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Will the use of double barrier result in sustained release of vancomycin? Optimization of parameters for preparation of a new antibacterial alginate-based modern dressing

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ABSTRACT

The aim of this research was to prepare and characterize an alginate-based wound dressing containing vancomycin immobilized at the silica surface. The silica samples functionalized with amine, diol and carboxylic acid groups were loaded with 7.8, 5.7 and 7.1 wt.% of the antibiotic respectively. The immobilized drug was encapsulated in alginate or gelatin/alginate gels and the average concentration of vancomycin was about 10 mg *per* g of the dried gel. The effect of functional organic groups at the silica surface on the release rate of the drug was investigated. Only the drug immobilized at Si-amine in alginate matrix was found to demonstrate slower release from the proposed wound dressing. The *in vitro* release profiles for other silica carriers did not show significant differences in relation to the free loaded drug. The presence of gelatin had a favourable impact on the slowing down of the drug release from the dressing with a double barrier. All the gels studied with vancomycin immobilized at the silica surface demonstrated antimicrobial activity against various bacteria. A reduction of the drug dose to a half had no effect on changing microbiological activity of gels.

1. Introduction

Dressings are important means used in the healing process of wounds. The optimal dressing should provide a quick healing of wounds at low cost with minimal patient discomfort (Boateng et al., 2008). Traditional dressings do not provide a moist wound environment thus they have been increasingly replaced by modern dressings. The main difference between the traditional and modern dressing is in the materials from which modern dressings are produced (Jones and San Miguel, 2006). The modern dressings are classified according to the material of production and according to their effect on tissue moisture: the ones that absorb exudates, maintain moisture and those that donate moisture (Ovington, 2007). For wounds with high exudates, it is necessary to use of absorbent dressings, which allow less frequent dressing changes, and thus the healing process is not disturbed. Alginate dressings are characterized by the ability to form gels after contact with exuding wounds.

Alginate is a polysaccharide composed of linear chains of guluronic (G block) and mannuronic (M block) acid residues (Baldwin and Kiick, 2010; George and Abraham, 2006; Hamidi et al., 2008). It is characterized by biocompatibility, non-toxicity and biodegradability. It forms hydrogels in the presence of divalent cations, mostly calcium ions acting as crosslinking agents. However, such crosslinked hydrogels are unstable in the presence of monovalent cations, thus leading to the material structure degradation. This undesirable process can limit the bioapplication of alginate biopolymer, thus it is often modified or combined with other materials to form stable hydrogels (Yang et al., 2011; Lin et al., 2010; Krishna Rao et al., 2006; Zhang et al., 2011; Li et al., 2011; Chen et al., 2011; Pal and Khanum, 2011; Ho et al., 2009). It is also important that at high enough concentration in water (at least 5% w/v), sodium alginate chains undergo entanglement and swelling. In such conditions, after extension of chains, a stable hydrogel is formed with a diffusion barrier. Therefore, alginates can be applied for delivery of different pharmaceutical agents, also in terms of antimicrobial dressings.

The active components incorporated in modern dressings prevent or combat infections. Many modern dressings contain

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incorporated silver (Meaume et al., 2005; Rujitanaroj et al., 2008). The pharmaceutical agent is released at the wound surface guarantying long-lasting antimicrobial action. If antibiotics are needed in the therapy, it is also crucial that local delivery of a drug from a dressing can limit of systemic antibiotic therapy. Antibacterial wound dressings can be loaded with *e.g.* vancomycin.

Vancomycin is a water soluble glycopeptides drug, active against gram-positive bacteria. The influence of different carriers on vancomycin release has been studied (Ravelingien et al., 2010; Zhanf et al., 2008). Antibacterial hydrogels with vancomycin can be applied as dressings for treatment of severe wounds (*e.g.* surgical infections). The drug is usually freely loaded to the biomaterial (Lin et al., 1999) or it is covalently linked to the biodegradable carrier (Lakes et al., 2014). It turns out that even the vancomycin via hydrophobic interaction can form a hydrogel, a new kind of a biomaterial (Xing et al., 2002).

Our research group has already proposed a method for the preparation of a dressing based on a double barrier with anti-inflammatory drug ibuprofen (Kurczewska et al., 2014). Mesoporous silica was charged with a model drug and then encapsulated in calcium alginate. The proposed model for a modern dressing has proved to be effective for a slower release of the active substance. On the other hand, the matrix constructed on the basis of the calcium alginate has been unstable for a long-term use. Therefore, we searched for other materials for encapsulating of silica carrying the bioactive substance. Very interesting model has been proposed by Thu et al. (2012) and Thu and Ng, (2013), who produced modern dressings based on a double layer of hydrocolloid film. Bilayer films were based on sodium alginate or a mixture of sodium alginate with gelatin providing a homogeneous distribution of the drug in the film.

In this study we used vancomycin as a model drug for a new antibacterial modern dressing. We have demonstrated earlier the influence of the type of bonding between the inorganic matrix and the drug on the controlled release and biological activity of vancomycin (Kurczewska et al., 2015). The aim of this research was to develop a model of a potential wound dressing containing ionically-bonded vancomycin encapsulated in alginate-based matrix. The system with a double barrier was designed to reduce the drug release in the initial phase, remain stable for at least 3 days, in order to reduce the frequency of dressing changes, and provide better antibacterial activity when compared to the free form of the drug.

2. Materials and methods

2.1. Materials

The inorganic matrices: silica-bound amine (Si-amine; 1.66 mmol g^{-1}), Silica-bound Diol (Si-diol; 1.12 mmol g^{-1}) and Silica-bound Carboxylic Acid (Si-carboxylic acid; 1.06 mmol g^{-1}) were purchased from SiliCycle®. Vancomycin hydrochloride was used as a commercial product of Xelia Pharmaceuticals ApS (Denmark). Alginic acid sodium salt, gelatin powder, dimethyl sulfoxide (DMSO), acetonitrile and glycerol were obtained from Aldrich, and were used as received. Demineralized water was used for aqueous solutions preparation.

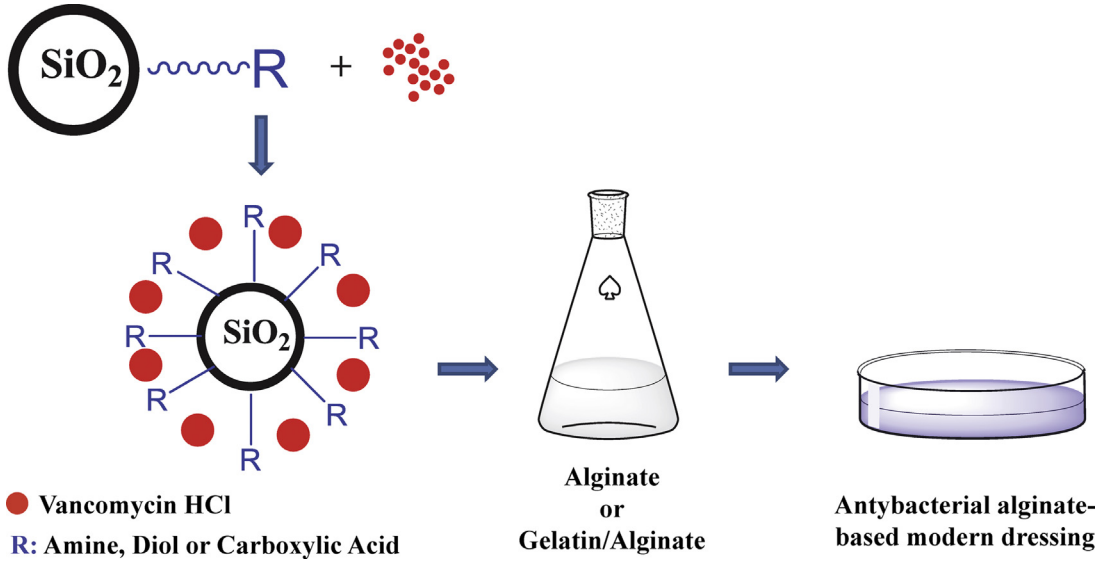
2.2. Drug loading and film preparation

For immobilization of Vancomycin at the silica surface, a portion of silica-bound amine, -diol or-carboxylic acid was suspended in anhydrous acetonitrile and mechanically stirred in the ultrasonic bath for 30 min at room temperature. Then a solution of vancomycin (0.1 g *per* 1.0 g of silica gel; in DMSO) was added dropwise and the resulting mixture was stirred for 48 h at room temperature. The materials were separated by centrifugation, followed by several times repeated washing with DMSO, acetonitrile and water in order to remove unreacted substrates and finally dried for 24 h to obtain the silicas with immobilized vancomycin. The drug loading was initially quantified gravimetrically.

The infrared spectra of the silicas studied were taken on an IFS 66 v/s Fourier transform infrared (FTIR) spectrophotometer from Bruker, equipped with an MCT detector (125 scans, resolution 2 cm^{-1}). The spectra were recorded in the 400–4000 cm^{-1} range for KBr pellets. The thermogravimetric studies were carried out in a Setsys 1200 apparatus (Setaram) at a heating rate of 10 °C/min under helium atmosphere.

Alginate-based dressings were prepared according to the following procedure:

Alginate: For the reference sample, without the antibiotic, 1.50 ± 0.02 g of sodium alginate (6%, w/v) was dissolved in 23.5 mL of water (40 °C). The solution was cooled and continuously stirred until a uniform gel formation. To the stirred solution, 1.5 mL of a plasticizer (glycerol) was added. For free drug-loaded alginate-dressing, 1.50 ± 0.02 g of sodium alginate (6%, w/v) was dissolved



Scheme 1. A schematic presentation of the preparation process of antibacterial alginate-based wound-dressing material.