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Synthesis and Evaluation of Starch Acetate as Microencapsulating Agent for Controlled Release of Carbamazepine

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The objective of the study is to synthesize starch acetate, a new starch based polymer and to evaluate for its application as microencapsulating agent for controlled release of carbamazepine. Controlled release formulations are needed for carbamazepine to avoid its erratic absorption, fluctuating plasma concentrations and associated toxicity. Starch acetate with a degree of acetyl substitution of 2.72 could be synthesized by acetylation of potato starch with acetic anhydride. Starch acetate microcapsules of carbamazepine were prepared by an industrially feasible emulsification-solvent evaporation method and the microcapsules were evaluated for controlled release. The starch acetate microcapsules prepared are spherical, discrete, free flowing and multi nucleate monolithic type. Microencapsulation efficiency was in the range 80-87 %. Carbamazepine release from the microcapsules was slow over 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. Drug release from the microcapsules was analyzed by Fickian diffusion mechanism. Good linear relationship was observed between wall thickness of the microcapsule and release rate. Starch acetate was found suitable as a new microencapsulating agent and the starch acetate microcapsules exhibited good controlled release characteristics. Carbamazepine release from starch acetate microcapsules, MC3 fulfilled the official (USP 30) release requirement prescribed for carbamazepine extended release tablets and these microcapsules were found suitable for once daily administration of carbamazepine.

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

INTRODUCTION

In the last two decades, controlled-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Drug release from these systems should be at a desired rate, predictable and reproducible. Polymers which are used as release retarding materials in the design of controlled-release dosage forms play a vital role in controlling the delivery of drug from these dosage forms. Though a wide range of

polymers and other release-retarding materials are available, there is a continued need to develop new, safe and effective release-retarding polymers for controlled release. Starch is a natural, biodegradable polymer and modified starches are reported[1,2] as fillers, disintegrants and dry binders. Carbamazepine is a widely used anticonvulsant drug belonging to the chemical category of iminostilbenes. It is used in doses of 100, 200 and 400 mg, 2 or 3 times a day. It is absorbed slowly and erratically after oral administration[3]. This erratic absorption may lead to fluctuations in plasma concentrations, which are responsible for its side effects and neurotoxicity[4]. Hence controlled release formulations are needed for carbamazepine to avoid erratic absorption, fluctuating plasma concentrations and associated toxicity. Controlled release formulations also improve patient compliance in the long-term therapy with carbamazepine. Carbamazepine extended release tablets are official in USP 30[5].

The objective of the present investigation is to synthesize starch acetate and to evaluate for its application as microencapsulating agent for controlled release of carbamazepine. Starch acetate microcapsules containing carbamazepine were prepared by an industrially feasible method of microencapsulation and the microcapsules were evaluated for controlled release of carbamazepine.

EXPERIMENTAL

Carbamazepine was a gift sample from M/s Ranbaxy Research Lab., Gurgaon. Acetic anhydride (Qualigens), chloroform (Merck), sodium carboxy methyl cellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1 % (w/v) solution at 25 °C, Loba-Chemie), sodium hydroxide and potato starch (Loba-Chemie) were procured from commercial sources. Starch acetate, a new starch polymer was prepared in the laboratory. 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 °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 °C for 2 h.

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

Determination of degrees of substitution (DS): A powdered starch acetate sample (1.0 g) was placed in a 250 mL flask and 50 mL of a 75 % ethanol in distilled water solution were added. The mixture was agitated, warmed to 50 °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 the starch. The acetylation level and the degree of substitution of the starch were calculated as follows:

$$\%\text{Acetylation} = \frac{[\text{blank(mL)} - \text{sample(mL)} \times \text{normality of acid} \times 0.043}{\text{Weight of the sample, g (dry basis)}} \times 100$$

$$\text{Degree of substitution (DS)} = \frac{162 \times \%\ \text{acetylation}}{4300 - (42 \times \%\ \text{acetylation})}$$

FT-IR spectra: The FT-IR spectra of starch and starch acetate were recorded by using KBr disc as reference on a FT-IR spectrophotometer (Model: NP-602378-14.002, instrument serial No. 72425).

Preparation of microcapsules: Starch acetate microcapsules containing carbamazepine were prepared by an emulsification-solvent evaporation method employing chloroform as the solvent for the polymer.

Starch acetate (2 g) was dissolved in chloroform (100 mL) to form a homogenous polymer solution. Core material, carbamazepine (0.8 g) was added to the polymer solution (10 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 500 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A medium duty stirrer (Remi Model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28 °C) for 3 h to produce spherical microcapsules. The micro-capsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. Different proportions of core to coat materials namely 9:1 (MC1), 8:2 (MC2) and 6:4 (MC3) were used to prepare microcapsules with varying coat thickness.

Estimation of carbamazepine: Carbamazepine content in the microcapsules was estimated by UV spectrophotometric method[6] based on the measurement of absorbance at 212 nm in 0.1N HCl. The method was validated for linearity, accuracy and precision. The method obeyed Beer-Lambert's law in the concentration range of 1-6 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.80 and 1.10 %, respectively. No interference from the excipients used was observed.

Characterization of microcapsules

Size analysis: For size distribution analysis, different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed.

Microencapsulation efficiency: Microencapsulation efficiency was calculated using the equation:

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated per cent drug content in microcapsules}}{\text{Theoretical per cent drug content in microcapsules}} \times 100$$

Scanning electron microscopy: The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S340, UK). Microcapsules were mounted directly on to the SEM sample stub, using double sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

Wall thickness: Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules was determined by the method described by Luu *et al.*[7] using the equation:

$$h = \frac{\bar{r}(1-p)d_1}{3[pd_2 + (1-p)d_1]}$$

where h = wall thickness, $\bar{r}$ = arithmetic mean radius of the microcapsule, d_1 = density of core material, d_2 = density of the coat material and 'p' = proportion of the medicament in the microcapsules. Mean radius of the microcapsules was determined by sieving. Densities were measured using petroleum ether as a displacement fluid at room temperature (28 ºC).

RESULTS AND DISCUSSION

Starch acetate was synthesized by acetylation of potato starch with acetic anhydride in alkaline medium. Starch acetate prepared was found to be a white crystalline powder. The percent acetylation was 42.38 % and the degree of substitution was 2.72. The IR spectrum 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.

Starch acetate microcapsules of carbamazepine could be prepared by an emulsion-solvent evaporation method employing chloroform as solvent for starch acetate. The method involves emulsification of the polymer (starch acetate) solution in chloroform containing the drug (carbamazepine) in an immiscible liquid medium as micro droplets and removal of solvent by continuous stirring to form rigid microcapsules of starch acetate. The microcapsules were found to be discrete, spherical and free flowing. SEM (Fig. 1) indicated that the microcapsules are spherical with smooth surface. The nature of the method of preparation indicates that the microcapsules

were multi-nucleated and monolithic type. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained. A large proportion of microcapsules were in the size range 20/30 (30-40 %) and 30/50 (35-40 %) mesh.

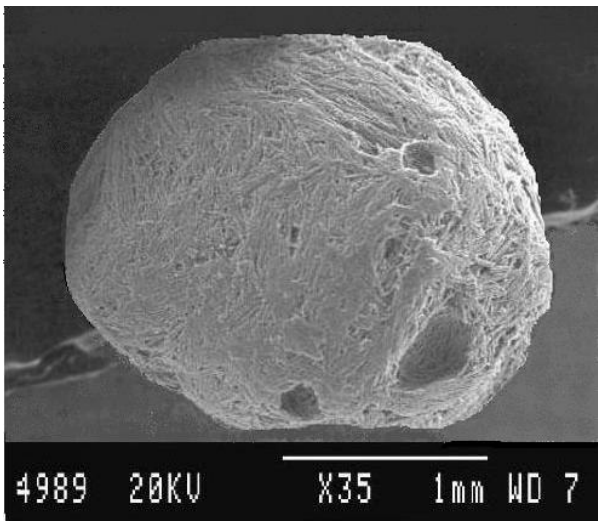

Fig. 1. SEM of starch acetate microcapsule, MC2 (size 20/30)

Low coefficient value (< 1.8 %) in percent drug content indicates uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range of 80-87 %. Drug content of the microcapsules was found to be nearly the same in different sieve fractions. As the microcapsules are spherical, the theoretical mean thickness of the wall that surrounds the core particles in the microcapsule was calculated[7]. Microcapsules prepared by employing various ratios of core:coat were found to have different wall thickness. Smaller microcapsules have thinner walls.

Carbamazepine release from the starch acetate microcapsules was studied in water (900 mL) as prescribed for carbamazepine extended release tablets in USP 30. Carbamazepine release from the starch acetate microcapsules was slow and spread over more than 24 h. The release data were analyzed as per zero order, first order, Higuchi[8] and Peppas[9] equation models. The correlation coefficient (R^2) values observed in fitting the release data into various kinetic models are given in Table-2. The drug release data more obeyed first order, Higuchi and Peppas equation models. When the release data were analyzed as per Peppas equation, the release exponent (n) was in the range 0.427-0.498 indicating Fickian diffusion as the drug release mechanism

TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE RATE OF STARCH ACETATE MICROCAPSULES OF CARBAMAZEPINE PREPARED

Micro-capsules (core:coat ratio)	Carbamazepine content (%)	Microen-capsulation efficiency (%)	Wall thickness (μm)	T_{90} (h)	Release rate K_1 (h^{-1})	'n' value in Peppas equation
Size 20/30						
MC1 (9:1)	76.53 (0.84)*	85.03	25.98	11.0	0.191	0.481
MC2 (8:2)	64.03 (1.08)	80.04	40.28	14.8	0.141	0.493
MC3 (6:4)	51.82 (0.98)	86.37	54.56	23.0	0.082	0.498
Size 30/50						
MC1 (9:1)	77.03 (0.29)	85.59	15.77	6.2	0.381	0.489
MC2 (8:2)	66.50 (1.35)	83.13	23.19	8.2	0.282	0.427
MC3 (6:4)	51.33 (1.80)	85.55	34.21	9.0	0.264	0.486

*Figures in parentheses are coefficient of variation (c.v) values.

TABLE-2
CORRELATION COEFFICIENT (R^2) VALUES IN THE ANALYSIS OF RELEASE DATA AS PER VARIOUS KINETIC MODELS

Microcapsules (core:coat ratio)	Regression coefficient (R^2) value			
	Zero order	First order	Higuchi model	Peppas equation
Size 20/30				
MC1 (9:1)	0.873	0.991	0.991	0.909
MC2 (8:2)	0.915	0.988	0.988	0.943
MC3 (6:4)	0.906	0.994	0.994	0.894
Size 30/50				
MC1 (9:1)	0.921	0.950	0.950	0.967
MC2 (8:2)	0.912	0.974	0.974	0.988
MC3 (6:4)	0.923	0.989	0.989	0.873

from the microcapsules. The release rate (K_1) depended on core:coat ratio, wall thickness and size of the microcapsules. As the proportion of coat increased, carbamazepine release rate decreased. The release rate was increased as the size of the microcapsules was decreased. Good linear relationship was observed between wall thickness of the microcapsules and drug release rate (K_1) (Fig. 2).

As the carbamazepine release from the starch acetate microcapsules was extended over 12-24 h depending on core:coat ratio, wall thickness and size, these microcapsules are considered suitable for oral controlled release of carbamazepine. Carbamazepine extended release tablets are

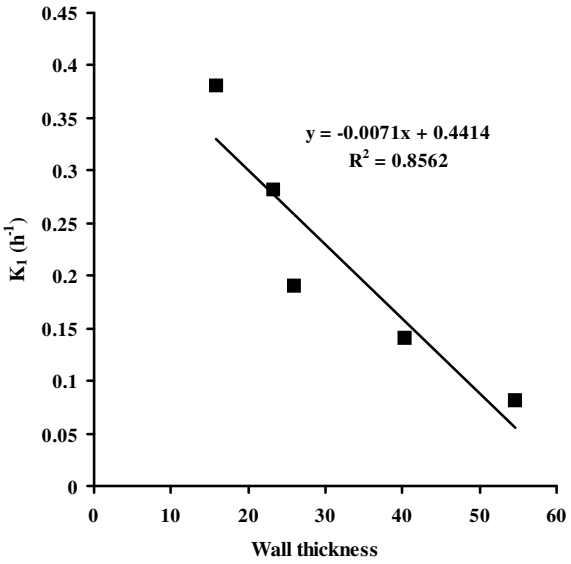

Fig. 2. Relationship between wall thickness and release rate (K_1) of starch acetate microcapsules

official in USP 30, which prescribed a release of 10-35 % in 3 h; 35-65 % in 6 h; 65-90 % in 12 h and NLT 75 % in 24 h. Starch acetate microcapsules, MC3 (size 20/30) gave release profiles fulfilling the official (USP 30) release requirements. Hence these starch acetate microcapsules (MC3, size 20/30) are considered suitable for once daily administration of carbamazepine.

Conclusion

(i) Starch acetate with a degree of acetyl substitution of 2.72 could be synthesized by acetylation of potato starch with acetic anhydride. (ii) Spherical starch acetate microcapsules of carbamazepine could be prepared by the emulsification-solvent evaporation method developed. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. (iii) Microencapsulation efficiency was in the range 80-87 %. (iv) Carbamazepine release from the starch acetate microcapsules was slow and extended over 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was by Fickian diffusion mechanism. (v) Good linear relationship was observed between wall thickness of the microcapsule and release rate. (vi) Starch acetate was found suitable as a new microencapsulating agent and starch acetate microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of carbamazepine.

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