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Polymeric Microcapsules for Drug Delivery

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ABSTRACT

Microencapsulation is a technique of enclosing a core material into a polymeric membrane such that the encapsulate may be released over a period of time by diffusion or spontaneously on collapsing the wall by a sudden pressure. Besides being used in the dyes, foodstuffs, and chemical industries, such a technique has also found applications in biomedicine for prolonged drug delivery. The present work discusses the possible use of cellulose acetate as an encapsulating material giving microcapsules for sustained drug delivery. The conditions of formation of such capsules containing testosterone as the drug, and its subsequent release from depots, are described. Scanning electron micrographs of these show formation of good, nearly spherical capsules in the range of 5-100 μm. The release of testosterone from the microcapsules sustains up to 35 d. Possible use of this system in medical applications is discussed.

INTRODUCTION

Microencapsulation is a process by which individual entities of a solid-liquid or gas are discretely enclosed in a shell of inert material of 5 to 500 μm in size [1]. These shells may be designed to release their ingradients at a specific rate under a given set of conditions or on collapsing under pressure to completely release the core material.

The technique of microencapsulation has varied applications. Specifically, it has received increasing attention in biomedical applications for a controlled and sustained release of drugs. Among the three methods of encapsulation (condensation, interfacial polymerization, and coacervation), the last one has been chosen in the present work. Various investigators have presented mathematical approaches to optimize and evaluate the coacervation process [2]. This process has been used for the preparation of microcapsules of higher cellulose ester [3] for a slow and prolonged release of acetylsalicylic acid and barbituric acid. The drug from microcapsules was released from these capsules by diffusion. Several other papers have been published on the release of drug through diffusion [4].

We report in this paper the results of our investigations on the release rates of testosterone from cellulose acetate microcapsules. Donsely and Parker [5] in studies on rats showed that implanted compressed pellets of crystalline androgens were highly effective in maintaining the secondary organs. Subsequent studies have confirmed that pellet implantation is from the physiological standpoint the most efficient method by which the androgens may be administered [6, 7] because absorption from the pellet is slow, continuous, and devoid of transient peaks which are wasteful of hormone. They have further shown that implanted testosterone in the form of pellets is 5 to 8 times more effective. However, placement of pellet subcutaneously involves incision. This may be avoided if microcapsules of steroids are prepared, since these can be easily injected.

MATERIALS AND METHODS

Capsules were prepared by a nonaqueous phase separation technique in which the wall material, being hydrophobic in nature, is precipitated by a suitable combination of organic solvent, polymer [8], and water.

Cellulose acetate and testosterone were obtained from B.D.H. (England). All the other reagents were of analytical grade.

FORMATION OF MICROCAPSULES

After trying different solvent-nonsolvent systems, acetone was chosen as the solvent and water as the nonsolvent. Cellulose acetate (CA) in acetone (0.15 g in 15 mL) was mixed with 50 to 80 mg of testosterone (TS). Thirty percent formalin containing 0.15 g of gum arabic [9] (GA) was dropped into the cellulose acetate solution and agitated in an ultrasonic vibrator for 10 min through a syringe-based apparatus for making microcapsules as described by Sparks et al. [10]. Fifteen milliliters of 20% Tween-20 solution was added to prevent agglomeration of capsules. The fluffy capsules precipitating

out were allowed to stand for 24 h. The supernatant was decanted and the capsules were dried at 40°C in an incubator for 24 h. The product was obtained as a white, free-flowing powder. Scanning electron micrographs of the capsules were taken by a Cambridge Steroscan 85 instrument. Release of the encapsulated drug was studied by following its elution into a Ringer phosphate buffer (pH 7.4) spectrophotometrically. For a typical experiment, 0.35 to 0.40 g of the microcapsules were equilibrated with 15 mL of the buffer for 24 h. The supernatant was separated by centrifugation and its optical density determined by absorbance at 248 nm. A fresh 15 mL of buffer was equilibrated till no more elution of the drug occurred.

RESULTS AND DISCUSSION

Scanning electron micrographs of cellulose acetate microcapsules (magnification 1.5 × 6000) containing testosterone are shown in Figs. 1 and 2. The capsules are near spherical in shape and their dimensions are in the range of 5-10 μm.

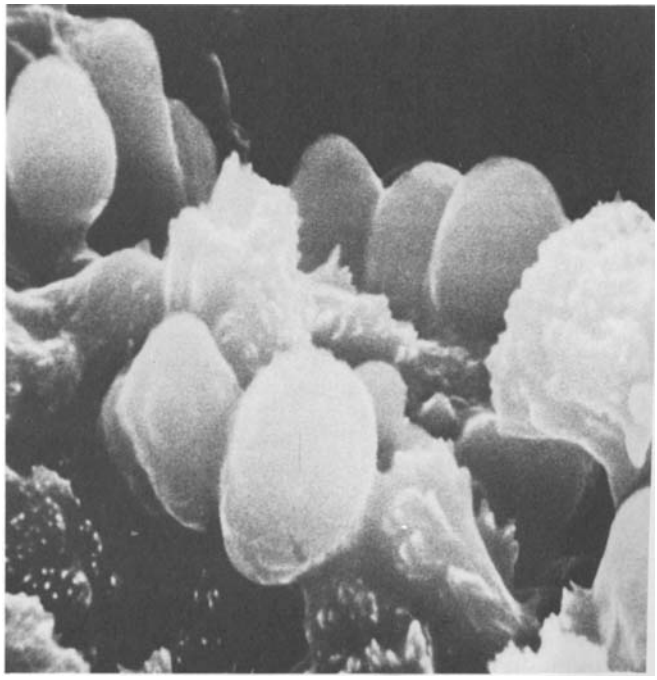

FIG. 1. Scanning electron micrograph of cellulose acetate containing testosterone.

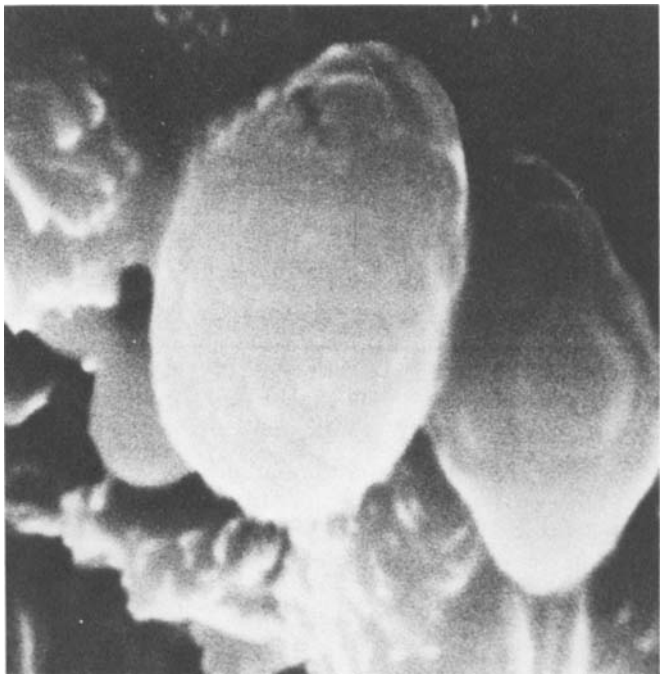

FIG. 2. Scanning electron micrograph of cellulose acetate containing testosterone.

The release from cellulose acetate microcapsules (300 mg) containing encapsulated testosterone from Preparations I, II, and III respectively was observed. The cumulative release data in milligrams of testosterone released are shown in Tables 1 and 2. It is seen that from Sample I a total of 32 mg is released in 30 d. This is 80% of the total testosterone used; that is, the amount encapsulated is 80% of the total core material taken. In Fig. 3 the release per day is plotted against time in days for Sample III. The release profiles are similar for the other samples. The amount released per day uniformly decreases without any spurt in the first few days (Fig. 3). This clearly indicates that there is no free steroid and that all the material is released by the same mechanism. The process is probably diffusion controlled. Since the conditions of encapsulation, including the amounts of wall materials, CA, and GA, were kept constant, the wall thickness may be approximately the same in all three cases. However, the amount of core material in the three capsules varied as III > II > I. The longest release is with III, indicating that prolonged release can be achieved by proportionally increasing the core material taken. However, in this case the dosage per day would also increase.

TABLE 1

Sample	Encapsulation in cellulose acetate material taken			Cumulative drug release at pH 7.4	
	CA (g)	GA (g)	TS (mg)	Total released (mg)	Depot exhausted (d)
I	0.15	0.15	40	32	30
II	0.15	0.15	50	38	32
III	0.15	0.15	60	50	35

TABLE 2. Release of Testosterone from Microcapsules Containing Different Concentrations of Drug

Time (d)	Cumulative release (mg) and % of testosterone containing different concentrations of drug					
	I	%	II	%	III	%
5	9.7	24	12.1	24.2	15.00	25
10	17.4	43	20.2	40.4	24.30	40
15	24.5	61	27.00	54.0	32.50	55
20	27.9	68	31.2	62.0	39.40	65
25	29.6	75	33.7	67.4	45.20	75
30	32.0	80	36.0	72.0	48.20	80
32	-	-	38.0	76.0	49.70	81
35	-	-	-	-	50.90	83

Possibly a longer rate of release at smaller dosages may be achieved by increasing the wall thickness.

The data on release were fitted into a first-order rate equation. In all cases the plots of log a/(a - x) vs t are linear (Fig. 5), where "a" is the total steroid encapsulated and "x" is the amount released. The values of the rate constant K were 0.95×10^{-1}, 1.1×10^{-1} and 1.0×10^{-1} d^{-1} for Samples I, II, and III, respectively.

Thus the three independent experiments give the same kind of release profile which is possibly diffusion controlled. Such a release in vivo can be of use where, instead of a constant zero-order release, a continuous but uniformly decreasing drug release is required. The

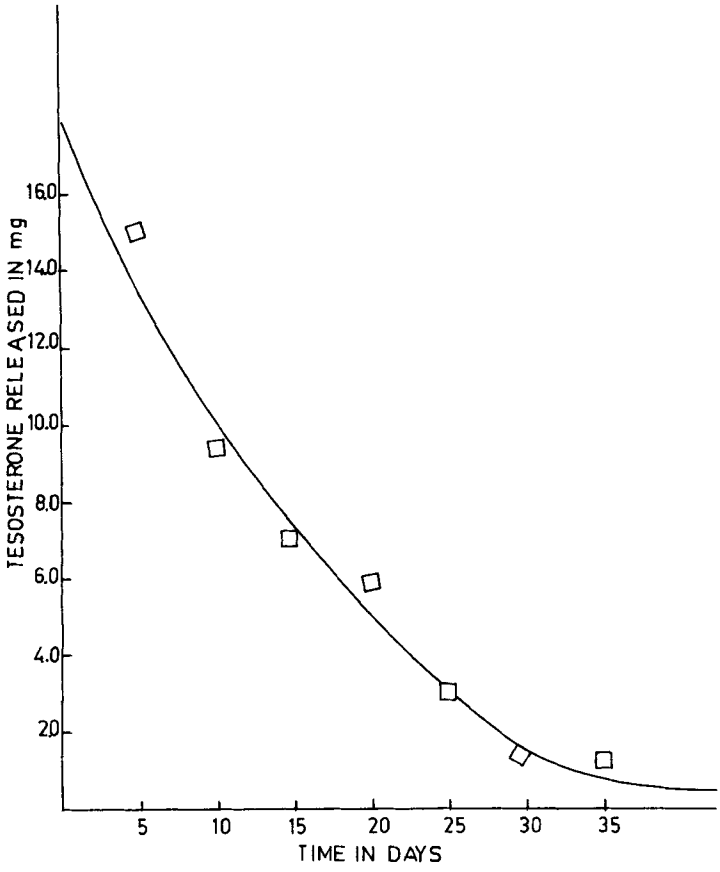

FIGURE 3.

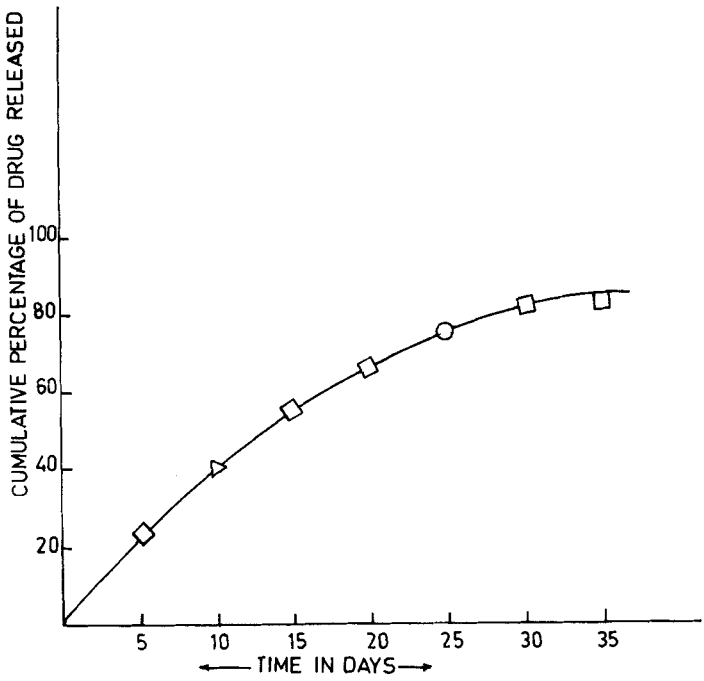

FIGURE 4.

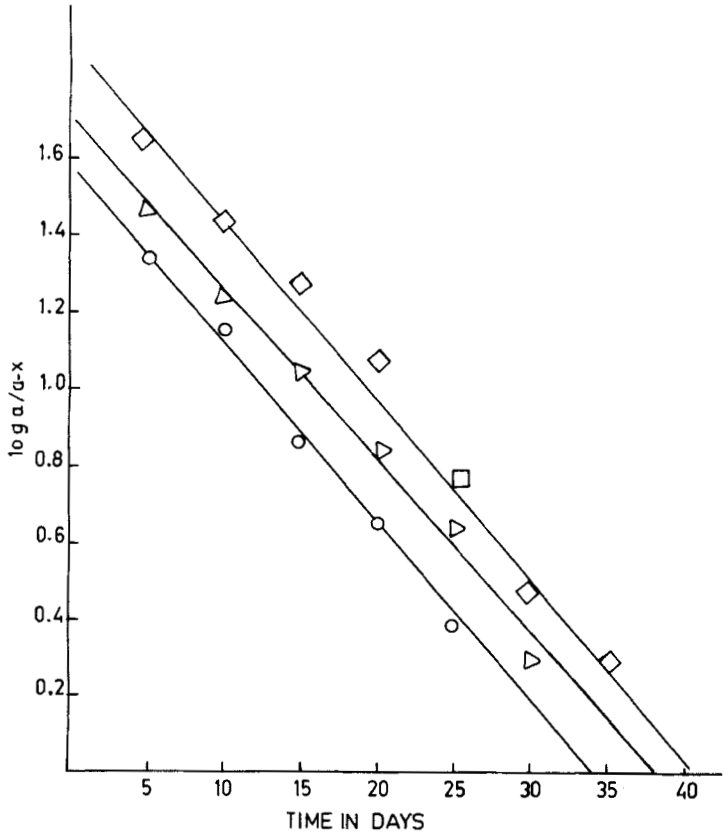

FIGURE 5.

rate of release may of course be quite different in vivo as compared to in vitro since the drug level would not only depend on the rate of release from the capsules but also on the removal of the drug from the system.

Gardner et al. [11] studied the "in vivo" release of estron from cellulose acetate butyrate microcapsules. They also reported sustained release of the steroid hormone estron over 20 d. After the first 8 d the amount coming out was only 8 μg/d. However, for highly potent drugs a release rate of a few μg/d may still be useful. In the light of the above, the present system has the potential for sustained drug delivery and the in vivo release is under study.

CONCLUSION

Good spherical microcapsules can be obtained from cellulose acetate under the conditions described with testosterone as the drug. The release of testosterone was sustained for about 35 d. These preparations may be useful in certain treatments where gradually decreasing dosages of the drug are required.

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