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Synthesis and characterization of tragacanth gum based hydrogels by radiation method for use in wound dressing application

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ABSTRACT

Keeping in view the inherent wound healing ability of tragacanth gum (TG), mucoadhesive and gel forming nature of polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), in the present work, an attempt has been made to prepare the antibiotic drug 'gentamicin' and analgesic drug 'lidocaine' loaded sterile TG-PVA-PVP hydrogel dressings for care of wound infection and wound pain together. These polymers were characterized by cryo-SEM, AFM, FTIR, XRD, ^{13}C NMR, TGA, DSC and swelling studies. Drug release mechanism and kinetic models, network parameters and other properties like haemolysis, mucoadhesion, water vapor permeability, microbial penetration, antioxidant activities and oxygen permeability were also determined. The results showed wound fluid absorption and slow drug release ability of hydrogel films. These polymer films were found to be blood compatible, permeable to water vapor and O_2, and impermeable to microorganism. Further, the synergic effects of mucoadhesive, antimicrobial and antioxidant nature of hydrogel dressings will make them suitable candidate for wound management.

1. Introduction

Recently, it has been reported that the tragacanth gum (TG) has inherent wound healing potential which fasten the wound healing. Tragacanth is also effective in the proliferation and remodeling phases of wound healing (Moghbel et al., 2005). Its antioxidant activity helps in wound healing processes (Yusufoglu et al., 2015; Kavoosi et al., 2013). TG and polyvinyl alcohol (PVA) based antibacterial nanofiber scaffold has been used for wound dressing applications. Adherence of nanofibers to human fibroblast cells and proliferation of the cells over these fibers have also been reported. TG is a natural hetero-polysaccharide derived from the *Astragalus gummifer* (Ranjbar-Mohammadi et al., 2013).

Polyvinyl pyrrolidone (PVP) is a water soluble, non cytotoxic polymer which is used in various biomedical applications. It has been used as a main component of wound dressing due to its transparency and biocompatibility (Higa et al., 1999; Lopes and Felisberti, 2003). It has been used as transdermal drug delivery system by Wang and coworkers (Wang et al., 2003). PVP crosslinking with PVA by high energy radiation forms the hydrogel wound dressings (Razzak et al., 1999). PVA is also a water soluble, non toxic, biocompatible polymer which provides the mechanical strength to the wound dressings (Stammen et al., 2001). Its excellent film forming properties make it suitable candidate for hydrogel wound dressing material (Kim et al., 2008; Varshney, 2007). Hydrogels are water swollen cross-linked network structure which provides resistance to dissolution and swell in water up to an equilibrium state and retain their original shape (Rosiak, 1994; Peppas, 1996). Hydrogel dressings are promising material for effective wound healing. Hydrogels absorb and retain the exudates, promotes fibroblast proliferation and keratinocyte migration leading to complete epithelialization of the wound (Bullock et al., 2010).

Gentamicin sulphate is an antibiotic drug and it has been used in wound infection by loading into a polymeric wound dressing (Hwang et al., 2010). At the same time, another important aspect of wound care is pain management which is often done via intravenous and oral drug delivery of analgesics, but, it is associated with various side effects (Gallagher et al., 2000; Chou et al., 2003). Lidocaine is a local anesthetic frequently used in various types of topical systems for sunburn, insect bites and for relieve from itching and pain (Mueller-Goymann and Frank, 1986; Kumar et al., 2012). However, topical application of antibiotics and analgesics is an alternative to minimize the side effects associated with conventional drug delivery system.

Keeping in view the above facts in consideration (i.e. inherent wound healing ability of TG, mucoadhesive and gel forming nature of PVP and PVA), in the present work, an attempt has been made to

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prepare antibiotic drug gentamicin and analgesic drug lidocaine loaded sterile TG-PVA-PVP hydrogel dressings for simultaneous care of wound infection and wound pain. These polymers were characterized by cryo-SEM, AFM, FTIR, XRD, ^{13}C NMR, TGA, DSC and swelling studies. Drug release mechanism, drug release kinetic models, network parameters and some other properties were also determined.

2. Experimental

2.1. Materials

Tragacanth gum and formaldehyde (Merck specialties private limited, Mumbai, India), polyvinyl alcohol (Merck Schuchardt, Germany), polyvinyl pyrrolidone (Sigma-Aldrich USA), lidocaine hydrochloride (AstraZeneca Pharma India Limited), gentamicin sulphate (Rainbow Biochem Pharmaceuticals industries ltd.) and glycerol (S.D. Fine-Chem Limited, Mumbai-India) were used as received.

2.2. Synthesis of polymer films

Synthesis of polymer films was carried out by radiation induced crosslinking by using definite concentration of tragacanth gum, polyvinyl pyrrolidone, polyvinyl alcohol and glycerol, taken in an aqueous reaction system. Homogenous solution of reaction mixture was prepared by stirring 100 rpm at 85 °C for 1 h at mechanical stirrer and then reaction content was autoclaved at 121 °C for 30 min at 15 psi. Thereafter, autoclaved reaction mixture was transferred to petri-plates in laminar flow. This solution was irradiated in ^{60}Co gamma rays at a dose rate of 0.765kGy/h. After irradiating at specific dose, the polymer films were taken out, washed with distilled water and were dried in air oven at 40 ± 2 °C for 96 h. Optimum reaction parameters for the synthesis of polymer films were determined by varying the irradiation dose (9.1 kGy–45.4 kGy), [polyvinyl alcohol] (2%–10% w/v)] and [polyvinyl pyrrolidone] (2% –10% w/v), on the basis of swelling and surface consistency maintained by hydrogel films after 24 h. Optimum conditions were obtained as irradiation dose=27.3 kGy, PVA=6% w/v and PVP=6% w/v. Polymer films were prepared at optimum reaction conditions were used to determine the biomedical properties, network parameters and drug release profile of drugs.

2.3. Characterizations

The polymer characterization was carried out by cryo scanning electron micrography (cryo-SEM), atomic force microscopy (AFM), Fourier transform infrared spectrum (FTIR), X-ray diffraction (XRD), ^{13}C-nuclear magnetic resonance (^{13}C NMR), thermo gravimetric analysis (TGA) and differential scanning calorimetry (DSC). cryo-SEM images of swelled and freeze dried polymer in liquid nitrogen at −190 °C were taken on Jeol (JSM 7600) scanning electron microscope (Japan) equipped with Quroum (UK) PP3000t cryo attachment. AFM of polymer film was taken on AFM (NT-MDT, RUSSIA) in contact mode to see the average surface roughness. FTIR of dried powdered samples was taken in KBr pellets on Nicolet 5700 FTIR THERMO (USA). X-Ray diffraction (XRD) measurements of the sample were made by using PAN analytical X'Pert Pro powder diffraction system (The Netherland). The definite amount of sample was scanned at 25 °C from 10° to 80° (2θ) and in step size of 0.05 and count time of 1.0 s, using an automatic divergence slit assembly and a proportional detector. The solid state ^{13}C NMR was carried on BRUKER DSX-300 solid state NMR spectrometer. The spectrophotometer was operated at a magnetic field of 9.1 T and at a frequency of 75.4 MHz for ^{13}C. TGA and DSC were conducted on a thermo-gravimetric analyzer STA 449 F3 Jupiter (NETZSCH) with a heating rate of 10 °C/min from 25 °C to 800 °C.

2.4. Swelling studies

Swelling studies of the polymer films were carried out in different media by gravimetric method (Singh, 2007). Known weight of polymers were taken and immersed in excess of solvent for different time intervals at 37 °C and thereafter polymers were removed, wiped with tissue paper to remove excess of solvent and weighed immediately. The difference in weight gave the gain in weight at different time intervals. Swelling studies of the polymer films were carried out in triplicate. Swelling of polymers was determined by using Eq. (1).

$$\text{Swelling of polymers} = (W_s - W_o)/W_o \quad (1)$$

where W_o is initial weight of dry polymer and W_s is weight of polymer after 24 h swelling.

Simulated wound fluid (SWF) was prepared by taking 0.68 g of NaCl, 0.22 g of KCl, 2.5 g of $NaHCO_3$, and 0.35 g of NaH_2PO_4 in 100 mL of distilled water in a volumetric flask. The pH of simulated wound fluid was observed to be 8.0 ± 0.2.

2.5. Determination of network parameters

Some important network parameters used to assess cross-linked network structure of hydrogel were determined which include polymer volume fraction in the swollen state (ϕ), molecular weight between two neighboring cross-links ($\bar{M}_c$), Flory-Huggins interaction parameter (χ), cross-link density (ρ), and mesh size (ξ). Swelling of polymer in distilled water was used to evaluate $\bar{M}_c$ by the Flory-Rehner Eq. (2) (Bajpai and Singh, 2006; Lira et al., 2009; Aithal et al., 1990; Kulkarni et al., 2000).

$$\overline{M}c = -\, d_p \nu_{m,1} \phi^{1/3} [\ln(1-\phi) + \phi + \chi\phi^2]^{-1} \quad (2)$$

Here, d_p is density of polymer, $\nu_{m,1}$ is the molar volume of the swelling agent, which is distilled water in present case, ϕ is the polymer volume fraction in the swollen state and χ is the Flory-Huggins interaction parameter. From the observed ϕ and $\bar{M}_c$ values, the further cross-link density (ρ), and mesh size were calculated using Eqs. (3 and 4) (Li et al., 2006; Jhaveri et al., 2009; Chung et al., 2005).

$$\rho = \frac{dp}{(\overline{M}c)} \quad (3)$$

$$\xi = \frac{0.071(\overline{M}c)^{1/2}}{(\phi)^{1/3}} \quad (4)$$

2.6. Drug release studies

The drug loading of both model drugs, lidocaine hydrochloride and gentamicin sulphate, into polymer matrix was carried out by swelling equilibrium method. The loading of drug and release of drug from the drug loaded polymers was determined from the standard curves of the drugs prepared at UV–Visible spectrophotometer (Cary-100 Bio, Varian). Standard curves for gentamicin sulphate was prepared at λ_{max}=255 nm (in DW, pH 2.2 buffer and SWF), at λ_{max}=256 nm (in PBS). For lidocaine hydrochloride, standard curves were prepared at λ_{max}=256 nm (in DW and pH 2.2 buffer), at λ_{max}=257 nm (in PBS) and at λ_{max}=295 nm (in SWF). The loading of drug was carried out in large number of polymer samples and then samples of constant loading were chosen for drug release study. The hydrogels were allowed to swell in the drug solution of known concentration (1000 μg/mL) (C_o) for 24 h at 37 °C. Thereafter, these polymers were taken out dried to obtain the drug release device. The drug concentration (C_f) of the final solution was measured from calibration graph which in turn gives the drug loaded in to the polymer sample. Drug entrapment efficiency is calculated from Eq. (5):