Semisolid Systems Containing Propolis for the Treatment of Periodontal Disease: *In Vitro* Release Kinetics, Syringeability, Rheological, Textural, and Mucoadhesive Properties

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ABSTRACT: Formulations containing poloxamer 407 (P407), carbopol 934P (C934P), and propolis extract (PE) were designed for the treatment of periodontal disease. Gelation temperature, *in vitro* drug release, rheology, hardness, compressibility, adhesiveness, mucoadhesion, and syringeability of formulations were determined. Propolis release from formulations was controlled by the phenomenon of relaxation of polymer chains. Formulations exhibited pseudoplastic flow and low degrees of thixotropy or rheopexy. In most samples, increasing the concentration of C934P content significantly increased storage modulus (G'), loss modulus (G''), and dynamic viscosity (η'), at 5°C, G'' exceeded G'. At 25 and 37°C, η' of each formulation depended on the oscillatory frequency. Formulations showed thermoresponsive behavior, existing as a liquid at room temperature and gel at 34–37°C. Increasing the C934P content or temperature significantly increased formulation hardness, compressibility, and adhesiveness. The greatest mucoadhesion was noted in the formulation containing 15% P407 (w/w) and 0.25% C934P (w/w). The work of syringeability values of all formulations were similar and very desirable with regard to ease of administration. The data obtained in these formulations indicate a potentially useful role in the treatment of periodontitis and suggest they are worthy of clinical evaluation. J Pharm Sci 96:2074–2089, 2007

Keywords: biodegradable polymers; buccal; natural products; mechanical properties; injectables; hydrogels; oral drug delivery

INTRODUCTION

Periodontal disease is a group of diseases, including gingivitis and periodontitis, associated with the structures supporting the teeth (periodontum).[1] In the development of periodontal disease, there is an initial extension to and accumulation of plaque at the gingival margin that, in turn, induces an inflammatory response, named gingivitis.[2] Periodontitis is the result of direct actions of both plaque and the induced inflammatory response within the deeper tissues, causing a space (pocket) to develop between the roots of the affected teeth and the soft tissues.[3] In this

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protected environment, bacteria accumulate and flourish. If the disease is allowed to progress, increased tooth mobility and ultimately tooth loss result.[3–5] Currently, the treatment of periodontal disease frequently involves mechanical removal of bacterial plaque and calculus. Moreover, given the role of specific bacteria in the etiology/progression of periodontal disease,[6,7] antimicrobial drugs (e.g., tetracycline, minocycline, clindamycin, metronidazole, and chlorhexidine) have also been used as adjuncts to mechanical treatment, particularly in treating early-onset and refractory cases.[8–10] A special case is propolis (bee glue), a strongly adhesive resinous product collected by honeybees and extracted from the beehive, which has been used against periodontal disease[11] in view of its pharmaceutical properties, including antimicrobial,[12–15] anti-inflammatory,[16,17] and antioxidant[18] activity. Moreover, propolis is relatively nontoxic, safe, and can display antimicrobial synergism when administered together with some antibiotic drugs.[16,19] Alone or incorporated in another dosage form, ethanolic extract of propolis is commonly used in the treatment of periodontal disease, due to its safety and efficacy.[11,16]

Additionally, the inability of antiseptic mouthrinses to penetrate into periodontal pockets, the short residence time of conventional topical agents at the site and the potential side-effects of administering systemic antibiotics have fuelled interest in the sustained delivery of therapeutic agents within the periodontal pocket.[3] Consequently, the release of drugs from several polymeric systems, together with their rheological, mechanical, and clinical evaluation, have been reported.[2,3,8,20–25] Cellulose fibers to deliver tetracycline (Actisite®), a semisolid system composed of glycerol mono-oleate and sesame oil to deliver metronidazole (Elyzol®), a semisolid system composed of poly (DL-lactide-coglycolide) and N-methyl-2-pyrrolidone to deliver doxycycline (Atridox®) and microspheres of polylactide coglycolide to deliver minocycline (Arestin®) are examples of commercially available systems.

The clinical efficacy of such treatments depends intrinsically on the drug release and mechanical properties of the formulation. Thus, ideal formulations should be easily inserted into the periodontal pocket (preferably using a syringe), show controlled release of drug into the crevicular fluid, exhibit retention within the pocket for the desired period of time (without the aid of mechanical bonding to tooth surfaces), be biodegradable, nontoxic, and nonirritant.[26] Few of the currently commercially available and experimental systems show prolonged retention within the periodontal pocket[3,26,27] and none was developed to deliver propolis. Thus, semisolid formulations consisting of mucoadhesive polymers such as polycarbophil, hydroxypropyl cellulose, polyvinylpyrrolidone, and carbopol have been proposed in order to improve intimacy of contact and also increase the residence time of a dosage form in the periodontal pocket.[8,26,28–30] Within the periodontal pocket environment, these polymers interact with the mucin-coated epithelial and tooth surfaces by means of specific interfacial forces in a process commonly referred as mucoadhesion, a special case of bioadhesion.[28] Furthermore, thermosensitive systems containing poloxamer have been investigated as a convenient dosage form of application into periodontal pocket.[31,32] Liquid dosage forms containing poloxamer injected into the periodontal pocket can undergo a transition to the gel state as a result of physical changes induced by rising temperature, improving their retention time in the pocket.[27]

This study, therefore, describes the development and characterization of semisolid systems containing propolis prepared from carbomer 934P and poloxamer 407 (P407), designed for application to the periodontal pocket for the treatment of periodontitis.

MATERIALS AND METHODS

Materials

P407 and Carbopol 934P (C934P) were purchased from Sigma (St. Louis, MO) and from B. F. Goodrich (Brecksville, OH), respectively. Triethanolamine (TEA), purchased from Galena (Campinas, SP, Brazil) was used as a neutralizing agent. Propolis was collected from an experimental apiary in the farm of the State University of Maringa (Parana State, Brazil) and propolis extract (PE) was obtained as described by Bruschi et al.[33] Hydroxyethylcellulose 4400 and sodium chloride were purchased from Union Carbide Corporation (São Paulo, Brazil) and Carlo Erba (Milano, Italy), respectively. All other chemicals were purchased from Merck (Darmstadt, Germany) and were of AnalaR, or equivalent, quality.

Preparation of Propolis-Containing Formulations

C934P (0.10, 0.25, or 0.50%, w/w) was initially dissolved in distilled water using a mechanical