Int. J. Chem. Sci.: 9(1), 2011, 177-187
ISSN 0972-768X

PREPARATION AND EVALUATION OF STARCH CITRATE: A NEW MODIFIED STARCH AS DIRECTLY COMPRESSIBLE VEHICLE IN TABLET FORMULATIONS

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ABSTRACT

The objective of the study is to prepare and evaluate starch citrate, a new chemically modified starch, as a directly compressible vehicle for tablets. Starch citrate prepared by reacting starch with citric acid at elevated temperatures, was found to be a white, crystalline and non-hygroscopic powder. Starch citrate powder of size 152 µm (80/120 mesh) exhibited excellent flow characteristics alone and after mixing drug and other excipients upto 30% and was found suitable for direct compression. Starch citrate was insoluble in water and aqueous fluids of acidic and alkaline pHs. It also exhibited good swelling (1500%) in water. It has no pasting or gelling property when heated at 100^0C in water for 30 min. Tablets of (i) gliclazide and (ii) pioglitazone were prepared by direct compression method employing starch citrate (70%) as directly compressible vehicle and the tablets were evaluated. The tablets of gliclazide and pioglitazone formulated employing starch citrate as directly compressible vehicle gave rapid and higher dissolution of the contained drug apart from fulfilling the official or GMP standards prescribed for uncoated tablets. A 1.68 and 3.92 fold increase in the dissolution rate (K_1) was observed, respectively with gliclazide and pioglitazone tablets formulated by direct compression method employing starch citrate, when compared to the corresponding commercial brand. The starch citrate, a new modified starch was found to be a promising directly compressible vehicle for the preparation of tablets by direct compression method.

Key words: Modified starch, Starch citrate, Directly compressible vehicle, Tablets, Gliclazide, Pioglitazone.

INTRODUCTION

Direct compression is the preferred method for the preparation of tablets[1]. It offers several advantages[2,3]. Notable among them are (i) It is economical compared to wet granulation since it requires fewer unit operations (ii) More suitable for moisture and heat

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sensitive APIs since it eliminates wetting and drying steps (iii) Changes in dissolution profiles are less likely to occur in tablets made by direct compression method on storage than in those made from granulations[4]. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms[5]. Disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. Though several directly compressible excipients are available, there is a continued need to develop new, safe and effective excipients for direct compression method. The objective of the present study is to prepare and evaluate starch citrate, a new chemically modified starch, as a directly compressible vehicle for tablets.

Wing[6] has reported reaction of starch with citric acid to yield starch citrate, a biodegradable product possessing high ion-exchange capacity. Wepner *et al.*[7] have described a process for the synthesis of citrate derivatives of starch. Starch citrate is investigated as resistant starch in food industry. No reports are available on its use as pharmaceutical excipient. In the present study, starch citrate is prepared, characterized and evaluated as directly compressible vehicle in the formulation of tablets. Tablets of (i) gliclazide (30 mg) and (ii) pioglitazone (30 mg) were prepared by direct compression method employing starch citrate and the tablets were evaluated in comparison to commercial brands in each case. The results are reported in this paper.

EXPERIMENTAL

Material and methods

Gliclazide and pioglitazone were gift samples from M/s Natco Pharma Ltd., Hyderabad. Potato starch and citric acid (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Preparation of starch citrate

Citric acid (40 g) 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 *et al.*[8] with some modifications. Citric acid (20 g) 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 50 g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28^{o}C). The tray was then placed in forced air oven and dried at 60^{o}C for 6

h. The mixture obtained was ground and further dried in a forced air oven at 130^{o}C 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^{o}C to remove the water/moisture completely. The product obtained was ground and sized.

Characterization of starch citrate

The starch citrate prepared was evaluated for following -

Solubility

Solubility of starch citrate was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents like alcohol, dichloromethane, chloroform, acetone and petroleum ether.

pH

The pH of a 1% w/v slurry was measured.

Melting point

Melting point was determined by using melting point apparatus as well as by DSC spectra.

Viscosity

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.

$$\text{S. I. (\%)} = \frac{\text{Volume of sediment in water - Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \times 100 \quad \ldots(1)$$

Test for gelling property

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^{o}C for 30 min.

Moisture absorption

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

Particle size analysis was done by sieving using standard sieves.

Density

Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Bulk density

Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Angle of repose

Angle of repose was measured by fixed funnel method.

Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V) after hundred tappings of a sample of starch citrate in a measuring cylinder. CI was calculated using equation

$$\text{Compressibility index (CI)} = \frac{V_o - V}{V_o} \times 100 \quad \ldots(2)$$

Preparation of tablets

Tablets of (i) gliclazide (30 mg) and (ii) pioglitazone (30 mg) were prepared by direct compression method employing starch citrate (70% in the formula) as directly compressible vehicle. Talc (2%), magnesium stearate (2%) and lactose (q.s. to 220 mg) were also included. All the materials were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd) to a hardness of 6 kg/cm^2 using 9 mm round and flat punches. In each case, 100 tablets were compressed.

Evaluation of tablets

Hardness of tablets was tested using Monsanto Hardness tester. Friability of the

tablets was determined in a Roche friabilator. Disintegration time was determined in a Thermonic tablet disintegration test machine using water as test fluid.

Estimation of drug content in the tablets

From each batch of tablets prepared, five tablets were accurately weighed and powdered. Tablet powder equivalent to 20 mg of drug was taken for assay into a 100 mL conical flask and extracted with 3 x 10 mL quantities of methanol. The methanolic extracts were filtered and collected into a 50 mL volumetric flask and the volume was made upto 50 mL with methanol. The solution was then suitably diluted with phosphate buffer of pH 7.4 in the case of gliclazide and 0.1N hydrochloric acid in the case of pioglitazone. The absorbance of the solution was measured at 229 nm for gliclazide and at 269 nm for pioglitazone. Drug content of the tablets was calculated using the standard calibration curve in each case.

Dissolution rate study

Dissolution rate of the tablets prepared was studied using 8 station dissolution rate apparatus (M/s Lab India Disso 2000) employing a paddle stirrer at 50 rpm and at 37 ± 1^{o}C. Hydrochloric acid 0.1 N (900 mL) was used as dissolution fluid for pioglitazone tablets. Phosphate buffer of pH 7.4 (900 mL) was used as dissolution fluid in the case of gliclazide tablets. Samples of dissolution fluid, 5 mL each were withdrawn at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min through a filter (0.45 µ). The samples were suitably diluted with the corresponding dissolution fluid and assayed for gliclazide at 229 nm and pioglitazone at 269 nm using the corresponding dissolution fluid as blank. Each sample withdrawn was replaced with an equal amount of drug free dissolution fluid. All dissolution experiments were conducted in triplicate.

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. 80 and retained on mesh No. 120 was collected. This powder has an average particle size of 152 µm. The starch citrate prepared was characterised by determining various physical properties. The properties of starch citrate are summarised in Table 1.

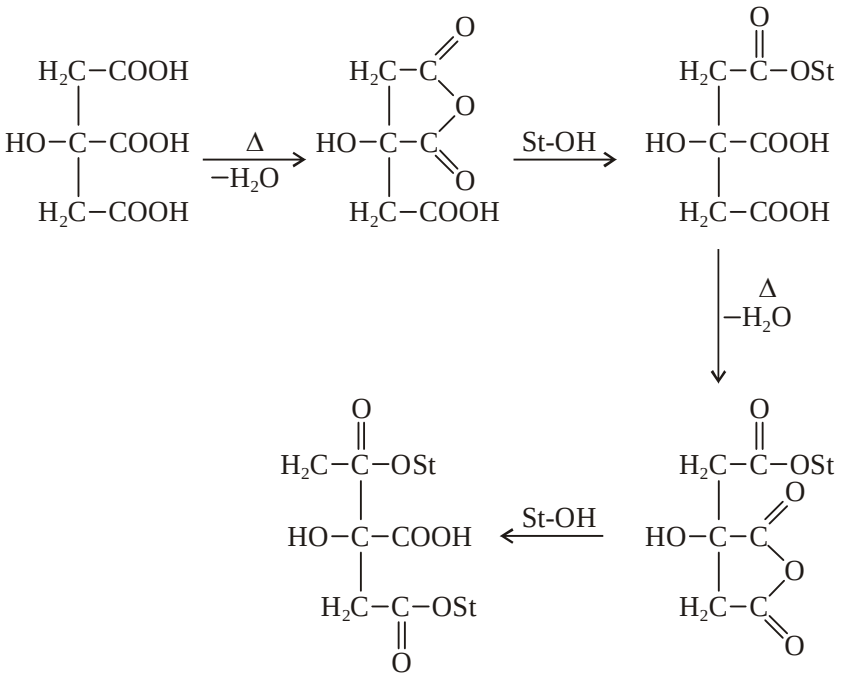

Fig. 1: Starch–citric acid reaction

Table 1: Physical properties of the starch citrate prepared

Property	Result
Solubility	Insoluble in all aqueous and organic solvents tested
pH (1% w/v aqueous dispersion)	7.72
Melting point	Charred at 210^{o}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

Cont…

Property	Result
Bulk density	0.834 g/cc
Angle of repose	21.04^{o}
Compressibility index	8.81 %

When tested for m.p., it charred at 220^{o}C. DSC also confirmed no melting, but charring at temperature above 220^{o}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 with the proposed structure of starch citrate. 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^{o}C for 30 min, where as potato starch formed a paste/gel during the above heat treatment. In the micromeritic evaluation, the angle of repose and compressibility index values revealed the excellent flow characteristic of starch citrate.

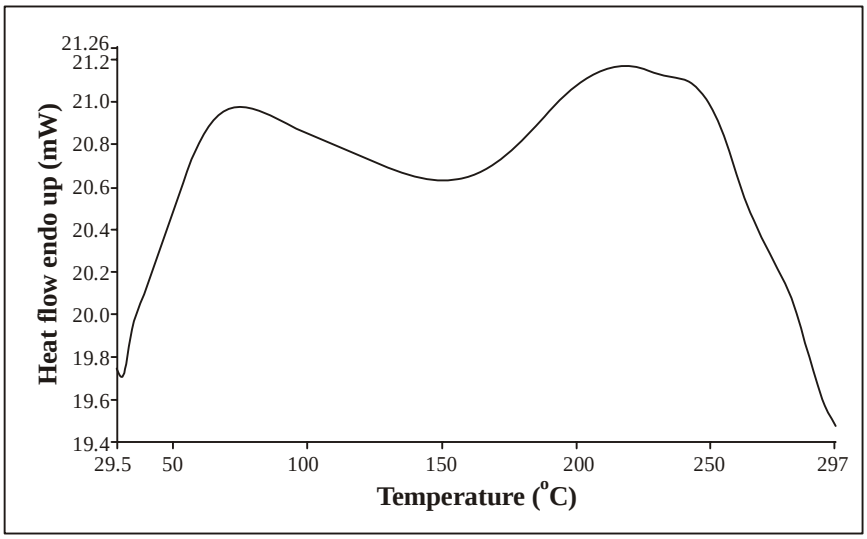

Fig. 2: DSC thermogram of starch citrate

All the physical properties studied indicated that starch citrate is a promising pharmaceutical excipient in tablets. Starch citrate is evaluated as a directly compressible

vehicle. Tablets of (i) gliclazide (30 mg) and pioglitazone (30 mg) were prepared by direct compression method. The blends of all ingredients in each case were evaluated for flow properties by determining angle of repose and compressibility index. The results shown in Table 2 indicated good flow characteristics of blends of all ingredients suitable for direct compression. The blends of ingredients, in each case were compressed into tablets and the compressed tablets were evaluated for all physical properties of tablets including dissolution rate. For comparison, one commercial brand in each case was also evaluated. In the test for uniformity of weight, the percentage deviation was less than 5.6 % in all the cases. Hardness was in the range 4 to 5 Kg/cm^2. Weight loss in the friability test was less than 1.80%. Drug content was within 100 ± 3 % of the labelled claim. The formulated tablets disintegrated rapidly within 23 seconds, when compared to commercial brands.

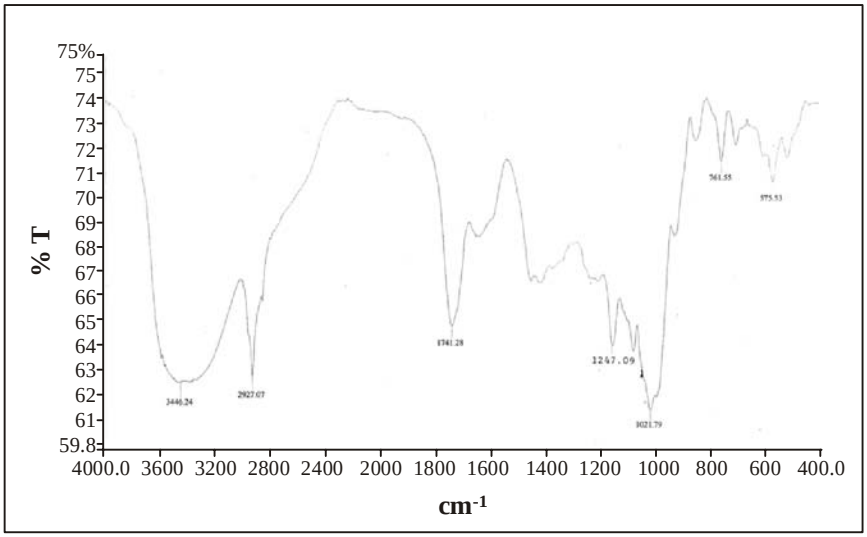

Fig. 3: IR spectra of starch citrate

Table 2: Flow properties of starch citrate and the blends prepared for compression

Formulation	Angle of repose (^{o})	Compressibility index (%)	Flow character
Starch citrate (Size: 80/120 Mesh)	21.04	8.81	Good
Gliclazide blend	23.41	19.53	Good
Pioglitazone blend	26.90	10.30	Good

The dissolution parameters of formulated and commercial brands are summarized in Table 3. All the formulated tablets gave very rapid and higher dissolution of the contained drug. The dissolution parameters given in Table 4 indicated rapid dissolution of the drug from the tablets formulated employing starch citrate, when compared to commercial brands. Drug dissolution from all the tablets followed first order kinetics. A 1.68 and 3.92 fold increase in the dissolution rate (K_1) was observed, respectively with gliclazide and pioglitazone tablets formulated by direct compression method employing starch citrate, when compared to the corresponding commercial brand.

Table 3: Drug content, hardness, friability, disintegration time and weight variation of tablets prepared employing starch citrate as directly compressible vehicle

Formulation	Drug content (mg/tab)	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration time (sec)	Weight variation (maximum % deviation)
Gliclazide tablets					
Formulated	30.9	5.0	1.80	23	5.6
Commercial	40.0	5.0	1.23	30	3.2
Pioglitazone tablets					
Formulated	29.30	5.0	1.15	16	4.2
Commercial	30.90	4.5	1.40	480	4.5

Table 4: Dissolution parameters of tablets prepared employing starch citrate as directly compressible vehicle

Formulation	PD_{10} (%)	DE_{15} (%)	K_1 (min^{-1})	R^2 in first order model
Gliclazide tablets				
Formulated	95.96	78.31	0.321	0.955
Commercial	79.3	68.46	0.191	0.961
Pioglitazone tablets				
Formulated	99.34	81.43	0.502	0.992
Commercial	48.86	38.74	0.128	0.984

CONCLUSIONS

(i) Starch citrate prepared by reacting potato starch with citric acid at elevated temperatures was crystalline, non-hygroscopic and was insoluble in water and aqueous fluids of acidic and alkaline pHs.

(ii) Starch citrate exhibited good swelling (1500%) in water. It has no pasting or gelling property, when heated at 100^0C in water for 30 min.

(iii) Starch citrate powder of size 152 µm (80/120 mesh) exhibited excellent flow characteristics alone and after mixing drug and other excipients upto 30% and was found suitable for direct compression.

(iv) The tablets of gliclazide and pioglitazone formulated employing starch citrate as directly compressible vehicle gave rapid and higher dissolution of the contained drug apart from fulfilling the official or GMP standards prescribed for uncoated tablets.

(v) A 1.68 and 3.92 fold increase in the dissolution rate (K_1) was observed, respectively with gliclazide and pioglitazone tablets formulated by direct compression method employing starch citrate, when compared to the corresponding commercial brand.

(vi) The starch citrate, a new modified starch was found to be a promising directly compressible vehicle for the preparation of tablets by direct compression method.

ACKNOWLEDGEMENTS

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

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Revised : 06.11.2010 *Accepted : 10.11.2010*