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Production and characterization of cornstarch/cellulose acetate/silver sulfadiazine extrudate matrices

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ABSTRACT

The production and evaluation of cornstarch/cellulose acetate/silver sulfadiazine extrudate matrices are reported herein. The matrices were melt extruded under nine different conditions, altering the temperature and the screw speed values. The surface morphology of the matrices was examined by scanning electron microscopy. The micrographs revealed the presence of non-melted silver sulfadiazine microparticles in the matrices extruded at lower temperature and screw speed values. The thermal properties were evaluated and the results for both the biopolymer and the drug indicated no thermal degradation during the melt extrusion process. The differential scanning analysis of the extrudate matrices showed a shift to lower temperatures for the silver sulfadiazine melting point compared with the non-extruded drug. The starch/cellulose acetate matrices containing silver sulfadiazine demonstrated significant inhibition of the growth of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. In vivo inflammatory response tests showed that the extrudate matrices, with or without silver sulfadiazine, did not trigger chronic inflammatory processes.

1. Introduction

Interest in the development of new biopolymer-based products has been growing worldwide following advances in the healthcare area [22]. In part, this increasing interest is due to the biocompatibility, biodegradability, low toxicity and favorable pharmacokinetics in the circulation of biopolymers as well as their natural sources in the environment [23,37]. Hence, they have been proposed as good candidates for various applications in food, personal care and pharmaceutical industries, e.g., as drug encapsulation and delivery systems and for wound dressings [17,20].

Ideally, an active wound dressing should (a) create and maintain a moist environment, (b) protect the wound from secondary infection, (c) promote flexibility, (d) offer durability/biodegradability and (e) absorb the wound fluids and exudates [11,17]. In recent years, different wound dressings based on synthetic polymers and biopolymers that target the treatment of both acute and chronic wounds have become available in the market [12,31]. Among these wound dressings, those prepared from biopolymers have gained particular relevance due to their unique properties, such as the stimulation of the physiological responses required for cellular regeneration due to the structural similarity among the biopolymers, protein and growth factors [34].

Furthermore, many of the biopolymers have hydrophilic features, thereby allowing large amounts of water to be absorbed and retained on contact. This feature is important during wound healing to avoid maceration, bacterial proliferation and potential infection [14,25]. However, hydrophilic biopolymers have poor mechanical strength, especially in swollen states, which may limit their application as wound dressings [7].

The blending of biopolymers with less hydrophilic biopolymers is one approach to overcome this limitation and provide more mechanical integrity in hydrated environments [2,10]. Gomes et al. [19] evaluated the water uptake of cornstarch/cellulose acetate blends produced by different techniques. The results showed that for the blends produced by extrusion there were less water uptake and more mechanical resistance compared with the pure biopolymers and blends obtained using other techniques.

The mechanical properties and retention of exudates determine the suitability of biopolymers for application as wound dressings. Equally important is the control of bacterial infections at a wound surface during the healing process [29]. Most wound infections involve aerobes (*Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pyogenes*) and anaerobes (*Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Peptostreptococcus* spp., *Clostridium* spp., *Prevotella* spp., and *Fusobacterium* spp.) [6]. Silversulfadiazine is the drug most commonly used in the treatment of

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superficial burns [26] because it exhibits a broad spectrum of antimicrobial activity acting against most Gram-positive and Gram-negative bacteria as well as certain fungal strains [8].

The aim of this study was to prepare starch/cellulose acetate matrices by hot melt extrusion. The extrusion parameters (barrel temperature and screw speed) were varied in order to verify their effect on the final properties of the matrices. Furthermore, to enhance the applicability of the starch/cellulose acetate matrices as wound dressings, silver sulfadiazine was incorporated in the matrices.

2. Materials and methods

2.1. Materials

The cornstarch/cellulose acetate blend (50/50 wt.%) (Trade name Mater-Bi® Y101U) was received from Novamont, (Novara, Italy) in the form of granules. This material has a glass transition temperature (Tg) of around 105 °C and can be processed at temperatures from 150 to 200 °C [5]. Silver sulfadiazine was purchased from Henrifarma (São Paulo, Brazil) with a particle size range of 975 nm to 3.5 μm. *S. aureus* (strain ATCC 25923) and *P. aeruginosa* (strain ATCC 27853) were purchased from Newprov (Brazil).

2.2. Production of matrices

The cornstarch/cellulose acetate granules and the silver sulfadiazine particles were firstly mixed using a mechanical agitator in order to obtain a homogenous dispersion before the hot melt extrusion. The matrices were prepared in a single screw Laboratory Mixing Extruder (LME; LAB-14 AX Plastic, Brazil) with a barrel length of 200 mm (L) and a screw diameter of 10 mm (D) (L/D = 20).

2.3. Extrudate characterization

2.3.1. Extrudate morphology

Scanning electron microscopy (SEM) was used to evaluate the surface morphology of the cornstarch/cellulose acetate and silver sulfadiazine as well as the hot melt extrudate matrices. The samples were then mounted on aluminum stubs using adhesive carbon tape and coated with a thin layer of gold using a sputter coater (D2 Diode Sputtering System). The microscopy was performed using a JEOL (JSM-6390LV) operating at an accelerating voltage of 15 kV.

2.3.2. Thermal analysis

A differential scanning calorimeter (DSC-50, Shimadzu) was employed to measure the thermal properties of the starting materials (cornstarch/cellulose acetate and silver sulfadiazine) and extrudate matrices. Thermal scans were performed from 25 to 300 °C at a heating rate of 10 °C/min under an N_2 atmosphere (50 mL/min). An empty pan was used as reference. The thermogravimetric analyzer (TGA) used in this study was a Shimadzu TGA-50 with samples of 10–11 mg being placed on the aluminum pan. The TGA was performed in the range of 25–900 °C under a nitrogen atmosphere (flow rate 50 mL/min) applying a heating rate of 10 °C · min^{-1}.

2.3.3. Attenuated total reflectance-Fourier transform infra-red (ATR-FTIR) spectroscopy

ATR-FTIR spectra were obtained on a Bruker spectrometer (TENSOR 27) in the range of 4000–600 cm^{-1}. The spectra for the silver sulfadiazine and cornstarch/cellulose acetate as well as the cornstarch/cellulose acetate/silver sulfadiazine extrudate matrices were collected using a horizontal ATR accessory with a single reflection diamond crystal.

2.3.4. High performance thin layer chromatography (HPTLC)

The stability of the material after the hot melt extrusion process and the silver sulfadiazine recovery were evaluated by HPTLC. The stability analysis was carried out by comparing the chromatograms obtained for the non-extruded and the extruded materials.

Firstly, the analytical method for the determination of the silver sulfadiazine recovery using HPTLC was developed and validated. The results verified that the method had an acceptable precision and accuracy. The calibration plot obtained in the linear regression analysis showed a good linear relationship (r = 0.995) over the concentration range of 0.5 to 1.4 μg.

2.3.4.1. Silver sulfadiazine assay. For the determination of the silver sulfadiazine recovery a standard solution was prepared by diluting 20 mg silver sulfadiazine in 10 mL ammonia hydroxide:methanol (3:7 v/v) according to the procedure described in the United States Pharmacopeia [30]. Different volumes of the standard solution were diluted in methanol in a 10 mL volumetric flask and used to plot the calibration graph for the HPTLC.

Silver sulfadiazine was extracted from the cornstarch/cellulose acetate extrudate matrices by dissolving 200 mg samples of the matrices in ammonia hydroxide in 10 mL volumetric flasks kept under agitation for 24 h.

The samples of silver sulfadiazine extracted from the extrudate matrices were applied with a Camag microliter syringe onto plates precoated with silica gel $60F_{254}$ (200 × 100 mm with 250 μm thickness—E. Merck), using a Camag Linomat IV sample applicator. The drug was separated out with a mobile phase consisting of ammonia hydroxide: methanol:chloroform (10:40:70 v/v/v). Linear ascending development was carried in a glass chamber (CAMAG ADC 2) saturated with the mobile phase for 20 min at room temperature. The length of the chromatogram run was 70 mm. Subsequent to the development, the bands of silver sulfadiazine on the HPTLC plates were quantitated with a densitometer CAMAG TLC-Scanner III in the absorbance-reflection mode, measuring the absorbance of the bands at 254 nm (maximum absorption of the drug).

2.3.4.2. Silver sulfadiazine recovery. The extraction efficiency was determined by comparing the peak area of known amounts of silver sulfadiazine ($P_{standard}$) with the peak area of the extrudate matrices containing the same amounts of silver sulfadiazine (P_{sample}). The percentage of drug recovery (%) was calculated using Eq. (1).

$$\text{Drug recovery}\,(\%) = \frac{P_{sample}}{P_{standard}} \cdot 100. \quad (1)$$

2.4. Antimicrobial activity studies

The antimicrobial activity of the cornstarch/cellulose acetate/silver sulfadiazine matrices against *S. aureus* (ATCC 25923) as the model Gram-negative bacteria and *P. aeruginosa* (ATCC 27853) as the model Gram-positive bacteria was investigated. The bacteria were cultured overnight at 37 °C in soybean-casein broth, which was further adjusted to obtain turbidity comparable to that of the McFarland standard. The assessment was conducted based on the disc diffusion method. Both the non-loaded (without silver sulfadiazine) and the loaded (with silver sulfadiazine) cornstarch/cellulose acetate matrices were cut into circular discs (5 mm in diameter) and sterilized by exposure to ultraviolet light for 3 min. The Petri dish containing Mueller Hinton agar was divided into quadrants and loaded matrices were placed in three quadrants. The non-loaded matrix (control) was placed in the last quadrant, followed by incubation at 37 °C for 24 h. In case of inhibition, there would be no growth of the bacteria as indicated by a clear zone around the disc specimens. The diameters of the inhibition zones were measured for further evaluation. The experiments were performed in triplicate.