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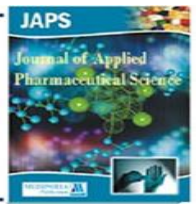

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Enhancement of Dissolution Rate and Formulation Development of Efavirenz Tablets Employing Starch Citrate-A New Modified Starch

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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 efavirenz. The feasibility of formulating solid dispersions of efavirenz in starch citrate into compressed tablets with enhanced dissolution rate was also investigated. Starch citrate was prepared by reacting 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 efavirenz 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 efavirenz when compared to pure drug. A 12.94 and 40.41 fold increase in the dissolution rate (K_1) of efavirenz was observed with solid dispersions SD-4 and SD-5 respectively. The DE_{30} was also increased from 10.66% in the case of efavirenz pure drug to 60.93% and 74.23% in the case of these solid dispersions. Efavirenz (50 mg) tablets were prepared employing efavirenz alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Efavirenz 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 7.01 and 15.30 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.

Key words: Starch Citrate, Efavirenz, Dissolution Rate, Formulation Development.

INTRODUCTION

Efavirenz, a widely prescribed HIV-1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) 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 (Chowdary et.al., 2005) 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 (Wing et.al., 1996) has reported reaction of starch with citric acid to yield starch citrate, a biodegradable product possessing high ion-exchange capacity. Wepner (Wepner et.al., 1999) have described a process for the synthesis of citrate derivatives of starch. Starch citrate is

investigated as resistant starch in food industry. We reported (Chowdary et.al., 2011) 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 (Chowdary et.al., 2011) 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 efavirenz. The feasibility of formulating solid dispersions of efavirenz in starch citrate into compressed tablets with enhanced dissolution rate was also investigated.

MATERIALS AND METHODS

Materials

Efavirenz was gift sample from M/s Dr. Reddys Laboratory, 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

Citric acid (40g) was dissolved in 100 ml of water and pH of the solution was then adjusted to 3.5 with 10 M sodium hydroxide. Starch citrate was prepared based on the method of Klaushfer (Klaushfer et.al., 1978) 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

The starch citrate prepared was evaluated for the following

Solubility

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 a 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 were 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 in a graduated cylinder (Martin., 2001). Angle of repose was measured by fixed funnel method(Cooper et.al., 1986). 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 equation (Aulton. ME., 1988).

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

Estimation of Efavirenz

An UV spectrophotometric method based on the measurement of absorbance at 245 nm in water containing 2% SLS was used for estimation of efavirenz. The method obeyed Beer-Lambert's law in the concentration range of 1-10 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 0.60% and 1.0% respectively. No interference from excipients used was observed.

Preparation of Solid Dispersions of Efavirenz in Starch Citrate

Solid dispersions of efavirenz 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. Efavirenz (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^oC until dry. The dried mass was pulverized and sieved through mesh no. 100.

Preparation of Efavirenz-SD Tablets

Compressed tablets each containing 50 mg of efavirenz were prepared by wet granulation method employing efavirenz 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 efavirenz as such and from its solid dispersions and tablets prepared was studied in water containing 2% SLS (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Sodium lauryl sulphate (SLS) was added to dissolution fluid to maintain sink condition. Efavirenz or its solid dispersions equivalent of 100 mg of efavirenz and one tablet containing 50 mg of efavirenz was used in each test. A temperature $37\pm1^{o}C$ 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 efavirenz at 245 nm. For comparison, dissolution of efavirenz 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.

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 and the swollen particles of starch citrate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.
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.

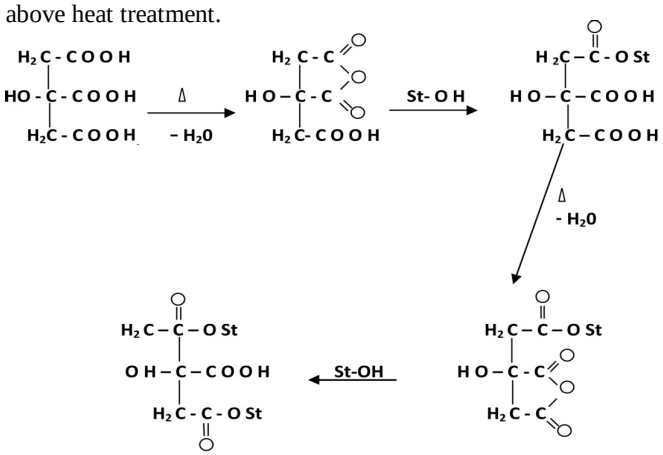

Fig. 1: Starch–Citric acid reaction.

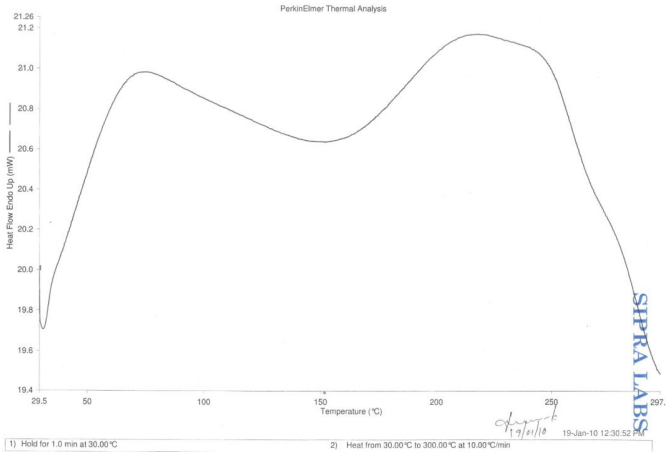

Fig. 2: DSC Thermogram of Starch Citrate

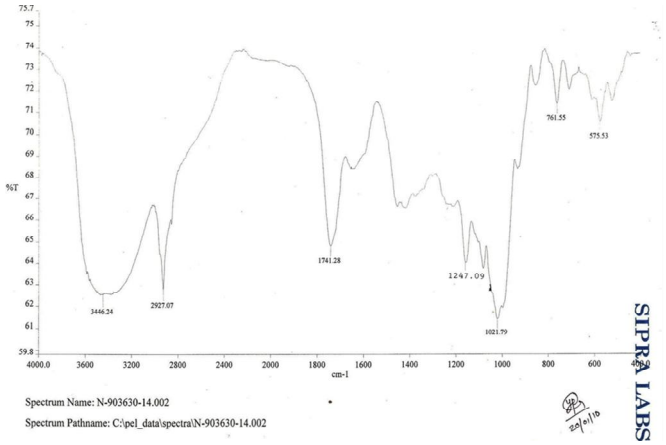

Fig. 3 IR spectra of Starch Citrate.

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 efavirenz 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 efavirenz alone and from its solid dispersions was studied in water containing SLS (2%). SLS was included in the dissolution fluid to maintain sink condition. All the solid dispersions prepared gave rapid and higher dissolution of efavirenz 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 model indicating that the dissolution of efavirenz 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 (Khan, K.A., 1975). The dissolution parameters of efavirenz and its solid dispersions are given in Table 2.

Solid dispersions of efavirenz showed superior dissolution properties when compared to efavirenz pure drug. Both dissolution rate (K_1) and DE_{30} values were much higher in the case of solid dispersions when compared to efavirenz 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 12.94 and 40.41 fold increase in the dissolution rate (K_1) of efavirenz was observed with solid dispersions SD-4 and SD-5 respectively.

Table 2 Dissolution Parameters of the Solid Dispersions of Efavirenz 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)
Efavirenz	10.66	>60	10.70	-	0.0042	-
SD-1	17.03	>60	20.90	1.95	0.0137	3.31
SD-2	26.42	52.0	26.80	2.50	0.0156	3.75
SD-3	27.92	27.0	31.26	2.92	0.0217	5.24
SD-4	61.69	7.0	60.93	5.69	0.0536	12.94
SD-5	71.10	< 5	74.23	6.93	0.1675	40.41

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.

The DE_{30} was also increased from 10.66% in the case of efavirenz pure drug to 60.93% and 74.23% in the case of SD-4 and SD-5 respectively. Thus solid dispersions of efavirenz prepared employing starch citrate as carrier showed marked enhancement in the dissolution rate (K_1) and DE_{30} of efavirenz.

The feasibility of formulating efavirenz solid dispersions in starch citrate into tablets retaining their rapid and higher dissolution rates was also investigated. Efavirenz (50 mg) tablets were prepared employing efavirenz alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. All the efavirenz tablets prepared were found to contain the efavirenz with in 100±3% of the labelled claim. Hardness of the tablets was in the range 6-8 Kg/sq.cm. Percentage weight loss in the friability test was less than 0.55% in all the cases. Tablets formulated employing solid dispersions disintegrated rapidly with in 2.0 min. Tablets formulated employing efavirenz pure drug disintegrated within 5-8 min. As such all the efavirenz 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.

Table 3 Dissolution Parameters of Efavirenz Tablets Formulated Employing Efavirenz 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	15.21	45	20.56	-	0.0250	-
TF2	76.48	< 5	80.58	3.92	0.175	7.01
TF3	94.07	< 5	89.41	4.35	0.382	15.30
Commercial	60.32	6	66.41	3.23	0.0913	3.652

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

Dissolution of efavirenz from all the tablets prepared followed first order kinetics with correlation coefficient 'R^2' values > 0.965. Efavirenz 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 7.01 and 15.30 fold increase in the dissolution rate (K_1) was observed with formulations TF2 and TF3 when compared to formulation TF1. A 1.92 and 4.12 fold increase in the dissolution rate (K_1) was observed with formulations TF2 and TF3 when compared to commercial formulation. Thus solid dispersions of efavirenz in starch citrate could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official standards.

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 efavirenz in starch citrate prepared

by solvent evaporation method employing various weight ratios of drug: starch citrate gave rapid and higher dissolution of efavirenz when compared to pure drug. Dissolution followed first order kinetics. . A 12.94 and 40.41 fold increase in the dissolution rate (K_1) of efavirenz 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 10.66% in the case of efavirenz pure drug to 60.93 % and 74.23% in the case of these solid dispersions. Efavirenz 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 7.01 and 15.30 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 efavirenz prepared employing starch citrate as carrier showed marked enhancement in the dissolution rate (K_1) and DE_{30} of efavirenz. These solid dispersions could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official (I.P.) standards.

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