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Preparation and evaluation of clindamycin phosphate loaded chitosan/alginate polyelectrolyte complex film as mucoadhesive drug delivery system for periodontal therapy

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ABSTRACT

In this study, Clindamycin phosphate loaded adhesive polyelectrolyte complex films for local periodontal therapy were prepared with alginate and chitosan. The thickness, drug content, structure, swelling, adhesion and in vitro drug release with release kinetics of formulations were evaluated. The effects of the varying concentration and molecular weight of polymers used and the volume of the polymer solutions on the characteristics of the films were investigated. Increasing the concentration of sodium alginate in total content of polymer mixture caused to higher adhesiveness. Chitosan molecular weight also affected to adhesiveness of complex films. The release rate of drug and release kinetics was affected from the complexation. The best complexation was obtained with the three times higher concentration and volume of alginate in combination with low molecular weight chitosan. Thus polyelectrolyte films that have delayed release together with high swelling ability and adhesiveness and high drug content were formed. Due to the heterogeneous structure of complex film, the release profiles of the formulations fitted to the anomalous transport mechanism. 3D structure of the drug loaded complex film was analyzed by Micro-CT imaging in this study and it was showed that using this method would be very advantageous for further studies about the investigation of complexation than the other imaging methods in order to determine the volume and the size of the formed complexes within the structure at the same time.

1. Introduction

Periodontitis is a chronic infectious and inflammatory disease resulting in destruction of the supporting tissues, progressive attachment loss and leading to tooth loss (Hiltunen et al., 2016; Lee et al., 2016; Van Dyke et al., 2015). The recent approach in periodontal therapy is mechanical removal of biofilm formed by periodontopathogenic species from periodontal tissue followed by peroral antibiotic administration (Schkarpetkin et al., 2016). Side effects of the systemic treatment of periodontitis due to antibiotics cause problems in the progression of the treatment. Therefore, local application of an antibiotic on the periodontal lesion is an appropriate treatment due to the high local drug concentration and minimum adverse effects (Kassem et al., 2015; Zupancic et al., 2015).

It is preferred that the drug delivery systems applied to the periodontal pocket are biodegradable and easy to place as well as produced with mucoadhesive polymers providing increased contact between dosage forms and mucosa (Kilicarslan et al., 2014b). The most convenient approaches for local delivery of drug in periodontal pocket include tablet, film, fiber, strip, injectable systems, gel, in situ gel, in situ implant, vesicular systems and particulate systems (Juliano et al., 2008; Kilicarslan et al., 2010; Kilicarslan et al., 2014a; Kilicarslan et al., 2014b; Madhumathi et al., 2018; Phaechamud and Setthajindalert, 2017; Do et al., 2014).

Films are dosage forms improving patient compliance during the periodontitis treatment. Anatomy of periodontal pocket provides a natural application reservoir for easy insertion of appropriate sized films (Kilicarslan et al., 2014b; Madhumathi et al., 2018; Mazzarino et al., 2014). Chitosan, alginate, gelatin and cellulose derived polymers such as ethylcellulose, hydroxyl propyl methylcellulose, sodium carboxymethyl cellulose among degradable natural polymers have been widely used as films for medical applications as well as medical studies

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(Karki et al., 2016; Kumar et al., 2011; Kumria et al., 2018; Lai et al., 2018; Xie et al., 2018). The effectiveness of the periodontitis treatment depends on the ability of the release system to prolong the drug release rate. In order to control drug release rate, cross-linking has a significant place among film-forming techniques (Kassem et al., 2015).

Polyelectrolyte complexes are macromolecular structures including repeating units and are formed by a network between oppositely charged polymeric molecules, proteins and nucleic acids in any ionizing solvent like water (Das and Tsianou, 2017; George and Abraham, 2006; Meka et al., 2017; Mirtic et al., 2018; Voron'ko et al., 2016; Wytrwal et al., 2016). Relatively easy ionic cross-linking natural polymers such as positively charged chitosan and an anionic polysaccharide, sodium alginate, are commonly used in preparation of drug delivery systems (Unagolla and Jayasuriya, 2018; Voron'ko et al., 2016). It has been shown in the studies of Yan et al. (2001) that chitosan and alginate polyelectrolyte complex is effective to retard the drug release because of the water insoluble complex. Alginate is a natural, anionic linear polysaccharide derived from brown marine algae (Kondaveeti et al., 2018; Ravichandran and Jayakrishnan, 2018). It is a highly preferred polymer in cosmetics, medicine, food and pharmaceutical industry due to its high water retention capacity, ion exchange capability, biocompatibility, low toxicity and low cost (Gierszewska et al., 2018; Gokila et al., 2017; Wang et al., 2017). Although water solubility of alginate makes it chemically unstable in aqueous conditions, it can solidify and form a stable structure easily by ionic gelation with the presence of multivalent cations such as Ca^{2+}, Zn^{2+}, chitosan and polyethylenimine (Conzatti et al., 2017; Lee et al., 2018; Mirtic et al., 2018; Sun et al., 2018; Valladares et al., 2016).

Chitosan being deacetylated derivative of the chitin is obtained from the external skeleton of a shellfish. It is chemically an active polymer due to its amino and hydroxyl groups. In addition, it is readily soluble in dilute acids (Bao et al., 2018; Sun et al., 2018; Venkatesan et al., 2017). The properties of chitosan such as being nontoxic, antimicrobial, anti-inflammatory, wound healing, having tissue regeneration activities, biodegradability, virucidal and fungucidal effects, muco/bioadhesivity has attracted attention in the field of dentistry (Gjoseva et al., 2018; Khajuria et al., 2018; Omid et al., 2018). Moreover, through the film forming ability of chitosan, it is used in most of the drug delivery systems as a convenient carrier for active substances on a wide scale from small molecules such as antibiotics to macromolecules such as proteins due to its ability to form the film (Ali and Ahmed, 2018; Ren et al., 2017). It is possible to obtain chitosan polyelectrolyte complexes in the form of gels, nano and microparticles, films/membranes and porous structures by means of changing the type of co-polyelectrolyte and reaction conditions (Gierszewska et al., 2018; Sun et al., 2018; Unagolla and Jayasuriya, 2018).

Clindamycin is a bacteriostatic lincosamide known as a broad-spectrum antibiotic for dental and periodontal therapies. Moreover, it has a molecular weight of 424.6 g/mol and its molecular formula is $C_{18}H_{33}N_2C_lO_5S$. It is a water-soluble drug and biological half-life is about 2.9 h (Ibrahim et al., 2017; Gonzalez et al., 2018; Karczewski et al., 2018; Kilicarslan et al., 2014a; Mohamed et al., 2015).

The aim of this study is to prepare clindamycin phosphate (CDP) loaded alginate-chitosan mucoadhesive polyelectrolyte complex films for periodontal applications and examine the effects of the concentration and molecular weight of polymers used and the volume of polymer solutions on the characteristics of the films. As far as we know, no published data is found on the literature regarding the stated drug and polymer combination as polyelectrolyte complex film for periodontal use. Another purpose of the study is to visualize the formation of 3D structure of the drug loaded complex by micro-CT analysis and this will be the first time in the literature.

2. Materials and methods

2.1. Materials

Chitosan (degree of deacetylation 75–85% (low (LC) and medium (MC) molecular weight) and sodium alginate (Alg) were supplied from Sigma-Aldrich (USA). Clindamycin phosphate (CDP) was kindly provided by DEVA (Turkey). Acetic acid was received from Merck (Germany). Propylene glycol and calcium chloride ($CaCl_2$) were purchased from Aklar Chemicals (Turkey). Acetonitrile and dialysis tubing cellulose membrane (Typical molecular weight cut off = 14,000) was supplied from Sigma-Aldrich (USA) and mucin was obtained from Carl Roth (Germany). Ultra-pure water received from a Millipore system was used to prepare all the solutions. The rest of the materials used in the study was pharmaceutical and had analytical grade.

2.2. Preparation of polyelectrolyte films

CDP loaded (1% (w/v)) polyelectrolyte complex films were prepared by solvent casting technique with Alg and chitosan having different molecular weight (LC and MC). Stock solution of Alg and LC or MC was prepared by dissolving in ultrapure water and 1.5% (v/v) acetic acid at room temperature respectively. $CaCl_2$ (0.1%, w/v) as a cross linker and propylene glycol (5%, v/v) as a plasticizer were added to the required amount of chitosan solutions and mixed until the formation of homogeneous dispersion. Then the chitosan solution was added drop wise to the Alg solution including CDP. This process was carried out with probe sonicator (Bandelin, Germany) in an ice bath for 20 min and then the dispersion mixed with an Ultra Turrax (IKA, Labotechnik, T25 basic, Germany) homogenizer for 10 min. Afterwards, the polymer gel was covered with perforated parafilm and sonicated in an ultrasonicator (Ultrasonic LC 30, Germany) for 10 min to remove any trapped air bubbles. The obtained mixture was poured into the petri dish and was allowed to dry at room temperature. The polyelectrolyte complex films were obtained by mixing 15 ml and 5 ml volumes of polymer solutions. These volume values were separately tested for different concentrations of LC, MC and Alg solutions (Table 1).

2.3. Thickness measurement

Diameter films with the thicknesses of 3.5 mm were measured by a manual micrometer (NSK Micrometer (25 mm), Japan) ($n = 6$).

2.4. Fourier transform infrared (FTIR) spectrum analysis

FTIR spectrums of the CDP, Alg, LC, MC and Alg-chitosan polyelectrolyte complex film samples were taken at room temperature using KBr disc method with Shimadzu FTIR-8040 (Japan) spectrophotometer. The spectra were recorded in 400–4000 cm^{-1} range with a resolution of 16 cm^{-1} and 30 scans.

2.5. Morphological analysis

2.5.1. Scanning electron microscopy (SEM)

The morphology of the polyelectrolyte complex films prepared with a constant concentration of polymers (2%:2%, Alg:MC) and a different volume ratio of polymer solution (1:3 or 3:1 Alg:MC) (F2 and F5) was observed by scanning electron microscopy (SEM), using a QUANTA 400F Field Emission SEM (Therma Fisher Scientific-FEI, Germany) operated at 15 kV accelerating voltage. All the samples were sputtered with a conductive gold layer by means of a sputter coater SC502.

2.5.2. Micro-CT scanning

A desktop Micro-CT system having a high resolution (Bruker Skyscan 1275, Kontich, Belgium) was used to scan the complex film formulation. The scanning conditions were as follows: 100 kVp, 100-