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DRUG RELEASE FROM DIRECTLY COMPRESSED TABLETS CONTAINING ZEIN

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ABSTRACT

The tablets prepared by the direct compression of spray-dried particles of a drug and zein were evaluated in vitro. The release of drug from the tablets was retarded compared with drug powder alone and tablets prepared from the physical mixtures. Drug release from the tablets was controlled by changing drug content and tablet weight.

INTRODUCTION

Drug release at the site of absorption and/or action at a controlled rate, over a required period of time is a contemporary therapeutic goal. In order to accomplish this objective, many biodegradable polymers have been utilized as drug carriers (1).

Zein is a natural polymer (corn protein) and has been used as edible coating for ingredients of food stuffs and pharmaceutical preparations due to its unique solubility characteristics (2, 3). However, there are few detailed reports of the effect of zein on the release of drugs or concerning the preparation of sustained-release tablets by the direct compression method. In this study, we investigated the release of drugs from zein tablets prepared from spray-dried particles in vitro.

EXPERIMENTAL

Materials

Zein was supplied by Nacalai Tesque, Inc. Salbutamol sulfate (SS) was kindly gifted from Hitachi Chemical Co., Ltd. Prednisolone (PD) and sodium cefazolin (CEZNa) were obtained from Wako Pure Chemical Ind. Ltd., and Fujisawa Pharmaceutical Co., Ltd., respectively. Pepsin isolated from porcine stomach

mucosa was obtained from Sigma Chemical Co. All other chemicals were of the finest grade available.

Spray-Drying

The spray-dryer used was GA-31 type (Yamato Scientific Co., Ltd.), having a drying chamber of 0.13 m in diameter. Each drug was dissolved in 70 (v/v) % ethanol and then zein was added to the solution (0.5 (w/v) %). Unless otherwise stated, the drug content in solid (drug + zein) was 9.1 (w/w) %. The solution was fed to the spray-dryer by using a roller pump (6 ml/min). The temperatures at the inlet and outlet of the drying chamber were 120 and 70 ± 5 °C, respectively. The amount of drying air supplied was adjusted to maintain this drying condition.

Tablet Preparation

A flat-faced 13 mm diameter tablet was prepared by compressing the spray-dried materials or the physical mixture of spray-dried zein particles and drug powder applying 600 kg/cm² force for 4 min using a Shimadzu hydraulic press (SSP-10 type).

Release Studies

The drug release studies were conducted in a JP XI dissolution test apparatus with a paddle stirrer at 37 ± 0.5 °C. The medium for the release studies was either distilled water or the JP XI disintegration test solution No. 1 (pH 1.2). Aliquots (0.1 ml) of the

medium were removed at appropriate intervals and analyzed for drug content. At the end of the experiments, tablets were taken out, rinsed and dissolved in 70 (v/v) % ethanol for residual drug analysis.

Analytical Methods

A Shimadzu LC-4A high performance liquid chromatograph (HPLC) equipped with a Shimadzu SPD-2AS spectrophotometric detector (set at 245 nm for PD, 270 nm for CEZNa) and ODS 120-T column (15 cm x 4.6 mm i.d.; 5 μm particle size) was employed to determine PD and CEZNa. The mobile phases were composed of 0.03 M KH_2PO_4 and methanol (70:30, v/v) for CEZNa and of acetonitrile, methanol and distilled water (30:30:40, v/v) for PD. A Shimadzu LC-6A HPLC equipped with a Shimadzu RF-535 fluorescence HPLC monitor (set at an excitation wavelength of 230 nm and an emission wavelength of 310 nm) and Zorbax C_8 column (25 cm x 4.6 mm; 5-6 μm particle size) was employed to determine SS. The mobile phase was a mixture of 5.8 mM phosphate buffer (pH 6.0) and methanol (69:31, v/v) (4).

SEM

After spray-drying the particles obtained were observed using a scanning electron microscope, Hitachi Akashi ALPHA-25A type.

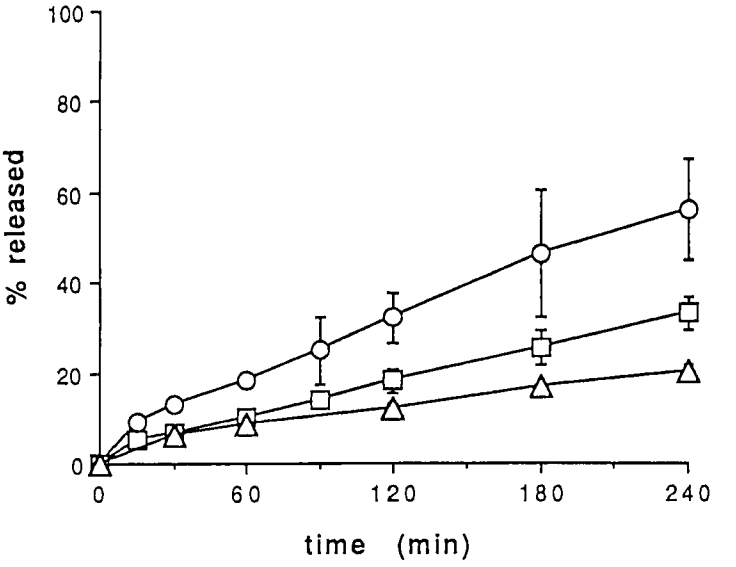

FIGURE 1

Release of drugs from zein tablets. The release media are JP XI Disintegration Medium No.1 (pH1.2) for prednisolone and salbutamol sulfate and distilled water for cefazolin Na. Each tablet weighs 80 mg and contains 9.1 (w/w) % of drug. The vertical bar represents the SD of 3 tablets.
○, SS; □, CEZNa; △, PD.

RESULTS AND DISCUSSION

Effect of Drug Solubility on The Release of Drug

The release patterns of 3 model drugs are shown in Fig. 1. All drugs showed an apparent zero-order release after a little burst. The release of these drugs from zein tablets was retarded compared with drug powder alone. In all cases, tablets did not disintegrate in the release medium. The release rates of water soluble drugs (SS, CEZNa) from the tablets were

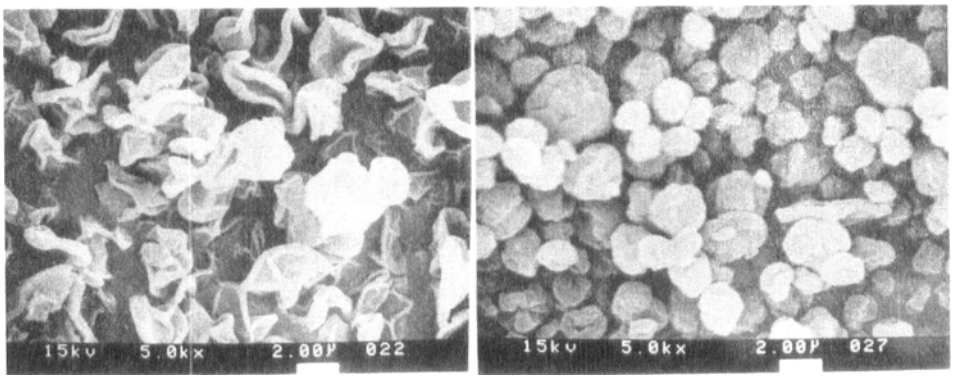

FIGURE 2
Scanning electron micrographs of zein particles. (A) without drug. (B) containing 9.1 (w/w) % of salbutamol sulfate.

greater than that of PD which is sparingly soluble in water. The spray-dried particles containing no drugs or PD were not spherical and not uniform in appearance, while those containing water soluble drugs became almost spherical (Fig. 2). The tablets containing drugs swelled in the release medium. Finally, it was found that the release of drugs from directly compressed tablets was retarded and depended on their solubility.

Effect of mixing ratio and type of mixtures on the release of drug

The release of SS from tablets (40 mg) loaded with different amounts of the drug (4.8, 9.1, 16.7 (w/w) %)

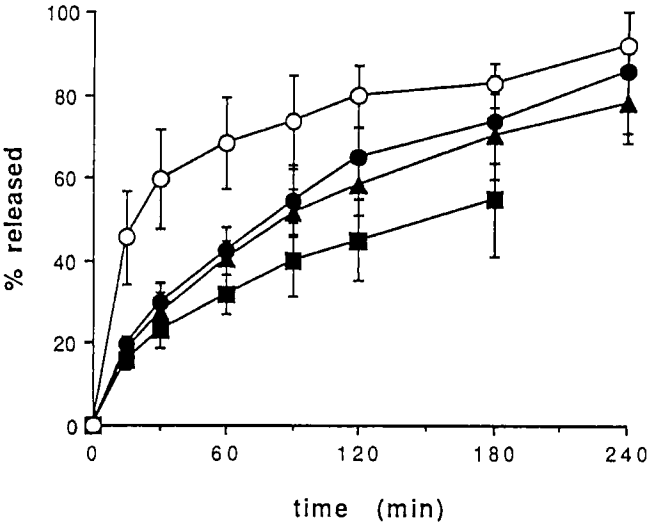

FIGURE 3
Effect of mixing ratio and type of mixtures on the release of salbutamol sulfate. Each tablet (40mg) contains 16.7 (●), 9.1 (▲) and 4.8 (■)(w/w) % of salbutamol sulfate. The tablet prepared from physical mixture (○) contains 9.1 (w/w) % of salbutamol sulfate. The vertical bar represents the SD of 3 tablets.

is shown in Fig. 3. The release rate of SS from the tablets containing 4.8 (w/w) % SS was smaller than those from the other tablets. In addition, these tablets proportionally swelled as the drug content increased. On the other hand, the tablets prepared from the physical mixture showed a greater initial burst than those from spray-dried particles. This might vary as a function of the distribution of the drug in the protein matrix and the nature of molecular interaction.

In conclusion, it was confirmed that the tablets made of spray-dried particles were superior to those of

the physical mixture in terms of sustained release of drug and it may be possible to control the drug release by changing drug ratio to zein in a tablet.

Effect of tablet weight on the release of drug

The effect of the tablet weight on release of drugs is shown in Fig. 4. The release of SS and CEZNa was proportionally retarded as tablet weight increased (Fig. 4). After a short burst phase, an apparent zero-order release was observed in 80 and 160 mg tablets. Since the swelling of the 40 mg tablet was much greater than that of the others during release experiments, it was suggested that the extent of swelling was affected by tablet weight. The characteristics of the tablets containing SS is summarized in Table I. It was difficult to explain the difference in release rates by total surface area and apparent density of tablets. Hydration of the tablets could be important for explanation of the difference (5, 6). Finally it was found that the release rate was a function of the tablet weight which is corresponding to zein weight in formulation.

Effect of pepsin on the release of drug

Zein is a protein and therefore it is important to investigate the nature of drug release in gastric fluid containing pepsin, a protease, if tablets are to be administered orally. Consequently, the effect of pepsin on the release of drug and disintegration of tablets was

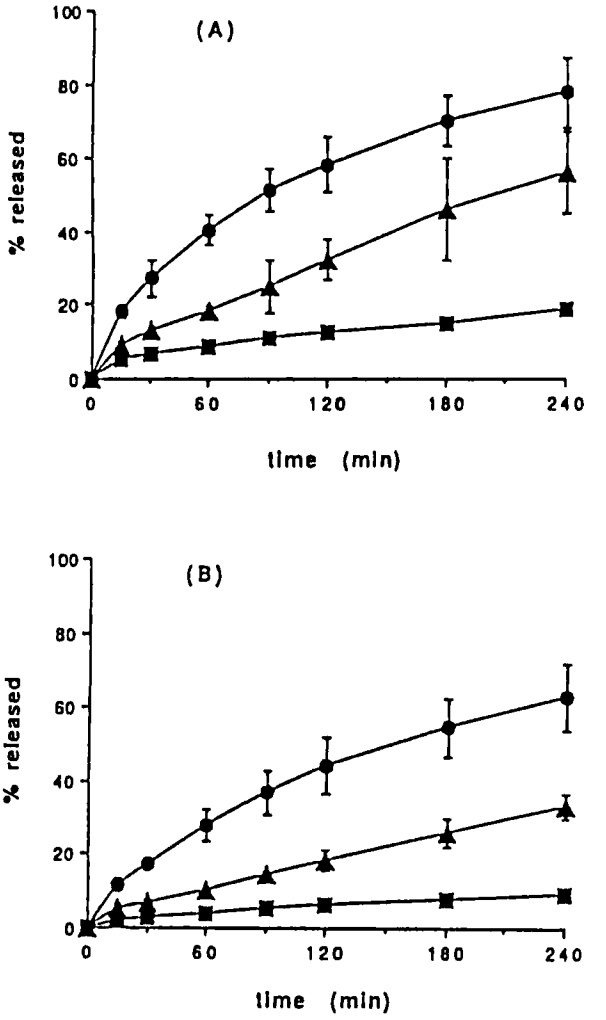

FIGURE 4
Effect of tablet weight on the release of drug. Each tablet contains 9.1 (w/w) % of salbutamol sulfate (A) or cefazolin Na (B). The vertical bar represents the SD of 3 tablets. ●, 40 mg tablet; ▲, 80 mg; ■, 160 mg.

TABLE 1

Characteristics of Zein Tablets Containing Salbutamol Sulfate

weight (mg)	SA[1] (mm^2)	volume (mm^3)	thickness (mm)	D,app[2] (mg/mm^3)
40	277	37.6	0.283	1.08
80	287	70.3	0.530	1.10
160	308	138.0	1.040	1.16

The diameter of the tablet is 13 mm.
[1] SA is total surface area of the tablet.
[2] D,app is apparent density of the tablet.

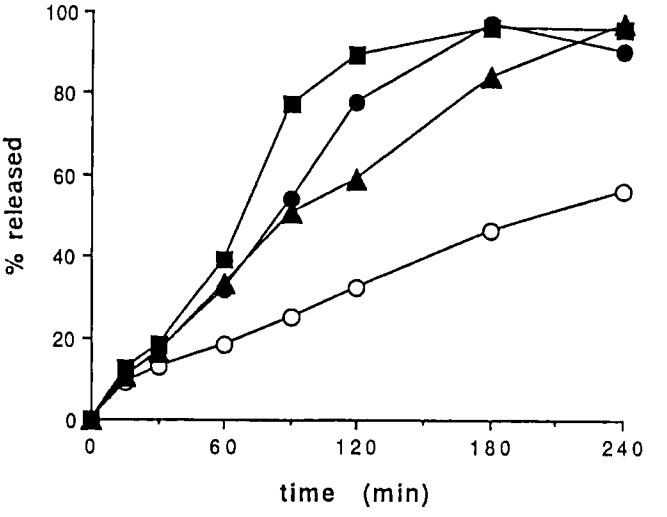

FIGURE 5
Effect of pepsin in release media on the release of salbutamol sulfate. Each tablet (80 mg) contains 9.1 (w/w) % of salbutamol sulfate. ■, + 500 mg pepsin in 500 ml of release media; ●, + 250 mg pepsin; ▲, + 50 mg pepsin; ○, no pepsin. n=2 or 3.

evaluated (Fig. 5). The amount of pepsin added into the release medium was determined according to the daily basic secretion amount of the enzyme in an adult (280 - 770 mg)(7). The drug release from each tablet containing SS was facilitated by increasing the amount of pepsin in the release medium. The SS-containing tablets disintegrated within 4 h, if the content of pepsin was more than 250 mg / 500 ml release medium. In the case of 50 mg pepsin, the tablet swelled but did not disintegrate. Finally, the release of drugs was affected by pepsin and that tablets were digested by the enzyme (> 0.5 mg/ml) as expected.

In conclusion, drug release from zein tablets, prepared by compressing spray-dried particles directly, was sustained and could be controlled by changing drug content and tablet weight.

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