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FORMULATION DEVELOPMENT OF RITONAVIR TABLETS EMPLOYING B CYCLODEXTRIN, SOLUTOL HS15 AND PVP K30

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ABSTRACT

Ritonavir, a widely prescribed anti retroviral drug belongs to class II under BCS and 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 objective of the study is to evaluate the feasibility of formulating ritonavir –βCD– Solutol HS15 /PVP K30 inclusion complexes into tablets and to evaluate the effects of βCD, Solutol HS15 and PVP K30 on the dissolution rate and dissolution efficiency of ritonavir tablets in 2^3 factorial study. Drug – βCD- Solutol HS15 / PVP K30 inclusion complexes were prepared by kneading method. Tablets each containing 100 mg of ritonavir were prepared by wet granulation method employing various βCD complexes as per 2^3 factorial design and the tablets were evaluated for dissolution rate and other physical properties.

Tablets formulated employing Ritonavir – βCD – Solutol HS15 / PVP K30 inclusion complexes disintegrated in 3-7 min and fulfilled the official (IP) disintegrating time specification of uncoated tablets. Ritonavir dissolution was rapid and higher from the tablets formulated employing drug- βCD- Solutol HS15/ PVP K30 inclusion complexes when compared to the tablets containing ritonavir alone. The individual as well as combined effects of the three factors involved i.e., βCD (factor A), Solutol HS15 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of ritonavir tablets. Among the three factors Solutol HS15 (factor B) gave highest enhancement (10.98 fold) in the dissolution rate (K_1) of ritonavir tablets. βCD alone gave a 2.93 fold increase in the dissolution rate (K_1) of ritonavir tablets.

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Whereas βCD in combination with Solutol HS15 and PVP K30 respectively gave 6.05 fold and 3.45 fold increase in the dissolution rate of ritonavir tablets.The dissolution efficiency (DE_{30}) was also much higher in the case of tablets formulated employing drug- βCD- Solutol HS15/ PVP K30 inclusion complexes when compared to the tablets containing ritonavir alone.Hence a combination of βCD with Solutol HS15 and / or PVP K30 or Solutol HS15 alone is recommended to enhance the dissolution rate and dissolution efficiency of ritonavir tablets.

Key words: *Ritonavir Tablets, β Cyclodextrin, Solutol HS15, PVP K30, Dissolution Rate, Factorial Study*

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. 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 [1]. 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 [2, 3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies [4, 5]. 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 [6] and paclitaxel [7] and as carrier in solid dispersions for increasing the dissolution rate and bioavailability of poorly soluble drugs such as curcumin [8] and biochanin A[9].

We reported [10] earlier that combination of βCD with Solutol HS15 and / or PVP K30 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 –βCD – PVP K30 inclusion complexes into tablets and to evaluate the effects of βCD, Solutol HS15 and PVP K30 on the dissolution rate of ritonavir tablets in a 2^3 factorial study.

MATERIALS AND METHODS

Materials:

Ritonavir was a gift sample from M/s. Hetero Drugs Limited, Hyderabad. β Cyclodextrin was a gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens), poly vinyl pyrrolidone (PVP K30) and Solutol HS15 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 210 nm in 0.1N hydrochloric acid was used for the estimation of ritonavir. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95% and 1.15 % respectively. No interference by the excipients used in the study was observed.

Preparation of ritonavir- βCD- Solutol HS15 / PVP K30 complexes:

Solid inclusion complexes of ritonavir, βCD, Solutol HS15 and PVP K30 were prepared as per 2^3 – factorial study by kneading method. Ritonavir, βCD, Solutol HS15 and PVP K30 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°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of ritonavir- βCD - Solutol HS15/ PVP K30 tablets:

Compressed tablets each containing 100 mg of ritonavir were prepared as per 2^3 – factorial study by wet granulation method employing Ritonavir-βCD - Solutol HS15/ PVP K30 inclusion complexes. The formulae of the tablets prepared are given in Table 1.

Table 1: Formulae of Ritonavir Tablets Prepared by Wet Granulation Method Employing Drug- βCD – Solutol HS15- PVP K30 Inclusion Complexes as per 2^3 Factorial Study

Ingredient (mg / tablet)	Ritonavir Tablet Formulation							
	T_1	T_a	T_b	T_{ab}	T_c	T_{ac}	T_{bc}	T_{abc}
Ritonavir (1)*	100.0	-	-	-	-	-	-	-
RV- βCD (1:2) (a)	-	300.0	-	-	-	-	-	-
RV – Solutol HS15(2%) (b)	-	-	102	-	-	-	-	-
RV - βCD (1:2) - Solutol HS15 (2%) (ab)	-	-	-	306	-	-	-	-
RV - PVP K30 (2%) (c)	-	-	-	-	102.0	-	-	-
RV - βCD (1:2) - PVP K30 (2%) (ac)	-	-	-	-	-	306	-	-
RV - Solutol HS15 (2%) - PVP K30 (2%) (bc)	-	-	-	-	-	-	104	-
RV - βCD (1:2) - Solutol HS15 (2%) - PVP K30 (2%) (abc)	-	-	-	-	-	-	-	312
Crospovidone	11.0	18.0	11.0	18.0	11.0	18.0	11.0	18.0
Talc	4.4	7.0	4.4	7.0.	4.4	7.0	4.4	7.0
Magnesium Stearate	4.4	7.0	4.4	7.0	4.4	7.0	4.4	7.0
Lactose	100.2	28.0	98.2.	22.0	98.2	22.0	96.2	16.0
Total weight	220.0	360.0	220.0	360.0	220.0	360.0	220.0	360.0

RV: Ritonavir; βCD: β cyclodextrin; PVP K30: poly vinyl pyrrolidone K30;

***** Figures in parentheses are codes as per 2^3 Factorial Design

Preparation of tablets by wet granulation method:

Lactose was used as filler. Crospovidone (5%), talc (2%) and magnesium stearate (2%) were incorporated, respectively as disintegrant and lubricants. Purified water was used as granulating fluid in wet granulation method. The required quantities of drug, drug- βCD- Solutol HS15 - PVP 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° C for 4 h. Dried granules were passed through mesh No. 16 to break aggregates. Crospovidone (5%) 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 (DE_{30}) values were calculated as suggested by Khan [11].

RESULTS AND DISCUSSION

The Ritonavir- βCD- Solutol HS15 / PVP K30 inclusion complexes as per 2^3 factorial design were prepared by kneading method with a view to enhance the solubility and dissolution rate of ritonavir, a BCS class II drug. All the solid inclusion complexes of Drug- βCD- Solutol HS15 / PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v) values (< 1%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate characteristics of these Ritonavir-βCD- Solutol HS15 / PVP K30 inclusion complexes were reported [10] earlier.

The feasibility of formulating Ritonavir- βCD - Solutol HS15/ PVP K30 solid inclusion complexes into tablets was evaluated by preparing ritonavir tablets employing the solid inclusion complexes by wet granulation method. To evaluate the individual and combined effects of βCD, Solutol HS15 and PVP K30 on the dissolution rate and efficiency of ritonavir tablets, tablets each containing 100 mg of ritonavir were formulated employing solid inclusion complexes of drug- βCD - Solutol HS15/ PVP K30 as per 2^3 factorial design. For this purpose two levels of βCD (0 and 1: 2 ratio of Drug : βCD) and two levels of each of Solutol HS15 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved in the formulation of tablets as per 2^3-factorial study were ritonavir pure drug (1); RV- βCD (1:2) inclusion binary complex (a); RV - Solutol HS15 (2%) binary mixture (b); RV - βCD (1:2) – Solutol HS15 (2%) ternary complex (ab); RV – PVP K30 (2%) binary mixture (c); RV - βCD (1:2) – PVP K30 (2%) ternary complex (ac); RV – Solutol HS15 (2%) - PVP K30 (2%) ternary complex (bc); RV - βCD (1:2)- Solutol HS15 (2%) - PVP K30 (2%) inclusion complex (abc). The formulae of ritonavir tablets prepared as per 2^3 factorial design employing the above mentioned cyclodextrin inclusion complexes are given in Table 1. All the prepared tablets were evaluated for drug content, hardness, friability and disintegration time and dissolution rate of ritonavir. The physical properties of the tablets prepared are given in Tables 2 and the dissolution parameters of the tablets prepared are summarized in Table 3.

All the tablets prepared were found to contain ritonavir within 100±5% of the labelled claim. Hardness of the tablets was in the range 4.5-6.5 Kg/cm^2. Percentage weight loss in the friability test was less than 0.75% in all the cases. Plain tablets formulated employing ritonavir alone disintegrated within 1 min. All the tablets prepared

employing βCD– Solutol HS15/ PVP K30 inclusion complexes disintegrated within 3-7 min.

Table 2: Physical Properties of Ritonavir Tablets Prepared Employing Drug- βCD – Solutol HS 15/ PVP K30 by Wet Granulation Method as per 2^3 Factorial Study

Formulation code as per 2^3 factorial design	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/tablet)
T_1	4.5	0.75	0-48	98.9
T_a	4.5	0.61	5-16	99.2
T_b	5.0	0.70	3-01	100.1
T_{ab}	4.5	0.69	4-24	100.5
T_c	5.5	0.55	5-45	98.6
T_{ac}	6.5	0.60	7-14	99.5
T_{bc}	5.0	0.73	6-02	98.7
T_{abc}	6.0	0.64	6-00	100.2

As such all the tablets prepared employing βCD– Solutol HS15/ PVP K30 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 parameters (T_{50}, K_1 and DE_{30}) of various tablets are summarized in Table 3.

Table 3: Dissolution Parameters of Ritonavir Tablets Prepared Employing Drug- βCD – Solutol HS15/ PVP K30 Inclusion Complexes as per 2^3 Factorial Study

Formulation code as per 2^3 factorial design	T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$) (min^{-1}) ($\bar{x}$) (cv)	Increase in K_1 (no. of folds)	Dissolution Efficiency (DE_{30}) (%) ($\bar{x}$) (cv)
T_1	30	1.27±0.00	-	34.61±0.60
T_a	15	3.71±0.00	2.93	48.95±1.13
T_b	3	13.91±0.01	10.98	81.07±0.61
T_{ab}	5	7.66±0.09	6.05	60.45±0.89
T_c	3	7.18±0.21	5.67	76.31±1.59
T_{ac}	8	4.38±0.20	3.45	59.66±0.98
T_{bc}	3	14.43±0.27	11.39	82.75±0.26
T_{abc}	4	6.63±0.06	5.24	56.58±1.19

Ritonavir dissolution was rapid and higher from the tablets formulated employing drug- βCD-Solutol HS15/ PVP K30 inclusion complexes when compared to the tablets containing ritonavir alone. Dissolution parameters, K_1 and DE_{30} in each case were subjected to ANOVA to find out the significance of the individual and combined effects of the three factors (βCD, Solutol HS15, PVP K30) in enhancing the dissolution rate and dissolution efficiency of ritonavir tablets. The individual as well as combined effects of the three factors involved i.e., βCD (factor A), Solutol HS15 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of ritonavir tablets. Among the three factors Solutol HS15 (factor B) gave highest enhancement (10.98 fold) in the dissolution rate (K_1) of ritonavir tablets.

βCD alone gave a 2.93 fold increase in the dissolution rate (K_1) of ritonavir tablets. Whereas

βCD in combination with Solutol HS15 and PVP K30 respectively gave 6.05 fold and 3.45 fold increase in the dissolution rate of ritonavir tablets. The dissolution efficiency (DE_{30}) was also much higher in the case of tablets formulated employing drug- βCD- Solutol HS15/ PVP K30 inclusion complexes when compared to the tablets containing ritonavir alone. Thus combination of βCD with Solutol HS15 or PVP K30 gave a significantly higher dissolution rate (K_1) and dissolution efficiency (DE_{30}) of ritonavir tablets. I.P 2010 prescribed a dissolution rate specification of NLT 75% in 60 min for ritonavir tablets. Ritonavir tablets formulated employing Ritonavir- Solutol HS15 (formulation T_b), Ritonavir- βCD - Solutol HS15 (formulation Ta_b), Ritonavir- βCD- PVP K30 (formulation T_{ac}) and Ritonavir- Solutol HS15-PVP (formulation $_{Tbc}$) inclusion complexes fulfilled the official (I.P) dissolution rate specification of ritonavir tablets. Whereas plain tablets formulated employing ritonavir alone (formulation T_1) and tablets formulated employing its βCD complexes (formulation T_a) did not fulfill the official dissolution rate specification. Hence a combination of βCD with Solutol HS15 and / or PVP K30 or Solutol HS15 alone is recommended to enhance the dissolution rate and dissolution efficiency of ritonavir tablets.

CONCLUSIONS

1. Tablets formulated employing Ritonavir – βCD – Solutol HS15 / PVP K30 inclusion complexes disintegrated in 3-7 min and fulfilled the official (IP) disintegrating time specification of uncoated tablets.
2. Ritonavir dissolution was rapid and higher from the tablets formulated employing drug- βCD- Solutol HS15/ PVP K30 inclusion complexes when compared to the tablets containing ritonavir alone.
3. The individual as well as combined effects of the three factors involved i.e., βCD (factor A), Solutol HS15 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of ritonavir tablets.
4. Among the three factors Solutol HS15 (factor B) gave highest enhancement (10.98 fold) in the dissolution rate (K_1) of ritonavir tablets.
5. βCD alone gave a 2.93 fold increase in the dissolution rate (K_1) of ritonavir tablets. Whereas βCD in combination with Solutol HS15 and PVP K30 respectively gave 6.05 fold and 3.45 fold increase in the dissolution rate of ritonavir tablets.
6. The dissolution efficiency (DE_{30}) was also much higher in the case of tablets formulated employing drug- βCD- Solutol HS15/ PVP K30 inclusion complexes when compared to the tablets containing ritonavir alone.
7. Hence a combination of βCD with Solutol HS15 and / or PVP K30 or Solutol HS15 alone is recommended to enhance the dissolution rate and dissolution efficiency of ritonavir tablets.

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