Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 3, Issue 4, 2011

Research Article

ENHANCEMENT OF DISSOLUTION RATE AND FORMULATION DEVELOPMENT OF RITONAVIR TABLETS EMPLOYING STARCH CITRATE

K.P.R. CHOWDARY* AND VEERAIAH ENTURI

University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530003 (A.P), India.
Email:prof.kprchowdary@rediffmail.com

Received: 13 September 2011, Revised and Accepted: 29 September 2011

ABSTRACT

The objective of the study is to prepare, characterize and evaluate starch citrate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of ritonavir. The feasibility of formulating solid dispersions of ritonavir in starch citrate into compressed tablets with enhanced dissolution rate was also investigated. Starch citrate was prepared by reacting potato starch with citric acid at elevated temperatures. It was insoluble in water and has good swelling (1500%) property without pasting or gelling when heated in water. Solid dispersions of ritonavir in starch citrate were prepared by solvent evaporation method employing various weight ratios of drug: starch citrate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of ritonavir when compared to pure drug. A 58.34 and 94.41 fold increase in the dissolution rate (K_1) of ritonavir was observed with solid dispersions SD-4 and SD-5 respectively. The DE_{30} was also increased from 6.80% in the case of ritonavir pure drug to 76.25% and 84.05% in the case of these solid dispersions. Ritonavir (50 mg) tablets were prepared employing ritonavir alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Ritonavir tablets formulated employing its solid dispersions in starch citrate gave rapid and higher dissolution rate and DE_{30} when compared to plain and commercial tablets. A 9.95 and 28.14 fold increase in the dissolution rate (K_1) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets.

Keywords: Starch Citrate, Ritonavir Tablets, Solid Dispersion, Dissolution Rate, Formulation Development

INTRODUCTION

Ritonavir, a widely prescribed antiretroviral protease inhibitor drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several 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 , microemulsions 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 dispersions in water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Wing[2] has reported reaction of starch with citric acid to yield starch citrate, a biodegradable product possessing high ion-exchange capacity. Wepner[3] have described a process for the synthesis of citrate derivatives of starch. Starch citrate is investigated as resistant starch in food industry. We reported[4] starch citrate, a new modified starch, as an efficient carrier in solid dispersions for enhancing the dissolution rate of poorly soluble drugs. Starch citrate, a new modified starch, was also reported[5] to be a promising directly compressible vehicle for the preparation of tablets by direct compression method.

The objective of the present study is to prepare, characterize and evaluate starch citrate as a carrier in solid dispersions for enhancing the dissolution rate of ritonavir. The feasibility of formulating solid dispersions of ritonavir in starch citrate into compressed tablets with enhanced dissolution rate was also investigated.

MATERIALS AND METHODS

Materials

Ritonavir was gift sample from M/s Hetero Drugs Pvt. Ltd., Hyderabad, starch citrate was prepared in the laboratory, Dichloromethane (Qualigens), potato starch (S.D Fine Chemicals), citric acid (Qualigens) Methanol (S.D Fine Chemicals), lactose, talc, magnesium stearate , acacia were procured from commercial sources.

Methods

Preparation of Starch Citrate

Starch citrate was prepared based on the method of Klaushfer[6] with some modifications. Citric acid (20g) was dissolved in 20 ml of water, the pH of the solution was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made upto 50 ml by adding water. The citric acid solution (50 ml) was mixed with 50g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28^0C). The tray was then placed in forced air oven and dried at 60^0C for 6 h. The mixture obtained was ground and further dried in a forced air oven at 130^0C for 2 h. The dry mixture was repeatedly washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50^0C to remove the water/moisture completely. The product obtained was ground and sized.

Characterization of Starch Citrate

Solubility of starch citrate was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether. The pH of 1% w/v slurry was measured. Melting point was determined by using melting point apparatus as well as by DSC spectra. Viscosity of 1% dispersion in water was measured using Ostwald Viscometer. Swelling Index: Starch citrate (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$S.I\ (\%) = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \times 100$$

The gelling property (gelatinization) of the starch and starch citrate prepared was evaluated by heating a 7% w/v dispersion of each in water at 100^0C for 30 min. The hygroscopic nature of starch citrate was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature. Particle size analysis was done by sieving using standard sieves. Density (g/cc) was determined by liquid displacement method using benzene as

liquid. Bulk density (g/cc) was determined by three tap method[7] in a graduated cylinder. Angle of repose was measured by fixed funnel method[8]. Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V) after hundred tapings of a sample of starch citrate in a measuring cylinder. CI was calculated using equaion[9]

$$\text{Compressibility index (CI)} = \frac{V_o - V}{V_o} \times 100$$

Estimation of Ritonavir

An UV spectrophotometric method based on the measurement of absorbance at 210 nm in 0.1N hydrochloric acid was used for estimation of ritonavir. The method obeyed Beer- Lambert's law in the concentration range of 0-10 µm/mL. When the standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.35% and 1.2% respectively. No interference from excipients used was observed.

Preparation of Solid Dispersions of Ritonavir in Starch Citrate

Solid dispersions of ritonavir and starch citrate were prepared in 2:1 (SD-1), 1:1 (SD-2), 1:2 (SD-3), 1:3 (SD-4) and 1:9 (SD-5) ratios of drug: carrier by solvent evaporation method. Ritonavir (1 g) was dissolved in dichloromethane (10 ml) in a dry mortar to get a clear solution. Starch citrate (1 g) was then added and mixed. The thick slurry was triturated for 15 min for complete evaporation of dichloromethane and then dried at 55°C until dry. The dried mass was pulverized and sieved through mesh no. 100.

Preparation of Ritonavir-SD Tablets

Compressed tablets each containing 50 mg of ritonavir were prepared by wet granulation method employing ritonavir alone and its solid dispersions (SD-3 and SD-4) in starch citrate. Lactose was used as diluent to adjust the weight of the tablet to 220 mg. acacia (2%), talc (2%) and magnesium stearate (2%) were incorporated respectively as binder and lubricants.

The tablet granules were prepared by wet granulation method and were compressed into tablets on a Cadmach 16-station rotary tablet punching machine (M/s Cadmach Engineering Co. Pvt. Ltd., Mumbai) using 9 mm concave punches. . In each batch 100 tablets were prepared. All the tablets prepared were evaluated for content of active ingredients, hardness, friability, disintegration time and dissolution rate as per official (IP) methods.

Dissolution Rate Study

Dissolution rate of ritonavir as such and from its solid dispersions and tablets prepared was studied in 0.1N hydrochloric acid (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Ritonavir or its solid dispersions equivalent of 100 mg of ritonavir and one tablet containing 50 mg of ritonavir was used in each test. A temperature 37+1°C was maintained in each test. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for ritonavir at 210 nm. For comparison, dissolution of ritonavir from one commercial brand was also studied. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Starch citrate was prepared by reacting starch with citric acid at elevated temperatures. When citric acid is heated, it will dehydrate to yield an anhydride. The citric anhydride can then react with starch to from starch citrate. The reactions involved are shown in Fig. 1. Starch citrate prepared was found to be white, crystalline, non hygroscopic powder and can easily be ground to different sizes. Powder that passes through mesh no.120 was collected. The starch citrate prepared was characterised by determining various physical properties. The properties of starch citrate are summarised in Table 1.

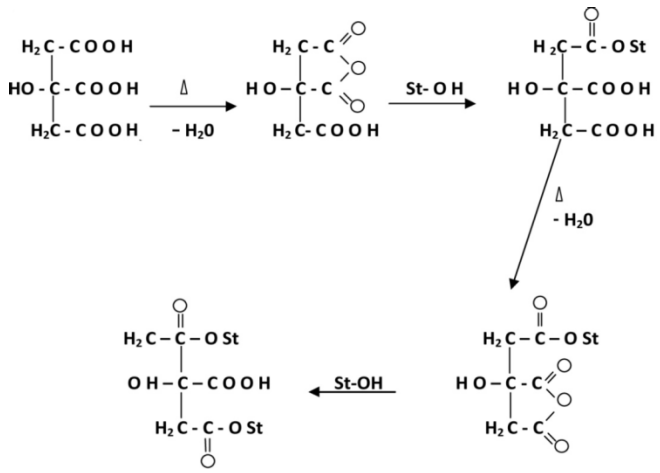

Fig. 1: Starch–Citric acid reaction

Table 1: Physical Properties of the Starch Citrate Prepared

Property	Result
Solubility	Insoluble in all aqueous and organic solvents tested
P^H (1% w/v aqueous dispersion)	7.72
Melting Point	Charred at 210°c
Viscosity (1% w/v aqueous dispersion)	1.01 cps
Swelling Index	1500
Gelling Property	No gelling
Moisture Absorption	4.5 %
Particle Size	152 µm (80/120 mesh)
Density	0.645 g/cc
Bulk Density	0.834 g/cc
Angle of Repose	21.04^0
Compressibility Index	8.81 %

When tested for m.p., it was charred at 220^{0}C. DSC also conformed no melting, but charring at temperature above 220^{0}C (Fig. 2). The IR-spectra of starch citrate (Fig. 3) showed characteristic peaks at 1741.2 cm^{-1} (due to C=O, carbonyl structure), 1021.79 cm^{-1} and 1247 cm^{-1} (due to C-O-C structure), 3446 cm^{-1} (due to C-OH) and 2927 cm^{-1} (due to C-H), which were absent in potato starch. The IR-spectra is in accordance in with the proposed structure of starch citrate shown in Fig. 3. Starch citrate prepared was insoluble in water, aqueous fluids of acidic and alkaline pH and several organic solvents tested. In water it exhibited good swelling (1500%). No gelling/pasting was observed with starch citrate when its aqueous dispersion was heated at 100^{0}C for 30 min, where as potato starch formed a paste/gel during the above heat treatment.

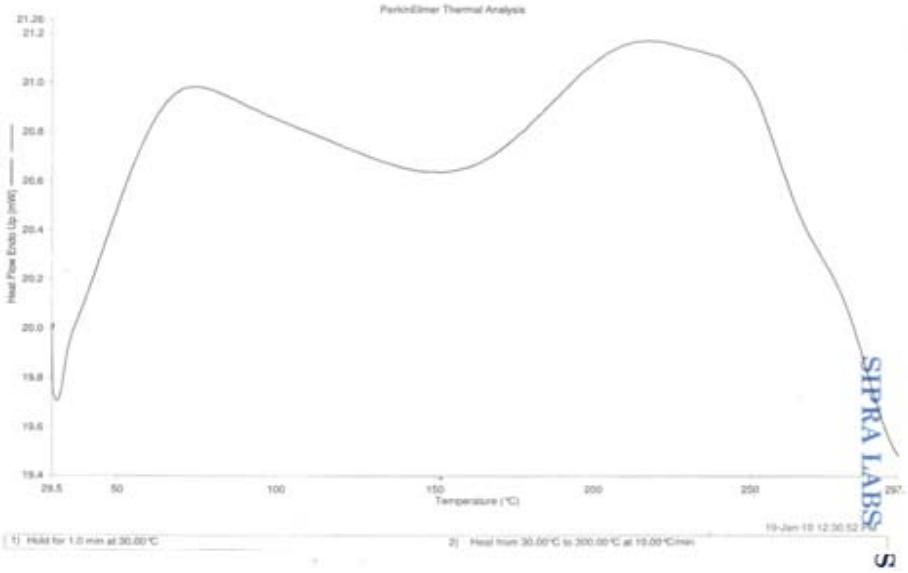

Fig. 2: DSC Thermogram of Starch Citrate

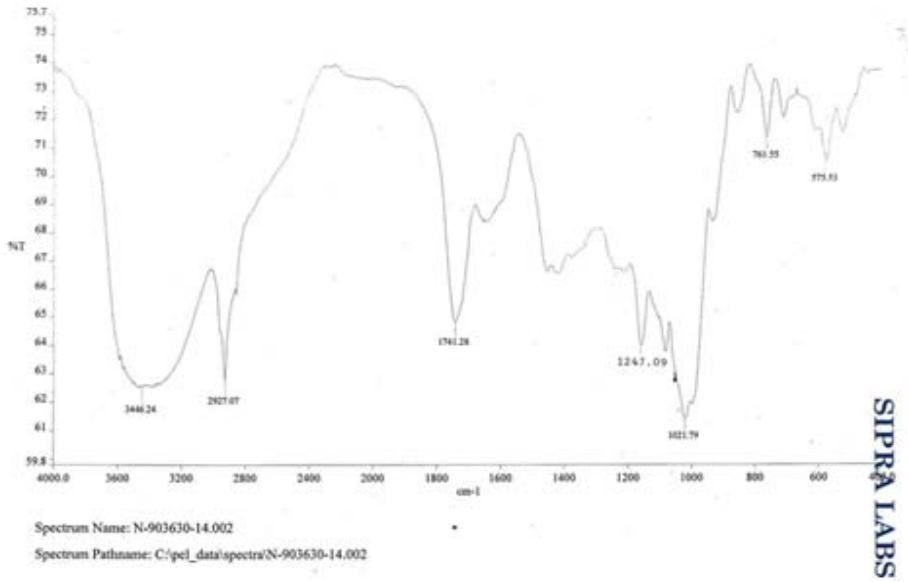

Fig 3: IR spectra of Starch Citrate

As starch citrate, a chemically modified starch was found to be insoluble in water and has good swelling property without pasting or gelling when heated in water it is considered as a promising carrier for solid dispersions for enhancing the dissolution rate of poorly soluble drugs. Solid dispersions of ritonavir in starch citrate were prepared by solvent evaporation method employing various weight ratios of drug: starch citrate.

All the solid dispersions prepared were found to be fine and free flowing powders with an angle of repose in the range 19^o – 21^o. Low C.V (< 1.0%) in the percent drug content indicated uniformity of drug content in each batch of solid dispersions prepared.

The dissolution rate of ritonavir alone and from its solid dispersions was studied in 0.1N hydrochloric acid. All the solid dispersions prepared gave rapid and higher dissolution of ritonavir when compared to pure drug. The dissolution data were analyzed as per zero order and first order kinetics in each case. The R^2 values were higher in the first order model than in the zero order models indicating that the dissolution of ritonavir as such and from its solid dispersions followed first order kinetics. 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 ritonavir and its solid dispersions are given in Table 2.

Table 2: Dissolution Parameters of the Solid Dispersions of Ritonavir Prepared Employing Starch Citrate as a Carrier

Formulation	PD_{10} (%)	T_{50} (min)	DE_{30} (%)	Increase in DE_{30} (No of Folds)	K_1 (min^{-1})	Increase in K_1 (No of Folds)
Ritonavir	5.97	> 60	6.80	-	0.0030	-
SD-1	43.90	19.0	40.88	6.01	0.0221	7.37
SD-2	46.46	17.0	43.19	6.35	0.0391	13.03
SD-3	65.92	7.00	71.01	10.44	0.1424	47.48
SD-4	68.89	<5	76.25	11.21	0.1750	58.34
SD-5	87.99	<5	84.05	12.36	0.2832	94.41

Ratio of drug: starch citrate in solid dispersions: SD-1 (2:1); SD-2 (1:1); SD-3 (1:2); SD-4 (1:3); SD-5 (1:9); PD_{10} : percent dissolved in 10 min; T_{50}: time for 50 % dissolution; DE_{30}: dissolution efficiency upto 30 min; K_1: first order dissolution rate.

Solid dispersions of ritonavir showed superior dissolution properties when compared to ritonavir pure drug. Both dissolution rate (K_1) and DE_{30} values were much higher in the case of solid dispersions when compared to ritonavir pure drug. The dissolution rate (K_1) and DE_{30} values increased as the proportion of starch citrate was increased. The number of folds of increase in dissolution rate (K_1) and DE_{30} observed with various solid dispersions are shown in Table 2. A 58.34 and 94.41 fold increase in the dissolution rate (K_1) of ritonavir was observed with solid dispersions SD-4 and SD-5 respectively.

The DE_{30} was also increased from 6.80% in the case of ritonavir pure drug to 76.25% and 84.05% in the case of SD-4 and SD-5 respectively. Thus solid dispersions of ritonavir prepared employing starch citrate as carrier showed marked enhancement in the dissolution rate (K_1) and DE_{30} of ritonavir.The feasibility of formulating ritonavir solid dispersions in starch citrate into tablets retaining their rapid and higher dissolution rates was also investigated. Ritonavir (50 mg) tablets were prepared employing ritonavir alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. All the ritonavir tablets prepared were found to contain the ritonavir with in 100±2% of the labelled claim. Hardness of the tablets was in the range 5-8 Kg/sq.cm. Percentage weight loss in the friability test was less than 0.75% in all the cases. Tablets formulated employing solid dispersions disintegrated rapidly with in 3.0 min. Tablets formulated employing ritonavir pure drug disintegrated within 6-7 min. As such all the ritonavir tablets prepared were of good quality with regard to drug content, friability, hardness and disintegration time and fulfilled the official (IP) specifications of uncoated tablets.

The dissolution parameters of the prepared tablets are given in Table 3. Dissolution of ritonavir from all the tablets prepared followed first order kinetics with correlation coefficient 'R^2' values > 0.925. Ritonavir tablets formulated employing its solid dispersions in starch citrate (TF2 and TF3) gave rapid and higher dissolution rate and DE_{30} when compared to plain (TF1) and commercial tablets. A 9.95 and 28.14 fold increase in the dissolution rate (K_1) was observed with formulations TF2 and TF3 when compared to formulation TF1. A 2.23 and 6.29 fold increase in the dissolution rate (K_1) was observed with formulations TF2 and TF3 when compared to commercial formulation. Thus solid dispersions of ritonavir in starch citrate could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official standards.

Table 3: Dissolution Parameters of Ritonavir Tablets Formulated Employing Ritonavir alone and its Solid Dispersions in Starch Citrate

Formulation	PD_{10} (%)	T_{50} (min)	DE_{30} (%)	Increase in DE_{30} (No of Folds)	K_1 (min^{-1})	Increase in K_1 (No of Folds)
TF1	24.59	28.0	25.98	-	0.0121	-
TF2	69.23	7.0	67.29	2.59	0.1208	9.95
TF3	85.45	<5	84.21	3.24	0.342	28.14
Commercial	35.41	20.00	44.67	1.72	0.0543	4.47

TF1: tablets formulated employing ritonavir alone and using lactose as diluent; TF2: tablets formulated employing ritonavir solid dispersion SD-3; TF3: tablets formulated employing ritonavir solid dispersion SD-4.

CONCLUSION

Starch citrate was prepared by reacting starch with citric acid at elevated temperatures was insoluble in water and has good swelling (1500%) property without pasting or gelling when heated in water. Solid dispersions of ritonavir in starch citrate prepared by solvent evaporation method employing various weight ratios of drug: starch citrate gave rapid and higher dissolution of ritonavir when compared to pure drug. Dissolution followed first order kinetics. A 58.34 and 94.41 fold increase in the dissolution rate (K_1) of ritonavir was observed with solid dispersions prepared at 1:3 and 1:9 ratios of drug: starch citrate respectively. The DE_{30} was also increased from 6.80% in the case of ritonavir pure drug to 76.25 % and 84.05% in the case of these solid dispersions. Ritonavir tablets formulated employing its solid dispersions in starch citrate also gave rapid and higher dissolution rate and DE_{30} when compared to plain and commercial tablets. A 9.95 and 28.14 fold increase in the dissolution rate (K_1) was observed with tablet formulations containing solid dispersions prepared at 1:2 and 1:3 ratios respectively when compared to plain tablets. Solid dispersions of ritonavir prepared employing starch citrate as carrier showed marked enhancement in the dissolution rate (K_1) and DE_{30} of ritonavir. These solid dispersions could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official (I.P.) standards.

ACKNOWLEDGEMENT

Authors are thankful to University Grants Commission, New Delhi for providing financial assistance in the form of UGC JRF to Veeraiah Enturi.

REFERENCES

1. Chowdary K. P. R and Madhavi B. L. R, Novel Drug Delivery Technologies for Insoluble Drugs, Indian Drugs 2005; 42(9):557-562.
2. Wing RE, Starch citrate: preparation and ion exchange properties, Starch 1996; 48: 275- 279.
3. Wepner B, Berghofer E, Miesenberger E, Tiefenbacher K, Ng PNK, Citrate starch: application as resistant starch in different food systems, Starch 1999; 5: 354-361.
4. Chowdary, K. P. R. and Veeraiah Enturi, Factorial Studies on The Enhancement of Dissolution Rate of Nimesulide Tablets Employing Starch Citrate - A New Modified Starch, PEG 4000 And PVP K-30, Int. J. Pharm. Res. Dev 2011; 3(1): 224-230.
5. Chowdary, K. P. R. ,Veeraiah Enturi and Sujatha, S. Preparation and Evaluation of Starch Citrate: A New Modified Starch as Directly Compressible Vehicle in
6. Tablet Formulations, Int. J. Chem. Sci 2011; 9(1):177-187.
7. Klaushofer H, Berghofer E, Steyrer W, Starch Citrates-Production and Technical Application Properties, Starch 1978; 30(2):47-51.

8. Martin A. Micromeritics. In: Martin A, ed. Physical Pharmacy. Baltimore, MD: Lippincott. Williams & Wilkins, 2001: 423-454.
9. Cooper. J and Gunn. C, Tutorial Pharmacy: Powder flow and compaction; In: Carter SJ. Eds, New Delhi, India: CBS Publications, 1986: 211-233.
10. Aulton ME, Wells TI. Pharmaceutics: The Science of dosage form design. 2nd ed. London, England: Churchill Livingstone, 1988: 89-90.
11. Khan K. A: The Concept of Dissolution Efficiency. J. Pharm. Pharmacol 1975; 27:48-49.