International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

ENHANCEMENT OF DISSOLUTION OF POORLY SOLUBLE RITONAVIR DRUG USING SYNTHETIC POLYMERS

A. Surendra*, M. Jhansirani, R. Aruna, A.M.S. Sudhakar babu

Department of Pharmaceutics, A.M.Reddy Memorial College of Pharmacy, Narsaraopet, Guntur district, A.P, India

***Corresponding author e-mail:** surianumula2@gmail.com

ABSTRACT

Development of solid dispersions of poorly water soluble drugs is one of the most widely used approaches to enhance the solubility as well as dissolution rate. In the current investigation, Ritonavir is selected as model drug to improve the solubility and dissolution rate by solid dispersion method. Solid dispersions were prepared using fusion method by incorporating carriers like polyethylene glycol 20000, Soluplus and Plasdone. Each carriers in different ratios (1:1, 1:2 and1:3) and evaluated for solubility studies, drug-carrier compatibility studies and *in vitro* dissolution studies. Based on the solubility and drug release studies, among all 10 formulations F_{10} formulation showed better drug release of 100% drug release at the end of 150^{th} minute compared to other 8 formulations and plain Ritonavir formulation. So F_{10} (containing 1:3 ratio of PEG 20000) is the optimized formulation. In each case tablets prepared employing carriers gave higher dissolution rates as compared to the tablets prepared using pure drug. Hence solid dispersion in polymers can be used for enhancing the solubility and dissolution of Ritonavir.

Keywords: Ritonavir, solid dispersions, fusion method and dissolution rate.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. But a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research
that focus on improving the oral bioavailability of active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs1,2

Several techniques[3] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility , microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches, solid dispersions in water dispersible excipients are a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs. These can be prepared by various methods. Solvent evaporation method and fusion method are widely used depending upon the requirement6.

Ritonavir, a widely prescribed antiretroviral protease inhibitor drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability.

The objective of the present research work was to investigate the possibility of improving the solubility and dissolution of Ritonavir by formulating solid dispersions of Ritonavir with carriers into tablets.

MATERIALS AND METHODS

Materials: Ritonavir was gift sample from Tejkamal pharmaceuticals Ltd., Bangalore, PEG 20000, Soluplus and Plasdone were obtained from Signet chemical corporation Pvt. Ltd., Mumbai. Lactose Sodium starch glycolate and Aerosil were supplied by NR CHEM, Mumbai. All chemicals used in the study were of analytical grade.

Preparation of solid dispersions by Fusion method: In fusion method, carriers i.e., PEG 2000, Soluplus and Plasdone s- 630 in different ratios were taken into a porcelain dish and melting those at there melting pointes and to this Ritonavir added with thorough mixing for 1 – 2 minutes followed by quick cooling. The dried mass was pulverized and sieved through mesh 100# and were stored in desiccators until use.

Preparation of Ritonavir-SD Tablets: Preparation of Ritonavir-SD tablets by direct compression method. The solid dispersion powder equivalent to 100 mg of Ritonavir, SSG and other tabletting excipients were passed through mesh 60#.The powdered solid dispersion was mixed with proper portion of Sodium Starch Glycolate. Then excipients other than glidant and lubricant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with talc and magnesium stearate for another 5 min and the resultant mixture was directly compressed into tablets using rotary tabletting machine.

Prior to compression, powder blends were evaluated for pre-compression parameters like Hausner's ratio [tapped/bulk density ratio using a tapped volumeter apparatus (Copley Scientific, UK)], Carr's compressibility index[4], and static angle of repose. To measure the angle of repose, 10 mL of powder was poured through a glass funnel onto a flat surface and the angle to the horizontal was measured. The measurements were performed in triplicate.

Characterization of tablets: Physical properties of the tablets were determined according to the USP 24 methods[5]. Weight variation was performed on 20 tablets selected at random. Hardness of the tablets was measured by recording the force to fracture a tablet on a hardness tester for 6 tablets from each formulation (SCHNEUNIGER). Friability was determined using Roche friabilator for 20 tablets at 100 rpm for 4 minutes. Six tablets were tested from each formulation for disintegration time at 37 ± 0.5 °C in water (ELECTROLAB – ED-2L). For determination of drug content, a total of 10 tablets were weighed and powdered. A powder mass equivalent to 50 mg of ritonavir was weighed, dissolved in 0.1N hydrochloric acid and filtered. The filtrate was collected, diluted suitably and analyzed for the content of ritonavir by UV- Double beam spectrophotometer at 238 nm (LABINDIA® UV-3000).

In vitro release study: The *in vitro* dissolution study was carried out according to the USP 24 specifications [5] with Apparatus II (n = 6) using an Electrolab dissolution apparatus TDT-08L. The dissolution medium consisted of 900 mL of 0.1N hydrochloric acid solution maintained at 37 ± 0.5 °C and stirred at 50 rpm. Aliquot samples (5 mL) were withdrawn at predetermined intervals, filtered through a 0.45-µm membrane filter (Millipore, USA) and replaced by an equivalent volume of fresh dissolution medium. The samples were suitably diluted and the amount of the drug dissolved was analyzed spectrophotometrically at 238 nm.

Drug content: 10 tablets are accurately weighed and powdered. Tablets powder equivalent to 20 mg of medicament was taken in the test tube and extracted with methanol. The methanolic extract collected into 50ml volumetric flask and volume made up to 50ml with 0.1N Hcl. The solution was subsequently diluted and assayed for drug content was analyzed spectrophotometrically at 238 nm.

RESULTS AND DISCUSSION

All the solid dispersions prepared were found to be fine and free flowing powders with an angle of repose in the range 23.72^0 – 29.26^0. Low C.V (< 1.0%) in the percent drug content indicated uniformity of drug content in each batch of solid dispersions prepared.

Prior to compression, the powder blends were evaluated for the most important parameters referring to flowability and compression. Table no.2 shows the pre-compression parameters of the powder blends used in the compression of ritonavir tablets. The blends were found to have passable flowability as determined by Hausner's ratio, compressibility index and angle of repose. The compressibility index ranged from 12.10 to13.91 %. Compressibility index values of up to 20 % generally indicate fair flow properties in regard to compressibility-flowability correlation data. Hausner's ratio was higher than 2 and the angle of repose ranged from 23.72-29.26° for all the formulation blends. Therefore, the values of pre-compression parameters were within the prescribed limits and indicated free flow properties.

Ritonavir (100 mg) tablets were prepared employing ritonavir alone and its solid dispersions (F2-F10) by direct compression method and were evaluated. The hardness test indicated good mechanical strength with non-significant differences in all formulations. All the tablets showed good mechanical resistance, as indicated by the friability test where it was less than 1 % for all tablets. Drug content was found to be consistent and almost uniform in all tablet formulations (>98 %) and no significant statistical mass variability was observed in the produced tablets. Therefore, our results, as indicated by the post-compression parameters presented in Table no.3, showed that an excellent degree of uniformity was achieved for all prepared tablet formulations. Tablets formulated employing solid dispersions disintegrated rapidly with in 3.30 min. Tablets formulated employing ritonavir pure drug disintegrated within 5-6 min. As such all the ritonavir tablets prepared were of good quality with regard to drug content, friability, hardness and disintegration time and fulfilled the official (IP) specifications of uncoated tablets.

All the tablets formulated employing solid dispersions in synthetic polymers gave rapid and higher dissolution of Ritonavir when compared to that of Ritonavir plain tablets (i.e. tablets formulated employing Ritonavir and lactose as diluent). Among all formulations F10 was shown (fig.1-4)100% of drug release with in 150min.

Ritonavir dissolution from all the tablets followed first order kinetic with correlation coefficient 'r' (table no. 4). The first order dissolution plots of various tablets are shown in Fig no.**5 & 6**.
The increasing order of dissolution rate of Ritonavir from tablets observed with various synthetic polymers was PEG 20000 > Soluplus > Plasdone > Plain Ritonavir Tablets.

CONCLUSION

The present work on enhancement of dissolution rate of Ritonavir tablets by solid dispersion fusion technique utilizing PEG20000, Soluplus and Plasdone to increase the solubility of the formulation in 3hrs time period. The formulations containing solid dispersions prepared at 1:1, 1:2 and 1:3 ratios respectively when compared to plain tablets. Among all 10 formulations F_{10} formulation showed better drug release of 100% drug release at the end of 150^{th} minute compared to other 8 formulations and plain Ritonavir formulation. So F_{10} (containing 1:3 ratio of PEG 20000) is the optimized formulation. Among the polymers used the role of PEG20000 is quite worthy compared to Soluplus and Plasdone in enhancing the dissolution rate.

Table.1 Formulations of Ritonavir solid dispersion tablets

MATERIALS	F1(with out carrier)	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ritonavir	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
PEG 20000	-	-	-	-	-	-	-	100mg	200mg	300mg
Soluplus	-	-	-	-	100mg	200mg	300mg	-	-	-
Plasdone	-	100mg	200mg	300mg	-	-	-	-	-	-
Lactose	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Sodium Starch Glycolate	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Aerosil	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Magnesium Stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg

Table .2 Pre-compression parameters of blend

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.52	0.62	27.14º	13.88	1.16
F2	0.53	0.68	29.14º	13.91	1.16
F3	0.57	0.66	25.14º	12.70	1.14
F4	0.58	0.69	28.38º	12.10	1.13
F5	0.54	0.65	29.26º	13.76	1.15
F6	0.31	0.36	26.46º	13.88	1.16
F_7	o.49	0.58	24.38^0	13.20	1.15
F_8	0.51	0.64	26.92^0	12.76	1.14
F_9	0.57	0.66	23.72^0	12.24	1.14
F_{10}	o.49	0.58	26.06^0	12.72	1.14

Table.3 Characterization of Ritonavir tablets

Tablet Formulation	Hardness (kg/cm^2)	Diameter (mm)	Thickness (mm)	Friability (%)	Drug content	Disintegration Time (Sec)
F_1	4.24	9.0	4.01	0.60	99.1	252
F_2	4.5	9.2	4.05	0.57	98.9	184
F_3	4.81	10.27	4.22	0.37	99	175
F_4	4.92	11.35	4.93	0.44	98.6	156
F_5	4.75	9.1	4.02	0.85	98.8	143
F_6	4.84	10.29	4.27	0.51	99.2	117
F_7	4.95	11.37	4.94	0.49	99.1	102
F_8	4.87	9.3	4.01	0.69	98.6	83
F_9	4.78	10.25	4.25	0.55	98.9	67
F_{10}	4.92	11.39	4.96	0.67	99.3	52

Table.4 **release kinetics of Ritonavir formulations**

Solid dispersion formulations	Correlation Coefficient (r)	
	Zero order	First order
F_1	0.9184	0.961
F_2	0.9457	0.994
F_3	0.9411	0.9884
F_4	0.8852	0.9569
F_5	0.9384	0.9542
F_6	0.8911	0.9912
F_7	0.9272	0.9901
F_8	0.9149	0.9747
F_9	0.8852	0.9287
F_{10}	0.9246	0.9392

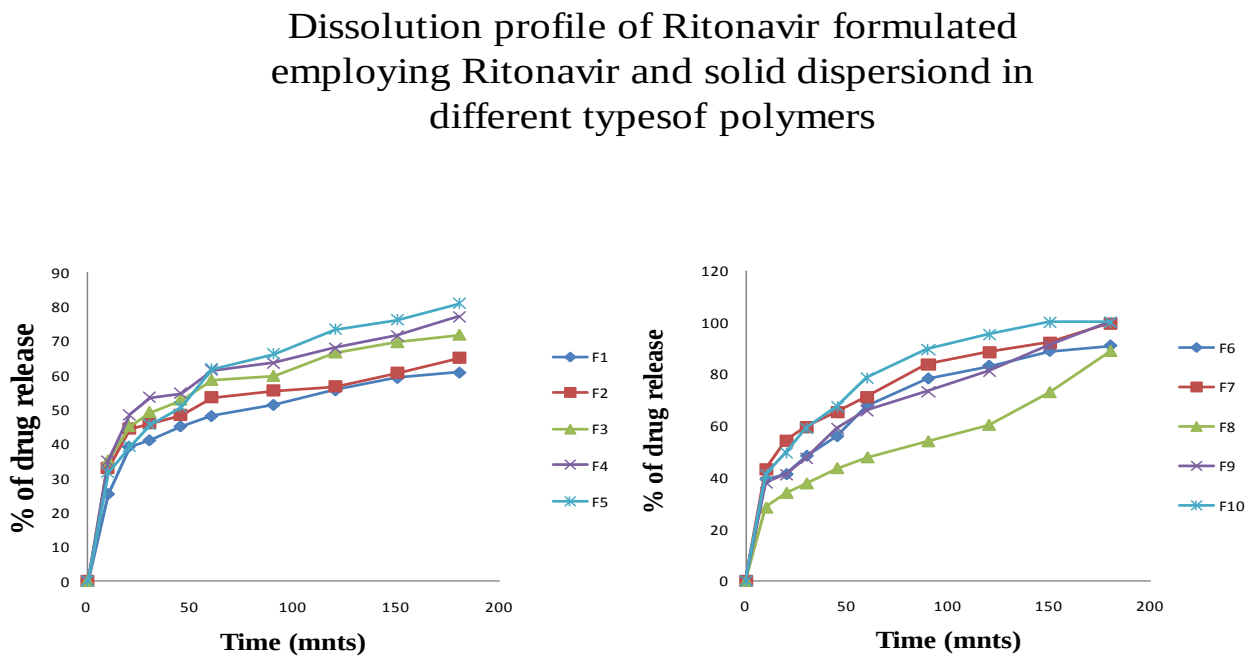

Fig.1. Dissolution profile of Ritonavir formulated employing Ritonavir and solid dispersion in different types of polymers

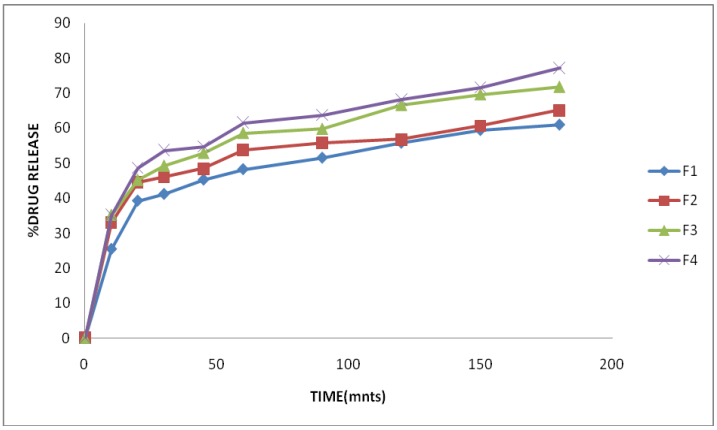

Fig 2. dissolution profile of Ritonavir – Plasdone

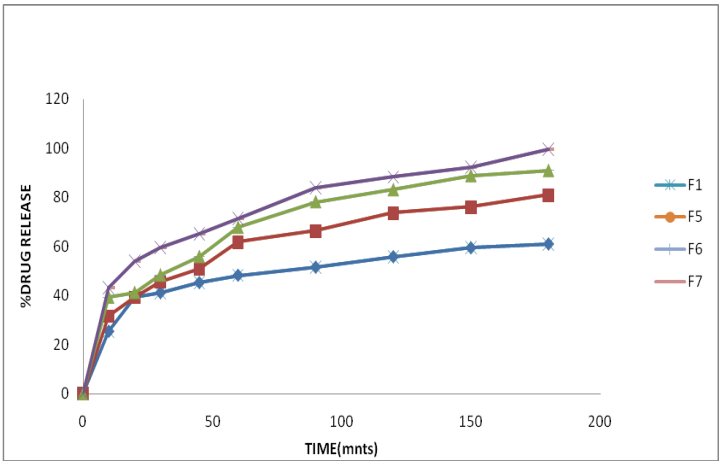

Fig 3. dissolution profile of Ritonavir – Soluplus

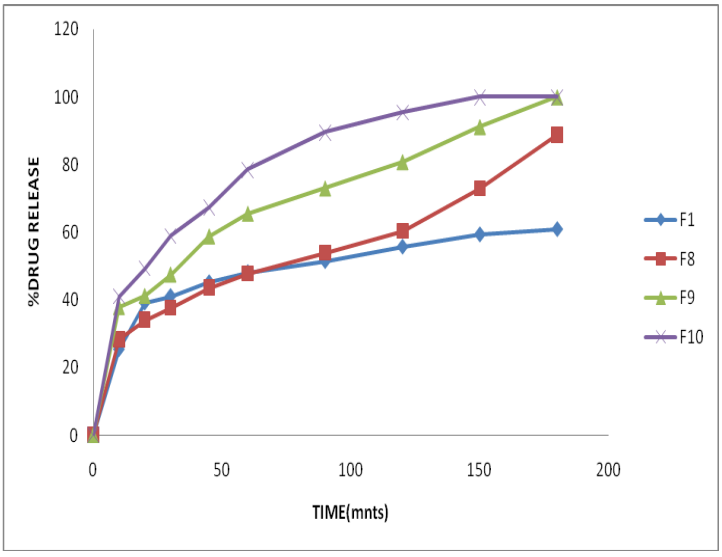

Fig. 4 dissolution profile of Ritonavir –PEG 20000

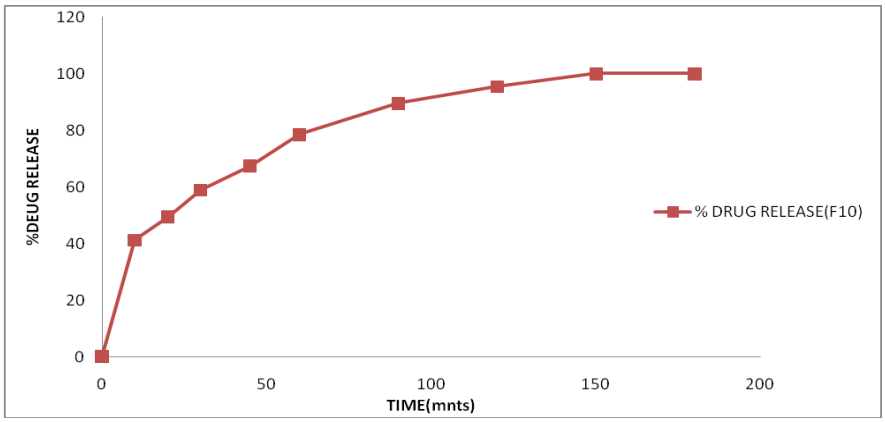

Fig.5. Zero order release of optimized formulation(f10)

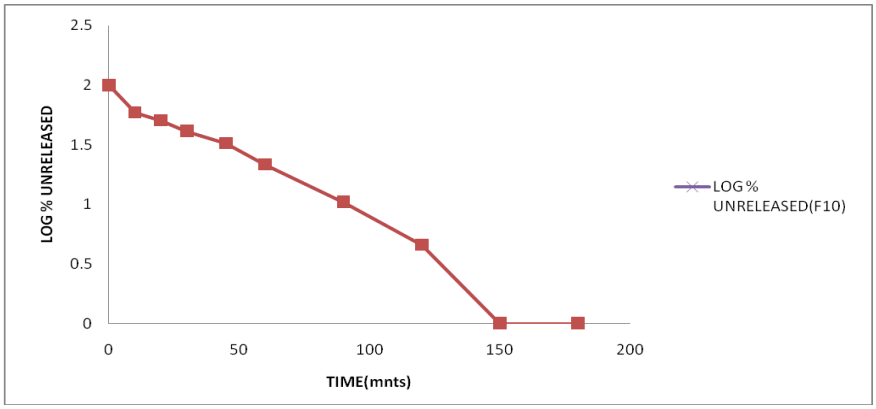

Fig. 6. First order release of optimized formulation (f10)

REFERENCES

1. Kaushik D, Dureja H, Saini TR. Mouth Dissolving Tablets: A Review. *Indian Drugs* 2004; 41: 87-193.
2. Patil MP, Gaikwad NJ. Preparation and characterization of gliclazide poly ethylene glycol 4000 solid dispersions. *Acta Pharm* 2009; 59: 57–65.
3. Chowdary KPR, Madhavi BLR. Novel drug delivery technologies for insoluble drugs. Indian Drugs 2005; 42(9):557-562.
4. Reddy KR, Mutalik S, Reddy S. Once-daily sustained release matrix tablets of nicorandil: formulation and in vitro evaluation, AAPS Pharm Sci Tech 2003; 4(61).
5. United States Pharmacopoeia 24, National Formulary *19*, USP Convention. Rockville (MD) USA; 2000.
6. Craig D.Q.M. The mechanisms of drug release from solid dispersions in water soluble polymers.International Journal of Pharmaceutics, 2002; 203, 131-144.
7. Hulsmann S., Backensfeld T., Keitel S., Bodmeier R. Melt extrusion-an alternative method for enhancing the dissolution rate of 17ß-estradiol hemihydrate, European Journal of Pharmaceutics and Biopharmaceutics, 2000; 49, 237-242.
8. Phillips E.M., Stella V.J. Rapid expansion from supercritical solutions, application to pharmaceutical processes. International Journal of Pharmaceutics, 1993; 94, 1-10.
9. Subramaniam B., Rajewski R.A., Snavely K. Pharmaceutical processing with supercritical carbon dioxide, Journal of Pharma Sciences, 1997; 86, 885-890.
10. Batra,V, Shirolkar, V.S,mahaparale P.R, kasture P.V, and Deshpande A.D. solubility and dissolution enhancement of Ritonavir by solid dispersion technique, International journal of pharmaceutical education and research, 2008, 373-378.
11. Dohrn R., Bertakis E., Behrend O., Voutsas E., Tassios D. Melting point depression by usingsupercritical CO2 for a novel melt dispersion micronization process. Journal of Molecular Liquids, 2007; 131-132.
12. Saleh A.M., Daabis, N.A. Study of the interaction of menadione with hydrotropic salts. Pharmazie, 1974; 29, 525-527.
13. Rasool A.A., Anwar A. H., Lewis W.D. Solubility enhancement of some water-insoluble drugs in the presence of nicotinamide and related compounds, Journal of Pharmaceutical Sciences, 2002; 80 (4), 387-393.