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SHORT COMMUNICATIONS

Sustained Release of Oxytetracycline from Chitin Tablet

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In recent years, much attention have been paid to the drug delivery systems using biodegradable polymers. Chitin, which is one of biodegradable polymers, is a natural mucopolysaccharide consisted of *N*-acetyl-D-glucosamine unit and chitosan is *N*-deacetylated product of chitin. It is important that the concentration of an administrated reagent in blood is maintained at a suitable level as long as a possible for the treatment and prophylaxis disease. There is a commercial long acting injectable solution "Teramycine/LA" (Pfizer Co., Ltd.) which contains oxytetracycline (OTC) and used at the treatment of infectious disease of cow or pig, however, this needs repeating injections at 3—5 day intervals and gives sharp pain at the injection. Tian-Rui *et al.* reported the dissolution properties of water-soluble drugs from directly compressed tablets using chitosan with high degree of polymerization, chitosan with low degree of polymerization, 60% deacetylated chitin or hydroxypropylchitosan, in considering a development of per-oral sustained release tablets.[1] One of our purposes is to develop the sustained release of oxytetracycline against dressing animals by subcutaneous administration for a long period. In the preceding paper, it was found that chitin and chitosan showed good biocompatibility in animal body.[2] Moreover, it was reported that some of chitin derivatives showed an immuno-adjuvant activity in mice.[3]

In this study, we prepared the tablet which contained OTC·HCl and chitin, followed by covering with various chitin derivatives such as carboxymethylchitin (CM-chitin), dihydroxypropylchitin (DHP-chitin), and partially deacetylated chitin (DAC), and observed the release of OTC·HCl from tablet in the phosphate buffer solution (pH = 7.1).

EXPERIMENTAL

Materials

Chitin of shrimp shell and oxytetracycline hydrochrolide (OTC·HCl) were purchased from Wako Pure Chemical Industries, Ltd. Partially deacetylated chitin (67% of deacetylation: DAC-67) was purchased from Katokichi Co., Ltd. Carboxymethylchitin (CM-chitin) and dihydroxypropylchitin (DHP-chitin) were prepared from chitin of squid pen (Nippon Suisan Co., Ltd.) according to the method of Tokura.[4] Other reagents were purchased from Nakarai Tesque, Inc. and used without further purification.

Preparation of Tablet Covered with Polysaccharide

A typical procedure to prepare the tablet covered with polysaccharide (CM-chitin and DHP-chitin) is as follows: chitin powder (shrimp shell) of 200 mg and 200 mg of

OTC·HCl were blended in a mortar. Flat-faced tablet with 400 mg weight, 2 mm of thickness, and 10 mm in diameter containing *ca.* 200 mg of OTC·HCl in tablet was prepared by compressing the mixture directly under 300 kg cm^{-2} at room temperature for 0.5—1 min with Riken MODEL P-16B hydraulic press. This core tablet was immersed in 100 ml of 1.5% aqueous CM-chitin or DHP-chitin solution for 1 min (covering reagent) and in 100 ml of acetone (coagulator), successively, then dried *in vacuo* to give an OTC·HCl releasing tablet covered with CM-chitin or DHP-chitin. In the case of DAC-67, the core tablet was immersed in 100 ml of 4 wt% aqueous acetic acid containing 0.5% of DAC-67. The amount of covering reagent was controlled by repetition of the above procedure.

Evaluation of OTC·HCl Releasing

The tablet was immersed in 200 ml of 0.1 M phosphate buffer solution (pH = 7.1) and shaken at 37°C in 70 cycle min^{-1} and 5 cm length, followed by decanting and adding the buffer at suitable intervals. The amount of released OTC·HCl in the decanted solution was determined by the ultraviolet absorption at 358 nm with a Shimadzu UV-120-02 spectrophotometer.

RESULTS AND DISCUSSION

The releases of OTC·HCl from tablets covered with various chitin derivatives are shown in Figure 1. Each tablet covered with chitin derivatives did not immediately disintegrate and gave the sustained release of OTC·HCl for a long period (more than 7 days). The release of OTC·HCl were suppressed more by the tablet covered with CM-chitin < DHP-chitin < DAC-67 in this order. These results are attributed to the followings: 1) CM-chitin used in this study immediately dissolved in phosphate buffer solution (pH = 7.1); 2) a part of DHP-chitin formed gel in buffer solution; 3) DAC-67 swelled a little in this buffer solution. In the case of a tablet without covering reagent, the releasing rate of OTC·HCl was similar to that of the tablet covered with CM-chitin. In addition, the releasing rate of OTC·HCl was dependent on the amount of chitin in the tablet without covering reagent (data not shown). From these facts, the releasing rate of OTC·HCl from tablet would depend not only on the rate of diffusion of OTC·HCl in the tablet but also on the solubility of chitin derivatives used as covering reagent in

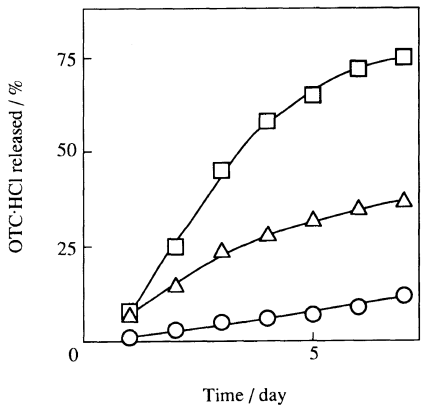

Figure 1. Release of OTC·HCl from tablets covered with various chitin derivatives; chitin, 200 mg; OTC·HCl, 200 mg; temp, 37°C; ○, DAC-67 (272 mg); △, DHP-chitin (289 mg); □, CM-chitin (310 mg).

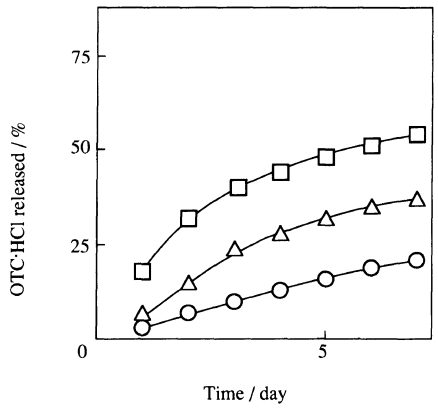

Figure 2. Effect of the amount of DHP-chitin on the release of OTC·HCl; chitin, 200 mg; OTC·HCl, 200 mg; temp, 37°C; DHP-chitin: ○, 392 mg; △, 289 mg; □, 197 mg.

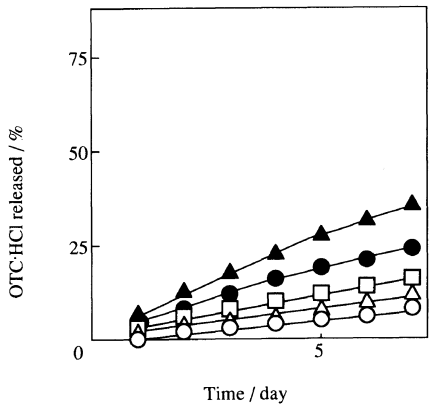

Figure 3. Effect of the amount of DAC-67 on the release of OTC·HCl; chitin, 200 mg; OTC·HCl, 200 mg; temp, 37°C; DAC-67: ○, 447 mg; △, 272 mg; □, 141 mg; ●, 98 mg; ▲, 67 mg.

phosphate buffer solution (pH = 7.1) and the permeability of OTC·HCl through the membrane of covering reagent.

Next we examined the control of the releasing rate of OTC·HCl from tablet by changing the amount of chitin derivative as covering reagent. In the case of CM-chitin, the releasing rate and the amount of the released OTC·HCl were not affected by the amount of CM-chitin (data not shown). In contrast, the amount of the released OTC·HCl depended on the amount of DHP-chitin covered. As shown in Figure 2, the amount of the released OTC·HCl decreased with the increase in the amount of DHP-chitin covered. In the case of DAC-67, the released OTC·HCl also decreased with the increase in the amount of covering reagent and the percentage of OTC·HCl released from the tablet covered with DAC-67 (447 mg) was only 8% after 7 days (Figure 3). From these results, it was suggested that the amount of the released OTC·HCl could be controlled successfully by changing the amount of DHP-chitin or DAC-67 used as covering reagent, but not controlled by CM-chitin.

As described above, the sustained release of OTC·HCl from tablet could be achieved for a long period by covering with DHP-chitin or DAC-67. The release of OTC·HCl supressed most by DAC-67 amoung covering reagent investigated in this study. Hence, these tablets would be useful as sustained release drugs for dressing animals.

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