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Mucoadhesive intestinal devices for oral delivery of salmon calcitonin

Vivek Gupta [1], Byeong Hee Hwang, JooHee Lee, Aaron C. Anselmo, Nishit Doshi, Samir Mitragotri *

Department of Chemical Engineering, University of California, Santa Barbara 93106, USA

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ABSTRACT

One of the major challenges faced by therapeutic polypeptides remains their invasive route of delivery. Oral administration offers a potential alternative to injections; however, this route cannot be currently used for peptides due to their limited stability in the stomach and poor permeation across the intestine. Here, we report mucoadhesive devices for oral delivery that are inspired by the design of transdermal patches and demonstrate their capabilities *in vivo* for salmon calcitonin (sCT). The mucoadhesive devices were fabricated by compressing a polymeric matrix containing carbopol, pectin and sodium carboxymethylcellulose (1:1:2), and were coated on all sides but one with an impermeable and flexible ethyl cellulose (EC) backing layer. Devices were tested for *in vitro* dissolution, mucoadhesion to intestinal mucosa and enhancement of drug absorption *in vitro* (Caco-2 monolayer transport) and *in vivo* in rats. Devices showed steady drug release with ≈75% cumulative drug released in 5 h. Devices also demonstrated strong mucoadhesion to porcine small intestine to withstand forces up to 100 times their own weight. sCT-loaded mucoadhesive devices exhibited delivery of sCT across Caco-2 monolayers and across the intestinal epithelium *in vivo* in rats. A ≈52-fold (pharmacokinetic) and ≈44-fold (pharmacological) enhancement of oral bioavailability was observed with mucoadhesive devices when compared to direct intestinal injections. Oral delivery of devices in enteric coated capsules resulted in significant bioavailability enhancement.

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1. Introduction

Macromolecules including proteins and polypeptides represent an increasingly significant component of therapeutic drugs [1]. However, these macromolecules must be delivered by injections which often limit their acceptance by patients. While oral delivery offers a highly compliant mode of administering these drugs, its utility is limited by proteolytic degradation in the stomach and intestine and by low permeability of the epithelial barrier [2,3]. Here, we focus on delivery of a representative polypeptide drug, salmon calcitonin (sCT), a 32 amino acid long analog of human calcitonin, which is secreted by parafollicular cells (C-cells) of thyroid gland in humans and it plays a role in regulating calcium metabolism in tandem with parathyroid hormone to maintain bone mass [4,5].

sCT has long been approved by the U.S. FDA for treatment of postmenopausal osteoporosis, Paget's disease, hypercalcemia and bone associated pain conditions [6,7]. Despite its therapeutic efficacy, full therapeutic potential of sCT has not been exploited due to limitations associated with the delivery route. sCT is currently administered primarily by the subcutaneous injections and to an extent by the intranasal route [8]. sCT injections are currently used as a second-line therapy after oral bisphosphonates due to lack of potency [9], in part due to the acceptance of oral administration; and is only prescribed to patients who develop contraindications to oral bisphosphonates. At the same time, oral bisphosphonates have also been associated with increased incidences of esophagitis and other GI disorders [10], which has led FDA to issue a safety alert for the same [11]. Nasal sCT, though painless, suffers from the disadvantages of local irritation after chronic administration.

In light of the chronic nature of sCT therapy, oral route is likely to be a highly preferred route of administration. Further, several recent reports have demonstrated additional therapeutic benefits associated with oral sCT including chondroprotective effects in osteoarthritis [12,13] and improved glucoregulatory functions [14–17]. Accordingly, several approaches have been tested for facilitating oral absorption of sCT; these approaches make use of formulation additives that either modulate the intestinal environment or target specific intestinal regions with favorable properties (*e.g.*, low residual volume, high absorptive surface area or reduced enzymatic activity) [5]. These strategies make use of: (i) chemical permeation enhancers (CPEs) including 5-SNAC [18], acyl carnitines [19], and other cationic/anionic surfactants [20,21], (ii) encapsulation technologies such as micro- and nanospheres [22–24], (iii) pH-sensitive hydrogels [25–28], (iv) protease inhibitors to protect sCT against enzymatic degradation in intestine [29], and (v) chemical modification of sCT to name a few [30–32]. Most of these approaches however have had limited success, and despite showing initial promise, have only been marginally successful in clinical studies, mainly because of a less favorable toxicity-efficacy profile.

* Corresponding author. Tel.: +1 805 893 7532; fax: +1 805 893 4731.
E-mail address: samir@engineering.ucsb.edu (S. Mitragotri).
[1] Current address: School of Pharmacy, Keck Graduate Institute of Applied Life Sciences, 535 Watson Dr., Claremont 91711, USA.

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Here, we describe a mucoadhesive, 'transdermal patch-like' system to enable delivery of sCT. Adhesive patch-like delivery systems have long been established for their efficacy in delivering drugs *via* transdermal and buccal routes [33]. However, their efficacy in promoting oral delivery of therapeutics has not been well investigated despite intestinal mucosa presenting an excellent platform for it. A few literature studies have reported on the use of mucoadhesive patches for oral delivery and have demonstrated their principles as well as benefits [34–37]. Here, we report on the use of these systems for delivering sCT.

2. Materials and methods

2.1. Materials

Pharmaceutical grade carbopol-934 was obtained from Lubrizol Advanced Materials Inc. (Cleveland, OH, USA). Sodium carboxymethylcellulose (SCMC), pectin, and ethyl cellulose (EC) were obtained from Sigma Aldrich (St. Louis, MO, USA). Salmon calcitonin (MW = 3432 da, ≥95%) was obtained from Anaspec, Inc. (Fremont, CA, USA). The transwell Caco-2 system was set up using 24 well BD-Biocoat™ HTS Caco-2 assay system (fibrillar collagen coated, 1 μm pore size) obtained from BD Biosciences (Bedford, MA, USA). Extraction-free ELISA kit for analysis of salmon calcitonin was obtained from Bachem Americas, Inc. (Torrance, CA, USA). Colorimetric assay kit for calcium measurements was obtained from ScienCell Research Laboratories (Carlsbad, CA, USA). Supplies for Caco-2 culture, cell viability studies and for confocal imaging were obtained from Fisher Scientific (Pittsburgh, PA, USA). All other chemicals used were of analytical grade and were obtained from various vendors.

2.2. Mucoadhesive devices

Polymeric mucoadhesive devices were prepared by direct compression of a homogenous mixture of carbopol 934/pectin/SCMC in a dry weight ratio of 1:1:2 as demonstrated by Whitehead et al. [34]. Briefly, all weighed polymers were mixed by grinding using a mortar and pestle. Salmon calcitonin (MW ≈ 3432 da) was added to the ground mixture so as to produce a final sCT concentration in the range of 0.1–10% w/w (dry weight %). The sCT loading of 0.1–10% mentioned here was based on the amount of sCT added to the mucoadhesive matrix during fabrication. 110 mg of homogenously powdered mixture was then poured into a 13 mm pellet press (Pike Technologies, Madison, WI, USA), and was compressed under a pressure of 3 tons using a hydraulic press (Carver Inc., Wabash, IN, USA) for 5 min. This procedure produced a 400 μm thick disk with a typical diameter of 13 mm. Disposable biopsy punches (Miltex Inc., Plainsboro, NJ, USA) were used to cut this disk into smaller disks with radii of 1–5 mm. These disks were placed on a support and coated on all sides but one using a solution of 5% w/v ethylcellulose (EC, Sigma) in acetone. Acetone was evaporated at room temperature. This procedure produced an EC layer of about 50 μm.

2.3. Morphology of the devices

Morphology of the mucoadhesive devices was determined by scanning electron microscopy (SEM). SEM images of the devices were taken on an FEI XL40 (Hillsboro, OR, USA) after 90 s of palladium sputter coating. The devices were imaged at 10 kV acceleration voltage at a 5 mm working distance for images over 100× magnification and at 50 mm working distance for images under 20× magnification. SEM images were taken for both the top and bottom surfaces, and also for the ethyl cellulose coated sides of the devices.

2.4. Adhesion force measurements

To determine the adhesive forces exerted by the mucoadhesive devices on the intestinal mucosa, *in vitro* experiments were performed using porcine small intestine obtained from Lampire Biologicals Inc. (Pipersville, PA, USA) following the protocols described by Whitehead et al. [34] with slight modifications. Briefly, devices were incubated with intestinal mucosa for time periods between 30 min and 2 h. Following the incubation, the adhesion force between the device and intestinal mucosa was quantified using a microbalance. The mucosal surface (with devices attached) was mounted onto a microbalance. A small plastic cylinder (2 cm in length and 1 mm in diameter) was attached using an acrylate adhesive to the backing side of one of the patches on the mucosa. The other end of the cylinder was attached to a string and passed over a pulley. The cylinder was gradually pulled until the patch detached from the mucosa. The detachment force (force of adhesion) at which the adhesive bond between the patch and the mucosa failed was calculated by recording the gradual reduction in weight readings on the microbalance. Similar experiments were performed in simulated intestinal fasting fluid (SIFF, Biorelevant Ltd, Surrey, United Kingdom) to establish system's efficacy in a biologically relevant system. Briefly, SIFF was prepared as per manufacturer's protocol, and the devices were incubated in SIFF with gentle shaking for specified time and adhesion forces were measured as mentioned earlier.

2.5. In vitro dissolution studies

To evaluate the efficacy of devices in providing sustained delivery of sCT, *in vitro* release experiments were performed. Briefly, a 5 mm (≈17 mg) device loaded with sCT (24 μg/device) was incubated with 10 ml sterile PBS (pH 7.4; room temperature) with gentle shaking so as to emulate mucociliary movement in small intestine. 100 μl samples of the release media were withdrawn at predetermined time intervals up to 5 h followed by immediate replenishment with fresh PBS. Withdrawn samples were analyzed to quantify the amount of sCT being released from the devices due to time-dependent swelling and degradation of the devices. Sample analysis was performed by using commercially available extraction sCT ELISA kit as mentioned in the Materials section. Similar studies were performed with sulforhodamine-B (SRB) loaded devices to determine possible peptide binding with mucoadhesive matrix.

Drug release kinetics was analyzed by assessing the r^2 value for the concentration–time curve for the release profile. Zero order release rate constant was calculated using the following equation [38]:

$$Q_t - Q_0 = K_0 \cdot t$$

where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. Dissolution exponent was calculated using the Korsmeyer–Peppas model [39]:

$$M_t / M_\infty = K \cdot t^n$$

where M_t/M_∞ is a fraction of drug released at time t, K is the release rate constant and n is the dissolution exponent.

2.6. Enhancement of sCT transport across Caco-2 monolayers

Efficacy of mucoadhesive devices in enhancing sCT transport across Caco-2 monolayers was assessed by a rapid 3-day Caco-2 transwell system following a protocol established in our laboratory [40]. Briefly, a rapid 3-day Caco-2 transwell system was developed using BD Biocoat ™ HTS Caco-2 assay system (BD Biosciences, Bedford, MA, USA) using Caco-2 cell line (HTB-37; American Type Culture Collection, Manassas, VA, USA) between 5th and 14th passages due to possible phenotypic

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