AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation Development of Ritonavir Tablets Employing B-Cyclodextrins, Hydroxy Propyl B -Cyclodextrin and Solutol Hs15

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ABSTRACT

Ritonavir, exhibits low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. The individual main and combined (interaction) effects of CDs and Solutol HS15 on the dissolution rate of ritonavir from tablet formulations was investigated in a series of 2^2 – factorial experiments. Ritonavir (100mg) formulated in to compressed tablets by wet granulation method employing selected combinations of CDs (βCD and HPβCD) and Solutol HS15. All the tablets prepared were of good quality fulfilling the official (I.P) standards with regard to hardness, friability, disintegration time and drug content. Drug dissolution from the tablets formulated followed first order kinetics and gave relatively higher rates of dissolution (K_1) and dissolution efficiency (DE_{30}) values when compared to those of ritonavir plain tablets. Formulations R4 and R8, gave much higher dissolution rates when compared to plain tablets, R1. A 21.35 and 16.85 fold increase in K_1 was observed respectively with formulations R4 and R8 when compared to formulation R1 (plain tablets). The dissolution efficiency (DE_{30}) was also increased from 7.29% for formulation R1 (plain tablets) to 43.32 % and 39.36 % respectively for formulations R4 and R8. In combination βCD-Solutol HS15 gave 21.35 fold increase in the dissolution rate HPβCD and Solutol HS15 alone gave an enhancement of 4.85 fold and 6.10 fold in the dissolution rate (K_1) of ritonavir tablets respectively. Whereas in combination, HPβCD and Solutol HS15 gave a 16.85 fold increase in the dissolution rate.

Keywords: Ritonavir Tablets, β-Cyclodextrin, HPβ-Cyclodextrin Solutol HS15, Dissolution Rate, Factorial Study.

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Received 4 March 2013, Accepted 12 March 2013

Please cite this article in press as: Yogananda R *et al.*, Formulation Development of Ritonavir Tablets Employing B -Cyclodextrins, Hydroxy Propyl B -Cyclodextrin and Solutol Hs15. American Journal of PharmTech Research 2013.

INTRODUCTION

Ritonavir, a widely prescribed HIV- 1 specific non–nucleoside reverse transcriptase inhibitor drug belongs to class II under BCS and exhibits low and variable oral bioavailability due to its poor aqueous solubility[1]. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersions and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS Class II drugs[2]. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[3,4]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[5,6]. Solutol HS15 (polyethyleneglycol660-12-hydroxystearate) is a non-ionic surfactant used for pharmaceutical purposes produced from 1 mol 12-hydroxystearic acid and 15 mol ethylene oxide. The product is very efficient in solubilising substances like fat-soluble vitamins, and active ingredients of hydrophobic nature. Solutol HS15 is approved by the HPB (Canada) for human application. Solutol HS15 has been used to enhance the solubility of insoluble drugs such as nifedipine[7],paclitaxel[8] and as carrier in solid dispersions for increasing the dissolution rate and bioavailability of poorly soluble drugs such as curcumin[9]and biochanin A[10]. The combination of βCD with Solutol HS15 and / or PVP K30[11] has markedly enhanced the solubility and dissolution rate of ritonavir, a BCS class II drug than is possible with them individually. The objective of the present study is to evaluate the feasibility of formulating Ritonavir – βCD– Solutol HS15 and Ritonavir –HPβCD – Solutol HS15 inclusion complexes into tablets and to evaluate the effects of βCD, HPβCD and Solutol HS15 on the dissolution rate of ritonavir tablets in a 2^2 factorial study.

MATERIALS AND METHODS

Materials:

Ritonavir was a gift sample from M/s Amoli Organics Pvt., Ltd**.,** Mumbai, β-cyclodextrin and hydroxy propyl β-cyclodextrin were gift samples from Signet Chemical Corporation Pvt., Ltd., Solutol HS15 was a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad. Cross carmellose sodium, gift sample from M/s Natco Pharma Ltd., Hyderabad. Methanol (Qualigens), poly vinyl pyrrolidone (PVP K30) and were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Estimation of ritonavir:

A UV Spectrophotometric method based on the measurement of absorbance at 210nm in 0.1N hydrochloric acid was used for the estimation of ritonavir[12]. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-25 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be less than 1%. No interference by the excipients used in the study was observed.

Preparation of ritonavir- βCD- Solutol HS15 and ritonavir-HP βCD- Solutol HS15 complexes

Solid inclusion complexes of ritonavir, βCD, Solutol HS15 and ritonavir-HP βCD- Solutol HS15 were prepared as per 2^2–factorial study by kneading method. Ritonavir, βCD, Solutol HS15 and ritonavir-HP βCD- Solutol HS15 were triturated in a mortar with a small volume of solvent consisting of a blend of water: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55^{o}C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of ritonavir- βCD - Solutol HS15 and ritonavir-HP βCD- Solutol HS15:

Compressed tablets each containing 100 mg of ritonavir were prepared as per 2^2–factorial study by wet granulation method employing Ritonavir- βCD - Solutol HS15 and ritonavir-HP βCD- Solutol HS15 inclusion complexes. The formulae of the tablets prepared are given in table-1(a) and 1(b)

Preparation of tablets by wet granulation method:

Lactose was used as filler. Crosscarmellose sodium (4.2%), talc (2%) PVP and magnesium stearate (2%) were incorporated, respectively as disintegrant, binding agent and lubricants. Purified water was used as granulating fluid in wet granulation method. The required quantities of drug, drug- βCD- Solutol HS15, drug- HPβCD- Solutol HS15 inclusion complexes and lactose were mixed thoroughly in a mortar by following geometric dilution technique. Water 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 60^0C for 4 h. Dried granules were passed through mesh No.16 to break aggregates. Cross carmellose sodium (4.2%) and lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No.100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Evaluation of tablets:

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution rate study:

The dissolution rate of ritonavir tablets prepared was studied in 900 ml of 0.1N hydrochloric acid using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37±1^{o}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 (0.45 µ) 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 has been applied in calculating the percent drug dissolved at various times. The dissolution experiments were replicated three times each (n=3).

Analysis of results:

Dissolution data were subjected to analysis as per zero order and first order kinetics and the corresponding dissolution rates were calculated. Dissolution efficiency (DE30) values were calculated as suggested by Khan[13].

RESULTS AND DISCUSSION

Results of the present investigation indicated that the complexation of ritonavir with CDs (βCD and HPβCD) has markedly enhanced their solubility and dissolution rates from CD complexes. Addition of surfactant Solutol HS15 has further enhanced the solubility and dissolution rate of ritonavir. Combined effects of CDs and surfactant in enhancing the solubility and dissolution rates of these two poorly soluble BCS class-II drugs are highly significant. Among all, Drug-CD-Solutol HS15 ternary complex systems gave higher enhancement in the dissolution rate of ritonavir. The feasibility of formulating the Drug-CD-Solutol HS15 complex systems in to compressed tablets with enhanced dissolution rate was investigated. The individual main and

combined (interaction) effects of CDs and Solutol HS15 on the dissolution rate of ritonavir from tablet formulations was investigated in a series of factorial experiments.

Table-1(a) Formulae of Ritonavir Tablets Prepared Employing βCD and Solutol HS15 as per 2^2 Factorial Design

Ingredient (mg/tab)	Formulation			
	R1(F_1)	R2(F_a)	R3(F_b)	R4(F_{ab})
Ritonavir	100	100	100	100
β-CD	--	200	--	200
Solutol HS15	--	--	5	5
Cross Carmellose Sodium	15	15	15	15
PVP	7	7	7	7
Talc	7	7	7	7
Magnesium stearate	7	7	7	7
Lactose	214	14	209	9
Total weight (mg)	350	350	350	350

Table-1(b) Formulae of Ritonavir Tablets Prepared Employing HPβCD and Solutol HS15as per 2^2 Factorial Design

Ingredient (mg/tab)	Formulation			
	R5(F_1)	R6(F_a)	R7(F_b)	R8(F_{ab})
Ritonavir	100	100	100	100
HPβ-CD	--	200	--	200
Solutol HS15	--	--	5	5
Cross Carmellose Sodium	15	15	15	15
PVP	7	7	7	7
Talc	7	7	7	7
Magnesium state	7	7	7	7
Lactose	214	14	209	9
Total weight (mg)	350	350	350	350

Drug-CD and Drug-CD-Solutol HS15 complex systems could be formulated in to compressed tablets by wet granulation method. The hardness, friability, drug content and disintegration time of the tablets prepared are given in Tables 2(a)(b).

Table 2(a): Physical Properties of Ritonavir Tablets Prepared Employing Drug- βCD – Solutol HS 15 by wet Granulation Method as per 2^2 Factorial Study

(code as per 2^{2-} Factorial Design)	Hardness (kg/sq.cm	Friability (%)	Disintegration Time (min.)	Ritonavir content (mg/tablet)
R1 (1).	7.0	0.54	3.5	99.4
R2 (a).	6.5	0.64	2.5	98.2
R3 (b).	6.0	0.35	2.0	100.6
R4 (ab).	7.5	0.65	2.0	98.8

Table 2(b): Physical Properties of Ritonavir Tablets Prepared Employing Drug- HPβCD - Solutol HS 15 by wet Granulation Method as per 2^2 Factorial Study

(code as per 2^2 – Factorial Design)	Hardness (kg/sq.cm	Friability (%)	Disintegration Time (min.)	Ritonavir content (mg/tablet)
R5 (1).	6.5	0.45	2.5	98.4
R6 (a).	6.0	0.65	2.0	101.2
R7 (b).	7.0	0.80	2.5	99.6
R8 (ab).	6.0	0.85	1.5	98.6

Hardness of the tablets was in the range 6.0 – 7.5 kg/sq.cm. Percent weight loss in the friability test was less than 0.85% with all the formulations. The disintegration time was in the range 1 – 3.5 min. with all the tablets prepared. Drug content of the tablets was within 100 ± 2% of the labeled claim.

As such all the tablets prepared employing drug-CD-Solutol HS15 inclusion complexes fulfilled the official (I.P) disintegration time specification of uncoated tablets. The dissolution rate of ritonavir from the tablets prepared was studied in 900 ml of 0.1N hydrochloric acid as prescribed in I.P 2010.Dissolution of ritonavir from all the tablets prepared followed first order kinetics. The correlation coefficient (r) values were higher in the first order model than those in the zero order model in all the cases. The dissolution profiles of the ritonavir tablets prepared are given in Table 3(a)(b) and in Figure. 1(a)(b).

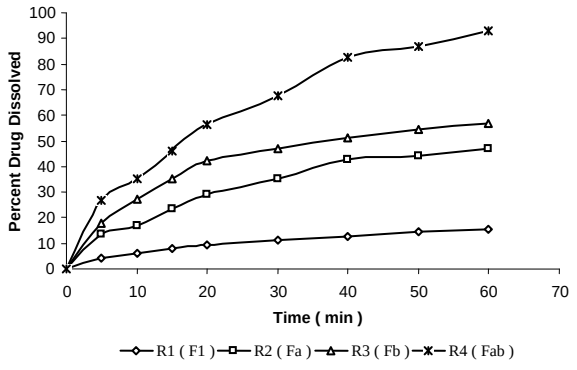

Figure.1(a) Dissolution Profiles of Ritonavir Tablets Formulated Employing βCD and Solutol HS15 as Per 2^2 Factorial Design

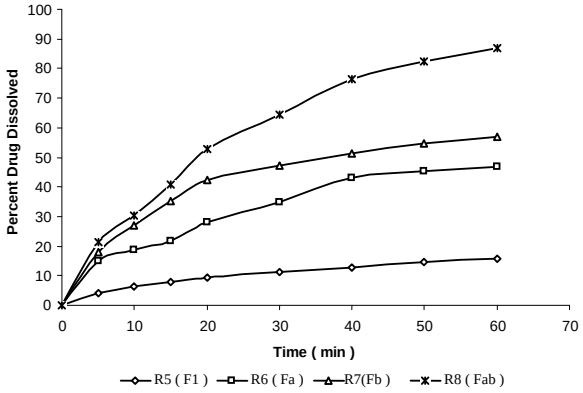

Figure.1 (b) Dissolution Profiles of Ritonavir Tablets Formulated Employing HPβCD and Solutol HS15 as Per 2^2 Factorial Design

Table -3(a) Dissolution Profiles of Ritonavir Tablets Formulated Employing βCD and Solutol HS15 as per 2^2 Factorial Design

Time (min)	Percent Ritonavir Dissolved ($\bar{x}$ ± sd)			
	R1 (1)	R2 (a)	R3 (b)	R4 (ab)
5	4.22±0.76	13.60±0.78	17.85±0.66	26.65±1.55
10	6.32±0.42	16.77±0.30	27.05±0.51	35.05±0.46
15	7.80±0.42	23.32±0.78	35.35±0.78	46.15±0.55
20	9.40±0.67	29.27±0.78	42.25±0.46	56.35±0.61
30	11.30±0.91	35.07±0.60	47.05±0.72	67.60±0.58
40	12.57±0.53	42.92±1.28	51.27±0.78	82.60±1.64
50	14.62±1.07	44.32±0.921	54.50±1.35	86.90±1.24
60	15.65±0.86	46.87±0.75	56.82±0.44	93.12±2.20

Table -3(b) Dissolution Profiles of Ritonavir Tablets Formulated Employing HPβCD and Solutol HS15 as per 2^2 Factorial Design

Time (min)	Percent Ritonavir Dissolved ($\bar{x}$ ± sd)			
	R5 (1)	R6 (a)	R7 (b)	R8(ab)
5	4.22±0.76	15.02±0.62	17.85±0.66	21.30±0.80
10	6.32±0.42	18.85±0.47	27.05±0.51	30.25±0.61
15	7.80±0.42	21.9±1.12	35.35±0.78	40.92±1.33
20	9.40±0.67	28.22±0.96	42.25±0.46	52.92±2.16
30	11.3±0.91	34.80±0.63	47.05±0.72	64.47±1.38
40	12.57±0.53	42.92±0.52	51.27±0.78	76.42±4.59
50	14.62±1.07	45.30±0.88	54.50±1.35	82.27±2.72
60	15.65±0.86	46.87±0.80	56.82±0.44	86.92±1.28

The dissolution parameters (K_1 and DE_{30}) of various tablets are summarized in Table 4(a)(b). Dissolution data were analyzed as per zero and first order kinetics. The correlation coefficient (r^2) values in the analysis of dissolution data indicated that the dissolution of ritonavir from all the tablets formulated followed first order kinetics. The correlation coefficient (r^2) values were in the range 0.8927-0.9978 with all the ritonavir tablets prepared. Tablets formulated employing CDs and Solutol HS15 gave relatively higher rates (K_1) of dissolution and dissolution efficiency (DE_{30}) values when compared to the ritonavir plain tablets (i.e. tablets formulated with ritonavir alone). The order of increasing dissolution rate (K_1) observed with various ritonavir tablets wasR1 (plain) < R2 (βCD)= R6 (HPβCD) <R3 (SolutolL HS15) <R8 (HP βCD-Solutol HS15) <R4 (βCD-Solutol HS15).

Formulations R4 and R8, which are formulated employing βCD-Solutol HS15 and HPβCD-Solutol HS15 respectively, gave much higher dissolution rates when compared to plain tablets, R1. A 21.35 and 16.85 fold increase in K_1 was observed respectively with formulations R4 and R8 when compared to formulation R1 (plain tablets). The dissolution efficiency (DE_{30}) was also increased from 7.29% for formulation R1 (plain tablets) to 43.32 % and 39.36 % respectively for

formulations R4 and R8. The dissolution rate (K_1) data of the ritonavir tablets formulated employing CDs and Solutol HS15 were subjected to ANOVA to assess the significance of their individual and combined effects on dissolution rate. ANOVA indicated that the individual main effects of βCD and Solutol HS15 and their combined effect in enhancing the dissolution rate (K_1) of ritonavir tablets were highly significant ($p < 0.01$). βCD and Solutol HS15 alone gave an enhancement of 4.75 and 6.10 fold in the dissolution rate (K_1) respectively. Whereas in combination βCD-Solutol HS15 gave 21.35 fold increase in the dissolution rate.

Table 4(a): Dissolution Parameters of Ritonavir Tablets Prepared Employing Drug- βCD – Solutol HS15 Inclusion Complexes as per 2^2 Factorial Study

Formulation	DE_{30} (%)		K_1 (min^{-1}) ×10^2	
	($\bar{x} \pm$ s.d.)	Increase in DE_{30} (N0.of folds)	($\bar{x} \pm$ s.d.)	Increase in K_1 (N0.of folds)
R1 (F1)	7.29	-	0.20± 0.0	-
R2 (Fa)	22.11	3.03	0.95± 0.0	4.75
R3 (Fb)	31.77	4.35	1.22± 0.0	6.10
R4 (Fab)	43.32	5.94	4.27± 0.4	21.35

Table 4(b): Dissolution Parameters of Ritonavir Tablets Prepared Employing Drug- HPβCD – Solutol HS15 Inclusion Complexes as per 2^2 Factorial Study

CD-Surfactant System	DE_{30} (%)		K_1 (min^{-1}) ×10^2	
	($\bar{x} \pm$ s.d.)	Increase in DE_{30} (N0.of folds)	($\bar{x} \pm$ s.d.)	Increase in K_1 (N0.of folds)
R5 (F1)	7.29	-	0.2 ± 0.0	-
R6 (Fa)	22.14	3.03	0.97 ± 0.057	4.85
R7 (Fb)	31.77	4.35	1.22± 0.057	6.1
R8 (Fab)	39.36	5.39	3.37±0.27	16.85

Results of ANOVA also indicated that the individual main and combined effects of HPβCD and Solutol HS15 in enhancing the dissolution rate of ritonavir tablets were highly significant ($p < 0.01$). HPβCD and Solutol HS15 alone gave an enhancement of 4.85 fold and 6.10 fold in the K_1 respectively. Where as in combination HPβCD and Solutol HS15 gave a 16.85 fold increase in the dissolution rate of ritonavir tablets. The ritonavir, tablets formulated employing Drug-CD-Solutol HS15 ternary complex systems gave markedly higher dissolution rate (K_1) and dissolution efficiency (DE_{30}) values. Formulations R4, and R8 are considered as best tablet formulations developed.

CONCLUSIONS

1. Drug-CD and Drug-CD-Solutol HS15 complex systems could be formulated in to compressed tablets by wet granulation method.
2. All the tablets prepared employing drug-CD and drug-CD Solutol HS15 complex systems

were of good quality fulfilling the official (I.P) standards with regard to hardness, friability, disintegration time and drug content.

3. Drug dissolution from the tablets formulated employing drug-CD and drug-CD-Solutol HS15 complexes followed first order kinetics.
4. Tablets formulated employing CDs and Solutol HS15 gave relatively higher rates of dissolution (K_1) and dissolution efficiency (DE_{30}) values when compared to those ritonavir.
5. The order of increasing dissolution rate (K_1) observed with various tablets was R1 (plain) < R2 (βCD)= R6 (HPβCD) < R3 (Solutol HS15) < R8 (HP βCD-Solutol HS15) < R4 (βCD-Solutol HS15).
6. Ritonavir tablet formulations R4 and R8, which are formulated employing βCD-Solutol HS15 and HPβCD-Solutol HS15 respectively, gave much higher dissolution rates when compared to plain tablets, R1. A 21.35 and 16.85 fold increase in K_1 was observed respectively with formulations R4 and R8 when compared to formulation R1 (plain tablets).
7. The dissolution efficiency (DE_{30}) was also increased from 7.29% for Formulation R1 (plain tablets) to 43.32 % and 39.36 % respectively for formulations R4 and R8.
8. ANOVA indicated that the individual main effects of βCD, HPβCD and Solutol HS15 and their combined effects in enhancing the dissolution rate (K_1) of ritonavir tablets were highly significant ($P< 0.01$).
9. βCD and Solutol HS15 alone gave an enhancement of 4.75 and 6.10 fold in the dissolution rate (K_1)of Ritonavir tablets respectively. Whereas in combination βCD-Solutol HS15 gave 21.35 fold increase in the dissolution rate.
10. HPβCD and Solutol HS15 alone gave an enhancement of 4.85 fold and 6.10 fold in the dissolution rate (K_1) of ritonavir tablets respectively. Where as in combination HPβCD and Solutol HS15 gave a 16.85 fold increase in the dissolution rate.

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