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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF STARCH ACETATE AS RATE CONTROLLING MATRIX FORMER FOR CONTROLLED RELEASE OF NIFEDIPINE

K. P. R. CHOWDARY[*] and G. V. RADHA[a]

University College of Pharmaceutical Sciences, Andhra University, VISAKHAPATNAM (A.P.) INDIA
[a]GITAM Institute of Pharmacy, GITAM University, Rushikonda, VISAKHAPATNAM (A.P.) INDIA

ABSTRACT

Starch acetate with a degree of substitution of 1.48 to 1.50 could be synthesized by acetylation of potato starch with acetic anhydride. Matrix tablets of nifedipine (20 mg) prepared employing starch acetate as matrix former in different proportions gave slow and controlled release over more than 24 h. Nifedipine 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 nifedipine formulated employing starch acetate gave controlled release of nifedipine over 24 h and fulfilled the official release specification of nifedipine extended release tablets.

Key words: Starch acetate, Matrix tablets, Nifedipine, 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

[*]Author for correspondence; E-mail: prof.kprchowdary@rediffmail.com

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. Matrix tablets of nifedipine were formulated employing starch acetate in different proportions of drug and polymer and the tablets were evaluated for drug release kinetics and mechanism. Nifedipine is an effective and widely prescribed antianginal drug. It requires controlled release owing to its short biological half life of 2.5 h. A few sustained release formulations of nifedipine are available commercially.

EXPERIMENTAL

Material and methods

Nifedipine 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^{o}C. 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^{o}C 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^{o}C, 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 -

$$\text{Acetylation (\%)} = \text{mL (blank)} - \text{mL (sample)} \times \text{Normality of acid} \times 0.043 \times 100 / \text{Weight of sample, g (dry basis)} \quad \ldots(1)$$

and the degree of substitution was calculated using the equation –

$$\text{Degree of substitution} = 162 \times \% \text{ Acetylation} / 4300 - (42 \times \% \text{ Acetylation}) \quad \ldots(2)$$

IR spectra

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

Preparation of matrix tablets

Matrix tablets of nifedipine (20 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^{o}C for 4 hours. 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/sq.cm using 9 mm round and flat punches.

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, 0.1N HCl and phosphate buffer of pH 6.8 containing 1% w/v sodium lauryl sulphate as test fluids.

Estimation of nifedipine

Nifedipine content of the microcapsules was estimated by UV spectrophotometric method based on the measurement of absorbance at 238 nm in phosphate buffer of pH 6.8 containing 1% w/v sodium lauryl sulphate. 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 percent, respectively.

Table 1: Formulae of nifedipine SR tablets prepared employing starch acetate

Ingredient (mg/tablet)	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8
Nifedipine	20	20	20	20	20	20	20	20
Lactose	186.8	180.2	169.2	158.2	-	-	-	-
DCP	-	-	-	-	186.8	180.2	169.2	158.2
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)

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^{o}C. Phosphate buffer of pH 6.8 containing 1% w/v sodium lauryl sulphate (900 mL) was used as dissolution fluid for nifedipine 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 238 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[5] square root time and Peppas[6] equation models to asses the release kinetics and mechanisms.

RESULTS AND DISCUSSION

Starch acetate prepared was found to be a white crystalline power. The percent acetylation was 28.38 % and the degree of substitution was 1.48 to 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.

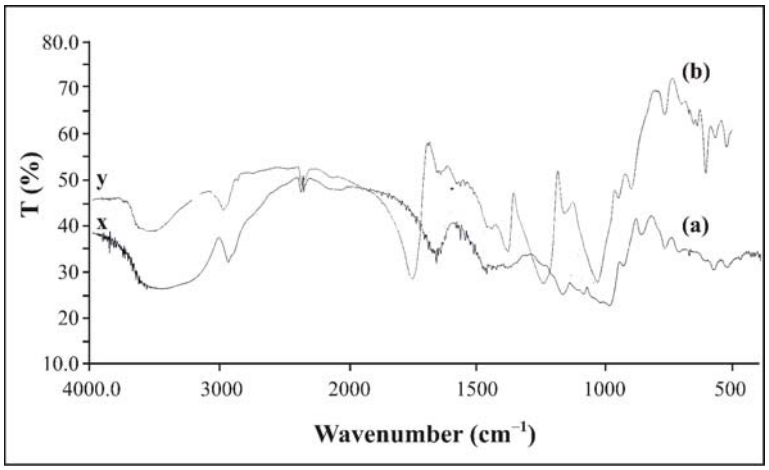

Fig. 1: FTIR Spectra of potato starch (A) and starch acetate (B)

Matrix tablets of nifedipine could be prepared employing different proportions of starch acetate by conventional wet granulation method. As nifedipine 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/sq. cm. 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 6.8) 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.

Nifedipine release from the matrix tablets prepared was slow and spread over more than 24 hours 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 nifedipine matrix tablets formulated employing starch acetate

Formulation	Percent polymer (%)	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	n in Peppas equation
NF1	2	4.5	9.5	1.715	0.834
NF2	5	7.1	13.0	1.34	1.012
NF3	10	8.2	15.0	1.217	1.101
NF4	15	11.5	20.1	0.910	1.067
NF5	2	9	15.8	1.15	1.012
NF6	5	12.9	22.8	0.781	1.046
NF7	10	13.9	23.9	0.768	1.070
NF8	15	16.2	> 24	0.670	1.031

Analysis of release data as per zero order and first order kinetic models indicated that the drug release from the matrix tablets followed zero order kinetics. The correlation coefficient (r) values were high in zero order model. When the release data were analysed as per Peppas equation, the release exponent 'n' was in the range (0.834-1.07) with all the matrix tablets indicating non-Fickian (anomalous) diffusion, as the release mechanism from the matrix tablets formulated employing starch acetate. Plots of percent released versus square root of time were found to be linear ($r > 0.9270$) 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 were increased, release rate was decreased, a good linear relationship was observed between percent polymer (starch acetate) and release rate (K_o) (Fig. 2). Drug release from the matrix tablets could be controlled by varying the proportion of drug : polymer in the matrix.

Nifedipine extended release tablets are official in USP XXIV for which a release of 5-17 % at 4 h; 43-60% at 12 h and NLT 80% at 24 h is prescribed. A comparison of drug release profiles of various nifedipine matrix tablets formulated employing starch acetate with the official release specification indicated that nifedipine matrix tablets **NF4** and **NF6** gave

drug release fulfilling the official specification. As such these tablets formulated employing starch acetate are considered as good sustained release formulations to provide controlled release of nifedipine over 24 h.

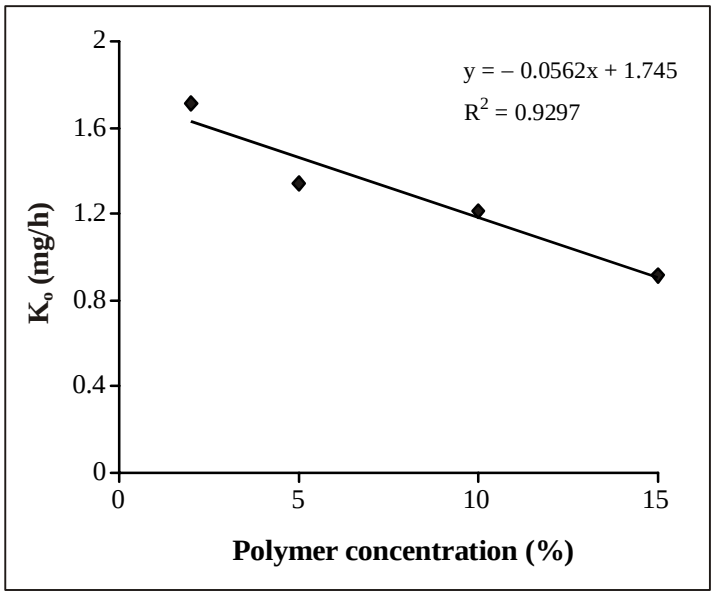

Fig. 2: Relationship between polymer concentration and release rate (K_0) for nifedipine matrix tablets formulated employing starch acetate

Short term accelerated stability testing was performed on formulations **NF4** and **NF6**. The tablets in screw capped HDPE bottles were stored at 40°C ± 1°C 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 percent 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.

CONCLUSIONS

(i) Starch acetate with a degree of substitution of 1.48 to 1.50 could be synthesized by acetylation of potato starch with acetic anhydride.

(ii) Matrix tablets of nifedipine (20 mg) prepared employing starch acetate as matrix former in different proportions gave slow and controlled release over more than 24 h.

(iii) Drug 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.

(iv) Good linear relationship was observed between percent of polymer (starch acetate) and release rate (K_0) of the matrix tablets.

(v) Release rate of the matrix tablets was stable and unaltered during short time accelerated stability study.

(vi) Starch acetate was found suitable as matrix former for controlled release and the matrix tablets of nifedipine formulated employing starch acetate (**NF4** and **NF6**) gave controlled release of nifedipine over 24 h and fulfilled the official release specification of nifedipine extended release tablets.

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