Jaya S. *et al.* / *International Journal of Pharmacy & Therapeutics*, 4(1), 2013, 51-58.

e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

ENHANCEMENT OF DISSOLUTION RATE AND FORMULATION DEVELOPMENT OF RITONAVIR TABLETS BY SOLID DISPERSION TECHNOLOGIES

S. Jaya[1], K.P.R. Chowdary[2], P. Rajeswara Rao[2]

[1]Anurag Pharmacy College, Ananthagiri (V), Kodad, Andhra Pradesh-508206, India.
[2]A.U College of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530003, India.

ABSTRACT

Ritonavir, a widely prescribed anti-retroviral drug, belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Ritonavir is practically insoluble in water and aqueous fluids. Its aqueous solubility was reported to be 2.56 mg/100 ml. As such oral absorption of ritonavir is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The objective of the present study is to enhance the dissolution rate of ritonavir by solid dispersion in water soluble and water dispersible carriers. The feasibility of formulating the solid dispersions in to compressed tablets with rapid dissolution was also investigated. A total of 21 solid dispersions of ritonavir were prepared and evaluated. The dissolution of ritonavir from all the solid dispersions prepared was rapid and several times higher than the dissolution of ritonavir as such. Among the three water soluble carriers PVP solid dispersions gave highest enhancement (9.93 fold) in the dissolution rate of ritonavir. The order of increasing dissolution rate observed with various water soluble carriers was PVP > HPC-L > HPMC. Water dispersible superdisintegrants gave much higher enhancement in the dissolution rate of ritonavir. Among the superdisintegrants tested, croscarmellose sodium and crospovidone gave markedly higher enhancement in the dissolution rate of ritonavir, 47.24 and 28.15 fold respectively. The order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone > primogel >Prosolve. FTIR indicated no interaction between ritonavir and the two carriers, PVP and croscarmellose sodium, which gave highest enhancement in the dissolution rate of ritonavir. Ritonavir is present is an amorphous form in the solid dispersions which contributed to the rapid dissolution of ritonavir from the solid dispersions. The dissolution rate and dissolution efficiency of ritonavir were markedly enhanced by solid dispersion of ritonavir in water soluble polymers and superdisintegrants. Solid dispersions of ritonavir in PVP, crospovidone and croscarmellose sodium could be formulated into tablets by both wet granulation and direct compression methods. Ritonavir tablets formulated employing solid dispersions gave much higher dissolution rates and DE_{30} values when compared to plain tablets.

Key Words:- Ritonavir, Solid Dispersions, Water soluble carriers, Water dispersible carrier's, Dissolution Rate.

INTRODUCTION

Many of the modern drugs belong to the Class II category under biopharmaceutical classification system (Anonymous 1) (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble in water and aqueous fluids in the pH range of 1.0 - 7.5 and exhibit low and variable dissolution and bioavailability. There is a great need to develop technologies for these 'BCS' Class II drugs for enhancing

Corresponding Author

K.P.R.Chowdary
Email:- prof.kprchowdary@rediffmail.com

their dissolution rate and bioavailability. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product development.

Ritonavir, a widely prescribed anti-retroviral drug (Cooper CL *et al*., 2003; Merry C *et al*., 1996; Bertz RJ and Granneman GR, 1997; Hsu A *et al*., 1997), belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Ritonavir is practically insoluble in water and aqueous fluids. Its aqueous solubility was reported (Chowdary KPR *et al*., 2012) to be 2.56 mg/100 ml. As such oral absorption of ritonavir is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The poor aqueous solubility of the drug gives rise to difficulties in the formulation of solid dosage forms such as tablets and capsules.

Among the various methods of enhancement of the dissolution rate and oral bioavailability, solid dispersion technologies (Dhirendra K *et al*., 2009; Patidar Kalpana *et al*., 2010) were found to be very successful with a number of drugs. In the present investigation, studies were carried out on enhancement of dissolution rate and oral bioavailability of ritonavir by solid dispersion technologies employing various water soluble and water dispersible carriers. New classes of tablet excipients called superdisintegrants were evaluated as carriers for solid dispersions and for enhancing the dissolution rate and oral bioavailability of ritonavir. The feasibility of formulating the solid dispersions developed into compressed tablets was also investigated.

MATERIALS AND METHODS

Ritonavir gift sample from M/s Hetero Drugs Ltd., Hyderabad. Polyvinyl Pyrrolidone Mfg.: BASF, PVPK-30 (Sigma), Hydroxy propyl cellulose - L NISSO, having a viscosity of 3.0 - 5.9 cps in 2% by weight aqueous solution at 20°C, HPC-L, Hydroxy propyl methyl cellulose having a viscosity of 50 cps in a 2% by weight aqueous solution at 20°C (HPMC), Primogel gift sample from M/s Natco Pharma Ltd., Hyderabad, Crospovidone gift sample from M/s Natco Pharma Ltd., Hyderabad, Croscarmellose sodium gift sample from M/s Natco Pharma Ltd., Hyderabad, Prosolve gift sample from M/s Orchid Health Care Ltd., Chennai, Acacia (Loba Chemie), Lactose I.P. Potato starch I.P. Talc IP. Magnesium stearate I.P. All other materials were used of pharmacopoeial grade.

Preparation of Solid Dispersions Employing Soluble Carriers

Solid dispersions of ritonavir in water soluble carriers (HPMC, PVP and HPC-L) were prepared by common solvent method employing method as solvent. The required quantities of drug and carrier were weighed and dissolved in the solvent in a round bottom flask to get a clear solution. The solvent was then removed by evaporation under reduced pressure (vacuum) at 60°C with constant mixing. The mass obtained was crushed, pulverized and shifted through mesh No. 100. The solid dispersions were prepared at different ratios of drug carrier namely 95: 5, 90: 10 and 80: 20 respectively (Table 1).

Preparation of Solid Dispersions Employing Super disintegrant

Solid dispersions of ritonavir in water insoluble carriers (Prosolve, Primogel, crospovidone and croscarmellose sodium) were prepared by solvent evaporation method. The required quantity of drug was dissolved in the solvent to get a clear solution in a dry mortar. Methanol was used as solvent. The water insoluble carrier (passed through 120 mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50°C for 4 h in a oven. The dried product was crushed, pulverized and shifted through mesh No. 100. In each case solid dispersions in the insoluble carriers were prepared at three different ratios of drug: excipient namely 3:1,1:1 and 1 : 2 or 25%, 50%, 66% concentration of the excipient respectively (Table 1).

Estimation of Drug Contents of Solid Dispersions

From each batch, 4 samples of 100 mg each were taken and analysed for the drug ritonavir. Solid dispersion (100 mg) was weighed in to a 100 ml volumetric flask. Solvent (60 ml) was added and mixed the contents thoroughly to dissolve the drug from the dispersion. Methanol was used as solvent for ritonavir. The solution was then filtered and collected carefully into another 100ml volumetric flask. The solution was made upto volume with the solvent. The solution was suitably diluted with 0.1N hydrochloric acid at 210 nm for ritonavir.

Preparation of Ritonavir Tablets

Compressed tablets each containing 100 mg of ritonavir were prepared employing selected solid dispersions by wet granulation and direct compression methods.

Wet granulation method

The required quantity of solid dispersion containing the medicament and other ingredients were taken in a mortar. The aqueous binder solution was added

and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 4 hr. The dried granules were passed through mesh No. 16 to break the aggregates. Talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 onto dry granules and blended in a polyethylene bag. The tablet granules were then compressed into tablets on a rotary multi-station tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm using 9 mm round and flat punches.

Direct compression method

For direct compression Prosolve was used as directly compressible vehicle. Solid dispersion containing the medicament, Prosolve and other excipients were blended thoroughly in a closed polyethene bag and were directly compressed into tablets on a rotary multi-station tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm using 9 mm round and flat punches.

Evaluation of Tablets

All the tablets prepared are evaluated for content of active ingredient, hardness, friability, disintegration time, dissolution rate and dissolution efficiency.

Hardness

Hardness of the tablets was tested using a Monsanto hardness tester.

Friability

Friability of the tablets was determined in a Roche friabilator.

Disintegration Time

Disintegration times were determined in thermionic tablet disintegration test machine using distilled water as fluid.

Dissolution Rate Study:

Dissolution rate of ritonavir as such and from various ritonavir solid dispersions and tablets was studied using Disso-2000 (Labindia) 8 station dissolution rate test apparatus with paddle stirrer. The dissolution rate was studied in 900ml 0.1N hydrochloric acid ritonavir (100mg) or solid dispersion equivalent to 100 mg of ritonavir, a speed of 50 rpm and a temperature of $37^0C \pm 1^0C$ were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45µ) at different time intervals, suitably diluted, and assayed for ritonavir by measuring absorbance at 210 nm. The dissolution experiments were conducted in triplicate.

X- Ray Diffraction Study

X – Ray powder diffraction patterns of ritonavir and its solid dispersions were obtained using X-ray powder diffractometer (Philips model) employing $F_C - K_a$ radiation. The diffractograms were run at 2.4^0 / min in terms of 2θ angle.

FT-IR Spectra

The FT-IR spectra of ritonavir and its solid dispersions were recorded by using KB_r disc as reference on a FTIR spectrophotometer (SHIMADZU).

RESULTS AND DISCUSSION

Solid dispersions of ritonavir in three water soluble polymers namely HPMC, PVP and HPC-L were prepared by common solvent method employing methanol as solvent. In each case solid dispersions were prepared at three different ratios of drug: carrier namely 95:5, 90:10 and 80:20. Solid dispersions of ritonavir in four water dispersible superdisintegrants namely Prosolve, Primogel, crospovidone and croscarmellose sodium were prepared by solvent evaporation method employing a blend of methanol as solvent for the drug. In each case solid dispersions in superdisintegrants were prepared at three different ratios of drug: carrier namely 3:1, 1:1 and 1:2. A total of 21 solid dispersions of ritonavir in water soluble and water dispersible carriers were prepared and evaluated. All the solid dispersions prepared were found to be fine and free flowing powders. Low s.d and c.v (< 2.0) in the percent drug content values indicated that the drug content was uniform in a batch of solid dispersion prepared in all the cases.

The dissolution rate of ritonavir as pure drug and from various solid dispersions was studied in 0.1N hydrochloric acid. The dissolution of ritonavir from all solid dispersions was rapid and several times higher than the dissolution of ritonavir as such. The dissolution data were fitted into zero order and first order kinetic models to assess the kinetics and mechanism of dissolution. The dissolution of ritonavir as such and from all solid dispersions followed first order kinetics. Plots of log percent remaining versus time were found to be linear with all the products. First order rate constant (K_1 min^{-1}) was calculated in each case from the slope of first order linear plots. The DE_{30} values were calculated in each case as per Khan *et al* (Khan *et al*., 1975). The dissolution parameters of various solid dispersions prepared are given in Table 2.

All the dissolution parameters (T_{50}, percent dissolved in 10 min, DE_{30} and K_1 values) indicated rapid and higher dissolution of ritonavir from solid dispersions

than that of ritonavir as such. Among the three water soluble carriers tested (HPMC, PVP and HPC-L), PVP solid dispersions gave higher dissolution rates than the other two solid dispersions. At 9:1 ratio of drug carrier, PVP, HPC-L and HPMC solid dispersions gave 9.93, 6.03 and 2.75 fold increases in the dissolution rate of ritonavir respectively. With all the three soluble carriers the dissolution rate was increased as the carrier concentration was increased from 5% to 10%. At 20% carrier concentration the rate was decreased due to the aggregation of solid dispersion particles resulting in a decrease in dissolution rate with all the three carriers. Hence a concentration of 10% carrier (corresponding to a drug: carrier ratio of 9 : 1) is considered optimum for enhancing the dissolution rate with the water soluble carriers PVP, HPC-L and HPMC. The order of increasing dissolution rate observed with various polymers was PVP > HPC-L >HPMC.

Water dispersible superdisintegrants gave much higher enhancement in the dissolution rate of ritonavir. All the superdisintegrants tested gave rapid and higher dissolution of ritonavir when compared to pure drug. The dissolution of ritonavir from these solid dispersions also followed first order kinetics. Among the superdisintegrants tested croscarmellose sodium and crospovidone gave much higher enhancement in the dissolution rate of ritonavir (Table 2).

A 47.24 and 28.15 fold increase in the dissolution rate of ritonavir was observed with the solid dispersions in croscarmellose sodium and crospovidone at 1: 1 ratio of drug: carrier respectively. At 1:1 ratio of drug: carrier, the order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone > Primogel > Prosolve. In each case the dissolution rate was increased as the concentration of carrier was increased from 25% to 50%. At 66% carrier concentration (a drug: carrier ratio of 1:2), there was no further increase in the dissolution rate in majority of the dispersions. Hence a drug: carrier ratio of 1:1 is considered optimum for enhancing the dissolution rate in the case of water dispersible superdisintegrants. Overall, all the superdisintegrants tested were found to be good carriers for solid dispersions and for enhancing the dissolution rate of ritonavir. Among all the carriers used in preparing solid dispersions the order of their efficiency in enhancing the dissolution rate of ritonavir was croscarmellose sodium > crospovidone > PVP > HPC-L > Primogel > Prosolve > HPMC. These carriers gave an enhancement of 47.24, 28.15, 9.93, 6.03, 5.08, 4.65 and 2.75 folds respectively.

Thus the dissolution rate and dissolution efficiency of ritonavir were markedly enhanced by solid dispersion of ritonavir in water soluble and water dispersible carriers. The observed increase in the dissolution rate of ritonavir from its solid dispersions is due to the possible reduction in particle size and deposition of the drug in 'miniscular' form on the surface of the water dispersible superdisintegrants used as carriers during the process of preparation by solvent evaporation; increased wettability of drug particles when they are dispersed in the hydrophilic water soluble polymers. The easy and rapid dispersibility of superdisintegrants might have also contributed to the increased dissolution rate. As the superdisintegrants used as carriers remain suspended in the dissolution medium the drug particles deposited on them are continuously exposed to the solvent action and undergo rapid dissolution. The absence of aggregation and agglomeration between drug particles due to the presence of carrier will also contribute to the increased dissolution rate.

The changes in the physical state of the drug in the solid dispersions were evaluated by XRD. X-ray diffractograms of ritonavir and its solid dispersions, which gave highest enhancement in the dissolution rate of ritonavir i.e. ritonavir - PVP (9:1) in the case of soluble carriers and ritonavir - croscarmellose sodium (1:1) in the case of superdisintegrants, were taken. X-ray diffractograms of ritonavir and its solid dispersions are shown in Fig. 1.

The X-ray diffractogram of ritonavir exhibited characteristic diffraction pattern indicating its crystalline nature. Several diffraction peaks were observed with varying intensity counts. The poor dissolution rate of ritonavir is due to its crystalline nature. In the X-ray diffractograms of solid dispersions the diffraction peaks of ritonavir were disappeared or much reduced indicating that the drug is present in amorphous form in the solid dispersions. The rapid dissolution of ritonavir from the solid dispersions is due to the conversion of crystalline drug into amorphous form in the preparation of solid dispersions.

Drug and carrier interactions in the solid dispersions prepared were evaluated by FTIR spectral study. The FTIR spectra of ritonavir and its solid dispersions, which gave highest enhancement in the dissolution rate of ritonavir i.e. ritonavir - PVP (9:1) in the case of soluble carriers and ritonavir - croscarmellose sodium (1:1) in the case of superdisintegrants, are compared. The FTIR spectra of ritonavir 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 spectra of ritonavir solid dispersions tested also showed the above characteristic

peaks. These spectral observations indicated no interaction between ritonavir and the carriers used in the solid dispersions.

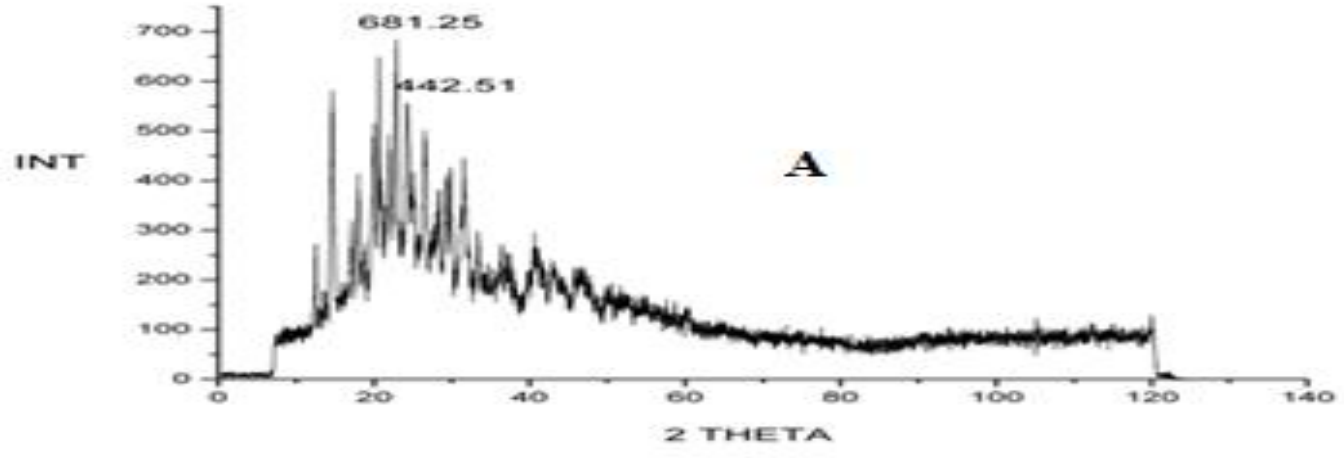
Solid dispersions in PVP (9:1) SD F5, crospovidone (1:1) SD F17 and croscarmellose sodium (1:1) SD F20 exhibited a marked enhancement in the dissolution rate and efficiency of ritonavir. The feasibility of formulating these solid dispersions into compressed tablets with enhanced dissolution rate was evaluated. These solid dispersions were formulated into tablets with usual tablet additives by wet granulation and direct compression methods as per the formulae given in Table 3.

All the tablets prepared contained ritonavir within 100 ± 5% of the labeled content. Hardness of the tablets was in the range 5-6 kg / sq.cm and was satisfactory. The percentage weight loss in the friability test was less than 0.95 in all the tablet formulations prepared. All the tablets formulated disintegrated rapidly within 7 min. Overall tablets formulated employing direct compression method, disintegrated more rapidly when compared to those tablets formulated with wet granulation method. However, all tablets fulfilled the official (I.P) disintegration time specification for uncoated tablets. Thus all the tablets formulated employing solid dispersions were found to be of good quality, fulfilling all official (I.P) and other requirements of compressed tablets.

All the tablets formulated employing solid dispersions gave rapid and higher dissolution of ritonavir when compared to that of ritonavir plain tablets (i.e. TF 29 and TF 33). Ritonavir dissolution from all the tablets prepared by wet granulation as well as direct compression method followed first order kinetics with correlation coefficient " r " above 0.846. The dissolution parameters estimated from the dissolution data of various tablets are summarized in Table 4. All dissolution parameters (K_1, DE_{30}, T_{50} and percent dissolved in 10 min.) indicated rapid and higher dissolution of ritonavir from tablets formulated employing its solid dispersions when compared to plain ritonavir tablets prepared by wet granulation (TF 29) and direct compression (TF 33) methods.

Ritonavir tablets formulated employing its solid dispersions and prepared by direct compression method gave rapid and higher dissolution of ritonavir when compared to the corresponding tablets prepared by wet granulation method. K_1 (min^{-1}) and DE_{30} values were higher in the case of tablets prepared by direct compression method when compared to those prepared by wet granulation method. In the wet granulation method, a 2.07, 7.01 and 14.85 fold increase in the dissolution rate (K_1) of ritonavir was observed with the tablets formulated employing solid dispersions in PVP (9 : 1), crospovidone (1:1) and croscarmellose sodium (1:1) respectively. Whereas in the direct compression method a 3.15, 6.56, and 16.47 fold, increase in the dissolution rate (K_1) of ritonavir was obtained with the tablets formulated employing solid dispersions in PVP (9:1), crospovidone (1:1) and croscarmellose sodium (1:1) respectively. In both the wet granulation and direct compression methods tablets formulated employing solid dispersions in croscarmellose sodium (1:1) gave highest enhancement in the dissolution rate and dissolution efficiency of ritonavir. The order of increasing dissolution rate observed with tablets formulated employing various solid dispersions was croscarmellose sodium > crospovidone > PVP.

Fig. 1. XRD of (A) Ritonavir, (B) Ritonavir-PVP (9:1) SD and (C) Ritonavir-Croscarmelose sodium (1:1) SD



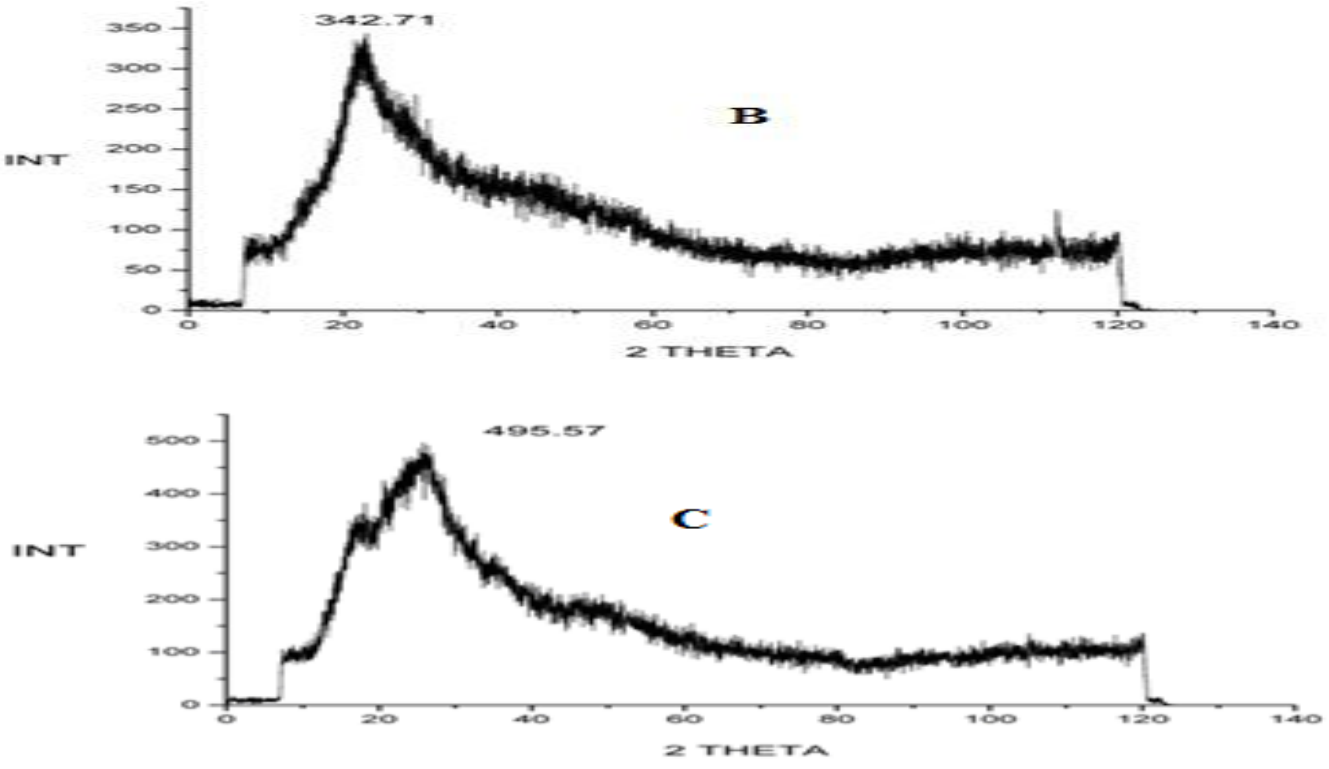


Table 1. Ritonavir Solid Dispersions Prepared and their Composition

S.No	Composition		
	Drug	**Carrier**	**SD Code**
1	Ritonavir (9.5)	HPMC(0.5)	SDF1
2	Ritonavir (9.0)	HPMC(1.0)	SDF2
3	Ritonavir (8.0)	HPMC (2.0)	SDF3
4	Ritonavir (9.5)	PVP (0.5)	SDF4
5	Ritonavir (9.0)	PVP(1.0)	SDF5
6	Ritonavir (8.0)	PVP (2.0)	SDF6
7	Ritonavir (9.5)	HPC-L (0.5)	SDF7
8	Ritonavir (9.0)	HPC-L(1.0)	SDF8
9	Ritonavir (8.0)	HPC-L(2.0)	SDF9
10	Ritonavir (3.0)	Prosolve(1.0) .	SDF10
11	Ritonavir (1.0)	Prosolve(1.0)	SDF11
12	Ritonavir (1.0)	Prosolve (2.0)	SDF12
13	Ritonavir (3.0)	Primogel(1.0)	SDF13
14	Ritonavir (1.0)	Primogel(1.0)	SDF14
15	Ritonavir (1.0)	Primogel (2.0)	SDF15
16	Ritonavir (3.0)	Crospovidone (1.0)	SDF16
17	Ritonavir (1.0)	Crospovidone (1.0)	SDF17
18	Ritonavir (1.0)	Crospovidone (2.0)	SDF18
19	Ritonavir (3.0)	Croscarmellose (1.0)	SDF19
20	Ritonavir (1.0)	Croscarmellose (1.0)	SDF20
21	Ritonavir (1.0)	Croscarmellose (2.0)	SDF21

Table 2. Dissolution Parameters of Ritonavir and its Solid Dispersions Prepared

Solid Dispersion	Carrier and Concentration (%)	T_{50} (min)	K_1 (min-1)	DE_{30} (%)	Percent Drug Dissolved in 10 min	Increase in K1 (no. of folds)
Ritonavir	--	>30	0.0058	22.07	21.59	--
SDF 1	HPMC (5)	>30	0.0076	29.72	28.8	1.31
SDF 2	HPMC (10)	28	0.016	37.29	36.24	2.75
SDF 3	HPMC(20)	30	0.0163	32.13	28.78	2.81
SDF4	PVP (5)	15	0.0157	47.59	47.9	2.7
SDF5	PVP (10)	3.2	0.0576	80.01	84.38	9.93
SDF6	PVP (20)	4	0.0562	76.89	78.45	9.68
SDF7	HPC – L (5)	3	0.0197	70.85	75.36	3.39
SDF 8	HPC – L (10)	2.5	0.035	82.27	88.28	6.03
SDF9	HPC – L (20)	4	0.0128	68.06	72.29	2.2
SDF10	Prosolve (25)	3	0.0191	73.79	80.48	3.29
SDF11	Prosolve (50)	3	0.027	77.05	84.14	4.65
SDF12	Prosolve (66)	3.6	0.021	72.52	77.99	3.62
SDF13	Primogel(25)	3.6	0.025	64.83	70.58	4.31
SDF14	Primogel(50)	3.4	0.0295	69.82	77.18	5.08
SDF15	Primogel(66)	3	0.055	80.67	87.8	9.45
SDF16	Crospovidone(25)	3.1	0.042	77.82	85.68	7.24
SDF17	Crospovidone(50)	3	0.1633	86.93	97.53	28.15
SDF18	Crospovidone(66)	3	0.1723	84.39	85.56	29.7
SDF19	Croscarmelose Sodium (25)	3.4	0.0218	71.97	76.89	3.75
SDF20	Croscarmelose Sodium (50)	3.2	0.274	88.84	101.39	47.24
SDF21	Croscarmelose Sodium (66)	3	0.0481	78.1	84.86	8.29

Table 3. Formulae of Ritonavir Tablets Prepared with Selected Solid Dispersions by Wet Granulation and Direct Compression Methods

Ingredient (mg / tab)	Formulation			
	TF29/TF33	TF30/TF34	TF31/TF35	TF32/ TF36
Ritonavir	100	-	-	-
SDF 5	-	111	-	-
SDF 17	-	-	200	-
SDF 20	-	-	-	200
Potato starch	45	45	45	45
Talc	6	6	6	6
Magnesium stearate	6	6	6	6
Acacia	6	6	6	6
Lactose/ Prosolve up to	300	300	300	300

Note: Formulations TF29-TF32 are prepared by wet granulation method using lactose as diluent and Formulations TF33-TF36 are prepared by direct compression method using Prosolve as directly compressible vehicle.

Table 4. Dissolution Parameters of Ritonavir Tablets Formulated with Selected Solid Dispersions

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Percent drug dissolved in 10 min
TF29	>30	0.0128	23.86	20.27±1.04
TF30	22	0.0266	36.38	30.16±1.02
TF31	6	0.0898	73.46	79.95±1.23
TF32	3.5	0.1812	80.53	83.69±1.47
TF33	22	0.0185	40.5	40.38±1.11

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Percent drug dissolved in 10 min
TF34	3	0.0584	76.43	73.62±1.66
TF35	3	0.1215	85.63	94.55±1.97
TF36	3	0.3048	85.8	96.44±1.74

CONCLUSIONS

- The dissolution of ritonavir from all the solid dispersions prepared was rapid and several times higher than the dissolution of ritonavir as such.
- Among the three water soluble carriers PVP solid dispersions gave highest enhancement (9.93 fold) in the dissolution rate of ritonavir. The order of increasing dissolution rate observed with various water soluble carriers was PVP > HPC-L > HPMC.
- Water dispersible superdisintegrants gave much higher enhancement in the dissolution rate of ritonavir.
- Among the superdisintegrants tested, croscarmellose sodium and crospovidone gave markedly higher enhancement in the dissolution rate of ritonavir, 47.24 and 28.15 fold respectively. The order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone > primogel >Prosolve.

The dissolution rate and dissolution efficiency of ritonavir were markedly enhanced by solid dispersion of ritonavir in water soluble polymers and superdisintegrants.

- FTIR indicated no interaction between ritonavir and the two carriers, PVP and croscarmellose sodium, which gave highest enhancement in the dissolution rate of ritonavir.
- Ritonavir is present is an amorphous form in the solid dispersions which contributed to the rapid dissolution of ritonavir from the solid dispersions.
- Solid dispersions of ritonavir in PVP, crospovidone and croscarmellose sodium could be formulated into tablets by both wet granulation and direct compression methods.
- Ritonavir tablets formulated employing solid dispersions gave much higher dissolution rates and DE_{30} values when compared to plain tablets.

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