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A potential bioactive wound dressing based on carboxymethyl cellulose/ZnO impregnated MCM-41 nanocomposite hydrogel

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ABSTRACT

Lack of antibacterial activity, deficient water vapor and oxygen permeability, and insufficient mechanical properties are disadvantages of existing wound dressings. Hydrogels could absorb wound exudates due to their strong swelling ratio and give a cooling sensation and a wet environment. To overcome these shortcomings, flexible nanocomposite hydrogel films was prepared through combination of zinc oxide impregnated mesoporous silica (ZnO-MCM-41) as a nano drug carrier with carboxymethyl cellulose (CMC) hydrogel. Citric acid was used as cross linker to avoid the cytotoxicity of conventional cross linkers. The prepared nanocomposite hydrogel was characterized using X-ray diffractometry (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Zeta potential and UV–vis spectroscopy. Results of swelling and erosion tests showed CMC/ZnO nanocomposite hydrogel disintegrated during the first hours of the test. Using MCM-41 as a substrate for ZnO nanoparticles solved this problem and the CMC/ZnO-MCM-41 showed a great improvement in tensile strength (12%), swelling (100%), erosion (53%) and gas permeability (500%) properties. Drug delivery and antibacterial properties of the nanocomposite hydrogel films studied using tetracycline (TC) as a broad spectrum antibiotic and showed a sustained TC release. This could efficiently decrease bandage exchange. Cytocompatibility of the nanocomposite hydrogel films has been analyzed in adipose tissue-derived stem cells (ADSCs) and results showed cytocompatibility of CMC/ZnO-MCM-41. Based on these results the prepared CMC nanocomposite hydrogel containing ZnO impregnated MCM-41, could serve as a kind of promising wound dressing with sustained drug delivery properties.

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1. Introduction

Skin is the largest organ in the human body and so cutaneous wounds severely affect human life and health. A wound dressing with perfect match to the demands of rapid wound closure has an important role in the entire management of wounds infection [1]. An ideal wound dressing should have appropriate mechanical properties, suitable oxygen and water vapor permeability, and keep the moisture in healing environment, and prevent wound from bacterial infection [2]. In addition, these dressings should be biocompatible and easily removed from wounds [3]. Hydrogels could absorb wound exudates due to their strong swelling ratio and give a cooling sensation and a wet environment [4,5]. Unique properties of natural polymers introduce them as very promising candidates for wound dressing materials [6].

Sodium carboxymethyl cellulose is a semi synthetic cellulose derivative that is biocompatible and biodegradable polymer and hence commonly used in wound dressings [7–9]. CMC alone has been used as dressing for burn wound dressing. It helps extracellular matrix formation and re-epithelialization due to its capability of maintaining an optimum moist environment in wound region [10–12]. Most of the available products are not clinically mature due to their characteristics and shortcomings [13]. For example, Ramli and Wong used non-crosslinked CMC films [14]. The membranes contain no antibacterial agent and have high degradation rate (films were changed every 6 h). Designing more effective dressing playing an active role in the wound healing process is in great demand. These bioactive dressings aim to deliver biomolecules including antibiotics and growth factors gradually [15,16]. Hence, combination of hydrogels with a drug delivery system is required to control and prolong the release of antibacterial agents to prevent wound infection during healing process. A wide variety of nanoparticles like Ag, ZnO and CuO nanoparticles are mixed with the polymeric network to obtain nanocomposite hydrogels with drug delivery and antibacterial properties [17–20].

ZnO is an eco-friendly and non-toxic material. It is widely used in drug delivery [21–23]. It has shown antibacterial activity and it is currently used in many cosmetic materials [24,25]. Furthermore, the Zn^{++} released from ZnO can enhance keratinocyte migration toward the wound site and promote healing [26,27]. In order to control the

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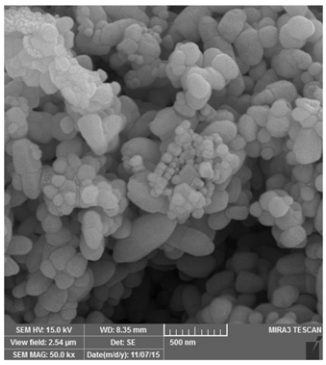

Fig. 1. SEM micrograph of the synthesized ZnO nanoparticles.

stability of the ZnO nanoparticles, ZnO have been loaded on mesoporous silica materials through impregnation leading to surface developing, life extension, chemical and thermal stability (dissolution to yield $Zn(OH)_2$) etc. [28,29].

MCM-41 (Mobil Composition of Matter No. 41, the number is added chronologically based on the date of discovery), one member of the mesoporous silica family, possess a highly ordered hexagonal array of one-dimensional cylindrical pores with changeable pore diameter between 1.5 and 30 nm [30]. Large surface area, large pore volume, and excellent biocompatibility make MCM-41 materials among the best candidates as hosts for many guest materials and have attracted significant interest as drug carriers [31,32]. Tian et al. prepared MCM-41 type mesoporous silica nanoparticles decorated with silver nanoparticles (Ag-MSNs). These Ag-MSNs possess an enhanced antibacterial effect [33]. Yu et al. used hyaluronic acid modified mesoporous silica nanoparticles for targeted drug delivery to cancer cells [34]. Buchtová et al. prepared nanocomposite hydrogels of mesoporous silica nano fibers interlinked with siloxane derived polysaccharide for cartilage tissue engineering. The prepared nanocomposite hydrogel showed enhanced mechanical properties and mesoporous silica acted as reservoirs for bioactive molecules [35].

Our group has shown previously that citric acid crosslinked carboxymethyl cellulose hydrogels could serve as potential wound dressings [36]. Here, for the first time, in order to design more effective dressing playing an active role in the wound healing process ZnO impregnated MCM-41 nanoparticles was added to the hydrogel. To maximize the antibacterial efficiency and reduce the chances of resistance development in the microbes by employing multiple targeting approaches TC was loaded to the nanoparticles. The prepared nanocomposite hydrogel was characterized using X-ray diffractometry (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Zeta potential and UV–vis spectroscopy. Effect of the nanoparticles on the swelling, erosion, gas permeability and TC delivery was studied. Finally, microbiological assay were conducted to examine the antimicrobial activity and drug delivery properties of the prepared nanocomposite hydrogel films against Gram-positive *S. aureus* and Gram-negative *E. coli*.

2. Experimental

2.1. Materials

Sodium carboxymethyl cellulose (CMC), degree of substitution (DS) 0.55–1.0, and viscosity 15,000 mPas/s (1% in H_2O, 25 °C) were obtained from Nippon Paper Chemicals Co., Ltd., Japan. Tetracycline hydrochloride was purchased from Sigma–Aldrich. Tetraethylorthosilicate (TEOS), cetyltrimethylammonium bromide (CTAB), $Zn(NO_3)_2 \cdot 6H_2O$, NaOH, citric acid, glycerol and all other materials were purchased from Merck.

2.2. MCM-41 synthesis

In a general synthesis, 2.74 mmol of (CTAB) were dissolved in 480 mL of NaOH aqueous solution (15.0 mM), and then 22.4 mmol of tetraethylorthosilicate (TEOS) was added dropwise to the solution. The mixture was vigorously stirred and heated to 80 °C for 2 h. Subsequently, the product was isolated by hot filtration, washed with distilled water and methanol, and dried. Finally, the resulted powder was calcinated at 600 °C in air for 6 h. To produce zinc impregnated MCM-41, a wet impregnation was performed. 0.33 g of calcinated MCM-41 was introduced into an aqueous solution of $Zn(NO_3)_2 \cdot 6H_2O$ (0.20 g/12 mL). After 1 h, the resulting mixture was dried at 80 °C. The resulting precipitate was then heated in 400 °C for 3 h to oxidize the impregnated zinc.

2.3. ZnO nanoparticles preparation

ZnO nanoparticles were synthesized according to an approach reported elsewhere with modifications [37]. Briefly 1.5 g CMC was added to 250 mL distilled water. After complete dissolution of CMC, 7.44 g (0.025 mol) of Zinc nitrate hexahydrate was added to the solution, and then 250 mL of sodium hydroxide solution (0.2 mol/L) was added drop-wise with constant stirring. After the complete addition of sodium hydroxide the solution was centrifuged at 8000 rpm for 20 min, the settled precipitate washed several times, dried and calcinated by 7 h at 540 °C to complete the reaction and remove CMC.

2.4. Characterization and analysis

UV–vis absorption spectra of the samples were recorded on a Shimadzu 1700 Model UV–vis spectrophotometer. The pattern of X-ray diffraction of the samples was obtained by Siemens diffractometer with Cu-kα radiation at 35 kV in the scan range of 2θ from 2 to 10° and scan rate of 1°/min. The diameter of channels of the synthesized MCM-41 was calculated using Bragg's equation where λ was 0.154 nm. The morphology of the dried samples was observed using a scanning electron micro-scope (SEM) (LEO 1430VP) operated at 15 kV after coating the dried samples with gold and silver films. Transmission electron micrograph (TEM) was conducted by LEO 906E transmission electron microscope operating at 100 kV. Zeta potential of the sample is analyzed by a Zeta Sizer 2000 (Malvern Instruments Ltd., UK). An Analytik Jena flame atomic absorption spectrometer model Nov. 400 (Jena, Germany; www.analytik-jena.de) furnished with an air–acetylene flame and a cadmium hollow cathode lamp, operated at 3.0 mA, was used for Zn determination.

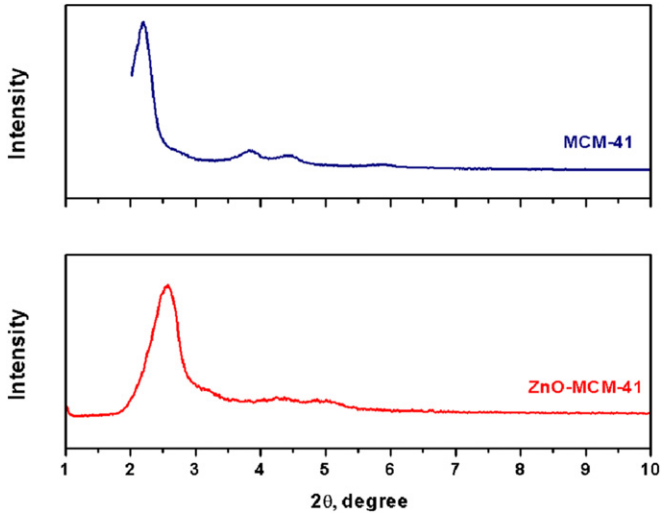

Fig. 2. XRD patterns of native MCM-41 and ZnO impregnated MCM-41.

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