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# Chitosan beads for the delivery of salmon calcitonin: preparation and release characteristics

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**Abstract**

Salmon calcitonin (sCT)-loaded chitosan beads were prepared by dropping a drug containing solution of chitosan into tripolyphosphate solution. The droplets instantaneously formed gelled spheres by ionotropic gelation. The mean diameter of beads was about 0.9 mm and encapsulation efficiency of drug was 54–59%. The drug was successfully encapsulated at pH 6. The amount of sCT did not affect the drug release from beads. Release data were examined kinetically and the mechanism was discussed. These results show that sCT-loaded chitosan beads could be prepared providing a controlled release property.

*Keywords:* Salmon calcitonin; Chitosan; Controlled-release; Chitosan-polyelectroylte complex

Salmon calcitonin (sCT) is a polypeptide comprised of 32 amino acid residues and is one of the most potent forms among calcitonins available for clinical use. It is used primarily for the treatment of postmenopausal osteoporosis and Paget's disease. These diseases generally require long-term therapy and sCT is a polypeptide subject to digestive degradation and having short half-life in the body (Segre and Dal Pra, 1985). An approach to solving the delivery problems of sTC is to incorporate it in a polymer matrix which can effectively protect the peptide and provide sustained release (Lee et al., 1991; Richardson et al., 1995).

Chitosan, a biopolymer, is also useful as a vehicle for sustained release preparations.

On the other hand, the gel bead, which is a spherical gel prepared by ionotropic gelation method, has received attention as a drug delivery vehicle for controlled release preparations (Bodmeier et al., 1989; Shirashi et al., 1993; Sezer and Akbuğa, 1995).

However there is no information about chitosan beads containing calcitonin. The purpose of this study is to explore the possible applicability of chitosan beads as a controlled release system of macromolecular drugs, such as calcitonin (Mol. wt. 3000). For the preparation of beads, salmon calcitonin (Sandoz, Switzerland) (666 $\mu$g/ml) was dissolved in 5 ml of a solution of chitosan (Sea Cure 340 Pronova A/S, Norway) in 1.5% v/v

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acetic acid. This solution was dropped through a glass syringe into gently agitated tripolyphosphate (Sigma, USA), (1% w/v) solution adjusted to pH 6. The beads were filtered and washed with distilled water and air-dried ($n = 3$). Beads were prepared by using different concentrations of SCT (500 and 600 mg/ml $KC_1$ and $KC_2$ respectively).

For release studies, beads were suspended in phosphate buffer (pH 6) contained in a glass bottle. This medium was stirred at 100 rpm in a shaker bath at 37°C. Samples were periodically removed and analyzed spectrophotometrically at 274 nm ($n = 3$) (Celebi et al., 1990). Drug content of beads was also spectrophotometrically determined after the extraction of beads.

By using ionotropic gelation method, spherical gel matrices were obtained. The viscosity of the chitosan sample has importance in the formation of beads. Chitosan beads could not be prepared from samples with viscosity below 966 cps. Extra high viscosity chitosan samples also did not form beads because of dropping difficulty. Chitosan solution having high viscosity values was not dropped through syringe easily. The size and drug loading capacity of beads are given in Table 1. The mean diamater of beads was about 0.9 mm. In contrast to an earlier report (Bodmeier and Paeratakul, 1989) size of sCT beads did not change with drug concentration ($P > 0.05$). As shown in Table 1, encapsulation efficiency of sCT was greater than 50%. The drug content of beads was not dependent on the initial drug concentration. This finding contrasts with the previous observation that sulfadiazine content of chitosan beads increased with increasing payload (Bodmeier et al., 1989). Moreover, this study suggested that 2 min were enough to obtain complete gelation.

Table 1
Size and drug-loading capacity of chitosan beads containing salmon calitonin

| Code | Bead size (mm ± SD) | Encapsulation efficiency (% ± SD) |
|---|---|---|
| 500 mcg/ml ($KC_1$) | 0.986 ± 0.05 | 59.4 ± 2.5 |
| 666 mcg/ml ($KC_2$ | 0.986 ± 0.07 | 54.2 ± 2.1 |

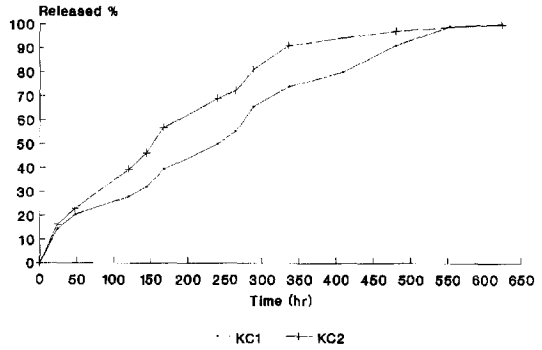


Fig. 1. Release profiles of sCT-loaded chitosan beads.

Fig. 1 shows the release profiles of sCT from the chitosan beads of various sCT content. As can be seen in this figure, marked retardation was observed in release profiles. The release sCT could be sustained for a period of 27 days from chitosan beads. A small burst effect of < 20% sCT release was observed during the first day. However the effect of drug concentration used in the preparation on the release was not significant ($P > 0.05$) (Fig. 1). In order to understand the mode of release of sCT from chitosan beads, the data ($\leq 60\%$) were fitted to the power law equation (Ritger and Peppas, 1987) ($M_t/M_\infty = kt^n$). The values of $n$ fell within the range of 0.47–0.48, indicating that drug release from chitosan beads is non-Fickian (Table 2). This kind of diffusion corresponds to a more predictable type of swelling-controlled system. Bodmeier et al. (1989), suggest this encapsulation procedure for the preparation of beads containing water-insoluble drug. However, by using this technique, a water-soluble, macromolecular drug, calcitonin was incorporated into chitosan beads.

In summary, this study demonstrates that controlled-release chitosan beads containing sCT were

Table 2
Coefficients and exponents of drug release functions according to $M_t/M_\infty = k \cdot t^n$ for chitosan beads containing salmon calcitonin

| | $r^2$ | $n$ | $k$ |
|---|---|---|---|
| $KC_1$ | 0.956 | 0.487 | 6.64 |
| $KC_2$ | 0.979 | 0.479 | 4.46 |

successfully prepared by gelling the cationic polysaccharide with the anionic counterion.

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