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Niflumic acid-collagen delivery systems used as anti-inflammatory drugs and analgesics in dentistry

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ABSTRACT

Collagen sponges are known to be safe and well-characterized supports for drug delivery systems. The aim of this study was to prepare, characterize and test drug delivery systems that contain collagen as support and niflumic acid as a drug. Type-I collagen and niflumic acid gels were cross-linked with different concentrations of glutaraldehyde and then freeze-dried in order to obtain collagen matrices (spongious form). The physical-chemical properties were assessed by infrared spectroscopy (FTIR) and morphological properties were evaluated by water absorption. Niflumic acid release from cross-linked collagen spongious forms was also investigated and the kinetic mechanism was discussed.

1. Introduction

Local pain management is the most critical point of patient care in dentistry and medicine [1] and anesthetics and anti-inflammatory drugs are commonly used [2]. These drugs develop therapeutic effects by their anti-inflammatory, analgesic, and antipyretic activities [3].

The systemic drug administration presents disadvantages due to the spreading of drugs throughout the body, which causes unwanted toxic effects to healthy organs [4]. Local controlled drug delivery received increasing attention since it presents a solution to characteristic problems of systemic drug administration [5–7].

Collagen sponges are safe and well-characterized supports for drug delivery systems, [8] since they are biocompatible and biodegradable biomaterials. The most used drugs in local topical administration are: antibiotics, steroids, cholinergic, anticoagulants, immuno-depressants [5,9]. Drug delivery systems in form of collagen sponges with doxycycline [10–12], gentamicin [13], triphala [14], tobramycin or ciprofloxacin [15] were studied successfully *in vitro* or *in vivo*.

Niflumic acid (NA) is an analgesic and anti-inflammatory agent, which could be used in pain management in dentistry and medicine. In our previous study, we developed some modern wound dressings such as controlled drug delivery systems based on collagen. For these materials, the maximum concentration of niflumic acid that did not produce toxicity was established [16]. Based on these results, the aim of this study was to continue our research in order to improve the solubility of the drug in aqueous solutions, the stability of the drug delivery systems and to control the release of niflumic acid. In this paper, a series of five spongious (3D) drug delivery systems based on collagen and niflumic acid cross-linked with different concentrations of glutaraldehyde were obtained and characterized by FTIR spectroscopy, water absorption and collagenase degradation. The niflumic acid release from cross-linked collagen spongious forms was also investigated and the kinetic mechanism was discussed.

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2. Materials and methods

2.1. Materials

Type-I collagen of bovine origin was provided by Collagen Department of Division Leather and Footwear Research Institute; it had been extracted by the currently used technology previously described [9]. The collagen (Coll) was obtained as a gel in its native form with fibrillar structure with an initial concentration of 2.5%, pH 2.5 and free of fat and ash. Niflumic acid (NA) was purchased from ICN Biomedicals Inc. (USA) and glutaraldehyde (GA) from Merck (Germany). The sodium hydroxide and the phosphate buffer solutions (PBS), pH = 7.4 were of analytical grade. All the chemicals used in this work were of analytical grade; water was distilled.

2.2. Preparation of niflumic acid - collagen delivery systems

The pH of collagen gel was adjusted at 7.4 under mechanical stirring with a 1 M sodium hydroxide solution. Niflumic acid 1 g/L was embedded into the collagen gel and then both collagen reference and collagen with niflumic acid were cross-linked with different concentrations of glutaraldehyde (GA) (0.25, 0.5, 0.75 and 1% with respect to the dry substance). All samples have a concentration of 4% of niflumic acid with respect to the dry substance (0.1% with respect to the collagen gel). The gels were then freeze-dried using the freeze-dryer Delta 2-24 LSC (Martin Christ, Germany), as previously described [17], in order to obtain 3D collagen systems (spongious forms).

2.3. FTIR analysis

Infrared analysis was performed using a PerkinElmer Spectrum 100 FTIR spectrophotometer in the attenuated total reflection mode on the spongious materials in order to evidence the presence of bonds between anti-inflammatory drug and collagen as well as the structural changes.

2.4. Water absorption analysis

Water absorption was evaluated as previously described [16]. Briefly, spongious materials with and without NA were weighted as such, and after immersion in water, at different time intervals until a stable mass was obtained. Then the percentage of water absorbed in spongious materials was evaluated.

2.5. In vitro kinetic studies

The *in vitro* niflumic acid release from collagen sponges was determined using a paddle dissolution equipment, as previously described [18,19]. Briefly, inside the apparatus release vessel, a transdermal sandwich device with the sponge sample is fitted. The phosphate buffer solution, pH 7.4, maintained at 37 °C, was used as release medium.

During the experiments (approximately 4 h), aliquots of 5 mL were withdrawn at predetermined time periods from the release medium and replaced with an equal volume of fresh phosphate buffer solution. The absorbance at 287 nm (PerkinElmer Spectrophotometer) was recorded for each sample and the released niflumic acid amount was evaluated based on the calibration curve previously determined ($A^{1\,cm}_{1\%} = 777$) [16].

3. Results and discussion

3.1. FTIR spectra

Figs. 1–3 and Table 1 present the IR spectra and the main wave numbers obtained for samples of collagen, niflumic acid and collagen with niflumic acid and cross-linking agent.

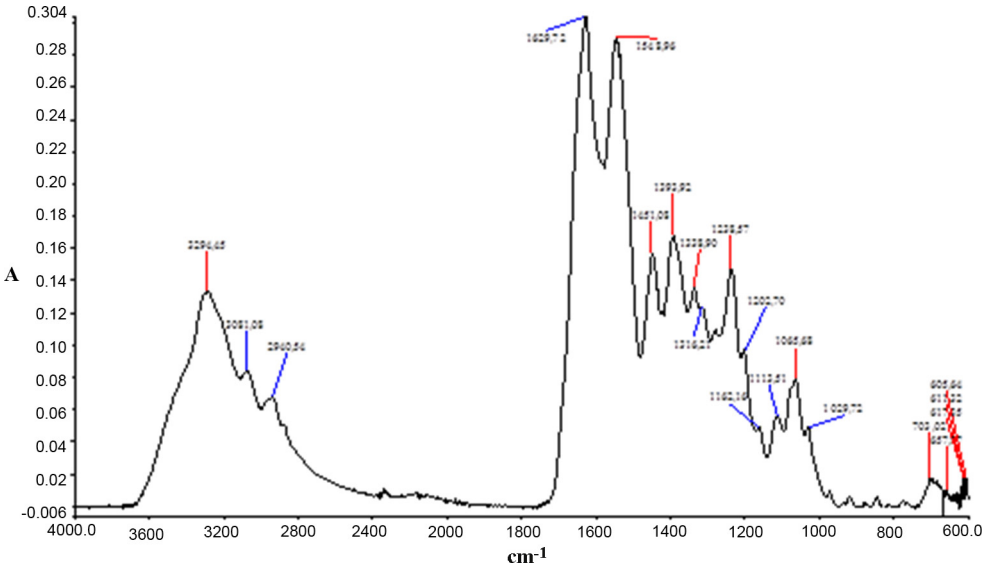

Fig. 1. Infrared spectrum of a collagen scaffold. Color available online.