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FORMULATION DEVELOPMENT AND OPTIMIZATION OF RITONAVIR TABLETS EMPLOYING STARCH 1500 AND SOLUPLUS

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ABSTRACT

The objective of the present study is to enhance the dissolution rate of Ritonavir by solid dispersion in Starch 1500 and Soluplus in its tablet formulation development and to optimse the Ritonavir tablet formulation employing Starch 1500(factor A) and Soluplus(factor B) by 2^2 factorial design to achieve NLT 85% dissolution in 10 min. Four Ritonavir tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. Ritonavir tablets were prepared by direct compression method and were evaluated. The individual and combined effects of the two factors, Starch 1500 and Soluplus are highly significant ($P < 0.01$) in influencing the dissolution rate of RITONAVIR tablets. Ritonavir tablet formulations F_{ab} and F_a disintegrated rapidly within one min and gave very rapid dissolution of Ritonavir, 99.4% and 89.9% in 10 min respectively. The increasing order of dissolution rate (K_1) observed with various formulations was $F_1 < F_b < F_a < F_{ab}$. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of starch1500(X_1) , soluplus (X_2) based on the observed results was found to be $\mathbf{Y = 77.74 + 16.92\ (X_1) + 9.42(X_2) - 4.67(X_1\ X_2).}$ Based on the above equation, the formulation of optimized Ritonavir tablets with NLT 85% dissolution in 10 min require starch1500 at 1:3.84 ratio of drug: starch1500, and Soluplus at 1% of drug and starch1500 content. The optimized Ritonavir tablet formulation gave 85.5% dissolution in 10min fulfilling the target dissolution requirement. Formulation of Ritonavir tablets with NLT 85% dissolution in 10 min could be optimized by 2^2 factorial design.

KEYWORDS: Formulation Development**,** Ritonavir tablets, Optimization, Factorial Design, Starch 1500, Soluplus.

INTRODUCTION

Optimization[1] of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. In a few studies[2-8] optimization by factorial designs was employed in the formulation development of BCS Class II drugs.

Several modern drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Ritonavir, a widely prescribed antiretroviral drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development.

Techniques[9] such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches, solid dispersion[10,11] in water soluble and water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs. Starch 1500 is a modified starch namely Pregelatinised starch used in tablets as diluent and directly compressible vehicle. It is also used as a carrier in solid dispersions in a few studies.[12-15]

Soluplus is a polymeric solubiliser with an amphiphilic chemical nature, which was particularly developed for solid solutions. Soluplus is polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol graft co-polymer. We have earlier reported[16] the enhancement of dissolution rate of Ritonavir by solid dispersion in Starch 1500 and soluplus alone and in combination.

In the present study solid dispersion of Ritonavir in Starch 1500 and Soluplus was used to enhance the dissolution rate of Ritonavir in its tablet formulation development. Ritonavir tablets with NLT 85% dissolution in 10 min was aimed in its formulation development. A 2^2 factorial design employing Starch 1500(Factor A) and Soluplus (Factor B) was used for Ritonavir tablet formulation development to achieve NLT 85% dissolution in 10 min. Thus the objective of the present study is optimization of Ritonavir tablet formulation employing Starch 1500, and Soluplus by 2^2 factorial design to achieve NLT 85% dissolution in 10 min.

EXPERIMENTAL

Materials

Ritonavir was a gift sample from M/s EASAI Pharma Technology Pvt. Ltd Visakhapatnam Ltd. Starch 1500 and Soluplus were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Estimation of Ritonavir

An UV Spectrophotometric method based on the measurement of absorbance at 240 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 1– 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 1.65% respectively. No interference by the excipients used in the study was observed.

Formulation of Ritonavir Tablets

For optimization of Ritonavir tablets as per 2^2 factorial design the Starch 1500 and Soluplus are considered as the two factors. The two levels of the factor A (Starch 1500) are 1:1 and 1:5 ratio of drug: Starch1500 and the two levels of factor B (Soluplus) are 0 and 2% of drug and Starch1500 content. Four Ritonavir tablet formulations employing selected combinations of

the two factors i.e. Starch 1500 and Soluplus as per 2^2 factorial design were formulated and prepared by direct compression method.

Preparation of Ritonavir Tablets

Ritonavir(100 mg) tablets were prepared by direct compression method as per the formula given in Table 1. The required quantities of Ritonavir, Starch 1500 and Soluplus as per the formula in each case were blended thoroughly in a closed polyethene bag. Talc and magnesium stearate were then added by passing through mesh no. 80 and blended. The blend of ingredients was then compressed directly into tablets using an 8- station RIMEK tablet punching machine employing 9mm or 12mm round and flat punches.

Evaluation of Tablets

All the Ritonavir tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability

The friability of the tablets was measured in a Roche friabilator using the formula

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Drug Content

Weighed tablets (10) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of Ritonavir was taken into 25 ml volumetric flask. Ethanol(20ml) was added and the contents were sonicated for ten minutes to dissolve the drug. The solution was made up to volume with ethanol. One ml of the drug solution was further diluted suitably with 0.1N Hydrochloricacid and assayed for Ritonavir at 240nm.

Disintegration time

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study

Dissolution rate of Ritonavir tablets prepared was studied in 0.1N Hydrochloric acid (900ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for Ritonavir at 240 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{20}) values were estimated as suggested by Khan.[17] Dissolution rate (K_1) values were analyzed as per ANOVA of 2^2 factorial experiments.

RESULTS AND DISCUSSION

The objective of the present study is to optimize the Ritonavir tablet formulation employing Starch 1500 and Soluplus by 2^2 factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Ritonavir tablets as per 2^2 factorial design the Starch 1500 and Soluplus are considered as the two factors. The two levels of the factor A (Starch 1500) are 1:1 and 1:5 ratio of drug: Starch1500 and the two levels of the factor B (Soluplus) are 0% and 2% of drug and Starch 1500 content. Four Ritonavir tablet formulations employing selected combinations of the two factors i.e. Starch 1500, and Soluplus as per 2^2 factorial design were prepared. The tablets were prepared by direct compression method as per the formulae given in Table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K_1) values were analysed as per ANOVA of 2^2 factorial design to find out the significance of the individual and combined effects of the two factors involved on the dissolution rate of Ritonavir tablets formulated.

Table 1: Fomulae of Ritonavir Tablets Prepared Employing Starch 1500 and Soluplus as per 2^2 Factorial Design.

Ingredients (mg/tablet)	Formulation code				
	F1	Fa	Fb	Fab	Fopt
RITONAVIR	100	100	100	100	100
Starch1500	100	500	100	500	384
Soluplus	-	-	4	12	4.84
Talc	4	12	4	12	10
Magnesium stearate	4	12	4	12	10
Total weight(mg)	208	624	212	636	508.8

F opt: Optimised Formulation to achieve NLT 85% Dissolution in 10 Minutes.

Table 2: Physical Properties of Ritonavir Tablets Prepared Employing Starch 1500 and Soluplus as per 2^2 Factorial Design.

Formulation code	Hardness (Kg per cm^2) ($\bar{x}$±SD)	Percent Wt. loss in FriabilityTest ($\bar{x}$±SD)	DT(sec) ($\bar{x}$±SD)	Content of active ingredient (mg per tablet) ($\bar{x}$±SD)
F_1	5.0 ± 0.07	0.85	30± 0.56	98.6±1.68
F_a	5.5±0.08	0.65	37.5±4.69	99.2±1.75
F_b	4.0±0.06	0.75	55±0.77	98.5±1.89
F_{ab}	4.5±0.07	0.95	65±1.36	99.5±1.59
F_{opt}	4.5±0.06	0.85	20±0.24	98.7±1.85

The physical parameters of the Ritonavirtablets prepared are given in Table 2. The hardness of the tablets was in the range 4.0-5.5 kg/cm^2. Weight loss in the friability test was less than 0.95% in all the cases. Ritonavir content of the tablets prepared was within 100±3%. Much variations were observed in the disintegration and dissolution characteristics of the Ritonavir tablets prepared. The disintegration times were in the range 20 to 65 sec. All the Ritonavir tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time. Dissolution of Ritonavir tablets prepared was studied in 0.1N Hydrochloric acid. The Dissolution parameters are given in Table 3.

Dissolution of Ritonavir from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.945. The first order dissolution rate constant (K1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K1) and DE_{30} values of the tablets prepared due to formulation variables.

Table 3: Dissolution Parameters of Ritonavir Tablets Prepared Employing Starch 1500 and Soluplus as per 2^2 Factorial Design.

Formulation code	PD_{10} (%) ($\bar{x}$±SD)	DE_{30} (%) ($\bar{x}$±SD)	$K_1 \times 10^2$ (min^{-1}) ($\bar{x}$±SD)
F_1	46.73 ± 0.75	40.70 ± 0.32	2.74 ± 0.02
F_a	89.92 ± 1.52	79.16 ± 1.57	4.67 ± 0.05
F_b	74.93 ±1.12	64.30 ± 1.09	3.36 ± 0.03
F_{ab}	99.47 ± 0.20	89.40 ± 1.45	45.5 ± 0.06
F_{opt}	85.95 ± 1.35	78.77 ± 1.33	7.18 ± 0.12

ANOVA of K_1 values indicated that the individual and combined effects of the two factors, Starch 1500 and Soluplus are highly significant ($P < 0.01$). Ritonavir tablet formulations F_{ab} and F_a gave very rapid dissolution of Ritonavirthan others. These tablets (F_{ab} and Fa) gave 99.47% and 89.92% in 10min respectively. Higher levels of Starch 1500 gave high dissolution rates of Ritonavir tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_1 < F_b < F_a < F_{ab}$.

Optimization

The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of starch 1500(X_1) and Soluplus (X_2) based on the observed results was found to be **$Y = 77.74 + 16.92(X_1) + 9.42(X_2) – 4.67(X_1\ X_2)$.** Based on the above equation, the formulation of optimized Ritonavir tablets with NLT 85% dissolution in 10 min require starch1500 at 1:3.84 ratio of drug: Starch 1500, and Soluplus at 1% of drug and starch1500 content.

To verify Ritonavir tablets were formulated employing the optimized levels of Starch 1500 and Soluplus. The formula of the optimized Ritonavir tablets is given in Table 1. The optimized Ritonavir tablet formulation was prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation are given in Table 2 and dissolution parameters are given in Table 3. The hardness of the optimized Ritonavir tablets was 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.85%. Disintegration time of the tablets was 20 sec. The optimized Ritonavir tablet formulation gave 85.5% dissolution in 10min fulfilling the target dissolution requirement. The dissolution results also indicated validity of the optimization technique employed. Hence formulation of

Ritonavir tablets with NLT 85% dissolution in 10 min could be optimized by 2^2 factorial design.

CONCLUSIONS

1. The individual and combined effects of the two factors, Starch 1500 and Soluplus are highly significant ($P < 0.01$) in influencing the dissolution rate of Ritonavir tablet.
2. Ritonavir tablet formulations F_{ab} and F_a disintegrated rapidly within one min and gave very rapid dissolution of Ritonavir, 99.4% and 89.9% in 10 min respectively.
3. The increasing order of dissolution rate (K_1) observed with various formulations was $F_1 < F_b < F_a < F_{ab}$.
4. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of starch1500(X_1), soluplus (X_2) based on the observed results was found to be $\mathbf{Y = 77.74 + 16.92(X_1) + 9.42(X_2) – 4.67(X_1\ X_2).}$ Based on the above equation, the formulation of optimized Ritonavir tablets with NLT 85% dissolution in 10 min require Starch1500 at 1:3.84 ratio of drug: starch1500, and Soluplus at 1% of drug and starch 1500 content.
5. The optimized Ritonavir tablet formulation gave 85.5% dissolution in 10min fulfilling the target dissolution requirement.
6. Formulation of Ritonavir tablets with NLT 85% dissolution in 10 min could be optimized by 2^2 factorial design.

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