International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2012; 2(5):224-229

Research Article

EFFECT OF SUPERDISINTGRANTS AND SOLUBILIZERS ON THE DISSOLUTION RATE AND DISSOLUTION EFFICIENCY OF RITONAVIR TABLETS

S. Jaya[1], K.P.R. Chowdary[2] and P. Rajeswara Rao[2]
[1]Anurag Pharmacy College, Kodad Andhra Pradesh-508206.
[2]A. U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh- 530003
(Received: 24 September 2012; Accepted: 15 October, 2012; Published: 29 October, 2012)
Corresponding Author's email: **prof.kprchowdary@rediffmail.com**

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. In the case of poorly soluble drugs formulation variables greatly influence their dissolution rate and bioavailability from solid dosage forms. The objective of the present work is to study the effect of five superdisintegrants and three solubilizers on the tablet qualities and dissolution rate of ritonavir tablets to optimize the formulation of ritonavir tablets. Compressed tablets each containing 100 mg of ritonavir were prepared by conventional wet granulation method using five superdisintegrants namely Prosolve, modified starch, croscarmellose sodium, Primogel, crospovidone and three solubilizers namely Tween 80, SLS and PEG 600 and the tablets were evaluated for content of active ingredient, hardness, friability, disintegration time, dissolution rate and dissolution efficiency. The superdisintegrant and solubilizer used has significant influence on the tablet qualities and dissolution rate of ritonavir from the tablets. The order of performance of the superdisintegrants based on increasing dissolution rate was Prosolve > modified starch > croscarmellose sodium > Primogel > crospovidone. Tablets formulated with Prosolve, modified starch and croscarmellose sodium exhibited higher dissolution rates and dissolution efficiency values fulfilling all other official (I.P) and GMP requirements of compressed tablets.Prosolve, modified starch and croscarmellose sodium were found to be better superdisintegrants for ritonavir tablets. The dissolution rate and dissolution efficiency of ritonavir tablets could be significantly enhanced by incorporating the solubilizers (Tween 80, PEG - 600 and SLS) in the tablets. The order of increasing dissolution rate observed with various solubilizers was Tween 80 > PEG - 600> SLS. The dissolution rate and efficiency of ritonavir from tablets could be enhanced by incorporating solubilizers in the tablets.

Key words: Ritonavir, Tablets, superdisintegrants, solubilizers, Dissolution rate, Dissolution Efficiency

INTRODUCTION

Many of the modern drugs belong to the Class II category under biopharmaceutical classification system[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 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[2-5], 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[6] 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. In the case of poorly soluble drugs formulation variables greatly influence their dissolution rate and bioavailability from solid dosage forms. Though ritonavir tablets are available commercially, no work was reported on the pharmaceutical formulation aspects of ritonavir. Ritonavir tablets are official in I.P. 2010 which prescribed a dissolution rate test specification of NLT 70 % in 60 min to check the quality of commercial brands.

In the present work the effect of five superdisintgrants and three solubilizers on the tablet qualities and dissolution rate of ritonavir

tablets was studied to optimize the formulation of ritonavir tablets. Disintegrant is a critical ingredient in tablets that influences the dissolution rate and bioavailability of the drug from tablets. The effect of disintegrants on the dissolution rate of poorly soluble drugs such as itraconazole and sparfloxacin from tablets was reported earlier[7, 8]. Formulation strategies of poorly soluble drugs include the use of surfactants and polyethylene glycols as solubilizers to enhance the absorption of poorly soluble drugs by enhancing drug dissolution[9-13]. Sodium lauryl sulphate (SLS), Tween 80 and polyethylene glycol 600 (PEG 600) were tried as solubilizers to enhance the solubility and dissolution rate of ritonavir from tablets.

EXPERIMENTAL

Materials

Ritonavir was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Polyvinyl pyrrolidone (Mfg: BASF, PVP K-30), Primogel (M/s Natco Pharma. Ltd., Hyderabad), Croscarmellose sodium (M/s Natco Pharma. Ltd., Hyderabad), Crospovidone (M/s Natco Pharma Ltd., Hyderabad), Prosolve (M/s Orchid Health Care Ltd., Chennai), modified Starch (M/s Natco Pharma Ltd., Hyderabad), Acacia (Loba Chemie), Sodium Lauryl Sulphate (Qualigens), Tween 80 (Sigma), PEG 600 (SD Fine Chemicals),Talc I.P and Magnesium stearate I.P. All other materials used were of Pharmacopoeial grade.

Preparation of Ritonavir Tablets

Compressed tablets each containing 100 mg of ritonavir were prepared by conventional wet granulation method using various superdisintegrants and solubilizers as per the formulae given in Table 1.

Method

The required quantity of medicament and other ingredients (Table 1) were taken in a mortar. The superdisintegrants were added after drying the granules. 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.Superdisintegrant, 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.

Evaluation of Tablets

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

Content of Active Ingredient

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 100 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 100 ml volumetric flask and the volume was made upto 100 ml with methanol. The solution was subsequently diluted with 0.1 N hydrochloric acid and assayed for the drug content by the UV spectrophotometric method at 210 nm.

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 Thermonic tablet disintegration test machine using distilled water as fluid.

Dissolution Rate Study

The dissolution rate of ritonavir from the tablets was studied in 900 ml of 0.1 N hydrochoric acid using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. One tablet containing 100 mg of ritonavir was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for ritonavir at 210 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid and a suitable correction was applied for the amount of drug removed in the sample of dissolution fluid at each time. The dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Ritonavir tablets could be prepared by wet granulation method employing various superdisintegrants and solubilizers. Superdisintegrants were added after drying the wet granules and before compression. All the tablets were found to contain the ritonavir within 100 ± 2% of the label claim. Hardness of the tablets was in the range 5.5 - 6.5 kg/sq.cm in all the batches of tablets. The percentage weight loss in the friability test was less than 1.1% with all the batches of tablets prepared. All the tablets formulated were disintegrated in 5-8 min. As such all the tablets prepared were of good quality fulfilling the official

(I.P) and GMP requirements of tablets.

Dissolution characteristics of various tablets prepared are shown in Tables 3 and 4 and in Figs. 1 and 2. Dissolution of ritonavir from all the tablets prepared followed first order kinetics with correlation coefficient (r) values in the range 0.962 - 0.997 with various tablet formulations. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[14]. Much variation was observed in the dissolution characteristics of tablets prepared with various superdisintegrants and solubilizers.

Table 1: Formula of Ritonavir Tablets Prepared with Various Superdisintegrants

Ingredient (mg/tab)	Formulation				
	TF1	TF2	TF3	TF4	TF5
Ritonavir	100	100	100	100	100
Acacia	5	5	5	5	5
Modified Starch	8	-	-	-	-
Primogel	-	8	-	-	-
Crospovidone	-	-	8	-	-
Croscarmellose Sodium	-	-	-	8	-
Prosolve	-	-	-	-	20
Talc	4	4	4	4	4
Magnesium stearate	4	4	4	4	4
Lactose up to (mg)	200	200	200	200	200

Table 2: Formula of Ritonavir Tablets Formulated Employing Various Solubilizers

Ingredient (mg/Tab)	TF6	TF7	TF8	TF9	TF10	TF11	TF12	TF13
Ritonavir	100	100	100	100	100	100	100	100
PVP	5	5	5	5				
Acacia					5	5	5	5
Tween 80	--	5	-	-	-	5		
PEG - 600	--	--	5				5	
SLS	--	-		5				5
Cross carmellose sodium	8	8	8	8	8	8	8	8
Talc	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4
Lactose up to (mg)	200	200	200	200	200	200	200	200

Table 3: Dissolution Parameters of Ritonavir Tablets Formulated with Various Superdisintegrants

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Percent Drug Dissolved in 10 min
TF1	48	0.0159	20.52	13.97± 1.32
TF2	>60	0.0112	20.44	16.35± 1.25
TF3	>60	0.0076	21.27	20.03± 1.14
TF4	45	0.0125	26.79	25.54± 1.42
TF5	22	0.0265	34.54	31.05± 1.22

Table 4: Dissolution Parameters of Ritonavir Tablets Formulated with Various Solubilizers

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Percent Drug Dissolved in 10 min
TF6	60	0.0073	29.57	29.70± 1.65
TF 7	18	0.0207	43.42	43.18± 1.08
TF 8	21	0.0196	40.44	38.11± 1.70
TF9	31	0.0200	30.89	26.59± 1.23
TF10	33	0.0137	33.99	32.48± 1.24
TF11	17	0.0201	48.32	48.38± 1.81
TF12	19	0.0172	42.80	42.44± 1.74
TF13	22	0.0156	39.95	41.82± 1.78

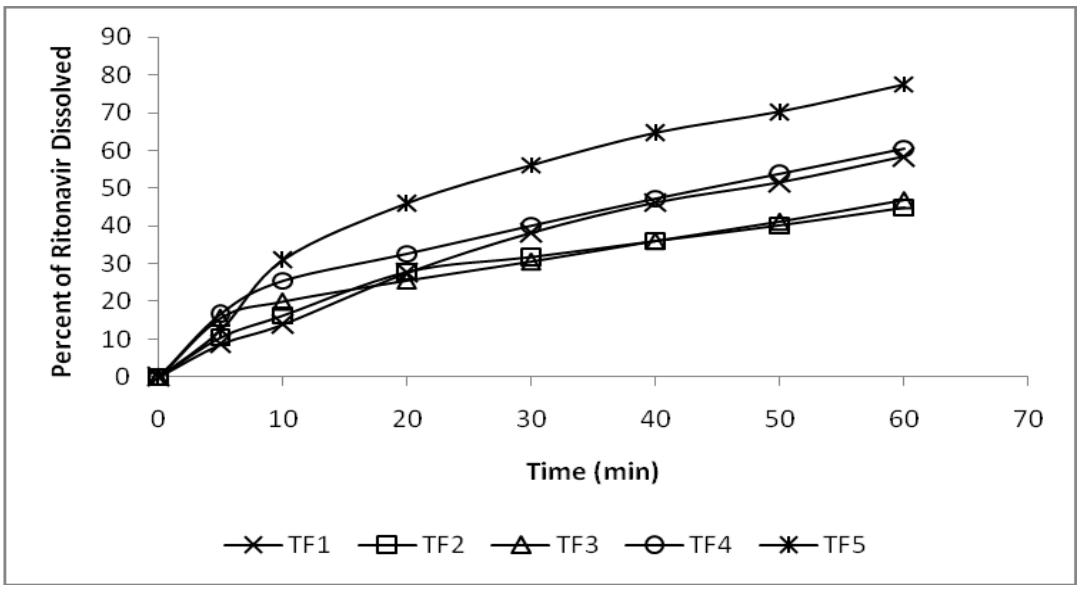

Fig 1: Dissolution Profiles of Ritonavir Tablets Prepared with Various Superdisintegrants

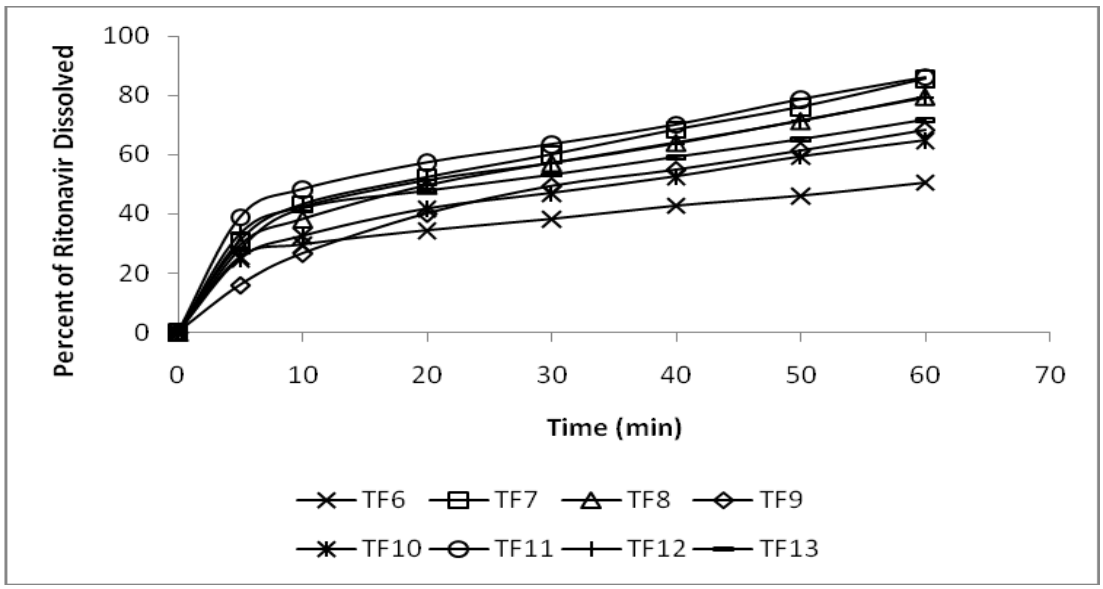

Fig 2: Dissolution Profile of Ritonavir Tablets Prepared by Using Various Solubilizers

The order of performance of superdisintegrants based on increasing dissolution rate was found to be Prosolve > modified starch > croscarmellose sodium > Primogel > crospovidone. Based on the dissolution efficiency the order of performance of superdisintegrants was Prosolve > croscarmellose

sodium > crospovidone > modified starch >Primogel. Tablets formulated with Prosolve, modified starch and croscarmellose sodium exhibited higher dissolution rates and dissolution efficiency among all and these tablets also fulfilled all official (I.P) and GMP requirements of compressed tablets. Prosolve is a commercial directly compressible vehicle consisting of microcrystalline cellulose (98%) and colloidal silicon dioxide (2%). Croscarmellose sodium is a cross-linked polymer of carboxymethyl cellulose sodium. Thus, Prosolve, modified starch and croscarmellose sodium were found to be better superdisintegrants for ritonavir tablets.

The feasibility of using the solubilizers in tablet formulations for enhancing the dissolution rate of ritonavir from tablets were also investigated.Tablets each containing 100 mg of ritonavir could be prepared by conventional wet granulation method employing SLS, Tween 80 and PEG – 600 as solubilizers. Tween 80, PEG 600 and SLS were used at concentration of 5 % in the formulae. All the dissolution parameters (K_1 DE_{30}, T_{50} and % dissolved in 10 min) indicated rapid and higher dissolution of ritonavir from tablets containing solubilizers when compared to control tablets without solubilizers. Formulations TF6, TF7, TF8 and TF9 were prepared employing PVP (2.5%) as binder. Formulations TF 6 is a control formulation without solubilizer. Formulations TF7, TF8 and TF9 contained Tween 80, PEG 600 and SLS respectively as solubilizers. Dissolution rate (K_1 min^{-1}) was found to be 0.0073, 0.0207, 0.0196 and 0.0200 respectively with formulations TF6, TF7, TF8 and TF9. The dissolution efficiency DE_{30} was also increased from 29.57% for formulation TF6 to 43.42% with formulation TF7 and to 40.44% with formulation TF8 and to 30.89% with formulation TF 9. The order of increasing dissolution rate (K_1 min^{-1}) and dissolution efficiency (DE_{30}) with various formulations was TF7 (Tween 80) > TF8 (PEG-600) > TF9 (SLS) > TF6 (control).Formulations TF10, TF11, TF12 and TF13 were formulated employing acacia (2.5%) as binder. Formulation TF10 is a control formulation without solubilizer. Formulations TF11, TF12 and TF13 contain Tween 80, PEG-600 and SLS respectively as solubilizers. With binder acacia also, the dissolution rate (K_1 min^{-1}) and dissolution efficiency (DE_{30}) were higher in the case of formulations containing solubilizers (TF11, TF12 and TF13) when compared to TF10 (control) .The order of increasing K_1 and DE_{30} observed with various formulations was TF11 (Tween 80) > TF12 (PEG - 600) > TF13 (SLS) > TF10 (control).

Thus with both the binders (PVP and acacia) the tablets formulated with solubilizers gave rapid and higher dissolution of ritonavir when compared to control formulations without solubilizers. With all the three solubilizers, formulations made with acacia as binder gave higher dissolution rate and dissolution efficiency of ritonavir when compared to those formulated with PVP as binder. Thus, the results of the study indicated that the dissolution rate and efficiency of ritonavir from tablets could be enhanced by incorporating solubilizers in the tablets.

CONCLUSIONS

1. The superdisintegrant and solubilizer used has significant influence on the tablet qualities and dissolution rate of ritonavir from the tablets.
2. The order of performance of the superdisintegrants based on increasing dissolution rate was Prosolve > modified starch > croscarmellose sodium > Primogel > crospovidone.
3. Tablets formulated with Prosolve, modified starch and croscarmellose sodium exhibited higher dissolution rates and dissolution efficiency values fulfilling all other official (I.P) and GMP requirements of compressed tablets. Prosolve, modified starch and croscarmellose sodium were found to be better superdisintegrants for ritonavir tablets.
4. The dissolution rate and dissolution efficiency of ritonavir tablets could be significantly enhanced by incorporating the solubilizers (Tween 80, PEG - 600 and SLS) in the tablets. The order of increasing dissolution rate observed with various solubilizers was Tween 80 > PEG - 600> SLS.
5. The dissolution rate and efficiency of ritonavir from tablets could be enhanced by incorporating solubilizers in the tablets.

REFERENCES

1. The Biopharmaceutics classification systems (BCS) guidance, Center for Drug Evaluation and Research, US Food and Drug Administration, **2001**; http://www.fda.gov/cder.
2. Cooper CL, Van Heeswijk RPG, Gallicano K and Cameron DW. Clin. A Review of Low-Dose Ritonavir in Protease Inhibitor Combination Therapy. *Infect. Dis.*, **2003**; 36(12): 1585.
3. Merry C, Barry M, Gibbons S, Mulcahy F and Back D., *Br. J. Clin. Pharmacol*., **1996**;42(6):l787.
4. Bertz RJ and Granneman GR., *Clin. Pharmacokinetic*., **1997**; 32(3): 210.
5. Hsu A, Granneman GR, Witt G, Locke C, Denissen J, Molla A, Valdes J, Smith J, Erdman K, Lyons N, Niu P, Decourt JP, Fourtillan JB, Girault J, and Leonard JM., Antimicrob. Agents. *Chemother.* **1997**; 41(5): 898.
6. Chowdary, K.P.R; Annamma Devi, G.S. and Swapna, Ch., *Res. J. Pharm. Biol. Chem. Sci*., **2012**; 3(4):294.
7. Chowdary, K.P.R., and Srinivasa Rao, S.K.

Int. J, Pharma. Excip., **1999**; 123.
8. Chowdary K.P.R., Radhika I. and Rajyalakshmi, Y., *Int. J. Pharma. Excip*., **2000**;181.
9. Poelma FG, Breas R, Tukker JJ and Crommelin DJ. Intestinal absorption of drugs. the influence of mixed micelles on on the disappearance kinetics of drugs from the small intestine of the rat, *J. Pharm. Pharmacol*, **1991**; 43: 317.
10. Shikha Agrawal, Nidhi Soni, Narendra K. Jain and G. P. Agrawal, solubility enhancement of poorly water soluble celecoxib for parenteral formulations, *International journal of Pharmaceutical Sciences and Research*, **2012**; 3(7): 2325-2336.
11. Md. Shaikhu, Millat Ibn Razzak, Ferdous Khan, Masuma Hossain, Tasmia Anika and Shamsad Afreen Moon. Impact of Sodium Lauryl Sulphate on the Release of Carbamazepine from Methocel K15M CR based Matrix Tablets, *Bangladesh Pharmaceutical Journal*, **2012**; 15(1): 79-82.
12. Mohamed Hassan G, Dehghana and Mohammad Jafarb. Improving Dissolution of Meloxicam Using Solid Dispersions, *Iranian Journal of Pharmaceutical Research,* **2006**; 4: 231-238.
13. Aleem AM, Dehghan MH and Rajesh Babu V. Solid dispersion- an approach to enhance the dissolution rate of Aceclofenac by using 3^2 factorial design. *International journal of Pharmaceutical Sciences and Research*, **2010**; 1(12): 203-208
14. Khan KA. The concept of dissolution efficiency. *J. Pharm. Pharmacol*, **1975**; 27: 48.