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Biodegradable soy wound dressings with controlled release of antibiotics: Results from a guinea pig burn model

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ABSTRACT

There is growing interest in the development of biodegradable materials from renewable biopolymers, such as soy protein, for biomedical applications. Soy protein is a major fraction of natural soybean and has the advantages of being economically competitive, biodegradable and biocompatible. It presents good water resistance as well as storage stability. In the current study, homogenous antibiotic-loaded soy protein films were cast from aqueous solutions. The antibiotic drug gentamicin was incorporated into the films in order to inhibit bacterial growth, and thus prevent or combat infection, upon its controlled release to the surrounding tissue. The current *in vivo* study of the dressing material in contaminated deep second-degree burn wounds in guinea pigs ($n = 20$) demonstrated its ability to accelerate epithelialization with 71% epithelial coverage compared to an unloaded format of the soy material (62%) and a significant improved epithelial coverage as compared to the conventional dressing material (55%). Our new platform of antibiotic-eluting wound dressings is advantageous over currently used popular dressing materials that provide controlled release of silver ions, due to its gentamicin release profile, which is safer. Another advantage of our novel concept is that it is based on a biodegradable natural polymer and therefore does not require bandage changes and offers a potentially valuable and economic approach for treating burn-related infections.

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1. Introduction

1.1. Soy protein

There is growing interest in the development of biodegradable materials from renewable biopolymers, such as soy protein, for biomedical applications [1–7]. Soy protein is a major fraction of natural soybean and can be found in several soybean derivatives in different quantities, depending on the extraction method: defatted soy flour contains 50–59% protein, soy protein concentrate contains 65–72% protein and soy isolate contains more than 90% protein [8]. Soy protein has been explored mainly in the polymer, food and agriculture fields. Use of soy protein as a food source is still increasing, due to its functional and nutritional value, availability and low price [9]. In the materials industry, soy protein was studied as an adhesive and as a ''green'' plastic [1]. Soy protein is an abundant plant protein and has the advantages of being economically competitive, biodegradable and biocompatible. It presents good water resistance as well as storage stability [4]. Soy protein is also very versatile and its properties can be tailored by physical, chemical, or enzymatic treatments [10], such that it can provide diverse requirements for different biomedical applications. It is known that local or systemic use of soybean or its components has an Ig E induced immunogenic effect more in children and less in adults, but in spite of it the soybean is used for the preparation of an intravenous medication widely used in surgery. As always, the public should be informed in the package insert. The statistics says that soybean affects approximately 0.4% of the children's population. Also, approximately 50% of children with soy allergy outgrew their allergy by age of 7 years. The soy protein extract used in the current study was provided by a company which sells it for the food industry and therefore it is considered as safe.

The suitability of soy protein for biomedical applications has been investigated, due to its low cost and bioactive properties [11]. Soy thermoplastics were found to be non-cytotoxic, and even encouraged cell proliferation during *in vitro* tests [12]. Proposed applications range from bone cement to hydrogel and membranes for wound-dressing applications. The most promising recent applications include drug delivery carrier films, temporary replacement implants and scaffolds for tissue engineering [13].

Snyders et al. [14] and Shingel et al. [15] investigated hybrid hydrogels made of poly(ethylene glycol) and soy protein for moist wound-dressing applications and concluded that these hydrogels can be considered as a safe, biocompatible and inflammatory inert wound-dressing material. Santos et al. [16] developed chitosan/soy (cht/soy)-based membranes as wound-dressing materials and showed that these new membranes possess the desired features for healing/repair stimulation, ease of handling, and final esthetic appearance, which are valuable properties for wound dressings.

1.2. Wound dressings

Various types of wounds result in tissue damage. These include burns, pressure ulcers, diabetic ulcers and trauma. The main goal in wound management is to achieve rapid healing with good functional and esthetic results. An ideal wound dressing can restore the milieu required for the healing process, while simultaneously protecting the wound bed against bacteria and environmental threats. The dressing should also be easy to apply and remove. Most modern dressings are designed to maintain a moist healing environment and to accelerate healing by preventing cellular dehydration and promoting collagen synthesis and angiogenesis [17]. However, over-restriction of water evaporation from the wound should be avoided, since accumulation of fluid under the dressing may cause maceration and facilitate infection. The physical and chemical properties of the dressing should therefore be adapted to the type of wound as well as to the degree of wound exudation.

Bacterial contamination of a wound seriously threatens its healing. In burns, infection is the major complication after the initial period of shock, and it is estimated that about 75% of the mortalities following burns are related to infections rather than to osmotic shock and hypovolemia [18]. This has encouraged the development of improved wound dressings that provide an antimicrobial effect by eluting germicidal compounds such as iodine (Iodosorb®, Smith & Nephew), chlorohexidine (Biopatch®, J&J), or, most frequently, silver ions (*e.g.*, Acticoat® by Smith & Nephew, Actisorb® by J&J and Aquacell® by ConvaTec). Such dressings are designed to provide controlled release of the active agent through a slow but sustained release mechanism which helps avoid toxicity yet ensures delivery of a therapeutic dose into the wound.

1.3. About the current study

It can be said that there is an increasing need to develop new biodegradable materials for use in wound-healing applications. Soy protein is a very promising natural biodegradable material, due to the abovementioned advantages. We therefore chose to develop and study soy protein films as a platform for wound-dressing applications, in all relevant aspects. We believe that a high quality soy protein film which is hydrophilic but also cross-linked and therefore exhibits desired relevant properties may provide properties that are usually achieved using the bilayer concept.

Homogenous antibiotic-loaded yellowish films were cast from aqueous solutions. A detailed description of the preparation process was published elsewhere [19]. The antibiotic drug gentamicin was incorporated into the films in order to inhibit bacterial infection upon its controlled release to the surrounding tissue. The mechanical and physical properties of these films, the antibiotic release profiles and their antimicrobial effects as well as cellular response results, were recently published by us [19,20]. Since these films are crosslinked and also contain plasticizer (glycerol), they are strong and flexible and can be easily handled. The new gentamicin-eluting soy protein wound dressing which exhibited the best properties in the above study was selected for the current *in vivo* study and compared to a neat soy protein wound dressing without the drug and to a standard Melolin dressing.

The guinea pig is often used as a dermatological and infection model [21–24]. Research on guinea pigs has included