International Journal of Pharmaceutics 520 (2017) 241–253

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A novel *in situ* silver/hyaluronan bio-nanocomposite fabrics for wound and chronic ulcer dressing: *In vitro* and *in vivo* evaluations

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ARTICLE INFO

Article history:
Received 10 December 2016
Received in revised form 27 January 2017
Accepted 1 February 2017
Available online 3 February 2017

Keywords:
In-situ silver
Hyaluronan
Cytotoxicity
Wound dressing

ABSTRACT

In-situ formed hyaluronan/silver (HA/Ag) nanoparticles (NPs) were used to prepare composite fibers/fabrics for the first time. Different concentrations of silver nitrate (1, 2 mg/100 ml) were added at ambient temperature to sodium hyaluronate solution (40 mg/ml), then the pH was increased to 8 by adding sodium hydroxide. *The in-situ* formed HA/Ag-NPs were used to prepare fibers/nonwoven fabrics by wet-dry-spinning technique (WDST). UV/vis spectroscopy, SEM, TEM, DLS, XPS, XRD and TGA were employed to characterize the structure and composition of the nanocomposite, surface morphology of fiber/fabrics, particle size of Ag-NPs, chemical interactions of Ag^0 and HA functional groups, crystallinity and thermal stability of the wound dressing, respectively. The resultant HA/Ag-NPs1 and HA/Ag-NPs2 composite showed uniformly dispersed throughout HA fiber/fabrics (SEM), an excellent distribution of Ag-NPs with 25 ± 2, nm size (TEM, DLS) and acceptable mechanical properties. The XRD analysis showed that the *in-situ* preparation of Ag-NPs increased the crystallinity of the resultant fabrics as well as the thermal stability. The antibacterial performance of medical HA/Ag-NPs fabrics was evaluated against gram negative bacteria E. coli K12, exhibiting significant bactericidal activity. The fibers did not show any cytotoxicity against human keratinocyte cell line (*HaCaT*). *In-vivo* animal tests indicated that the prepared wound dressing has strong healing efficacy (non-diabetics/diabetics rat model) compared to the plain HA fabrics and greatly accelerated the healing process. Based on our results, the new HA/Ag-NPs-2 mg nonwoven wound dressing fabrics can be used in treating wounds and chronic ulcers as well as cell carrier in different biological research and tissue engineering.

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1. Introduction

Wound healing is a complex, multi-step process including the activation of a variety of cell types. Re-epithelization during the early phase of wound healing, occurs only after migration and proliferation of keratinocyte cells in the epidermal layer from the wound edge as well as by differentiation of stem cells residing in the bulge of hair follicles (Tjong, 2012; Zanette et al., 2011). Bio-nanocomposites represent a fascinating interdisciplinary area that brings together biology, materials science and nanotechnology. Generally, polymer nanocomposite results from the combination of a suitable biopolymer and filler particles at the nanometer scale. The extraordinary versatility of these new materials stems from the large selection of biopolymers and fillers available (Paul and Robeson, 2008; Potts et al., 2011; Regiel et al., 2013; Tjong, 2012).

Abbreviations: HA, hyaluronan (hyaluronan sodium salt); Ag^0, silver nanoparticles; mg, milligram; WDST, wet-dry-spinning technique; SEM, scanning electron microscope; XRD, x-ray diffraction; IPA, isopropyl alcohol; DLS, dynamic light scattering; *E.coli K12*, *Escherichia coli* K12; *HaCaT*, keratinocytes cell line; UV/Vis, ultraviolet/visible spectroscope; TEM, transmission electron microscope; rpm, revolutions per minute; *MTT*, 3-(4.5-dimethylthiazol-2-yl)-2.5-diphenyl tetrazolium bromide; S, loose crust; G, granulation tissue; N, necrotic tissue; Ep, epithelial tissue.

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http://dx.doi.org/10.1016/j.ijpharm.2017.02.003
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The interaction between filler and polymer enables the NPs to act as molecular bridges greatly affecting properties of the polymer matrix (Kalathi et al., 2014; Potts et al., 2011; Tjong, 2012; Zeng et al., 2005). Bio-nanocomposites add a new biological dimension to these enhanced properties introducing bioactivity, biocompatibility and/or resorb-ability.

Sodium hyaluronate (HA) is natural polysaccharide with composed units of D-glucuronic acid and *N*-acetyl glucosamine, present in different connective tissues such as cartilage, bone, and it's the central component for structuring the connective tissue (Abdel-Mohsen et al., 2012c; Harris et al., 1972; Lapčík et al., 1998; Reineck et al., 2003). Moreover, they are environmentally friendly green chemicals. It is also used as a diagnostic marker for different diseases such as cancer, tumor diseases (Alkrad et al., 2003). Recently Raman spectroscopy is used to examine the chemical structure of bulk hyaluronan films (Kvitek et al., 2005; Tao et al., 2003). In order to avoid wound or chronic ulcer infection by bacteria, antibacterial agents must be introduced into neat hyaluronan (Abdel-Mohsen et al., 2013, 2012c). Among various antimicrobial agents, silver (Ag^0) is the most common and well-studied type of the antibacterial agent due to its wide antibacterial spectrum (Abdel-Mohsen et al., 2014, 2012a, 2013, 2012c). Silver nanoparticles are reported to be effectively against a wide range of gram positive/negative bacteria, fungi and viruses (Barbinta-Patrascu et al., 2014; Cong et al., 2014; Loza et al., 2014; Marsich et al., 2013; Nocchetti et al., 2013; Schneid et al., 2014; Shi et al., 2015; Taheri et al., 2014). Silver nitrate is used as antimicrobial agent for wounds as far back as World War I; the current use of silver agents has been reduced to topical silver derivatives like silver sulfadiazine (cream/gel) in the treatment of burn wounds due to the unique properties of excellent and effective antibiotics (Sun et al., 2013; Szegedi et al., 2014).

Silver nanoparticles (Ag-NPs) are clusters of silver atoms that area in diameter from 1 to 100 nm and attracted interest as antibacterial and antifungal agents for applications in cosmetics (Kokura et al., 2010), textile (Abdel-Mohsen et al., 2012a; Bober et al., 2014) and medicine (Abdel-Mohsen et al., 2012a; Stevens et al., 2011). They are used for coatings on various materials like

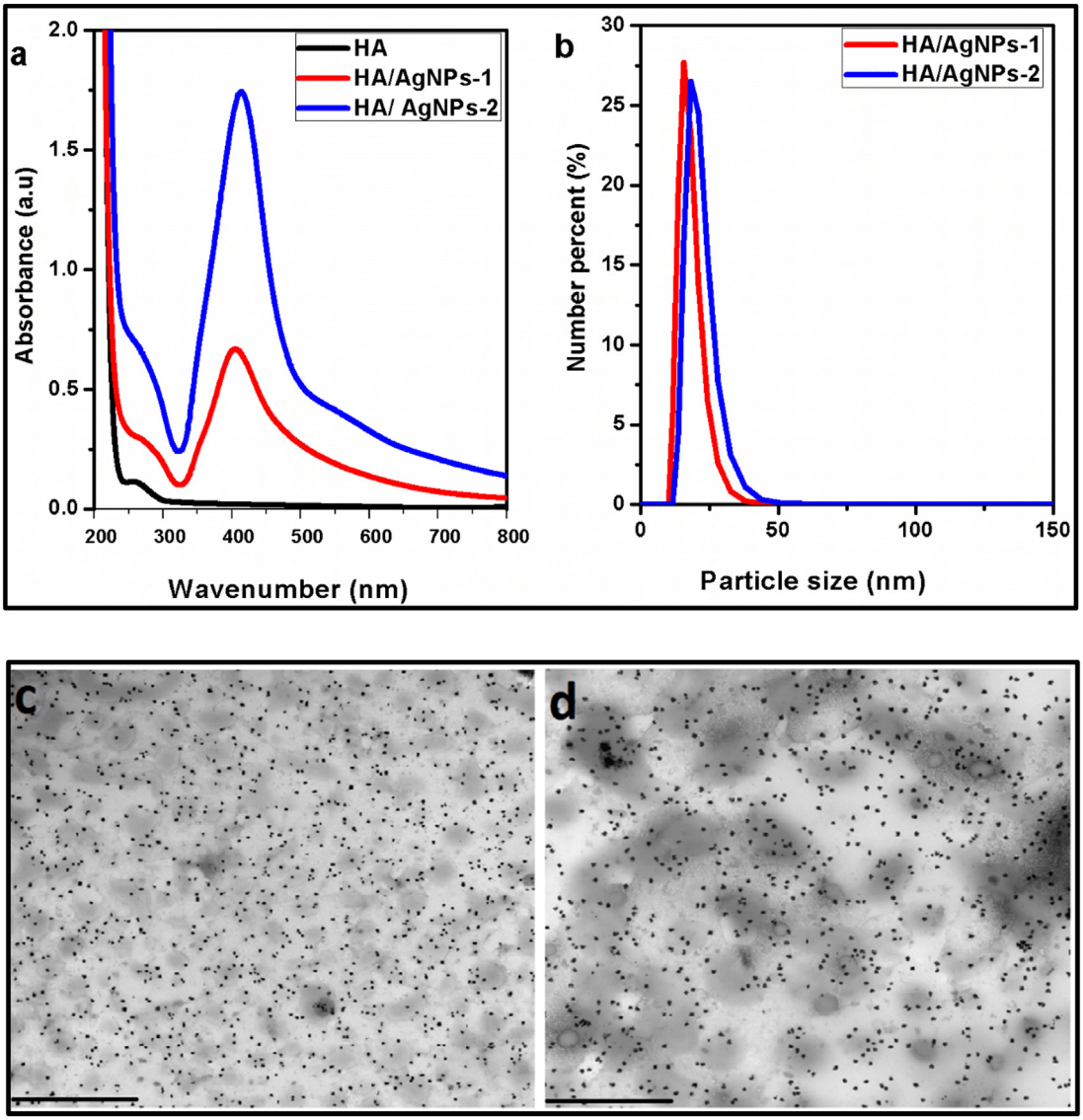

Fig. 1. UV/Vis spectra of plain HA and HA/Ag-NPs-1 mg and HA/Ag-NPs-2 mg (a); DLS of HA/Ag-NPs-1 mg and HA/Ag-NPs-2 mg (b), TEM of HA/Ag-NPs-1 mg (c); TEM of HA/Ag-NPs-2 mg (d); scale bars = 1 μm.

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