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Synthesis, Characterization and Evaluation of Starch Acetate as Microencapsulating Agent for Controlled Release of Glipizide

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Starch acetate with a degree of substitution about 1.5 could be synthesized by acetylation of potato starch with acetic anhydride. Starch acetate microcapsules of glipizide were prepared by an industrially feasible emulsification-solvent evaporation method and the microcapsules were studied with a view to evaluate starch acetate as microencapsulating agent. The starch acetate microcapsules prepared are spherical, discrete, free flowing and multinucleate, monolithic type. Microencapsulation efficiency was in the range 94-98 %. Glipizide release from the microcapsules was slow over 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release was by Fickian diffusion mechanism. Good linear relationships were observed between wall thickness of the microcapsules and release rate. Starch acetate was found suitable as microencapsulating agent and the starch acetate microcapsules exhibited good controlled release characteristics.

Key Words: Starch acetate, Microencapsulation, Glipizide, Controlled release.

INTRODUCTION

Microencapsulation has been widely accepted as a means to achieve controlled release[1,2]. Polymers and release retarding materials used as coat in microencapsulation play a vital role in controlling the drug release from the resulting microcapsules. Though a variety of polymeric materials are available to serve as release retarding coat materials, there is a continued need to develop new, safe and effective release retarding coat materials for microencapsulation.

Modified starches have been used[3,4] 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[5,6] 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 microencapsulating agent. Studies were carried out on microencapsulation of glipizide by starch acetate and evaluation of the resulting microcapsules for controlled release. 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[7]. 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 v/v) 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 synthesized starch acetate 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 for 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: IR spectra were recorded on Perkin-Elmer spectrometer, 1000 Model, using chloroform as solvent.

Preparation of microcapsules: An emulsification solvent evaporation method was tried to prepare starch acetate microcapsules. Starch acetate (0.2 g) was dissolved in chloroform (10 mL) to form a homogeneous solution. Core material, glipizide (0.8 g) was added to the polymer (starch acetate) solution (5 mL) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 mL of an aqueous mucilage of sodium CMC (0.5 % w/v) contained in a 450 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi medium duty stirrer with speed meter (model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28 ºC) for 3 h to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. Different proportions of core:coat namely 9:1 (MC1), 8:2 (MC2), 7:3 (MC3) were used to prepare microcapsules with varying coat thickness.

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.

Evaluation of microcapsules: For the size distribution analysis, different fractions in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed. Encapsulation efficiency was calculated using the equation, encapsulation efficiency = (estimated % drug content/theoretical % drug content) × 100. Theoretical mean wall thickness of the microcapsules was determined by the method of Luu *et al.*[8] using the equation, $h = \bar{r}(1 - p)\, d_1/3[pd_2 + \backslash(1-p)\, d_1]$ where h is the wall thickness, is the mean radius of the microcapsules, d_1 is the density of the core material, d_2 is the density of the coat material and p is the proportion of the medicament in the microcapsules.

Drug release study: Release of glipizide from the microcapsules of size 20/30 and 30/50 was studied in phosphate buffer of pH 7.4 (900 mL) using an 8 station dissolution rate test apparatus (model Disso-2000, M/s Lab. India) with a paddle stirrer at 50 rpm and 37 ± 0.5 ºC. A sample of microcapsules equivalent to 10 mg of glipizide were used in each test. Samples (5 mL) were withdrawn through a filter (0.45 µ) at different time intervals over 24 h and were assayed at 223 nm for glilpizide using a Shimadzu UV-150 double beam spectrophotometer. The sample (5 mL) taken at each sampling time was replaced with fresh dissolution medium (5 mL). The drug release experiments were conducted in triplicate.

Analysis of release data: Drug release data were analyzed as per zero order, first order, Higuchi[9] square root time and Peppas[10] 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 carbonyl 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.

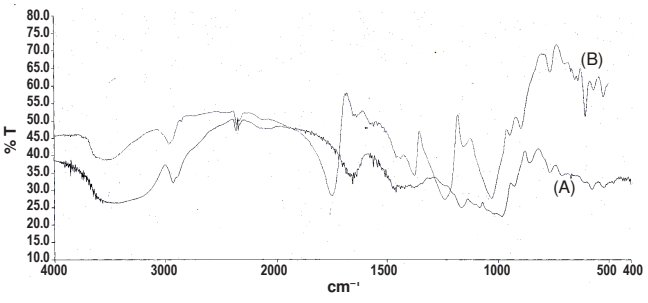

Fig. 1. FTIR spectra of potato starch (A) and starch acetate (B)

An emulsification - solvent evaporation method was developed for microencapsulation of glipizide by starch acetate. The method involves emulsification of the polymer (starch acetate) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5 % w/v solution of sodium CMC) as microdroplets, followed by removal of the solvent, chloroform by continuous stirring to form rigid microcapsules. The microcapsules were found to be discrete, spherical and free flowing. The nature of the method of preparation indicated that the microcapsules were of multinucleate and monolithic type.

The sizes could be separated by sieving and a more uniform size range of microcapsules could readily be obtained. The sieve analysis of different microcapsules showed that 42-45 and 32-35 % of microcapsules in a batch were in the size range of -20 + 30 (715 µm) and -30 + 50 (443.5 µm), respectively. A log-normal size distribution of the microcapsules was observed in all the batches prepared.

Low coefficient of variation in per cent drug content (< 2.0 %) indicated uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range 94-98 %. Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical, the theoretical average wall thickness of the microcapsules was calculated according to Luu *et al.*[8]. Microcapsules prepared with various ratios of core: coat were found to have different wall thickness (Table-1).

Glipizide release from the microcapsules was studied in phosphate buffer pH 7.4. Drug release parameters of the

TABLE-1
GLIPIZIDE CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF STARCH ACETATE MICROCAPSULES

Microcapsules (size)	Glipizide content (%)	Micro encapsulation efficiency (%)	Wall thickness (μ)	T_{50} (h)	T_{90} (h)	K_1 (h^{-1})	'n' in Peppas equation
MC1 (20/30)	87.48 (1.30)*	97.20	20.95	5.0	16.0	0.1736	0.4320
MC1 (30/50)	87.21 (1.20)	96.90	12.96	3.6	14.1	0.2069	0.3748
MC2 (20/30)	75.60 (1.50)	94.50	38.60	6.3	17.8	0.1642	0.3984
MC2 (30/50)	76.24 (1.60)	95.30	23.91	3.8	14.8	0.1765	0.3655
MC3 (20/30)	67.20 (1.90)	96.00	53.10	9.5	>24	0.0493	0.3814
MC3 (30/50)	66.85 (1.80)	95.50	33.20	7.0	> 24	0.0607	0.3770

*Figures in parentheses are coefficient of variation (CV) values; T_{50} is the time for 50 % release; T_{90} is time for 90 % release, K_1 is the first order release rate constant and 'n' is the release exponent in Peppas equation.

microcapsules are given in Table-1. Glipizide release from the microcapsules was slow and spread over a period of 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. As the proportion of the coat was increased, glipizide release rate was decreased. Smaller microcapsules gave higher release rate due to increased surface area.

Analysis of the release data as per zero and first order kinetic models indicated that the drug release from the microcapsules followed first order kinetics (r > 0.960). When the release data were analyzed as per Peppas equation[10], the release exponent 'n' was less than 0.5 with all the microcapsules indicating that the drug release from the microcapsules was by Fickian diffusion mechanism. Plots of percent released *vs.* square root of time were found to be linear (r > 0.980) indicating that the drug release from the microcapsules was diffusion controlled. Linear relationships were observed between wall thickness of the microcapsules and release rate (K_1) (Fig. 2).

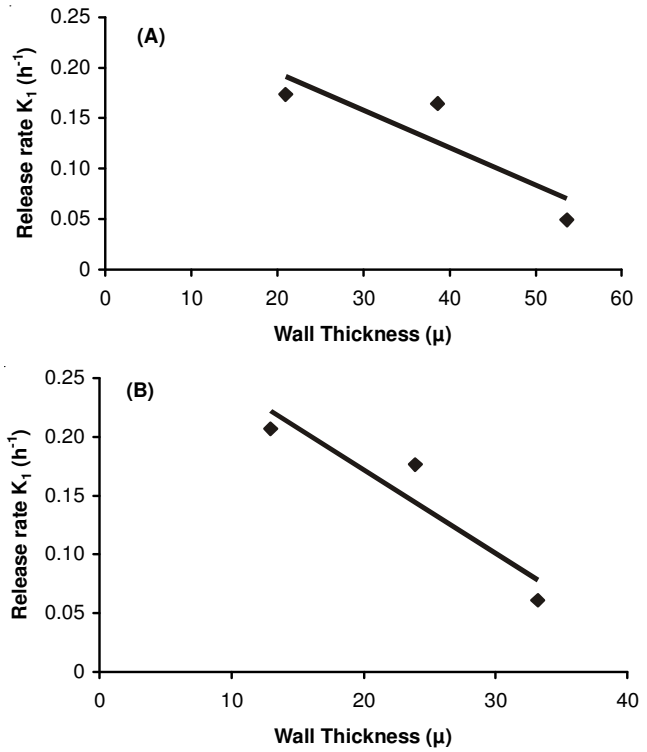

Fig. 2. Relationship between wall thickness and release rate of starch acetate microcapsules, size 20/30 (A) and size 30/50 (B)

Conclusion

Starch acetate with a degree of substitution about 1.5 could be synthesized by acetylation of potato starch with acetic anhydride. Spherical starch acetate microcapsules of glipizide could be prepared by the emulsification-solvent evaporation method. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. Microencapsulation efficiency was found to be in the range 94-98 %. Glipizide release from the starch acetate microcapsules was slow and extended over longer periods of time and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release from the starch acetate microcapsules was by Fickian diffusion mechanism. Good linear relationships were observed between wall thickness of the microcapsules and release rate (K_1). Starch acetate, thus, was found suitable as microencapsulating agent and the starch acetate microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release products.

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