20,000 and inclusion complexes of Hydroxy propyl beta cyclodextrins.

Key words: Polymeric Dispersion · Ritonavir · Polyethylene Glycols (Pegs) · Cyclodextrins

INTRODUCTION

Ritonavir shows more release than that of pure drug due to nano size dispersion and the solid dispersion prepared by solvent evaporation method is a promising approach for the bioavailability enhancement of Ritonavir [1]. The approaches used to overcome the insufficient bioavailability are reduction of particle-size which includes microsizing and nanosizing, salt formation, solubilization, use of surfactants, polymorphism, liquisolid technique [2, 8] and complexation with β cyclodextrins to increase the oral bioavailability of poorly water-soluble drugs [3]. Solid dispersion can produce a solid dosage form having the active in an amorphous state or in a molecular dispersion state. The solid dispersion is used to enhance the dissolution rate by drug particle size reduction, solublization effect of the carrier, invention of amorphous state and molecular interaction between the drug and carrier [4]. Ritonavir is practically insoluble in water. It is used for the treatment of human immune deficiency disease. The selected drug belongs to BCS class II basing on their solubility and permeability. Ritonavir is an anti HIV drug which acts by inhibiting the protease enzymatic action. Ritonavir pure drug is known to have high purity and satisfactory stability. However, it has low solubility in water and thus is not suitable for oral administration. Conversion of Ritonavir pure drug into an amorphous form leads to high water solubility and improves the usefulness of Ritonavir in the therapy of disease. But amorphous materials are thermodynamically

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unstable and therefore show some tendency to crystallize spontaneously to variations in the pH, temperature and moisture[5-7]. Hence in the present work it was planned to prepare Ritonavir polymer dispersions for improving the dissolution and physical stability. For this, we have selected various grades of Polyethylene glycol. i.e. PEG 4000, PEG 6000, PEG 8000, PEG 20000, Beta cyclodextrins and Hydroxy propyl beta cyclodextrins. These polymer dispersions were prepared by various techniques and evaluated for their effectiveness in improving the dissolution rate and improving the physical stability of Ritonavir.

The primary objective of the present work was to improve the solubility of poorly soluble drug by preparing polymeric dispersions and characterizes the properties of polymeric dispersions formulation using analytical methods like DSC and FTIR studies. The study also includes observation of the effect of different polymers and their concentration on the drug solubility parameters to improve the bioavailability of the drug. The present work involves preparation and evaluation of Ritonavir polymer solid dispersions.

MATERIALS AND METHODS

Ritonavir was received as a gift sample from Hetero drug limited (Hyderabad, India). Polyethylene glycol 4000, 6000, 8000 and 20000 were procured from S.D. Fine Chemicals Ltd. (Mumbai, India). Beta cyclodextrins and hydroxyl propyl beta cycldextrins purchased from Cavitron, USA. Other chemicals and reagents used were purchased from Merck Limited (Mumbai, India) and were of analytical grade.

Methods: In this present study, the polymeric dispersions were prepared by different methods. Polyethylene glycols (PEG 4000, PEG 6000, PEG 8000, PEG 20000), beta cyclodextrins and hydroxyl propyl beta cyclodextrins were used for the preparation of polymeric dispersions. All the polymeric dispersions were prepared from drug to polymer ratios about 1:0.25, 1:0.5, 1:1, 1:2, 1:3 and 1:4. Physical mixing technique is used for preparation of polymeric dispersions in various ratios of 1:0.25, 1:0.5, 1:1 and 1:2 in a mortar and pestle for 20 minutes as well as solvent evaporation technique (dissolved in methanol, then removed by evaporation under reduced pressure) is used for preparation of polymeric dispersions in various ratios of 1:0.25, 1:0.5, 1:1, 1:2, 1:3 and 1:4. Melting technique (carrier is melted and added the drug to carrier at same temperature, cooled) is used for preparation of polymeric dispersions in various ratios of 1:0.25, 1:0.5, 1:1, 1:2 and 1:3. Hydroxy propyl beta cyclo dextrins and cyclo dextrins were also used in various proportions.

Calibration Curve of Ritonavir in 0.1 N Hcl: Analytical Methods: In this present study, UV spectroscopic method was employed to determine absorbance maxima(max) and construct the standard calibration curve of Ritonavir in 0.1 N HCl.

Preparation of 0.1 N HCl: 8.5 ml of hydrochloric acid was added to 200 ml of distilled water and the final volume was made up to the 1000 ml with water.

Estimation of Ritonavir in 0.1 N HCl

Determination of λ_{max}: First the drug was dissolved in about 1 ml of methanol and the volume was made up to get various standard solutions using 0.1N HCl media. Most of drugs absorbs light in UV region (200-400 nm), since they are generally aromatic or contain double bonds. An absorption maximum was determined using 0.1 N HCl. Solutions ranging from 10-50 µg/ml was scanned from 200-400 nm using double beam UV spectrophotometer (SL 210, M/s Elico Pvt. Ltd., India) to determine absorption maximum of Ritonavir. The absorption maximum was found to be 245 nm.

Preparation of Ritonavir Standard Stock Solution: Stock solution of 1000 µg/ml solutions was prepared by dissolving 100 mg of Ritonavir in 100 ml of 0.1 N HCl, in a 100 ml volumetric flask. From this solution 10 ml was taken and diluted to 100 ml of 0.1 N HCl to give a concentration 100 µg/ml. From the above standard stock solution, Ritonavir was subsequently diluted with above selected solvent media to obtain a series of dilution containing 10, 20, 30, 40 and 50 µg of Ritonavir /ml. The absorbance of the above dilutions were measured at 245 nm using double beam UV spectrophotometer (SL 210, M/s Elico Pvt. Ltd., India) at 245 nm using pure solvent as blank. The absorbance values were plotted against concentration of Ritonavir Fig. 1. The method obeyed beer's law in the concentration ranges from 10-50 µg/ml. Reproducibility of the method was tested by analyzing six separately weighed samples of Ritonavir. The relative standard deviation (RSD) in estimated values was found to be <1. The low RSD values indicated that the method is reproducible. Thus the method was found to be suitable for the estimation of Ritonavir contents in the dissolution fluids.

Drug-Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopy (FT-IR): The pure drug and drug-excipients compatibility studies were carried out by Fourier Transform Infrared Spectroscopy (FT-IR). The pellets were prepared on KBr under hydraulic pressure of 150 kg/ cm^2, the spectra were scanned over the wave number range of 4000 to 400 cm^{-1} at the ambient temperature. The results were shown in Fig. 2.

Differential Scanning Calorimetry (DSC): DSC study was performed using DSC-60 Calorimeter. Samples were sealed in aluminum crucibles (40 µL) and the DSC thermograms were reported at a heating rate of 20°C/ min under dry air flow between 30°C-300°C. The results were shown in Fig. 3.

Phase Solubility Studies: Phase solubility studies showed a linear increase of drug solubility with an increase of the concentration of each examined carrier and have been attributed to the probable formation of weak complexes. On the other hand, the enhancement of the drug solubility in the aqueous carrier solution could be equally well explained by the co-solvent effect of the carrier. It has been found that hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole and dipole- to –dipole bonds) even though other types of forces, such as Vander Waals forces and hydrogen bonds, can frequently play a role in the drug carrier interaction. The drug solubility increased linearly with increasing polymer concentration.

Drug Content: The formulations (equivalent to 25 mg of Ritonavir) were dissolved in small amount of methanol, then final volume made up to 100 ml of 0.1 N HCl, then filtered and diluted with 0.1 N HCl, then find out the drug content using UV spectrophotometer at 245 nm. The percentage of drug content for all the formulations was found to be 86.14 ± 1.09- 99.09 ± 1.98% of Ritonavir, it complies with official specifications. The results were shown in Table 1.

***In vitro* Studies:** All the prepared formulations of Ritonavir were subjected to *in vitro* release studies these studies were carried out using USP type II dissolution apparatus, 900 ml of pH1.2 hydrochloric acid buffer at 37±0.5°C, 50 rpm and 5 ml of sample were withdrawn and replaced with fresh media to maintain sink conditions. The results were shown in Fig. 4 to Fig. 15. The results obtained in *in vitro* release studies were plotted in different model of data treatment as follows:

- Cumulative percent drug released vs. time (zero order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Log cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential Equation)
- Cubic root of unreleased fraction of drug verses time (Hixon Crowel)

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy (FT-IR) Studies: When FT-IR was performed, the drug spectrum indicated characteristic peaks at 3,480 cm^{-1} (N–H stretching amide group), 2,964 cm^{-1} (hydrogen-bonded acid within the molecule), 1,716 cm^{-1} (ester linkage), 1,645, 1,622 and 1,522 cm^{-1} (–C-C– stretching aromatic carbons). The FT-IR spectra of solid dispersion of Ritonavir prepared by solvent evaporation and melt method was taken and analyzed. Two main band formations were observed between drug and carrier on the basis of FT-IR spectra. Intermolecular hydrogen bonding was observed due to the peak at 3,380 cm^{-1}. A number of indistinguishable peaks appeared in the region of 3,400–4,000 cm^{-1} in the solid dispersion which was absent in the crystalline drug. A broad and strong absorption peak at 1,108 cm^{-1} indicated formation of secondary hydrogen bond which was absent in pure drug. The presence of strong absorption peak at 1,735 cm^{-1} and 2,720 cm^{-1} were indicative of characteristic C–H stretching band and C-O stretching band of aliphatic aldehydic group. This band was absent in the spectra of the crystalline drug. The hydrogen bonding and aldehydic group formation between drug and carrier indicated interaction between the two, which could be attributed to the cause of enhanced dissolution rate of the solid dispersion as compared to pure drug. In case of melt method, both the aldehydic group and hydrogen bond peaks were present but were very broad as compared to that obtained in solvent evaporation. The interaction between drug and carrier was due to hydrogen bond and aldehydic linkages resulting in the increase solubility of drug.

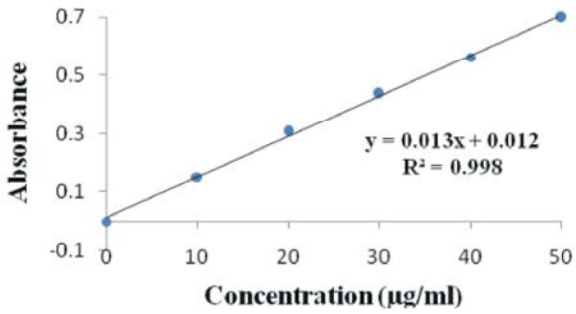
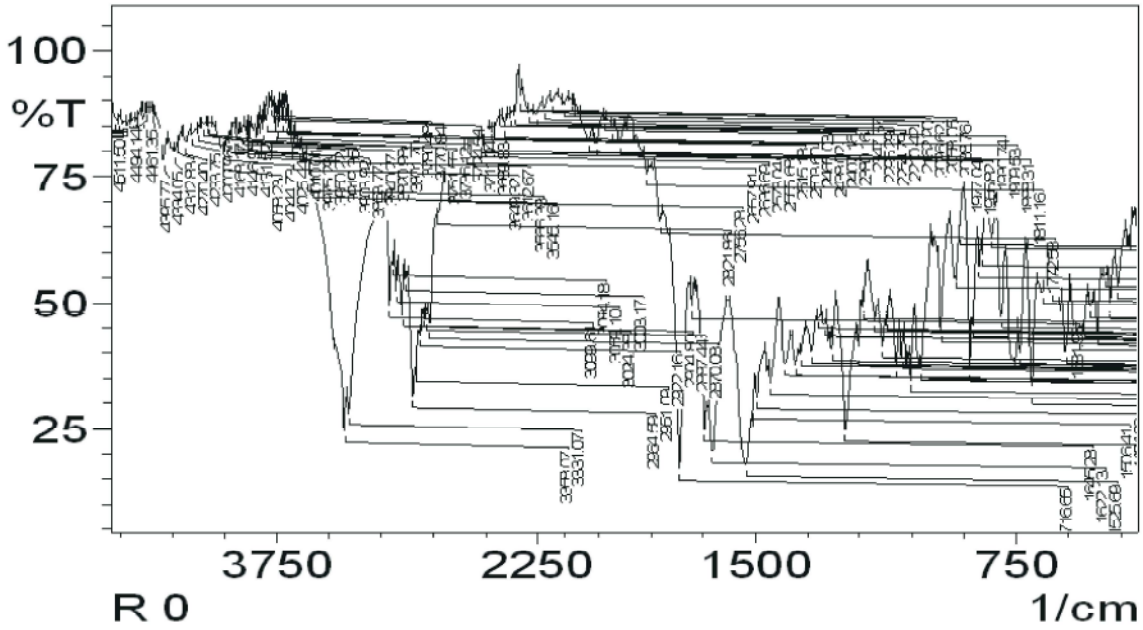
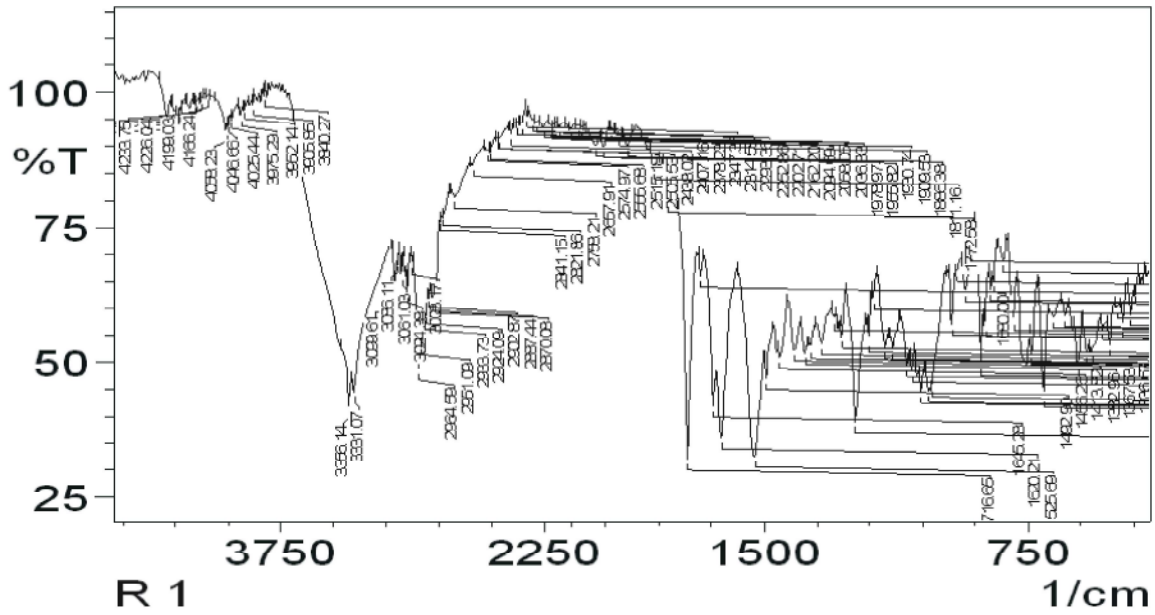


Fig. 1: Standard graph of Ritonavir pure drug



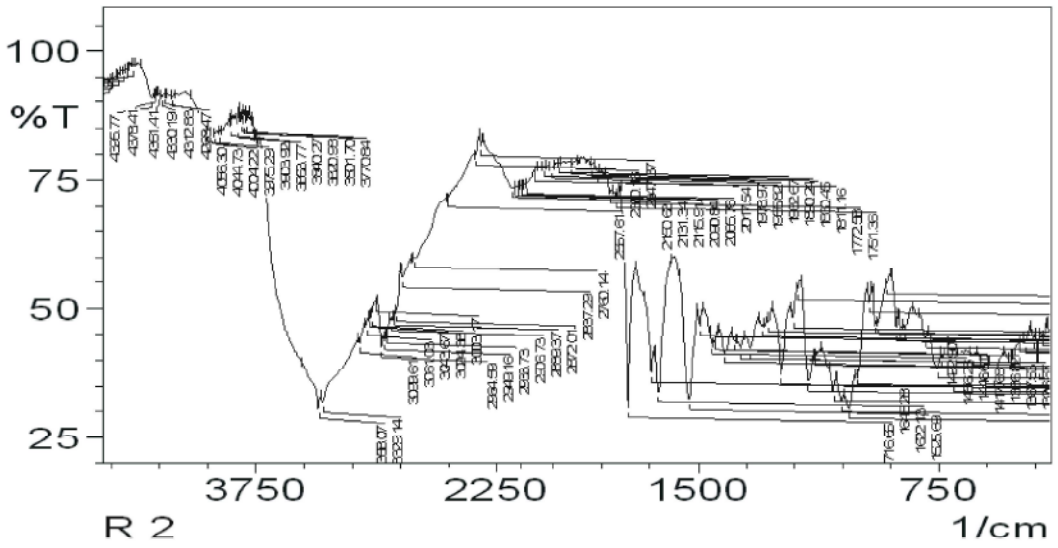
(A)



(B)

Fig. 2: Continued

(C)



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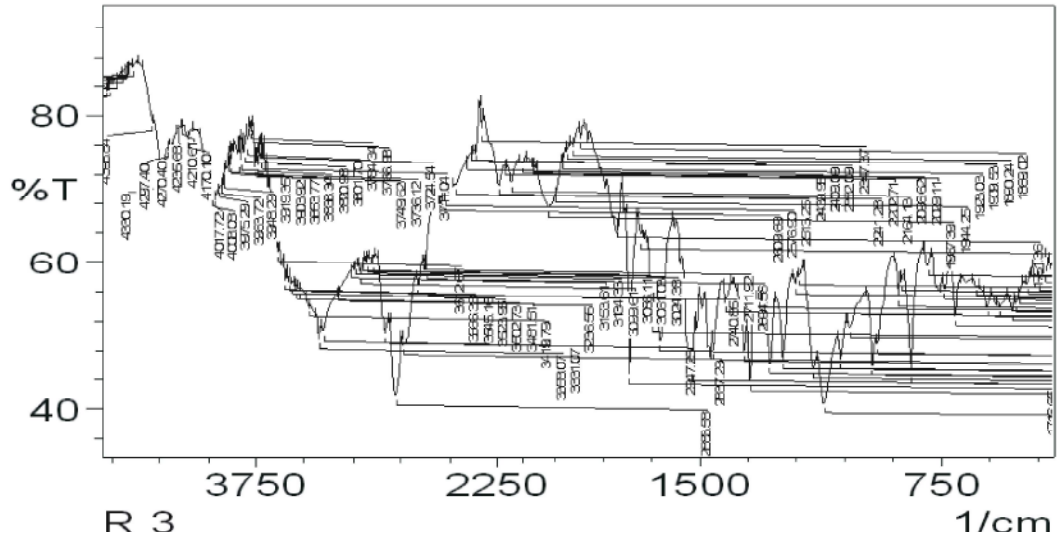

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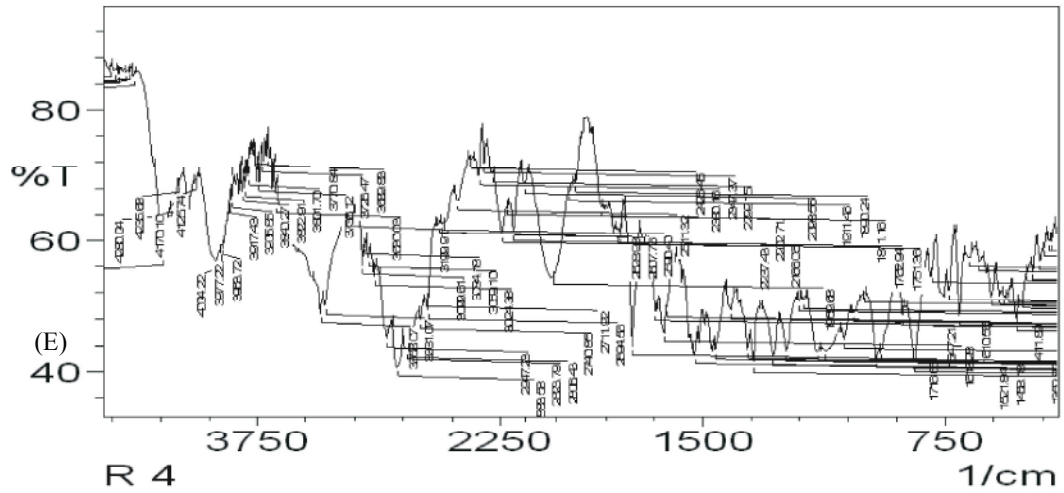
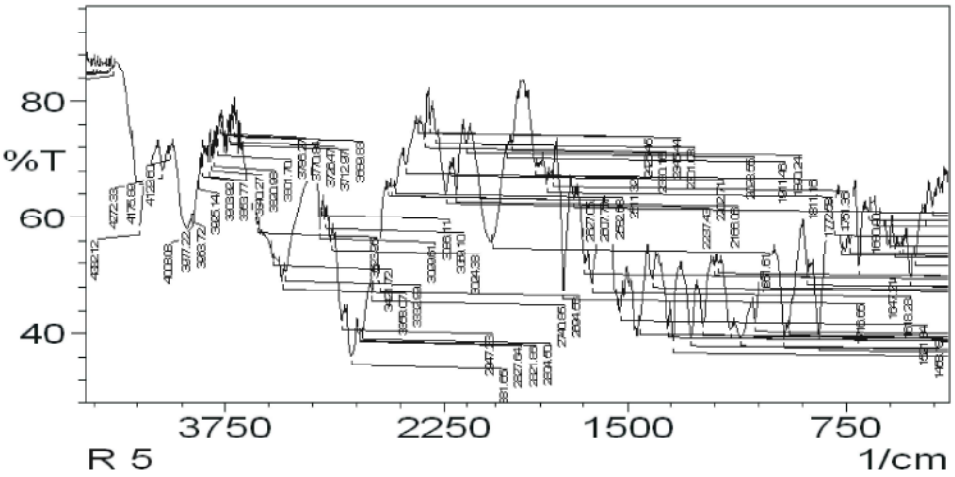


Fig. 2: Continued



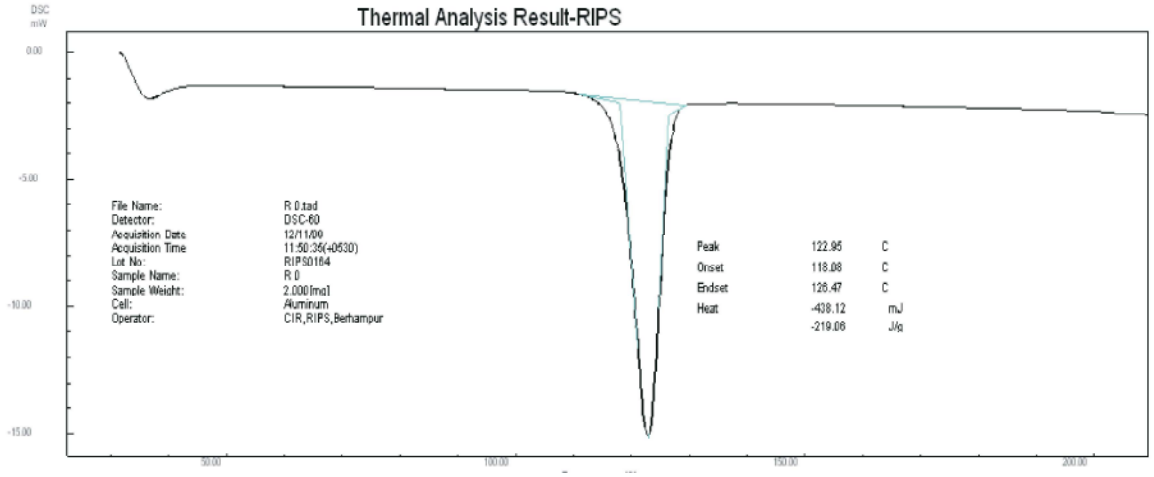
(F)

Fig. 2: FT-IR Spectra of A) pure drug Ritonavir; B) Kneading 1:0.5 HP Beta CD;C) Kneading 1:3 Beta CD;D) 1:3 Melting PEG 20,000; E) 1:4 Solvent evaporation PEG 20,000; F)1:4 Solvent evaporation PEG 4000

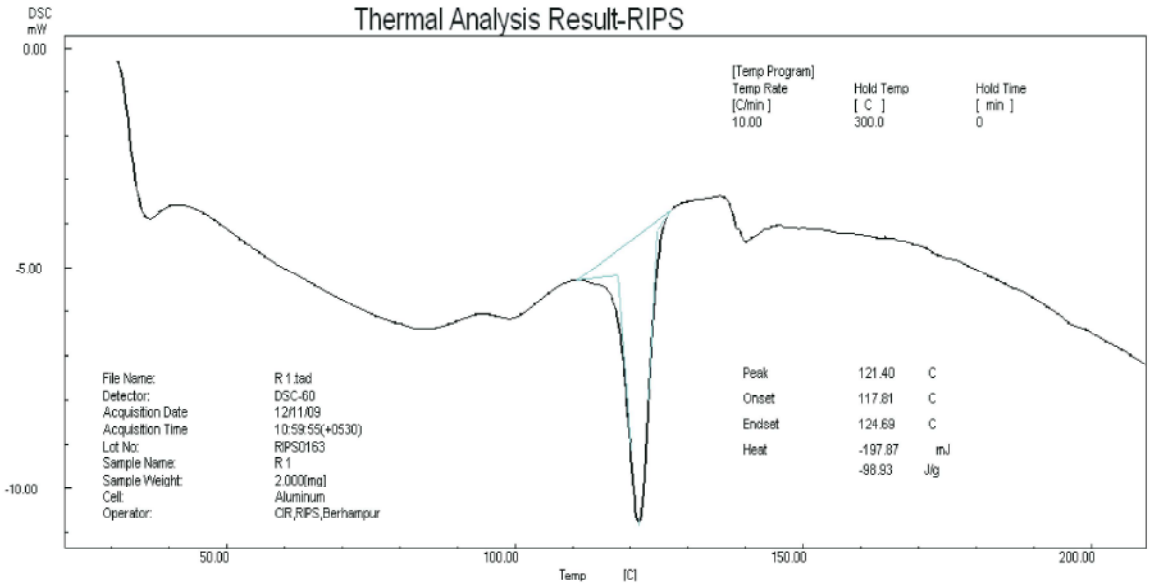
Differential Scanning Calorimetry (DSC): DSC studies of various solid dispersion of Ritonavir were taken. It was concluded on the basis of scans that DSC of the sample prepared by the solvent method, kneading, physical mixing and melt method showed absence of any significant drug peak at 120°C but presence of prominent peak of carrier with no change in melting point. This suggested the formation of a monotectic system where the melting point of the carrier is unchanged in the presence of drug. The results suggested formation of the eutectic solid dispersion where the drug is present as ultrafine crystals in polymer matrix.

Phase Solubility Studies: Phase solubility diagrams showed a linear increase in drug solubility with an increase in the concentration of each examined carrier. At 2%, 6% & 8% w/v concentration of β-CD, HP β-CD and PEGs, the solubility of Ritonavir increased significantly. Analogous results were found for these same carriers, probably due to the formation of weakly soluble complexes. Hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole and dipole-to-dipole bonds), even though other types of forces, such as Vander Waals forces and hydrogen bonds, can frequently play a role in the drug–carrier interaction. The drug solubility increased linearly with increasing polymer concentration. The values of Gibbs free energy (ΔG) associated with the aqueous solubility of Ritonavir in presence of carrier were all negative for carriers at various concentrations, the spontaneous nature of drug solubilization. The values decreased with increasing carrier concentration, demonstrating that the reaction became more favorable as the concentration of carrier increased.

***In vitro* Dissolution Studies:** All formulations of Ritonavir were subjected to *in vitro* dissolution studies using 0.1N HCl as the dissolution medium to assess various dissolution properties. All SD formulations with various polymers exhibited higher rates of dissolution than Ritonavir pure drug and corresponding physical mixtures. The pure drug showed up to 48 % dissolution over 60 min, but its solid dispersions prepared by solvent evaporation 1:4 w/w) showed dissolution of greater than 80%. Solid dispersions of β-CD and HP β-CD prepared by kneading and physical mixture showed nearly similar dissolution. The dissolution enhancing effect of various carriers used in this study followed the order: 20,000PEG>4000 PEG>8000PEG>6000 PEG and HP β-CD > β-CD. Among various ratios of drug with PEG, ratio at 1:4 w/w solid dispersions prepared by solvent evaporation technique showed better enhancement of solubility. Among various ratios of drug with HP β-CD at ratio 1:0.5 w/w inclusion complexes in the form of solid dispersions by kneading technique at room temperature exhibited improved aqueous solubility leading to superior *in vitro* dissolution profile. Among various ratios of drug with β-CD at ratio 1:3 w/w solid dispersions prepared by kneading technique at room temperature exhibited improved aqueous solubility leading to superior *in vitro*



(A)



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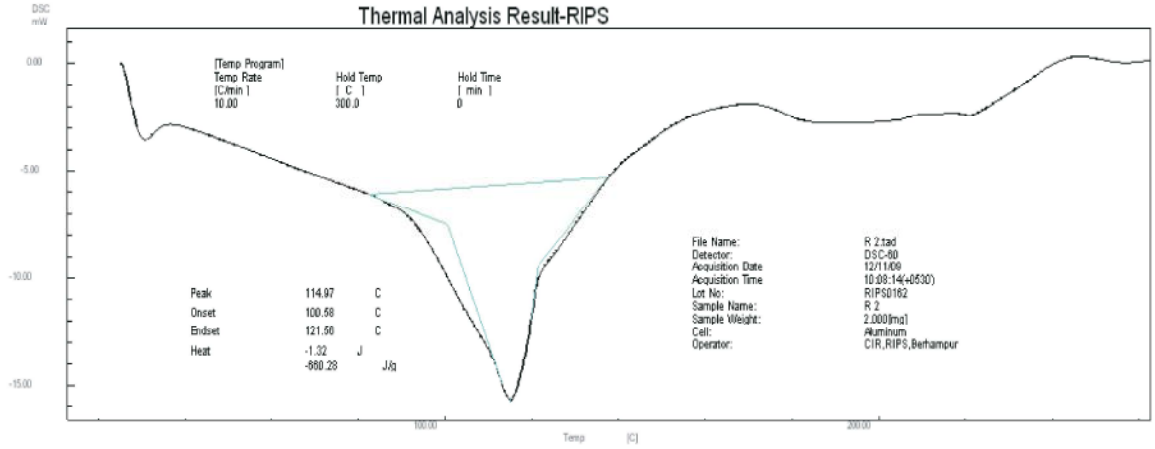
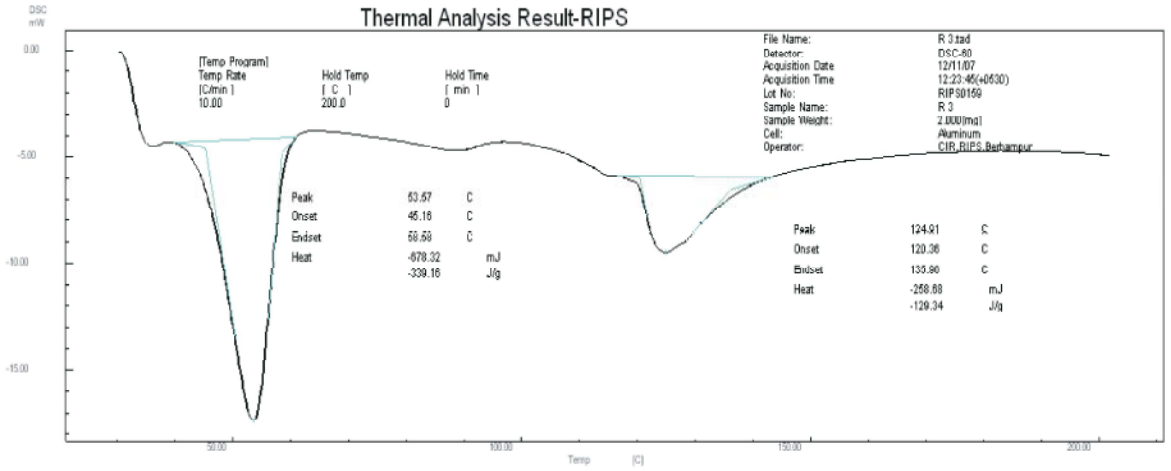


C)

Fig. 3: Continued



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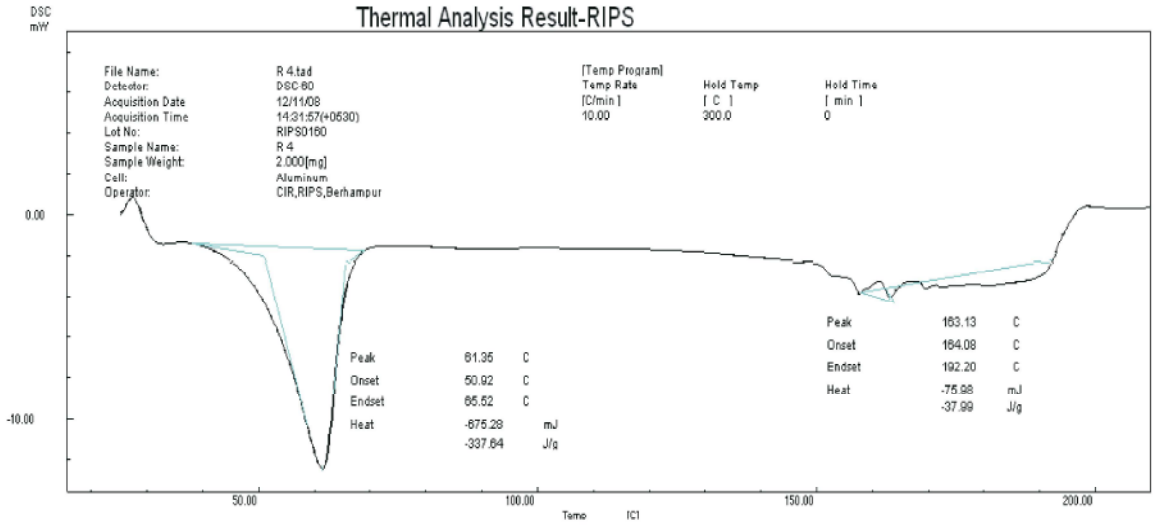

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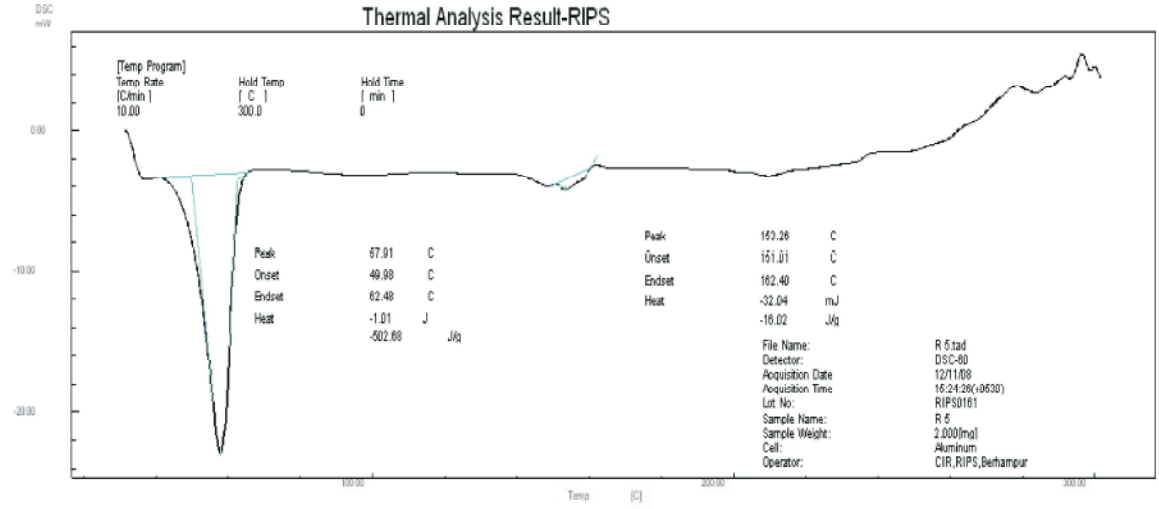

(F)

Fig. 3: DSC thermograms of A) pure drug Ritonavir; B) Kneading 1:0.5 HP Beta CD;C) Kneading 1:3 Beta CD;D) 1:3 Melting PEG 20,000; E) 1:4 Solvent evaporation PEG 20,000; F)1:4 Solvent evaporation PEG 4000

Pure Drug Dissolution Profile:

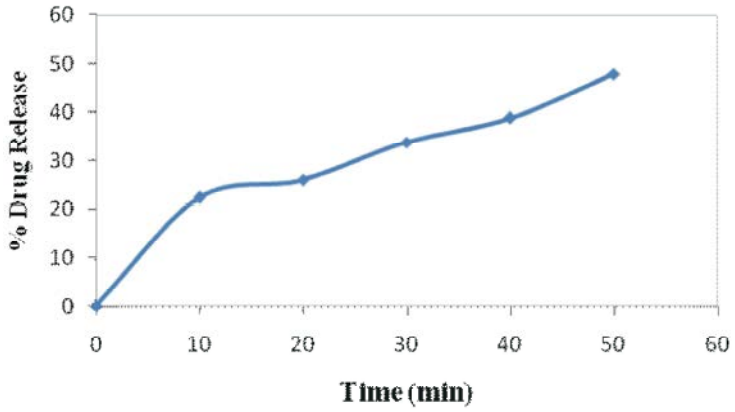

Fig. 4: *In vitro* dissolution profile of Pure drug

***In vitro* Dissolution Profile of Formulations Prepared by Physical Mixing:**

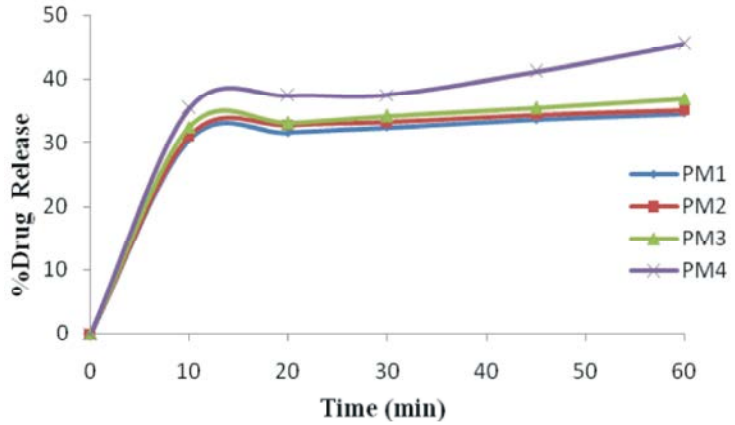

Fig. 5: *In vitro* dissolution profile of PM1 (1:0.25), PM 2 (1:0.5), PM 3 (1:1) and PM 4 (1:2) containing PEG 4000 by Physical Mixing

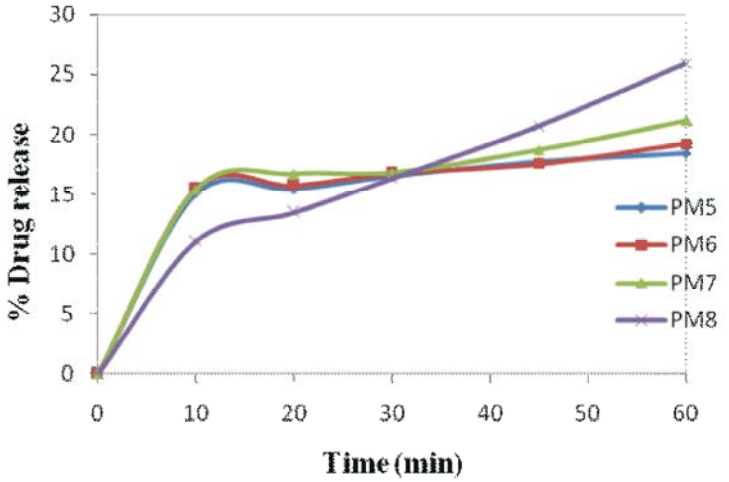

Fig. 6: *In vitro* dissolution profile of PM5 (1:0.25), PM 6 (1:0.5), PM 7 (1:1) and PM 8 (1:2) containing PEG 6000 by Physical Mixing

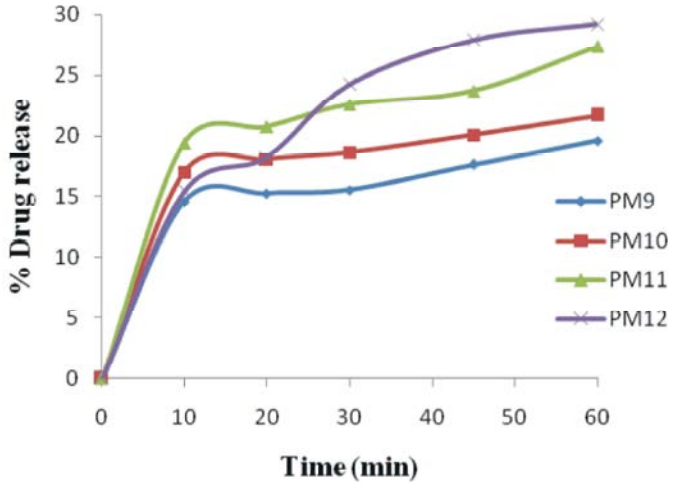

Fig. 7: *In vitro* dissolution profile of PM9 (1:0.25), PM 10 (1:0.5), PM 11 (1:1) and PM 12 (1:2) containing PEG 8000 by Physical Mixing

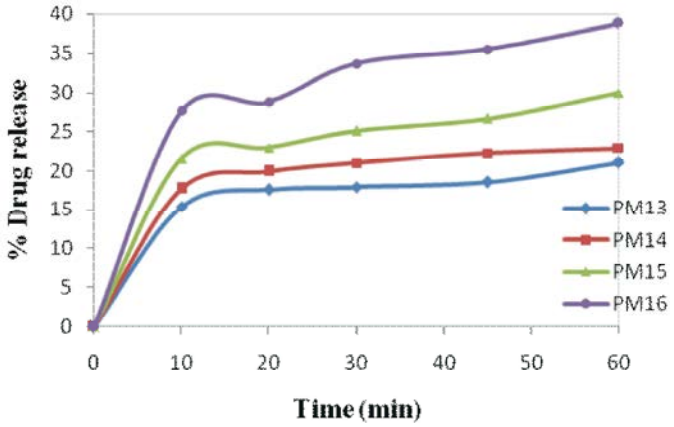

Fig. 8: *In vitro* dissolution profile of PM 13(1:0.25), PM 14 (1:0.5), PM 15 (1:1) and PM 16 (1:2) containing PEG 20000 by Physical Mixing

***In vitro* Dissolution Profile of Formulations Prepared by Solvent Evaporation:**

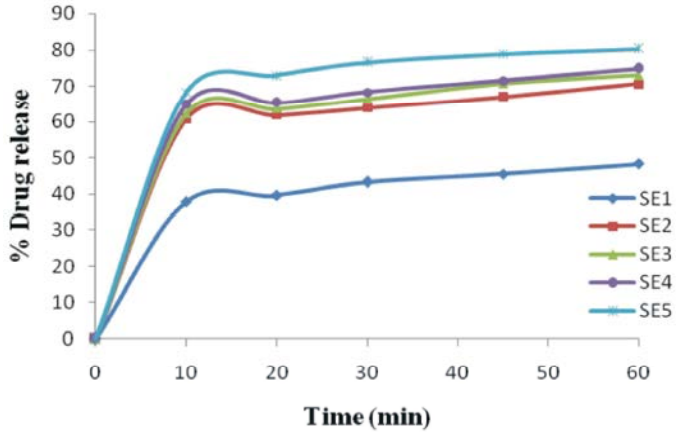

Fig. 9: *In vitro* dissolution profile of SE1 (1:0.5), SE2 (1:1), SE3 (1:2), SE4 (1:3) and SE5 (1:4) containing PEG 4000 by Solvent Evaporation

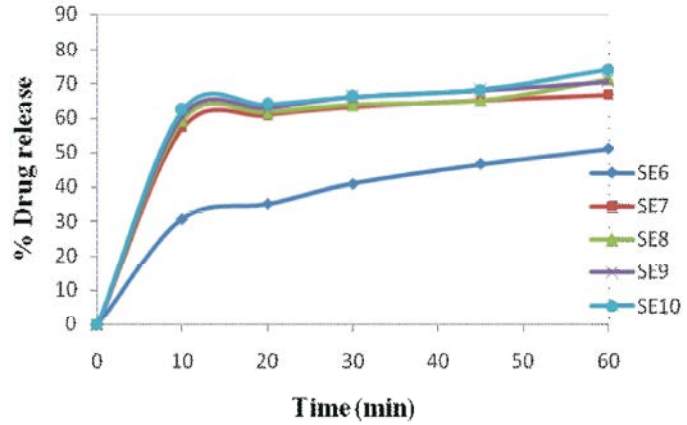

Fig. 10: *In vitro* dissolution profile of SE 6(1:0.5), SE7 (1: 1), SE8 (1:2),SE 9 (1:3) and SE 10 (1:4) containing PEG 6000 by Solvent Evaporation

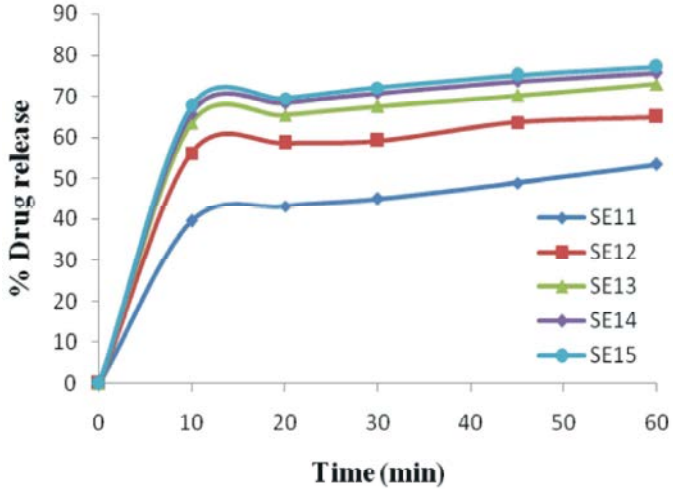

Fig. 11: *In vitro* dissolution profile of SE 11(1:0.5), SE12 (1: 1), SE13 (1:2),SE 14 (1:3) and SE 15 (1:4) containing PEG 8000 by Solvent Evaporation

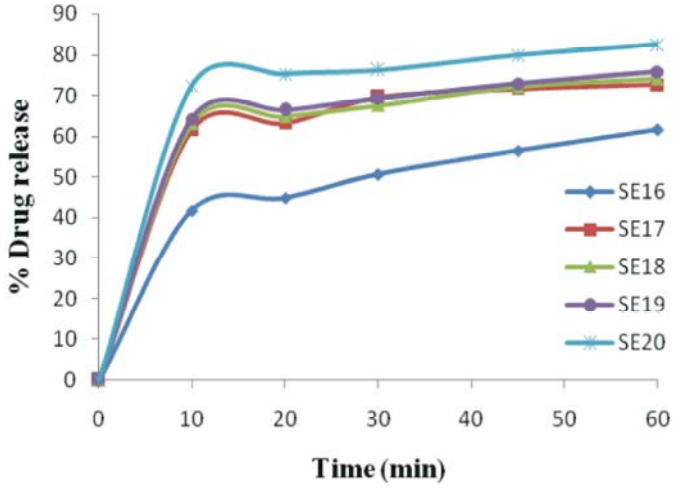

Fig. 12: *In vitro* dissolution profile of SE 16(1:0.5), SE17 (1: 1), SE18 (1:2), SE 19 (1:3) and SE 20 (1:4) containing PEG 20000 by Solvent Evaporation

***In vitro* Dissolution Profile of Formulations Prepared by Melt Fusion:**

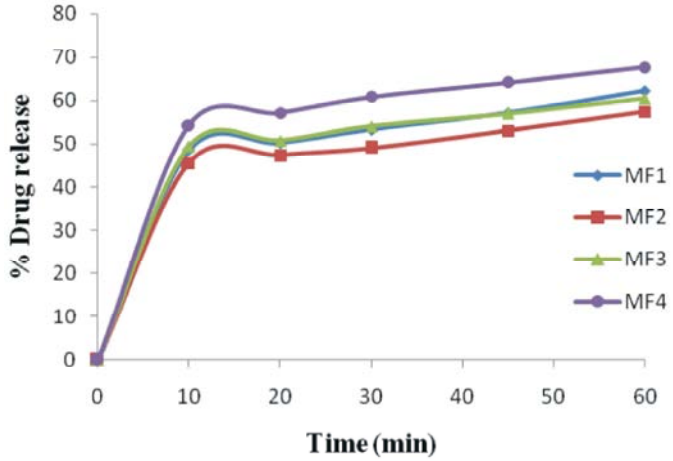

Fig. 13: *In vitro* dissolution profile of MF1(1:3), MF2(1:3), MF3(1:3) and MF4(1:3) containing by PEG 4000,6000,8000 and 20000 respectively (Melt fusion technique).

***In vitro* Dissolution Profile of Formulations Prepared by Kneading Method:**

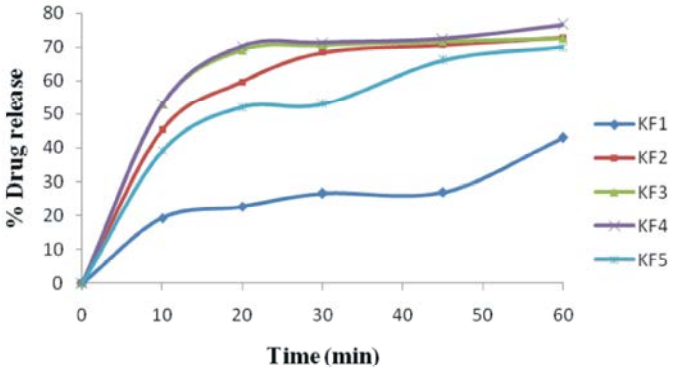

Fig. 14: *In vitro* dissolution profile of KF1 (1:0.5), KF2(1:1), KF3(1:2) KF4(1:3) (Kneading Method)and KF5 (1:0.5-Physical Mixing method) containing by Beta cyclodextrins

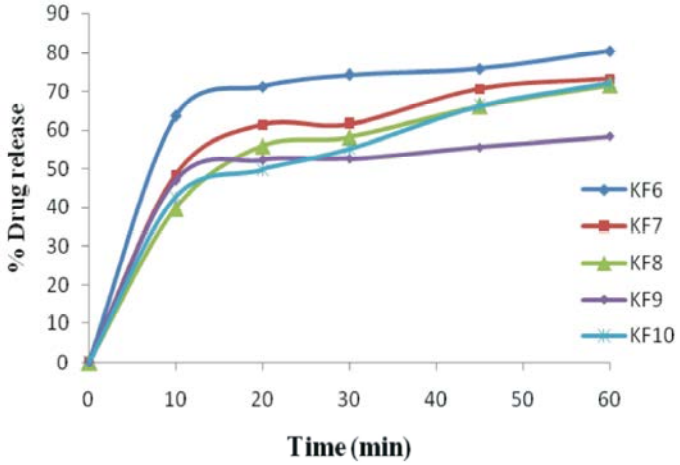

Fig. 15: *In vitro* dissolution profile of KF6 (1:0.5), KF7 (1:1), KF8(1:2) KF9(1:3) (Kneading Method) and KF10 (1:3-Physical Mixing method) containing by Hydroxy propyl Beta cyclodextrins

Table 1: Drug content estimation of Ritonavir polymeric dispersions by various carriers

Formulations code	Method	% Drug Content ± SD
PM 1	Physical Mixing Technique	91.01 ± 1.34
PM2	Physical Mixing Technique	92.01 ± 1.29
PM3	Physical Mixing Technique	92.91 ± 1.32
PM4	Physical Mixing Technique	93.28 ± 1.01
PM5	Physical Mixing Technique	86.14 ± 1.09
PM6	Physical Mixing Technique	86.61 ± 1.91
PM7	Physical Mixing Technique	86.56 ± 1.89
PM8	Physical Mixing Technique	86.97 ± 1.70
PM9	Physical Mixing Technique	87.87 ± 1.34
PM10	Physical Mixing Technique	87.88 ± 1.70
PM11	Physical Mixing Technique	87.89 ± 1.65
PM12	Physical Mixing Technique	87.89 ± 1.99
PM13	Physical Mixing Technique	94.32 ± 1.42
PM14	Physical Mixing Technique	95.68 ± 1.23
PM15	Physical Mixing Technique	96.07 ± 1.23
PM16	Physical Mixing Technique	99.09 ± 1.98
MF1	Melt Technique	93.24 ± 1.94
MF2	Melt Technique	86.28 ± 1.87
MF3	Melt Technique	89.81 ± 1.43
MF4	Melt Technique	99.01 ± 2.11
SE1	Solvent Evaporation Technique	92.12 ± 1.77
SE2	Solvent Evaporation Technique	92.23 ± 1.01
SE3	Solvent Evaporation Technique	92.24 ± 1.23
SE4	Solvent Evaporation Technique	93.56 ± 1.65
SE5	Solvent Evaporation Technique	93.52 ± 1.98
SE6	Solvent Evaporation Technique	86.35 ± 1.96
SE7	Solvent Evaporation Technique	86.84 ± 1.21
SE8	Solvent Evaporation Technique	86.85 ± 1.31
SE9	Solvent Evaporation Technique	86.87 ± 1.67
SE10	Solvent Evaporation Technique	86.89 ± 1.42
SE11	Solvent Evaporation Technique	88.12 ± 2.42
SE12	Solvent Evaporation Technique	88.14 ± 2.43
SE13	Solvent Evaporation Technique	88.23 ± 1.99
SE14	Solvent Evaporation Technique	88.34 ± 2.90
SE15	Solvent Evaporation Technique	89.31 ± 1.89
SE16	Solvent Evaporation Technique	94.12 ± 1.94
SE17	Solvent Evaporation Technique	95.01 ± 1.86
SE18	Solvent Evaporation Technique	96.02 ± 1.89
SE19	Solvent Evaporation Technique	97.03 ± 1.01
SE20	Solvent Evaporation Technique	98.04 ± 1.02
KF1	Kneading Method	96.42 ± 1.01
KF2	Kneading Method	96.26 ± 1.23
KF3	Kneading Method	96.91 ± 1.21
KF4	Kneading Method	97.13 ± 1.23
KF5	Physical Mixing Technique	95.42 ± 2.34
KF6	Kneading Method	90.92 ± 2.54
KF7	Kneading Method	91.12 ± 1.43
KF8	Kneading Method	92.16 ± 1.24
KF9	Kneading Method	91.34 ± 1.07
KF10	Physical Mixing Technique	93.88 ± 1.06

Table 2: Kinetics data for various polymeric dispersions

	Higuchi	Krosmeyer-Peppas model			Hixon Crowell	First order	Zero order
Formulations code	R	R	K	n	R	R	R
PM1	0.997	0.974	25.70	0.069	0.994	0.994	0.993
PM2	0.978	0.985	26.66	0.065	0.945	0.946	0.942
PM3	0.972	0.923	27.16	0.070	0.997	0.997	0.997
PM4	0.895	0.835	25.50	0.128	0.946	0.944	0.951
PM5	0.968	0.926	11.22	0.117	0.980	0.980	0.979
PM6	0.928	0.868	11.48	0.116	0.972	0.972	0.973
PM7	0.906	0.861	10.37	0.160	0.952	0.951	0.954
PM8	0.965	0.960	3.53	0.467	0.993	0.922	0.996
PM9	0.897	0.832	9.74	0.156	0.955	0.954	0.956
PM10	0.970	0.933	12.35	0.129	0.993	0.993	0.994
PM11	0.939	0.910	12.50	0.178	0.968	0.966	0.970
PM12	0.958	0.962	6.19	0.386	0.928	0.930	0.923
PM13	0.913	0.912	10.81	0.153	0.913	0.913	0.913
PM14	0.970	0.994	12.82	0.143	0.919	0.920	0.915
PM15	0.965	0.936	14.02	0.175	0.986	0.985	0.987
PM16	0.956	0.928	17.10	0.194	0.960	0.962	0.957
MF1	0.955	0.905	34.43	0.135	0.985	0.982	0.991
MF2	0.946	0.982	33.34	0.123	0.982	0.979	0.987
MF3	0.973	0.929	37.15	0.113	0.992	0.992	0.992
MF4	0.993	0.972	40.27	0.123	0.994	0.995	0.989
SE1	0.982	0.957	27.03	0.137	0.982	0.983	0.979
SE2	0.951	0.890	48.97	0.083	0.985	0.982	0.990
SE3	0.968	0.921	49.09	0.093	0.985	0.985	0.985
SE4	0.949	0.887	52.23	0.082	0.982	0.980	0.983
SE5	0.961	0.990	55.08	0.093	0.924	0.934	0.900
SE6	0.994	0.984	25.31	0.290	0.991	0.993	0.985
SE7	0.978	0.997	46.77	0.087	0.942	0.947	0.929
SE8	0.939	0.896	46.77	0.095	0.962	0.956	0.972
SE9	0.988	0.977	48.97	0.086	0.978	0.980	0.971
SE10	0.910	0.853	48.97	0.086	0.943	0.936	0.958
SE11	0.982	0.960	26.85	0.160	0.993	0.992	0.993
SE12	0.958	0.925	45.91	0.082	0.965	0.965	0.964
SE13	0.988	0.953	52.48	0.076	0.998	0.998	0.998
SE14	0.998	0.983	53.70	0.079	0.990	0.993	0.983
SE15	0.991	0.963	56.23	0.075	0.993	0.994	0.989
SE16	0.984	0.957	23.98	0.222	0.995	0.995	0.993
SE17	0.917	0.921	47.86	0.103	0.887	0.892	0.877
SE18	0.976	0.938	48.97	0.094	0.985	0.986	0.983
SE19	0.990	0.963	51.28	0.089	0.993	0.994	0.989
SE20	0.981	0.950	60.25	0.070	0.990	0.989	0.988
KF1	0.944	0.970	74.64	0.123	0.923	0.935	0.892
KF2	0.931	0.949	25.88	0.224	0.914	0.927	0.881
KF3	0.946	0.957	38.01	0.314	0.935	0.951	0.893
KF4	0.955	0.963	36.30	0.113	0.935	0.940	0.925
KF5	0.990	0.979	21.37	0.298	0.994	0.994	0.989
KF6	0.782	0.798	48.30	0.382	0.826	0.817	0.843
KF7	0.871	0.922	29.58	0.265	0.820	0.839	0.779
KF8	0.686	0.778	20.13	0.166	0.604	0.619	0.576
KF9	0.757	0.824	36.39	0.186	0.712	0.736	0.664
KF10	0.960	0.964	21.57	0.322	0.954	0.959	0.934

dissolution profile. The dissolution rate enhancing effect of various grades of PEG carriers used in this study followed the order 20,000 PEG> 4000PEG> 8000PEG> 6000PEG. The solubility enhancing effect in the case of complex forming polymers HP β-CD showed relatively higher dissolution enhancement in comparison with β-CD. The dissolution enhancing effect of various SD preparation methods followed the order solvent evaporation technique>kneading technique>melting technique>physical mixing technique. Experience with solid dispersions indicates that this is a very fruitful approach to improve the release rate and oral bioavailability of poorly soluble drugs. This could potentially lead to an increase in the bioavailability that is so great that that the dose administered can be lowered.

CONCLUSION

Although numerous methods are available to improve the solubility of pure drugs, the most promising method for promoting dissolution is the formation of solid dispersions. The negative values of Gibbs free energy of transfer from water to an aqueous solution of hydrophilic carriers indicated the spontaneity of drug solubilization. Increased solubility was also observed with all types of hydrophilic carriers used in the preparation of solid dispersions. Highest solubilizing power of HP β-CD and 20,000 grade of poly ethylene glycol towards Ritonavir were shown by Phase solubility and dissolution studies. The solubility and dissolution rate of ritonavir can be enhanced by the formulations of SDs of Ritonavir with Poly ethylene glycol 8000, Poly ethylene glycol 4000, Poly ethylene glycol 6000 and β-CD. The solubilization effect of PEGs may be contributed due to reduction of particle aggregation of the drug, absence of crystallinity, increased wettability, dispersibility and alteration of the surface properties of the drug from its solid dispersion. Among the various ratios, drug: PEG 20,000 and drug: HP β-CD showed satisfactory solubility enhancement. From FTIR spectroscopy studies, it was concluded that there was no well defined chemical interactions between Ritonavir - PEG 20,000 and Ritonavir-HP β-CD.

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