

## Preparation and Evaluation of Starch Acetate Coated Microcapsules of Glipizide for Controlled Release

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Starch acetate was evaluated as microencapsulating agent and to prepare starch acetate coated microcapsules. Starch acetate coated microcapsules of glipizide were prepared by an industrially feasible emulsification-solvent evaporation method and the microcapsules were investigated. The starch acetate coated microcapsules are spherical, discrete, free-flowing and multinucleate monolithic type. Microencapsulation efficiency was found to be in the range 87.5-98.8 %. Glipizide release from the SA coated 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 microcapsules was by non-fickian diffusion mechanism. Good linear relationship was observed between wall thickness of microcapsules and release rate ( $k_0$ ) and ( $k_1$ ). Starch acetate was found suitable as microencapsulating agent and the starch acetate coated microcapsules of glipizide exhibited good controlled release characteristics and were found suitable for oral controlled release products.

**Key Words: Starch acetate, Microcapsules, Glipizide, Controlled release.**

### INTRODUCTION

Microencapsulation and microcapsules have been widely accepted for achieving controlled release. Polymers and release retarding materials used as a coat play a vital role in controlling the drug release from the microcapsules. Microencapsulation by various polymers and their applications are described in standard text books<sup>1,2</sup>. 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.

Starch acetate (SA) is a novel modified starch that is produced by acetylating raw starch. Starch acetate is reported<sup>3</sup> to have good potential for application in coating because of its film forming properties. Though starch acetate has good film forming properties it has not been studied for controlled release application. In present work, starch acetate was evaluated as coating material in microencapsulation.

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Studies were carried out on microencapsulation of glipizide by starch acetate and evaluation of the starch acetate coated microcapsules of glipizide for controlled drug release.

Glipizide, an effective antidiabetic (100 times more potent than tolbutamide in evoking pancreatic secretion of insulin<sup>4,5</sup> requires controlled release formulation owing to its short biological half-life<sup>6</sup> of  $3.4 \pm 0.7$  h and is rapidly eliminated. Controlled release formulation is needed for glipizide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficacy, to reduce g.i. disturbances and to enhance patient compliance. A few controlled release formulations of glipizide are available commercially.

## EXPERIMENTAL

Glipizide was a gift sample from M/s Micro Labs Ltd., Pondicherry. Starch acetate (DS 2.75) was synthesized in the laboratory by acetylating potato starch with acetic anhydride in alkaline medium. Chloroform AR (Merck) and sodium carboxy methyl cellulose (with a viscosity of 1500-3000 cps of a 1 % w/v solution at 25 °C, Loba-chemie) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

### Methods

**Preparation of microcapsules:** Starch acetate (0.5 g) was dissolved in warm chloroform solvent (25 mL) to form a homogenous polymer solution. Core material, glipizide (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 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 °C) 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 (SAMC1), 8:2 (SAMC2) and 7:3 (SAMC3) were used to prepare microcapsules with varying coat thickness.

**Estimation of glipizide:** Glipizide content of the microcapsules was estimated by UV spectrophotometric method<sup>7</sup> 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 per cent, respectively.

**Microencapsulation efficiency:** Microencapsulation efficiency was calculated using the following equation:

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

**Wall thickness:** Theoretical mean wall thickness of the microcapsules was determined by the method of Luu *et al.*<sup>8</sup> using the equation,  $h = \bar{r} (1-p)d_1/3[(pd_2+1-p)d_1]$  where  $h$  is the wall thickness,  $\bar{r}$  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 starch acetate coated microcapsules of size 20/30-30/50 was studied in phosphate buffer of pH 7.4 using an eight station dissolution rate test apparatus (model Disso-2000, M/s. Lab., India) with a paddle stirrer at 50 rpm and  $37 \pm 0.5$  °C. A sample of microcapsules equivalent to 20 mg of glipizide were used in each test. Samples (5 mL) were withdrawn through a filter (0.45  $\mu$ ) at different time intervals over 24 h and were assayed at 223 nm for glipizide 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.

**FTIR spectra:** To confirm that drug is not interacting with the polymer under experimental conditions FTIR spectra of glipizide, starch acetate and starch acetate microcapsules (SAMC2) were taken on Perkin Elmer, Japan. The IR spectrum obtained was elucidated for different chromatophore group. The infrared absorption spectra of all the formulations were run between 600-4000  $\text{cm}^{-1}$ .

**Scanning electron microscopy:** The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S430, UK). For SEM, the microcapsules were mounted directly onto the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

## RESULTS AND DISCUSSION

Starch acetate (SA) coated microcapsules of glipizide could be prepared by the emulsification-solvent evaporation method developed. The method involves emulsification of the polymer (SA) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5 % w/v solution of sodium CMC) as micro droplets, followed by removal of the solvent chloroform by continuous stirring to form rigid microcapsules. The microcapsules were found to be discrete, nearly spherical and free flowing. The nature of the method of preparation indicated that the microcapsules were of multinucleate and monolithic type. The sieve analysis of different microcapsules showed that 55-60 % and 30-35 % of microcapsules in a batch were in the size range of 20/30-30/50 mesh, respectively.

Low coefficient of variation in per cent drug content (< 1.0 %) indicated uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range 87.5-98.8 %. Drug content of the microcapsules was found to be the same in different sieve fractions. Microcapsules prepared with various ratios of core: coat were found to have different wall thickness (Table-1).

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

Microcapsules (core: coat ratio)	Glipizide content (%)	Microencapsulation efficiency (%)	Wall thickness ( $\mu\text{m}$ )	Release rate	
				$K_0$ (mg/h)	$K_1$ ( $\text{h}^{-1}$ )
Size:20/30					
9:1(SAMC1)	89	98.88	20.95	0.63	0.06
8:2(SAMC2)	78	97.50	38.60	0.58	0.06
7:3(SAMC3)	69	98.57	53.60	0.52	0.05
Size : 30/50					
9:1(SAMC1)	89	96.66	12.96	1.65	0.14
8:2(SAMC2)	80	87.50	23.91	1.43	0.09
7:3(SAMC3)	67	95.70	33.20	0.77	0.02

Glipizide release from the starch acetate microcapsules was studied in phosphate buffer of pH 7.4. Glipizide release from the starch acetate microcapsules was slow and spread over a period of more than 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 rates due to increased surface area.

Analysis of the release data as per zero and first order kinetic models indicated that both the models are equally applicable to describe the release data. The  $R^2$  value were nearly the same in both the models. When the release data were analyzed by Ritzer and Peppas<sup>9</sup> equation the release exponent 'n' was in the range of 0.47-0.72 indicating non-Fickian diffusion as the release mechanism from the starch acetate microcapsules. Plots of per cent released *versus* square root of time were found to be linear ( $r > 0.97$ ) indicating that the drug release from the microcapsules was diffusion controlled. A good linear relationship was observed between wall thickness of the microcapsules and release rate ( $k_0$ ) and ( $k_1$ ) (Fig. 1).

The FTIR spectra of pure drug, starch acetate and SA microcapsules (SAMC2) are shown in Fig. 2. From the spectra, it is clear that the characteristic peaks at 3323 (asymmetry N-H stretching), 3249 (symmetry N-H stretching), 2937 and 2856 (aliphatic C-H stretching), 1689 (monoamide C-O stretching), 1649 (diamide C-O stretching), 1528, 1444 (C-C and C-N stretching), 1331 (asymmetry S-O stretching), 1158 (symmetry S-O stretching), 1032, 899 (S-O-C stretching) are present in both pure glipizide and its starch acetate microcapsules without any change in their position, indicating no chemical interaction between glipizide and starch acetate.

The microcapsules were found to be discrete, nearly spherical and free flowing. SEM (Fig. 3) indicated that the microcapsules are spherical with smooth surface and completely covered with the polymer coat. The nature of the method indicates that the microcapsules were multi-nucleated, mono-lithic type.

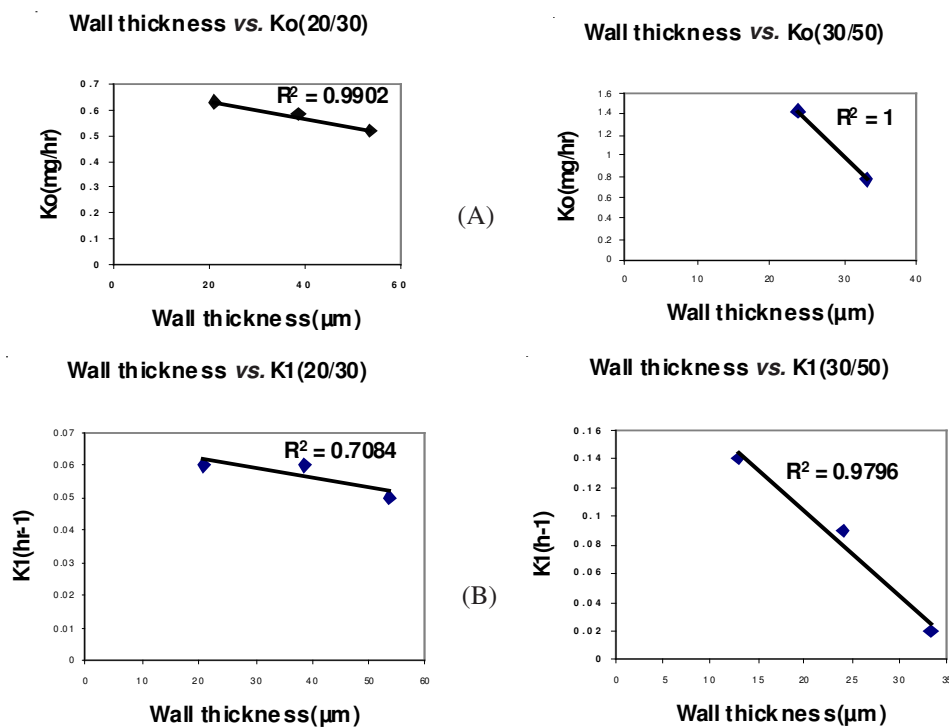


Fig. 1. Relationship between wall thickness and release rate of starch acetate microcapsules: (A) Wall thickness vs. zero order release rate ( $K_o$ ), (B) Wall thickness vs. first order release rate ( $K_i$ )

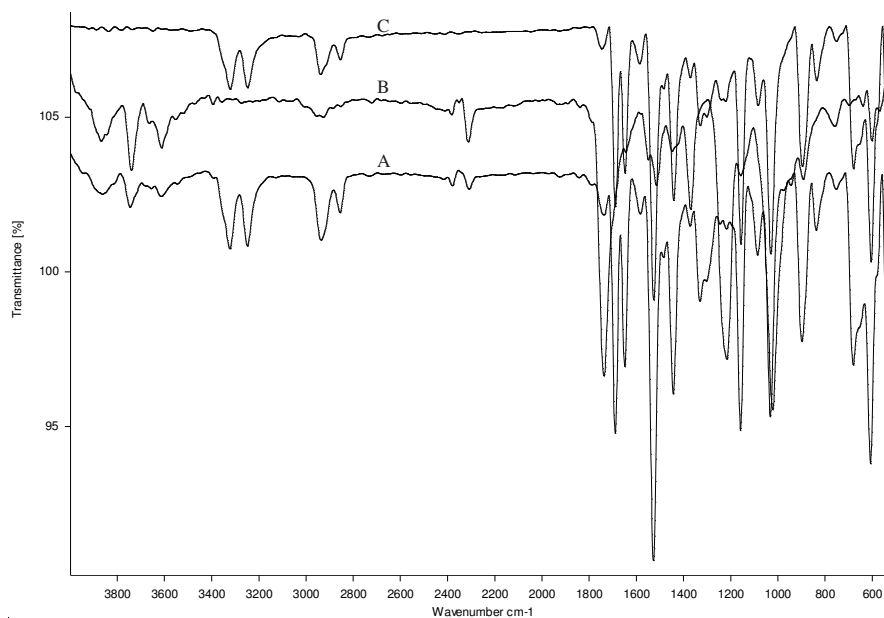


Fig. 2. FTIR spectra of A: Pure drug; B: Starch acetate; C: Microcapsules (SAMC2)

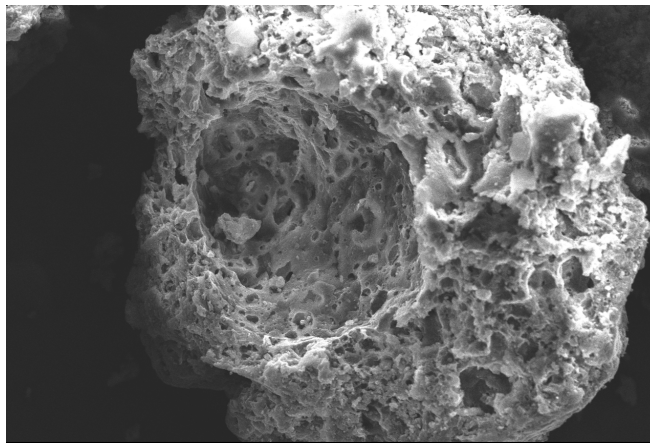


Fig. 3. SEM photograph of microcapsule (SAMC2)

### Conclusion

1. Spherical starch acetate (SA) coated microcapsules of glipizide could be prepared by emulsification-solvent evaporation method developed. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. 2. Microencapsulation efficiency was found to be in the range 87.5-98.8 %. 3. Glipizide release from the starch acetate coated microcapsules was slow and extended over longer periods of time and depended on core: coat ratio, wall thickness and size of the microcapsules. 4. Drug release from the microcapsules was by an non-Fickian diffusion mechanism. 5. Good linear relationship was observed between wall thickness of microcapsules and release rate ( $k_o$ ) and ( $k_i$ ). 6. starch acetate was found suitable as microencapsulating agent and the starch acetate coated microcapsules of glipizide exhibited good controlled release characteristics and were found suitable for oral controlled release products.

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(Received: 10 February 2009;

Accepted: 14 November 2009)

AJC-8048