CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2597460

Available online at: http://www.iajps.com Research Article

PREPARATION AND EVALUATION OF SOLID DISPERSIONS OF RITONAVIR IN STARCH 1500 AND SOLUPLUS ALONE AND IN COMBINATION

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Article Received: December 2018 **Accepted:** February 2019 **Published:** March 2019

Abstract:

Ritonavir, a widely prescribed antiretroviral drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy. The objective of the present study is to prepare and evaluate solid dispersions of Ritonavir in Starch 1500 and Soluplus alone and in combination for enhancing the dissolution rate and dissolution efficiency of Ritonavir. The individual and combined effects of the two carriers, Starch 1500 and Soluplus in enhancing the dissolution rate and dissolution efficiency of Ritonavir were evaluated in a 2^2 factorial study. Solid dispersions of Ritonavir in Starch 1500 alone were prepared using four ratios of drug: carrier namely 2:1, 1:1, 1:2 and 1:3 by solvent evaporation method. Solid dispersions of Ritonavir in Soluplus alone were prepared at three concentrations namely 0.5, 1.0 and 2% by common solvent method. Solid dispersions of Ritonavir in combined carriers namely Starch 1500 and Soluplus were prepared as per 2^2 factorial design. All the solid dispersions prepared were evaluated for drug content uniformity, dissolution rate and dissolution efficiency in comparison to Ritonavir pure drug.

The dissolution rate and dissolution efficiency of Ritonavir could be significantly enhanced by solid dispersion in Starch 1500 and Soluplus alone and in combination. The individual and combined effects of Starch 1500 and Soluplus in enhancing the dissolution rate and dissolution efficiency of Ritonavir are highly significant ($P < 0.01$). Soluplus gave significant enhancement in the dissolution rate of Ritonavir at very low concentrations where as a large proportion of Starch 1500 is required for a similar enhancement in the dissolution rate of Ritonavir. Combination of Starch 1500 and Soluplus resulted in a much higher enhancement in the dissolution rate and dissolution efficiency of Ritonavir than is possible with them individually. A 7.56 and 3.12 fold increase in the dissolution rate of ritonavir was observed with starch1500 and soluplus respectively .whereas in combination they gave a 11.67 fold increase in the dissolution rate of ritonavir. Combination of Starch 1500 and Soluplus is recommended for enhancing the dissolution rate and dissolution efficiency of Ritonavir.

Key words: *Ritonavir, Solid dispersion, Dissolution Rate, Starch 1500, Soluplus, Factorial study.*

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Please cite this article in press K. P. R. Chowdary et al., ***Preparation And Evaluation Of Solid Dispersions Of Ritonavir In Starch 1500 And Soluplus Alone And In Combination.,*** *Indo Am. J. P. Sci, 2019; 06(03).*

INTRODUCTION:

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 and pose challenging problems in their pharmaceutical product development process. Ritonavir, a widely prescribed antiretroviral drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy.

Techniques[1] 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 , micro emulsions 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 dispersion[2, 3] 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. In solid dispersions the poorly soluble drug is dispersed in an inert water-soluble carrier such as urea, polyethylene glycol, poly vinyl pyrrolidone and surfactants at solid state. In the case of solvent deposited dispersions the drug is deposited in minuscular form on an inert water insoluble excipient such as silica gel, starch and modified starches at solid state.

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 [4-7]. In the present study Starch 1500 is evaluated as carrier for solid dispersions for enhancing the dissolution rate of Ritonavir.

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. Soluplus increased the solubility and enhanced the bioavailability of drugs in solid solutions. Itraconazole and fenofibrate showed significant increase in the bioavailability with Soluplus[8]. The solubility and dissolution rate of valsartan was effectively enhanced by using Soluplus in the form of solid dispersions[9].

The objective of the present study is to prepare and evaluate solid dispersions of Ritonavir in Starch 1500 and Soluplus alone and in combination for enhancing the dissolution rate and dissolution efficiency of Ritonavir. The individual and combined effects of the two carriers, Starch 1500 and Soluplus in enhancing the dissolution rate and dissolution efficiency of Ritonavir were evaluated in a 2^2 factorial study.

EXPERIMENTAL:

Materials:

Ritonavir was a gift sample from M/s EASAI Pharma Technology Pvt. Ltd., Visakhapatnam Soluplus and Starch 1500 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 Hydrochloricacid 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 noticed.

Preparation of Solid Dispersions in Starch 1500

Solid dispersions of Ritonavir in Starch 1500 using various ratios of drug: carrier were prepared by solvent evaporation method. The required quantity of Ritonavir was dissolved in ethanol (10 ml) to get a clear solution in a dry mortar. Starch 1500 was added to the drug solution in the mortar and mixed. The mixture was triturated continuously for 20 min to evaporate the solvent. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50^0 C for 1 h in hot air oven. The dried product was powdered and passed through mesh no 100 in each case.

Preparation of Solid Dispersions in Soluplus:

Solid dispersions of Ritonavir in different concentrations of Soluplus were prepared by common solvent method. The required quantity of Ritonavir and Soluplus were dissolved in ethanol (10 ml) to get a clear solution in a dry mortar. The solution was triturated continuously for 20 min to evaporate the solvent. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50^0 C for 1 h in hot air oven. The dried product was powdered and passed through mesh no 100 in each case.

Preparation of Solid Dispersions in Combined Carriers:

Solid dispersions of Ritonavir in Starch 1500 and Soluplus as per 2^2 factorial design were prepared by kneading method. The required quantities of drug and Soluplus were dissolved in the solvent ethanol to get a clear solution in a dry mortar. Starch 1500 was added to the drug- surfactant solution in the motor and mixed. The mixture was kneaded for 30 min by continuous trituration. Small volume of the solvent was added to maintain the mixture as thick slurry during kneading process. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50°C for 1 hour in a hot air oven. The dried product was powdered and passed through mesh no. 100 in each case.

Estimation of Drug Content of Solid Dispersions:

From each batch four samples of solid dispersion equivalent to 20 mg of the medicament was taken into a 100 ml conical flask and extracted with 3 x 10 ml quantities of ethanol. The ethanolic extracts were filtered and collected into 50 ml volumetric flask and the volume was made up to 50 ml with ethanol. The solution was subsequently diluted with 0.1N Hydrochloric acid and assayed for the Ritonavir content at 240 nm.

Dissolution Rate Study:

Dissolution rate of Ritonavir from various solid dispersions prepared was studied in water (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Lab India Disso 8000) with a paddle stirrer at 50rpm. A temperature of 37±1°C was maintained throughout the study. Ritonavir or its solid dispersion equivalent to 100 mg of Ritonavir was used in the test. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45 µm) at different intervals of time, suitably diluted and assayed for Ritonavir at 240nm. The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction is made in calculating the amount of drug dissolved. All dissolution rate experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION:

The objective of the present study is to prepare and evaluate solid dispersions of Ritonavir in Starch 1500 and Soluplus alone and in combination for enhancing the dissolution rate and dissolution efficiency of Ritonavir, a BCS class II drug. Solid dispersions of Ritonavir in Starch 1500 alone were prepared using four ratios of drug: carrier namely 2:1, 1:1, 1:2, and 1:3 by solvent evaporation method. Solid dispersions of Ritonavir in Soluplus alone were prepared using three concentrations of carrier namely 0.5, 1.0 and 2% by common solvent method. Solid dispersions of Ritonavir in combined carriers namely Starch 1500 and Soluplus were prepared as per 2^2 factorial design by kneading method with a view to evaluate the individual main effects and combined (interaction) effects of Starch 1500 (factor A) and Soluplus (factor B) on the dissolution rate and dissolution efficiency (DE_{30}) of Ritonavir. For this purpose two levels of Starch 1500 (0 and 1:2 ratio of drug : carrier) and two levels of Soluplus (0 and 1%) were selected and the corresponding four treatments involved in the 2^2 factorial study were Ritonavir pure drug (1); Ritonavir - Starch 1500 (1:2) solid dispersion (a); Ritonavir - Soluplus (1.0%) solid dispersion (b) and Ritonavir - Starch 1500 (1:2) - Soluplus (1.0%) solid dispersion (ab). The above mentioned solid dispersions were prepared by kneading method.

All the solid dispersions prepared were found to be fine and free flowing powders. Low C.V (< 1.2 %) in the percent drug content indicated uniformity of drug content in each batch of solid dispersions prepared. The dissolution of Ritonavir as such and from various solid dispersions was studied in water. Water (900ml), a relatively poor solvent for Ritonavir was used as dissolution fluid to identify the differences in dissolution rate of various solid dispersions prepared. The dissolution profiles of various solid dispersions prepared are shown in Fig 1.The dissolution parameters of Ritonavir and its solid dispersions prepared are given in Tables 1 and 2.

All solid dispersions prepared gave rapid and higher dissolution of Ritonavir when compared to Ritonavir pure drug. The dissolution data were analyzed as per zero order and first order kinetics in each case. The coefficient of determination (R^2) values were higher in the first order model than in zero order model indicating that the dissolution of Ritonavir as such and from its solid dispersions followed first order kinetics. The coefficient of determination (R^2) values in the first order model were found to be in the range of 0.910 - 0.975. The corresponding dissolution rate (K_1) values of various products were estimated. Dissolution Efficiency (DE_{30}) values were calculated as described by Khan[10].The dissolution parameters of various solid dispersions are summarized in Tables 1 and 2.

All dissolution parameters (PD_{10}, K_1 and DE_{30}) indicated rapid and higher dissolution of Ritonavir from all solid dispersions when compared to Ritonavir. With both Starch 1500 and Soluplus the dissolution rate and dissolution efficiency of

Ritonavir was increased as the concentration of carrier in the solid dispersion was increased. In the case of Starch 1500 the dissolution rate was increased by 2.64, 5.24, and 7.56,8.52 folds respectively, in the case of SDs prepared at drug: carrier ratio of 2:1, 1: 1, 1:2 and 1:3. In the case of SDs prepared with Soluplus, 1.73, 3.12,and 6.47 folds increase in the dissolution rate was observed at 0.5, 1.0 and 2.0 percent concentration of carrier. In the case of Soluplus (Surfactant) a low concentration of carrier gave a significant increase in the dissolution rate when compared to Starch 1500.

The dissolution profiles of solid dispersions prepared in starch1500 and Soluplus alone and in combination are given inFig :1.The results of factorial study given in Table 2 indicated that the dissolution rate and dissolution efficiency of Ritonavir were markedly increased by solid dispersion in Starch 1500 and Soluplus alone and in combination. Analysis of Variance (ANOVA) indicated that the Individual and combined effects of Starch 1500 (Factor A) and Soluplus (Factor B) are highly significant ($P< 0.01$). Solid dispersion in Starch 1500 alone gave a 7.56 fold increase in the dissolution rate of Ritonavir at a drug: carrier ratio of 1:2. Soluplus at 1.0 percent concentration gave a 3.12 fold increase in the dissolution rate of Ritonavir whereas in combination they (dispersion ab) gave a 11.67 fold increase in the dissolution rate of Ritonavir. In combination Starch 1500 and Soluplus gave higher enhancement in the dissolution rate of Ritonavir than is possible with them individually. The higher enhancement in the dissolution rate is due to the combined effects of the two carriers. The drug is deposited in miniscular form on the carrier Starch 1500 particles, which increases the surface area of drug resulting in the enhancement of Dissolution rate of Ritonavir. Soluplus being a surfactant increases the wettability of drug particles by reducing interfacial tension and thus increases the dissolution rate of Ritonavir. Hence a combination of Starch 1500 and Soluplus are recommended for enhancing the dissolution rate and dissolution efficiency of Ritonavir, a BCS class II drug..

CONCLUSIONS:

1. The dissolution rate and dissolution efficiency of Ritonavir could be significantly enhanced by solid dispersion in Starch 1500 and Soluplus alone and in combination.
2. The individual and combined effects of Starch 1500 and Soluplus in enhancing the dissolution rate and dissolution efficiency of Ritonavir are highly significant ($P < 0.01$) .
3. Soluplus gave significant enhancement in the dissolution rate of Ritonavir at very low concentrations, where as a large proportion of Starch 1500 is required for a similar enhancement in the dissolution rate of Ritonavir.
4. Combination of Starch 1500 and Soluplus resulted in a much higher enhancement in the dissolution rate and dissolution efficiency of Ritonavir than is possible with them individually.
5. A 7.56 and 3.12 fold increase in the dissolution rate of ritonavir was observed with starch1500 and soluplus respectively .whereas in combination they gave a 11.67 fold increase in the dissolution rate of ritonavir
6. Combination of Starch 1500 and Soluplus is recommended for enhancing the dissolution rate and dissolution efficiency of Ritonavir.

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Table .1: Dissolution Parameters of Solid dispersions of Ritonavir in Starch 1500 and Soluplus

SD	System	PD_{10} (%)	$K_1 \times 10^2$ (min -1)	Increase in K_1 (No of folds)	DE_{30} (%)
1	R	42.4	5.84	-	38.6
2	R-St(2:1)	68.2	15.45	2.64	69.6
3	R-St(1:1)	84.8	30.65	5.2 4	77.8
4	R-St(1:2)	94.6	44.2	7.56	82.4
5	R-St(1:3)	97.9	49.8	8.52	89.5
6	R-Sol (0.5%)	58.6	10.12	1.73	60.4
7	R-Sol (1%)	69.2	18.24	3.12	68.2
8	R-Sol (2%)	98.4	37.8	6.47	88.6

SD – Solid dipersion ; R- Ritonavir ;St-Starch 1500 ; Sol - Soluplus

Table.2: Dissolution Parameters of Ritonavir Solid Dispersions in Starch 1500 and Soluplus Prepared as per 2^2- Factorial Design

SD	System	PD_{10} (%)	$K_1 x 10^2$ min^{-1}	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)
1	R	42.4	5.84	---	38.6	---
a	R-St (1:2)	94.6	44.2	7.56	82.4	2.13
b	R-Sol (1%)	69.2	18.24	3.12	68.2	1.76
ab	R-St (1:2) - Sol (1%)	99.9	68.2	11.67	96.4	2.49

SD -Solid dipersion; R- Ritonavir; St-Starch 1500; Sol - Soluplus

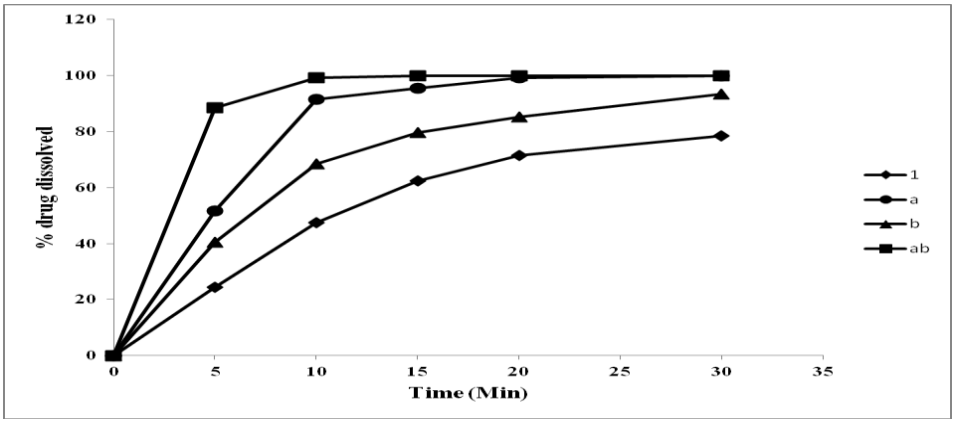

Fig. 1: Dissolution Profiles of Ritonavir Solid Dispersions in Starch 1500 and Soluplus Prepared as per 2^2- Factorial Design