

Antibiotic-eluting bioresorbable composite fibers for wound healing applications: Microstructure, drug delivery and mechanical properties

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Abstract

Novel antibiotic-eluting composite fibers designed for use as basic wound dressing elements were developed and studied. These structures were composed of a polyglyconate core and a porous poly(DL-lactic-co-glycolic acid) shell loaded with one of three antibiotic drugs: mafenide acetate, gentamicin sulphate and ceftazidime pentahydrate. The shell was prepared by the freeze-drying of inverted emulsions. The fiber investigation focused on the effects of the emulsion's formulation on the shell microstructure and on the resulting profile of drug release from the fibers. Albumin was found to be the most effective surfactant for stabilizing the inverted emulsions and also to have a beneficial holdup effect on the release kinetics of the hydrophilic antibiotic drugs, especially mafenide acetate, probably through a specific interaction. An increase in the organic:aqueous phase ratio, polymer content or molecular weight of the host polymer resulted in a decrease in the burst release and a more moderate release profile due to changes in shell microstructure. The first two parameters were found to be more effective than the third. The diverse release profiles obtained in the current study and the good mechanical properties indicate that our new composite fibers have good potential for use in wound healing applications.

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1. Introduction

Wound dressings aim to restore the milieu required for skin regeneration and to protect the wound from environmental threats and penetration of bacteria. Although traditional gauze dressings offer some protection against bacteria, this protection is lost when the outer surface of the dressing becomes moistened by wound exudate or external fluids. Furthermore, traditional gauze dressings do not greatly restrict moisture evaporation and may cause dehydration of the wound bed. This can lead to adhesion of the dressing, particularly as wound fluid production diminishes, causing pain and discomfort to the patient when removed [1]. Most modern dressings are designed according to the well-accepted bilayer structure concept,

i.e. an upper dense “skin” layer to prevent bacterial penetration and a lower spongy layer designed to adsorb wound exudates and accommodate newly formed tissue [2,3]. Unfortunately, dressing material which has absorbed wound discharge provides conditions that are also favorable for bacterial growth. This has encouraged the development of a new generation of wound dressings with improved curative attributes that provide an antimicrobial effect by eluting various germicidal compounds. These dressings still require frequent changing, which may be painful to the patient, harm the vulnerable underlying skin and increase the risk of secondary contamination. Biore-sorbable dressings successfully address this shortcoming, since they do not need to be removed from the wound surface once they have fulfilled their role. Film dressings made of lactide–caprolactone copolymers such as Topkin[®] (Biomet, Europe) and Oprafof[®] (Lohmann & Rauscher, Germany) are currently available [4]. Biodegradation of

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these films occurs via hydrolysis of the copolymer into lactic acid and 6-hydroxycaproic acid. However, film dressings are better suited for small wounds, since they lack absorbence and are impermeable to water vapor and gases, both of which cause accumulation of wound fluids on larger wound surfaces.

Some recently reported work has focused as an alternative on the development of more complex biodegradable fiber-based wound dressings with antibiotic delivery [5–8]. Fiber-based dressings composed of either continuous fibers that form a non-woven fiber mesh or a fabric made from woven fibers offer a high surface area for controlled release, absorbency and pliability. However, the main challenge in designing a device for the release of low molecular weight (MW) hydrophilic antibiotics is to overcome the rapid discharge of the drug from the device. This drawback has also been reported for other antibiotic-eluting devices such as periodontal devices [9,10] and vascular grafts [11,12]. The local antibiotic release profile should exhibit a considerable initial release rate in order to respond to the elevated risk of infection from bacteria introduced during the initial trauma, followed by a release of antibiotics at an effective level long enough to inhibit latent infection [13]. The location, size and degree of injury, as well as the rate of tissue regeneration (depending on the patient's age and other parameters), affect the wound healing process. Hence, characteristic healing has been reported to take 3–7 weeks [14]. Common strategies that have been described in an attempt to overcome the problem of rapid drug release include the entrapment of the hydrophilic drug within a hydrophobic substance as a means to delay water penetration and outward drug diffusion [15,16], or enhancement of drug bonding to the carrying matrix [11,12,17]. The latter can be achieved either by selecting or modifying a matrix material to support the formation of covalent bonds, Van der Waals dispersion forces, hydrogen bonds, or ionic interactions between the drug and the matrix. Vascular grafts sealed with albumin and gelatin have been shown to promote such interactions and therefore demonstrate a reduced burst release of antibiotics compared to uncoated grafts [11,12]. A wound dressing based on succinylated collagen, which behaves as an anion after swelling, has been shown to delay the release of the cationic drug ciprofloxacin via ionic interactions [17].

Incorporation of antibiotics in the process of fiber spinning (e.g. electrospinning or melt and solution spinning) is associated with the disadvantages of poor mechanical properties due to drug incorporation and limitations in drug loading. Furthermore, many drugs and proteins do not tolerate melt processing and organic solvents. The main goal of the current study was therefore to develop and study new fiber structures loaded with antibiotics. Our composite fibers combine a dense polymer core fiber and a drug-loaded porous shell structure, i.e. the drug is located in a separate compartment (a “shell”) around a melt spun “core” fiber. The shell is prepared using freeze-drying of inverted emulsions. This fabrication process uses

mild processing conditions and is designed to produce a structure with good mechanical properties as well as the desired drug-release profile. These new fibers are ideal for forming thin, delicate, biomedically important structures such as wound dressings. Our fibers were loaded with one of three antibiotic drugs: gentamicin sulphate, ceftazidime pentahydrate and mafenide acetate. The first two antibacterial drugs are broad-spectrum antibiotics which can be used systemically or locally, whereas the third is typically used in burn dressings. The drugs' physicochemical properties and antibacterial spectra are presented in Table 1. The effects of the emulsion's formulation parameters on the shell microstructure and on the resulting drug-release profile and mechanical tensile properties are presented.

2. Materials and methods

2.1. Materials

Maxon™ polyglyconate monofilament sutures with a diameter of 0.20–0.25 mm (United States Surgical Inc., USA) were used as core fibers.

Bioresorbable porous structures (the shell coating) were made of 75/25 poly(DL-lactic-co-glycolic acid) (PDLGA), inherent viscosity (i.v.) = 0.4, 0.65 and 1.13 dl g⁻¹ (in CHCl₃ at 30 °C), MW approximately 50, 100, 240 kDa, respectively (Absorbable Polymer Technologies, Inc., USA).

2.1.1. Drugs

Gentamicin sulfate (cell-culture tested), 590 µg gentamicin base per mg of salt (Sigma, G-1264).

4-Aminomethylbenzenesulfonamide acetate salt (mafenide acetate) (Sigma, A-3305).

Ceftazidime hydrate, 90–105% (Sigma, C-3809).

2.1.2. Surface active agents

Bovine serum albumin (BSA), MW = 66,000 Da (Sigma, A-4503).

Poly(vinyl alcohol) (PVA), 87–89% hydrolyzed, MW = 13,000–23,000 Da (Aldrich, 36,317-0).

2.1.3. Reagents

Isopropyl alcohol (propanol) was purchased from Frutarom, Israel.

1,1,1,3,3,3-hexafluoro-2-propanol (H1008) was purchased from Spectrum Chemical Mfg. Corp.

2.2. Preparation of core-shell fiber structures

2.2.1. Fiber surface treatment

The sutures were surface-treated in order to dispose of the original fiber coating and to enhance adhesion between the core fiber and the coating. The Maxon™ fibers were gently wrapped around flexible Teflon frames and dipped in a Petri dish containing 1,1,1,3,3,3-hexafluoro-2-propanol for 40 s. The fibers were then washed with 70% ethanol and dried.

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