



CELLULOSE ACETATE AS COATING MATERIAL : DESIGN AND DEVELOPMENT OF DICLOFENAC MICROCAPSULES

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ABSTRACT

Diclofenac sodium microcapsules were prepared with a view to develop oral controlled release of diclofenac by employing solvent evaporation technique in presence of coating material cellulose acetate. The microcapsules were evaluated for size analysis, angle of repose, bulk density, true density, per cent compressibility, drug content, microencapsulation efficiency, wall thickness, drug release characteristics and surface characteristics. The method gave discrete, large sized, free flowing spherical microcapsules. Diclofenac release from the microcapsules was slow, followed first order kinetics and influenced by the size of the microcapsules, wall thickness and coat : core ratio. IR spectral studies indicated that the drug and polymer are compatible with each other.

Key words : Diclofenac, Microcapsule, Cellulose acetate

INTRODUCTION

The ultimate goal of any drug delivery system is to deliver a therapeutic amount of drug to the exact location of the body, to achieve promptly and then maintain, the desired pharmacological response (s) and to reduce the incidence and severity of unwanted side effects¹. Microcapsules are small particles that contain an active agent or core material surrounded by a coating or shell. Commercial microcapsules typically have a diameter between 3 and 800 μm and contain 10 – 90 wt. per cent core. A wide range of core materials has been encapsulated including adhesives, agrochemicals, live cells, active enzymes, flavors, fragrances and pharmaceuticals. Most capsule shell materials are organic polymers, but fats and waxes are also used². Diclofenac sodium, which requires oral controlled release because of its short biological half – life of 2.0 h and gastro – intestinal irritation if present in larger concentration^{3,4} was used as core in the microencapsulation. The results are reported here.

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MATERIALS AND METHODS

Cellulose acetate having a viscosity of 6% solution in 95% acetone–water mixture at 20 °C is 140 cS was provided by G. S. Chemical Testing Lab. & Allied Industries, Mumbai. Diclofenac sodium I. P. was provided by Natco Pharmaceuticals, Hyderabad. All solvents and reagents used were AR grade. The spectrophotometer was an Elico UV–Vis model.

Preparation of microcapsules

Cellulose acetate microcapsules containing diclofenac sodium were prepared by an emulsion solvent evaporation method employing dichloromethane with coat : core ratio 3 : 7. The polymer (1.5 g) was dissolved in the polymer solvent (25 mL) to form a homogeneous polymer solution. Core material, diclofenac sodium (1.4 g) was added to the polymer solution (10 mL) and mixed thoroughly. The resulting mixture was then added in a thin stream to 100 mL of 0.1N HCl containing sodium CMC (0.5% w/v) contained in a 450 mL beaker while stirring at 200 RPM to emulsify the added droplets. A Remi medium duty stirrer with speedometer (Model RQT 124) was used for stirring. Stirring was continued for 5 min to disperse the added mixture as fine droplets. The dispersion was transferred to Buchner flask and stirring was continued with magnetic stirrer. The solvent was then removed by evaporation at RT (28°C) under reduced pressure (8 in. Hg Abs) to produce spherical microcapsules. The microcapsules were collected by decantation and washed with water. The product was then dried at 45°C for 4 h to obtain discrete microcapsules.

Preformulation study

The compatibility of diclofenac with the polymer cellulose acetate was initially investigated by using FTIR impact – 410, Nicolet, USA.

Evaluation of microcapsules

Microcapsules characteristics such as angle of repose, bulk density, true density and per cent compressibility were studied.

Size analysis

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

Estimation of diclofenac sodium

Diclofenac sodium content in the microcapsules was calculated by an UV spectro–photometric method based on the measurement of absorbance at 285 nm⁵. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 0–10 µg/mL. When a standard drug solution assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.8% and

1.2%, respectively. The amount of diclofenac sodium estimated from different samples and sizes are depicted in Table 1.

Microencapsulation efficiency

Microencapsulation efficiency was calculated using the formula.

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

The microencapsulation efficiency values are reported in Table 1.

Wall thickness

Wall thickness of microcapsules was determined by the method of Luu et al⁶ using the equation.

$$h = \frac{\bar{r} (1 - P) d_1}{3 [Pd_2 + (1 - P)d_1]}$$

Where h is the wall thickness,

r is the arithmetic mean radius of the microcapsules,

d₁ is the density of the core material,

d₂ is the density of the coat material and

P is the proportion of medicament in the microcapsules

The wall thickness of different microcapsules is reported in Table 1.

SEM studies

The microcapsules were observed under a scanning electron microscope (SEM – LEICA, S430, UK). For SEM, the microcapsules were mounted directly on to the SEM sample stab, using double – sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr). The SEM photograph of microcapsules is represented in Fig. 1.

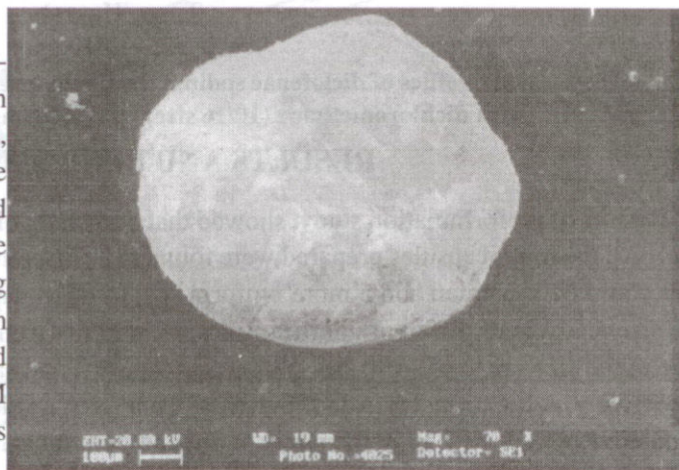


Fig. 1. SEM photograph of CA microcapsules of diclofenac sodium prepared by employing dichloromethane

Drug release studies

Release of diclofenac sodium from the microcapsules of size 10/16 and 22/44 was studied in phosphate buffer of pH 7.4 (900 mL) using an USP XXXIII dissolution rate test apparatus (M/s. Campbell Electronics, Mumbai) with a paddle stirrer at 100 rpm and at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. A sample of microcapsules equivalent to 100 mg of diclofenac sodium were used in each test. Samples were withdrawn through a filter (0.45μ) at different time intervals and were assayed at 285 nm for diclofenac sodium using an Elico double beam UV spectrophotometer. The drug release experiments were conducted in triplicate. The dissolution profiles are shown in Fig. 2–3.

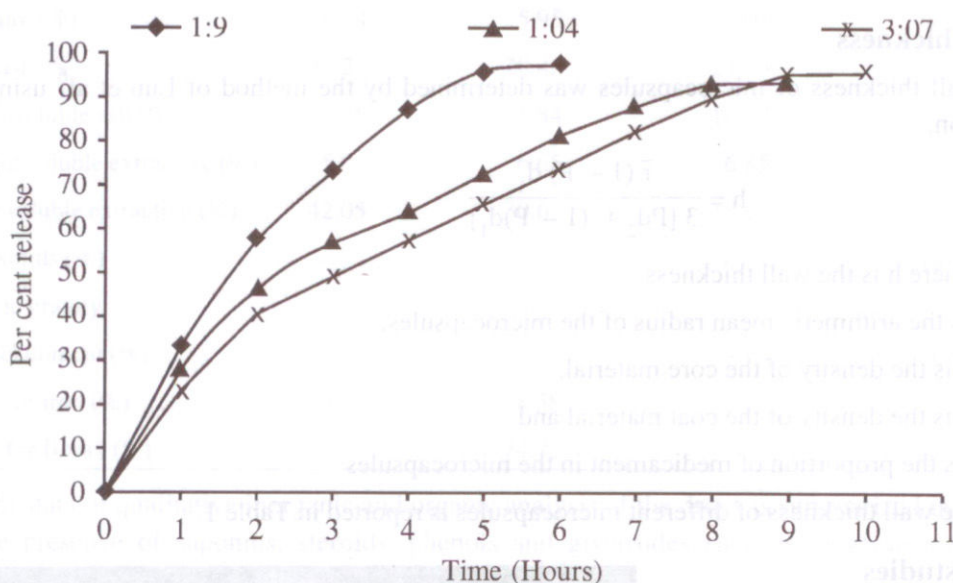


Fig. 2. Dissolution profiles of diclofenac sodium from cellulose acetate microcapsules prepared with dichloromethane (10/16 size) by employing coat : core ratio

RESULTS AND DISCUSSION

Results of preformulation study, showed that drug and polymer were compatible with each other. All the microcapsules prepared were found to be discrete, spherical and free flowing. The sizes could be separated and a more uniform size of microcapsules could readily be obtained. The size analysis of different microcapsules showed that generally about 12%, 25% and 36% were in the size range of $-10 + 16$ (1350μ), $-16 + 22$ (855μ) and $-22 + 44$ (532.5μ) mesh size, respectively. A lognormal size distribution of the microcapsules was observed in all the batches prepared. Low CV (< 2.0) in the per cent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical, the wall thickness of the microcapsules was calculated as per Luu et al.⁶

Table 1 : Wall thickness, micro encapsulation efficiency, drug content and release characteristics of cellulose acetate microcapsules

Coat : Core ratio	Size	Wall thickness	Micro encapsulation Efficiency	Drug content	Dissolution rate constant K_1 (hr ⁻¹)	T ₅₀
1 : 9	10/16	80.88	96.04	86.44	0.620	1.012
1 : 9	22/44	34.16	94.93	85.44	0.673	1.030
1 : 4	10/16	143.84	93.52	74.82	0.310	2.210
1 : 4	22/44	55.47	94.32	75.46	0.524	1.320
3 : 7	10/16	180.50	96.57	67.60	0.260	2.690
3 : 7	22/44	73.35	94.98	66.49	0.463	1.500

SEM photographs (Fig. 1) indicated that the microcapsules are discrete, nearly spherical and covered with continuous coating of the polymer.

Diclofenac release from the microcapsules was studied in phosphate buffer of pH 7.4 for a period of 12 h. Diclofenac release from all the microcapsules was slow and spread over an extended period of time. Release followed first order kinetics and controlled by diffusion mechanism. The drug release depended on size of the microcapsules and the coat : core ratio (Fig. 2–3).

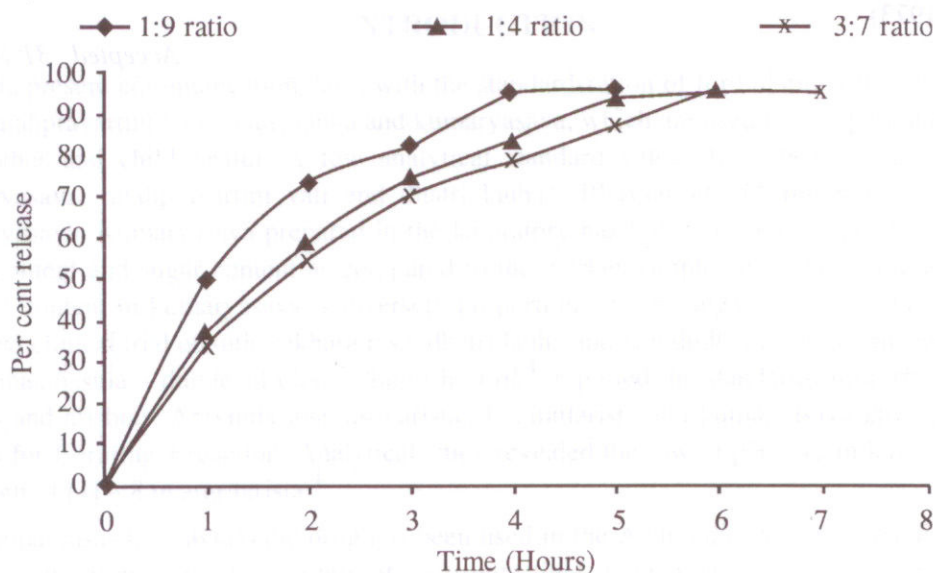


Fig.3. Dissolution profiles of diclofenac sodium from cellulose acetate microcapsules prepared with dichloromethane (22/44 Size) by employing coat : core Ratio

Large sized spherical microcapsules of cellulose acetate containing diclofenac sodium as core could be prepared by an emulsion solvent evaporation method. Drug release from the microcapsules can be controlled by the size of the microcapsules and the coat : core ratio employed in the preparation of microcapsules.

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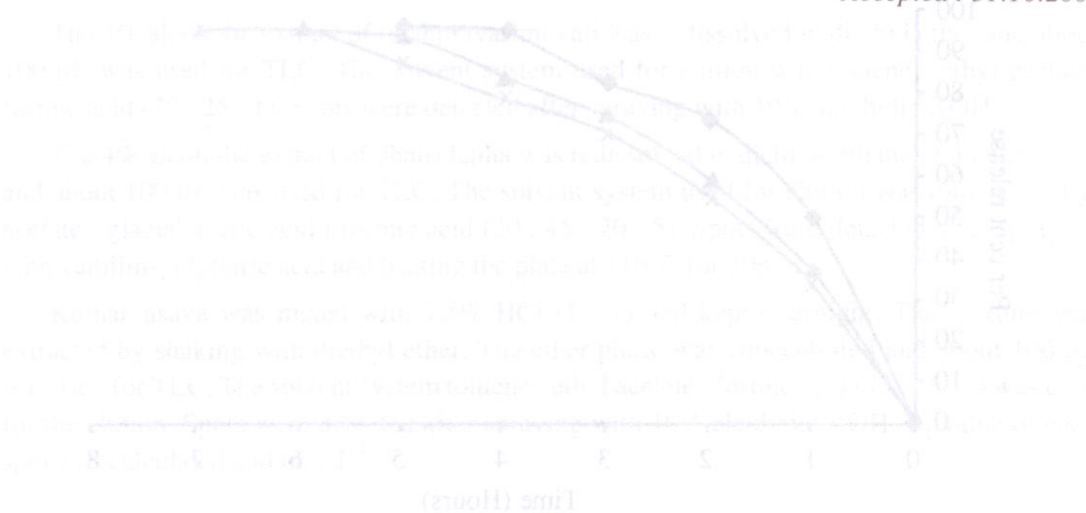


Fig. 1. Release profile of diclofenac sodium from cellulose acetate microcapsules prepared with diclofenac: cellulose acetate (1:1, 1:2, 1:4) by employing coat : core Ratio