Asian Journal of Chemistry; Vol. 23, No. 2 (2011), 502-504

ASIAN JOURNAL OF CHEMISTRY

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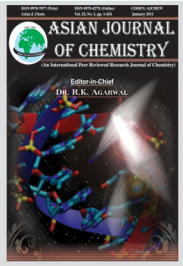

Synthesis, Characterization and Evaluation of Starch Acetate as Rate Controlling Matrix Former for Controlled Release of Glipizide

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(*Received*: 4 January 2010; *Accepted*: 17 September 2010) AJC-9094

Starch acetate with a degree of substitution of 1.48-1.50 could be synthesized by acetylation ofpotato starch with acetic anhydride. Matrix tablets of glipizide (10 mg) prepared employing starch acetate as matrix former in different proportions gave slow and controlled release over more than 24 h. Glipizide release was diffusion controlled and dependent on strength (%) of starch acetate and type of diluent in the tablets. Non-fickian diffusion was the release mechanism from these tablets. A good linear relationship was observed between per cent of polymer, starch acetate and release rate (K_0) of the matrix tablets. Release rate of the matrix tablets was stable and unaltered during short time accelerated stability study. Starch acetate was found suitable as matrix former for controlled release and the matrix tablets of glipizide formulated employing starch acetate (5 %) gave controlled release of glipizide over 24 h.

Key Words: Starch acetate, Matrix tablets, Glipizide, Controlled release.

INTRODUCTION

Among various approaches preparation of drug embedded matrix tablets is one of the least complicated approaches for obtaining controlled release and is widely used in industry. Polymers and release retarding materials used as matrix formers in matrix tablets play a vital role in controlling the drug release from the tablets. Though a variety of polymeric materials are available to serve as release retarding matrix materials, there is a continued need to develop new, safe and effective release retarding matrix materials for matrix tablets for controlled release.

Modified starches have been used[1,2] for various pharmaceutical purposes such as fillers, superdisintegrants and matrix formers in capsules and tablet formulations. One of the important modification of starch is acetylated starch. Starch acetate is reported[3,4] to have excellent bond forming ability and suitable for coating and controlled release applications. Much of the literature on starch acetate and its industrial applications are patented, the details of which are not known. In the present work starch acetate was synthesized, characterized and evaluated as rate controlling matrix former for controlled release of glipizide. Matrix tablets of glipizide were formulated employing starch acetate in different proportions of drug and polymer and the tablets were evaluated for drug release kinetics and mechanism. Glipizide is an effective and widely prescribed antidiabetic drug. It requires controlled release owing to its short biological half life of 3.4 ± 0.7 h[5]. A few sustained release formulations of glipizide are available commercially.

EXPERIMENTAL

Glipizide was a gift sample from M/s Micro Labs Limited, Pondicherry. Potato starch (SD Fine Chemicals), acetic anhydride (qualigens), sodium hydroxide (Qualigens) and chloroform (qualigens) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Synthesis of starch acetate: Potato starch (20 parts), acetic anhydride (80 parts) and sodium hydroxide 50 % solution (4.4 parts) were mixed and refluxed for 5 h at 150 ºC. The reaction mixture was added to cold water to precipitate the starch acetate formed. The product was collected by vacuum filtration, washed repeatedly with water and dried at 80 ºC for 2 h.

Characterization of starch acetate: The starch acetate synthesised was characterized by determining the extent of acetylation and degree of substitution and by IR spectra. Solubility characteristics were also tested.

Determination of degree of substitution: A powdered starch acetate sample (1.0 g) was placed in a 250 mL flask and 50 mL of 75 % ethanol in distilled water solution were added. The mixture was agitated, warmed to 50 ºC, held at that temperature for 0.5 h and cooled, then 40 mL of 0.5 N potassium hydroxide were added. The mixture was then allowed to stand 72 h with occasional swirling. The excess

alkali was back titrated with standard 0.5 N hydrochloric acid using phenolphthalein as indicator. A blank was titrated in the same way using an original sample of starch. The acetylation level was calculated using the equation, acetylation (%) = mL (blank) - mL (sample) × normality of acid × 0.043 × 100/ weight of sample, g (dry basis) and the degree of substitution was calculated using the equation, degree of substitution = 162 × % acetylation/4300 - (42 × % acetylation).

IR spectra were recorded on Perkin-Elmer spectrometer, 1000 Model, using chloroform as solvent.

Preparation of matrix tablets: Matrix tablets of glipizide (10 mg) were prepared as per the formulae given in the Table-1. The required quantities of medicament, diluent (lactose/ DCP) and matrix material (starch acetate) were mixed thoroughly in a mortar by following geometric dilution technique. The granulating fluid (solvent blend of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60 ºC for 4 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants, talc and magnesium stearate were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a tablet punching machine (M/s Cadmach machinery Co. Pvt. Ltd.,) to a hardness of 8 kg/cm^2 using 9 mm round and flat punches.

TABLE-1
FORMULAE OF GLIPIZIDE SR TABLETS
PREPARED EMPLOYING STARCH ACETATE

Ingredient (mg/tablet)	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8
Glipizide	10	10	10	10	10	10	10	10
Lactose	196.8	190.2	179.2	168.2	–	–	–	–
Dicalcium phosphate	–	–	–	–	196.8	190.2	179.2	168.2
Starch acetate	4.4	11	22	33	4.4	11	22	33
Talc	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Granulating fluid*	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

*A solvent blend of alcohol:water (1:1).

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, 0.1 N HCl and phosphate buffer of pH 7.4 as test fluids.

Estimation of glipizide: Glipizide content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 223 nm in phosphate buffer of pH 7.4. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 1-10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 %, respectively.

Drug release study: Drug release from the matrix tablets prepared was studied using 8-station dissolution rate test apparatus (M/s Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37 ± 1 ºC. Phosphate buffer of pH 7.4 (900 mL) was used as dissolution fluid for glipizide tablets. Samples of 5 mL each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. The samples withdrawn were analysed at 223 nm by using a Shimadzu UV-150 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate.

Analysis of release data: Drug release data were analyzed as per zero order, first order, Higuchi[6] square root time and Peppas[7] equation models to asses the release kinetics and mechanisms.

RESULTS AND DISCUSSION

Starch acetate prepared was found to be a white crystalline power. The per cent acetylation was 28.38 % and the degree of substitution was 1.48-1.50. The IR spectrum (Fig. 1) of starch acetate showed the acetyl carobonyl stretching at 1749 cm^{-1}, which was absent in the IR spectrum of potato starch, indicating the acetylation of the native starch. The starch acetate prepared was insoluble in water, aqueous buffers of pH 1.2 and 7.4, methanol, petroleum ether, dichloromethane and cyclohexane. It is freely soluble in chloroform.

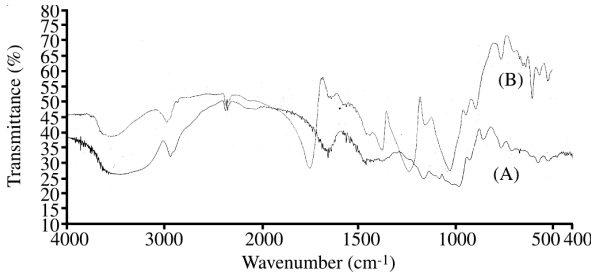


Fig. 1. FTIR spectra of potato starch (A) and starch acetate (B)

Matrix tablets of glipizide could be prepared employing different proportions of starch acetate by conventional wet granulation method. As glipizide is a potent drug with low dose, a diluent was also incorporated in the tablets. Two diluents namely lactose (water soluble) and DCP (water insoluble) were included in the formulations to assess their influence on drug release characteristics of starch acetate matrix tablets. Starch acetate was added at 2, 5, 10 and 15 % strength in the matrix. Hardness of the tablets was in the range 8-10 kg/cm^2. Weight loss in the following test was less than 0.5 % in all the cases. All the prepared tablets contained the drug within 100 ± 3 % of the labeled claim. All the matrix tablets prepared employing starch acetate were found to be non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such the prepared tablets were of good quality with regard to drug content, hardness and friability. As they were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

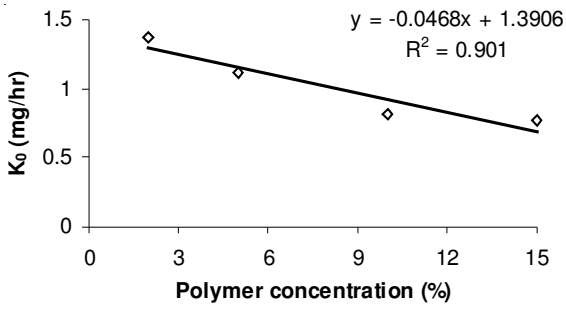
Glipizide release from the matrix tablets prepared was slow and spread over more than 24 h and depended on the concentration (%) of starch acetate in the tablets and nature/type of diluent. The release parameters are given in Table-2 As the concentration of starch acetate in the matrix tablets was increased, drug release was decreased. Release was relatively faster with water soluble diluent lactose when compared to water insoluble diluent DCP at all concentrations of starch acetate.

TABLE-2
DRUG RELEASE PARAMETERS OF GLIPIZIDE MATRIX TABLETS FORMULATED EMPLOYING STARCH ACETATE

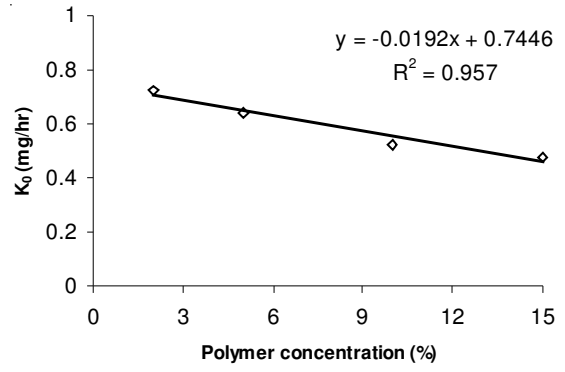
Formulation	Per cent polymer (%)	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	n in Peppas equation
GF1	2	2.0	5.50	1.370	0.6535
GF2	5	2.9	6.30	1.114	0.6756
GF3	10	5.0	8.20	0.818	0.6641
GF4	15	7.2	11.00	0.767	0.762
GF5	2	4.5	8.12	0.723	0.615
GF6	5	5.8	13.50	0.642	0.619
GF7	10	7.8	16.60	0.523	0.609
GF8	15	10.3	21.50	0.477	0.930

Analysis of release data as per zero order and first order kinetic models indicated that both the models were equally applicable to describe the release data of the tablets. The correlation coefficient (r) values were nearly the same in both the models. When the release data were analyzed as per Peppas equation, the release exponent 'n' was in the range 0.609-0.930 with all the matrix tablets indicating non-fickian (anomalous) diffusion as the release mechanism from the matrix tablets formulated employing starch acetate. Plots of per cent released versus square root of time were found to be linear ($r > 0.8998$) with all the matrix tablets prepared indicating that the drug release from these tablets was diffusion controlled.

As the starch acetate proportion (%) in the matrix tablets was increased release-rate was decreased. A good linear relationship was observed between per cent polymer (starch acetate) and release rate (K_0) (Fig. 2). Drug release from the matrix tablets could be controlled by varying the proportion of drug: polymer in the matrix.



(A)



(B)

Fig. 2. Relationship between polymer concentration and release rate (K_0) for glipizide matrix tablets formulated employing starch acetate. Diluent:lactose (A); DCP (B)

For comparison glipizide release from glynase XL SR tablets (a commercial SR product) was also studied. A comparison of the release profiles of commercial and various starch acetate matrix tablets indicated that GF6 (glipizide matrix tablets formulated employing 5 % starch acetate and DCP as diluent) gave a release similar to that of glynaseXL SR tablets. Drug release profiles of formulated tablets GF6 and glynase XL SR tablets were compared by calculating difference factor f_1 and similarity factor f_2. The values of f_1 and f_2 were found to be 3.98 and 113, respectively for the comparison of release profiles of GF6 and glynase XL SR tablets indicating that the release profiles of these two products are similar. Hence glipizide matrix tablets GF6 formulated employing 5 % starch acetate and DCP as diluent are considered as the best controlled release formulation suitable for controlled release of glipizide over 24 h.

Short term accelerated stability testing was performed on formulation GF6. The tablets in screw capped high density polyethylene bottles were stored at 40 ± 1 ºC and 75 % RH for 3 months. The drug content and dissolution rate of the stored products were determined and compared with those of freshly made products. No visible changes were observed in starch acetate matrix tablets after storage. No significant difference ($p > 0.05$) was observed in the per cent drug content before and after storage for 3 months. The drug release characteristics of all the matrix tablets tested remained unaltered during the storage period.

Conclusion

Starch acetate with a degree of substitution of 1.48-1.50 could be synthesized by acetylation of potato starch with acetic anhydride. Matrix tablets of glipizide (10 mg) prepared employing starch acetate as matrix former in different proportions gave slow and controlled release over more than 24 h. Glipizide release was diffusion controlled and dependent on strength (%) of starch acetate and type of diluent in the tablets. Non-fickian diffusion was the release mechanism from these tablets. A good linear relationship was observed between percent of polymer, starch acetate and release rate (K_0) of the matrix tablets. Release rate of the matrix tablets was stable and unaltered during short time accelerated stability study. Starch acetate was found suitable as matrix former for controlled release and the matrix tablets of glipizide formulated employing starch acetate (5 %) gave controlled release of glipizide over 24 h.

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