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Report

Modification of Gelatin Beadlets for Zero-Order Sustained Release

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A three-phase suspension process was used for the preparation of gelatin beadlets containing succinylsulfathiazole. When the beadlets were hardened with 10% formalin at 5°C for varying periods of time up to 24 hr, the 6-hr hardening time gave the slowest release rate. Drug release rate from gelatin beadlets was slower in simulated gastric fluid (SGF) than in simulated intestinal fluid (SIF) but the sustained effect was too limited to be useful for most applications. When the hardened gelatin beadlets were coated with cellulose acetate butyrate (CAB) by an emulsion–solvent evaporation method, a more pronounced sustained effect and a nearly zero-order release were found in SIF. The effects of the amount of gelatin used, the amount of CAB employed, and the length of hardening time on drug release were investigated. The treatment of gelatin beadlets with formalin reduced the swelling action of gelatin in aqueous medium. A nonzero-order drug release rate was observed when the gelatin swelled sufficiently to rupture the CAB coating. The drug release rate can be adjusted by using different ratios of hardened gelatin beadlets and CAB coating in which the gelatin enhances the release rate and the CAB serves as a barrier.

KEY WORDS: gelatin beadlets; cellulose acetate butyrate-coated microcapsules; zero-order release; sustained release.

INTRODUCTION

In order to treat a disease effectively, the drug dose regimen should be scheduled so that the plasma level does not decrease below the minimum effective concentration. However, frequent administration is a burden to a patient. Thus, ways to maintain an effective plasma level for a longer period of time are often desired. Microencapsulation has been recognized as an effective method to achieve a sustained release effect (1). Although several microencapsulation processes are available, e.g., simple coacervation (2) and complex coacervation (3,4) processes, the three-phase suspension process which was first reported in 1939 (5) is a simple and easily controlled method when gelatin is used as an encapsulant. Tanaka *et al.* (6) modified this technique in 1963 and showed that only simple equipment is needed. Paradissis and Parrott (7) and Goto *et al.* (8) employed the same technique to encapsulate drugs. Leucuta (9) prepared magnetic microspheres of gelatin containing metronidazole which were coated with ethyl cellulose to extend the release time. These coated microspheres showed spherical matrix release kinetics in 0.1 *N* HCl. There have been few reports on the dissolution behavior of gelatin beadlets in simulated intestinal fluid (SIF).

This study investigates the dissolution behavior of gelatin beadlets in simulated gastric fluid (SGF) and SIF and develops an optimum reservoir-type microcapsule system from cellulose acetate butyrate (CAB)-coated gelatin beadlets to achieve a zero-order sustained-release rate.

EXPERIMENTAL

Preparation of Gelatin Beadlets

A known quantity of succinylsulfathiazole (SST) was added to a specified concentration of gelatin solution (Table I) which was maintained at 55–65°C and dispersed by using a magnetic bar. After the drug was uniformly suspended in the solution, the mixture was added to 150 ml mineral oil which was preheated to 55–65°C. The suspension was stirred mechanically at a constant speed until the gelatin droplets formed. The droplets were solidified by cooling rapidly to 2–5°C in an ice bath. Stirring was continued for at least an hour, then 150–225 ml of 10% formalin–isopropanol was added and stirring was continued for another 30 min. The formed gelatin beadlets were then refrigerated at 5°C for 4, 6, and 24 hr, respectively. After hardening, the gelatin beadlets were washed with two portions of isopropanol and dried at room temperature for 15–16 hr. The beadlets were then washed with three portions of *n*-hexane to eliminate residual mineral oil and dried for 4 hr.

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Table I. Formulations of Gelatin Beadlets Containing Succinylsulfathiazole (SST)

Formulation	Gelatin (g)	SST (g)	Water (ml)	Hardening time (hr)
1	12.5	10	50	6
2	10.0	10	40	6
3	7.5	10	30	6
4	5.0	10	20	6
5	7.5	10	30	0
6	7.5	10	30	4
7	7.5	10	30	24

Encapsulation of Gelatin Beadlets with CAB

Gelatin beadlets containing SST were suspended in a CAB–acetone solution. When a uniform suspension was formed it was emulsified in heavy mineral oil, then the acetone was evaporated while stirring continued. The rigid microcapsules were separated from the dispersing medium by centrifugation and filtration. Three portions of *n*-hexane were used to wash the microcapsules, which were then dried in a desiccator for 4 hr.

Dissolution Studies

A method similar to the USP paddle method was used. A 50-mg sample of microcapsules was placed in a dissolution vessel containing 1000 ml of dissolution medium (SGF or SIF with 0.02% Tween 80, without enzyme). The temperature of the dissolution medium was maintained at 37 ± 0.5°C, the stirring speed was fixed at 100 ± 1 rpm. At appropriate time intervals, samples (4 ml) were withdrawn and assayed spectrophotometrically at 257 nm. After analysis the samples were immediately returned to the dissolution vessel. Each dissolution data point is the average of six determinations.

RESULTS AND DISCUSSION

The particle size of gelatin beadlets depended mainly upon the speed of agitation during the formation of the gelatin droplets. The faster the agitating speed, the smaller the particle size. Particles having an average size of 335 μm (passed on 420 μm, retained on 250 μm) were chosen as the core because this size was found to be the most suitable for subsequent coating with CAB. During coating, smaller particles tended to aggregate to form multicore microcapsules which were easily broken in the dissolution test.

Dissolution studies were carried out in both SGF and SIF. Figure 1 shows that the dissolution of both SST powder and uncoated gelatin beadlets was slower in SGF than in SIF. The release of the drug from uncoated gelatin beadlets was dependent on the pH value of the dissolution medium. Nixon *et al.* (10) and Khalil and El Gamal (11) have reported similar results for other drugs. Since dissolution is more rapid in SIF and sustained-release beadlets would normally be exposed to an environment similar to SIF for the majority of time in the body, SIF was employed for the remaining studies.

The drug release rate from hardened gelatin beadlets showed some sustained effects (Fig. 2). Different formalin exposure times gave different extents of sustained release, with the 6-hr hardening time possessing the longest sustained effect. Longer hardening times allowed more rapid loss of the drug, possibly because of the formation of cracks or fracture lines in the beadlets, similar to results reported by Madan *et al.* (12) for microcapsules. After coating the beadlets with CAB, much slower release rates were observed. There were apparent differences between the formalin-hardened and the unhardened gelatin beadlets (Fig. 3). A near zero-order release rate was achieved when hardened gelatin beadlets were coated with CAB.

The optimum hardening time for minimum swelling and lowest release rate was 6 hr. Treatment of gelatin beadlets for 24 hr resulted in fracture lines on the beadlets, a greater surface area, and a greater porosity. Thus, the release rate was higher than for the beadlets treated for a shorter time.

Figure 4 shows that when the CAB-to-gelatin ratio was maintained constant, the higher the gelatin-to-drug ratio, the faster the drug was released. This can be explained by the stronger swelling action of the larger gelatin proportion. Figure 5 shows that the smaller the amount of CAB employed to coat the gelatin beadlets, the faster the drug was released

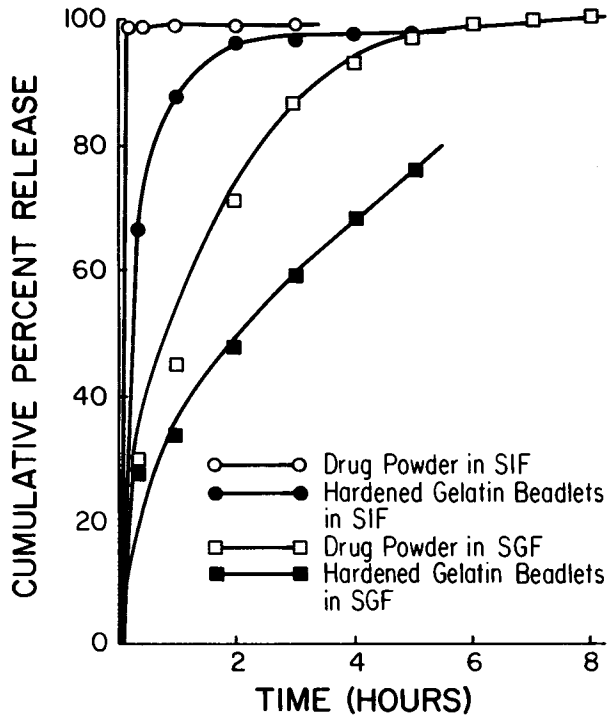

Fig. 1. Dissolution of succinylsulfathiazole from uncoated gelatin beadlets hardened with 10% formalin for 6 hr in SIF and SGF.

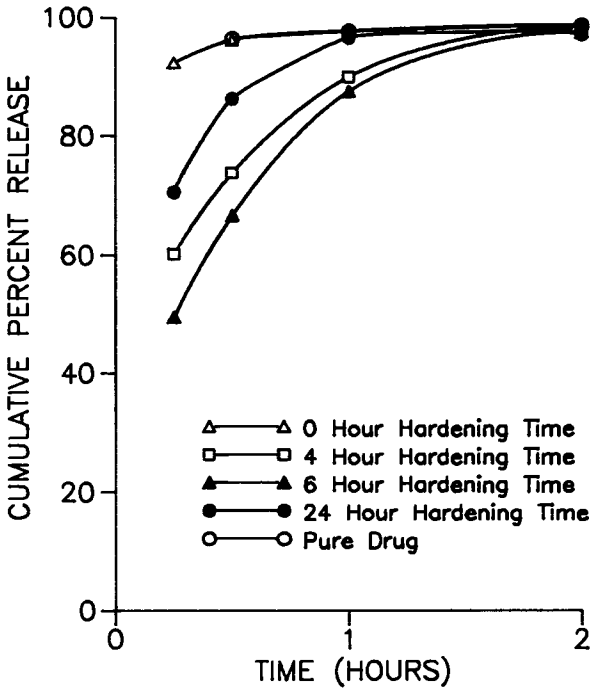

Fig. 2. Effect of gelatin hardening time on drug release from gelatin beadlets in SIF.

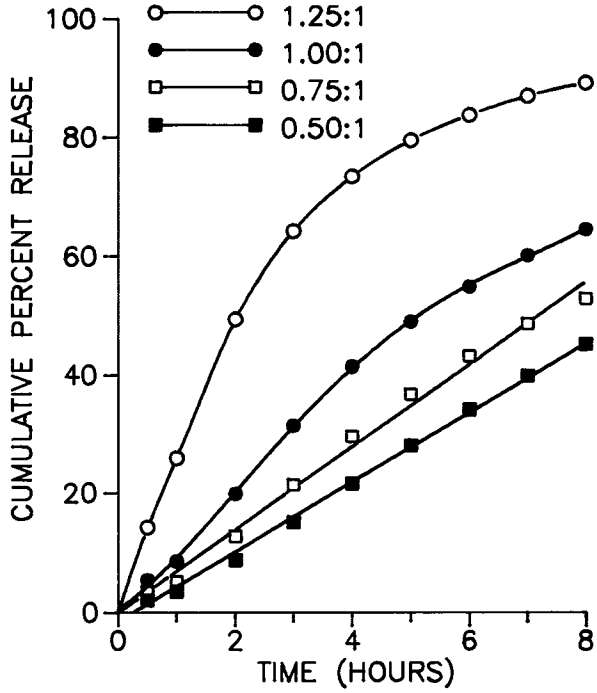

Fig. 4. Effect of gelatin-to-drug ratio in gelatin beadlets on drug release from cellulose acetate butyrate microcapsules in SIF (constant CAB amount).

from microcapsules. This can be attributed to the reduced thickness of the microcapsule wall caused by the decreased amount of polymer available.

When the amount of gelatin used was halved, the zero-order release pattern was always kept, even when the CAB to gelatin beadlets ratio was decreased further, to 0.5 to 1.

From microscopic observation of spent microcapsules, it is clear that the key factor for keeping zero-order release was whether the gelatin swelled sufficiently to rupture the CAB coating. When the amount of the gelatin used was halved,

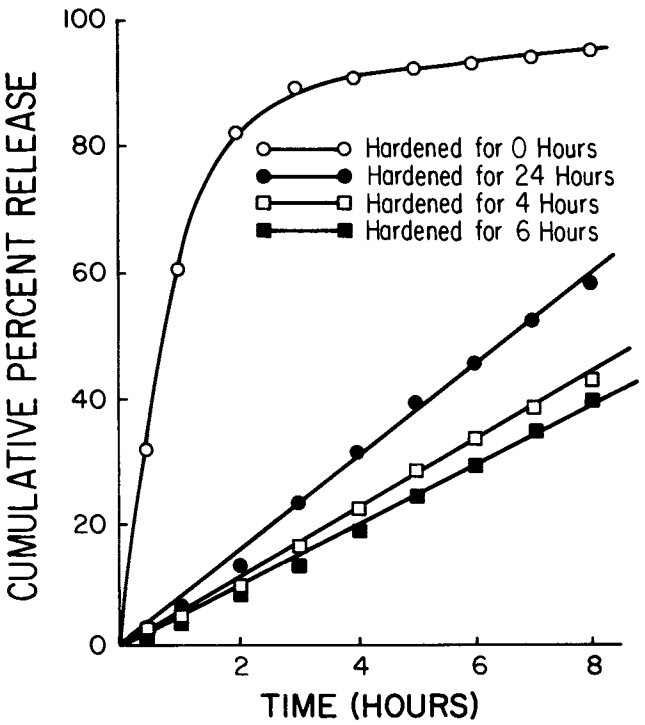

Fig. 3. Effect of gelatin hardening time on drug release from cellulose acetate butyrate microcapsules in SIF.

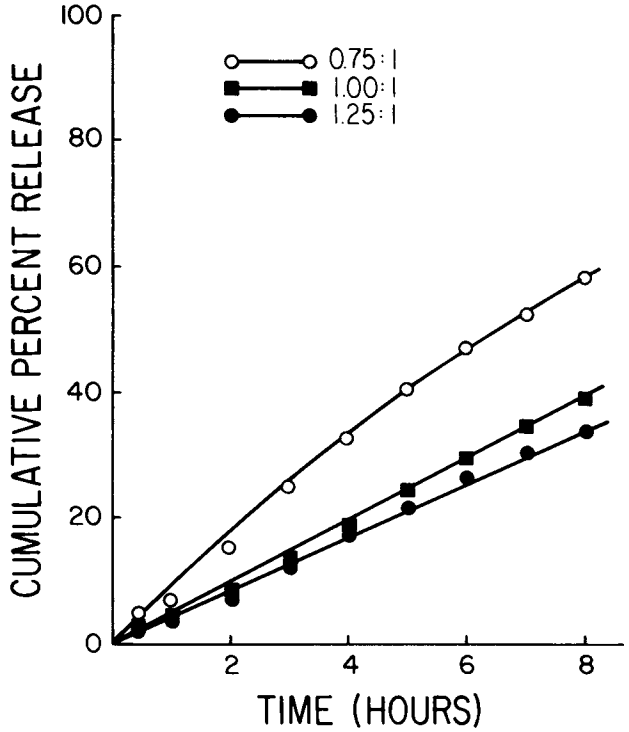

Fig. 5. Effect of cellulose acetate butyrate-to-gelatin beadlets ratio on drug release of microcapsules in SIF.

the swelling action was reduced and was less likely to rupture the coating.

CONCLUSION

(1) Formalin-hardened gelatin beadlets showed some sustained effect compared to unhardened beadlets, but the most pronounced effect was found in gelatin beadlets coated with cellulose acetate butyrate.

(2) The higher the cellulose acetate butyrate-to-gelatin beadlets ratio, the slower the release rate.

(3) Zero-order release rate can be accomplished by coating hardened gelatin beadlets with cellulose acetate butyrate.

(4) The amount of gelatin employed in making gelatin beadlets has a determinative effect on drug release from cellulose acetate butyrate microcapsules.

(5) The relative amounts of gelatin and cellulose acetate butyrate employed can be adjusted to control the drug release rate. Increased gelatin enhances the release rate, while cellulose acetate butyrate serves as a barrier membrane.

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