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Acacia gum polysaccharide based hydrogel wound dressings: Synthesis, characterization, drug delivery and biomedical properties

Baljit Singh [a,*], Sushma Sharma [b], Abhishek Dhiman [a]

[a] Department of Chemistry, Himachal Pradesh University, Shimla 171005, India
[b] Department of Biosciences, Himachal Pradesh University, Shimla 171005, India

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ABSTRACT

Keeping in view the importance of polysaccharide gums for wound care, in the present article, an attempt has been made to explore antioxidant nature of gum acacia in designing hydrogel wound dressing to improve its wound healing potential. These polymers were prepared by using acacia gum-polyvinylpyrollidone/carbopol and were characterized by ^{13}C NMR, FTIR, SEM, AFM, cryo-SEM, XRD, TGA, DSC and elemental analysis techniques. Some important biomaterial properties of wound dressings such as wound fluid absorption, haemo-compatibility, bioactive assessment, gaseous/water/microbial permeability, mechanical properties, bio-adhesion, drug release, and histology of wound healing were also determined. Hydrogel wound dressings were found non-haemolytic, antioxidant and mucoadhesive in nature. Release of drug occurred through non-Fickian diffusion mechanism and release profile best fitted in Higuchi model.

1. Introduction

Design of innovative bioactive materials for wound care is a necessity of the present era in order to accelerate wound healing processes. Mimicry of the human skin by the hydrogels has led to exploration of their potential as wound dressings materials. Nowadays, hydrogels have been widely accepted as biomaterial scaffolds for tissue-engineering applications due to their crosslinked three dimension structures which have ability to encapsulate cells and bioactive molecules, efficient mass transfer, and easily manipulated physical properties (Bonifacio, Gentile, Ferreira, Cometa, & Giglio, 2017; Fan et al., 2017 Shankar et al., 2017). Highly hydrated hydrogels provide ideally cellular microenvironments for cell proliferation and differentiation. Hydrogels also possess structural and functional similarities to the natural extracellular matrices (Paladini, Pollini, Sannino, & Ambrosio, 2015). Natural polymers have frequently been used to make hydrogel dressings for tissue-engineering applications owing to their biocompatibility, inherent biodegradability, and critical biological functions (Hoffman, 2012). Keeping in view the importance of natural polysaccharide based hydrogel in wound dressing applications, in the present work, an attempt has been made to design a hydrogel dressing using gum-acacia (GA), polyvinylpyrollidone [poly(NVP] and carbopol. Further, these hydrogel dressings have been loaded with antibiotic drug moxifloxacin to enhance their wound healing potential (Jacobsen et al., 2011). Hence, the proposed antibiotic drug loaded hydrogel wound dressings will not only provide protection from infection for longer period (due to antibiotic drug) but can also absorbed simulated wound fluid which is necessary for wound debridement and maintenance of moist wound environment for rapid wound healing. GA, poly(NVP) and carbopol are briefly discussed here.

Gum arabic is a dried exudation obtained from the stems and branches of *Acacia Senegal* or closely related species of acacia (fam. Leguminosae). It consists mainly of higher molecular weight polysaccharides and their calcium, magnesium and potassium salts, which on hydrolysis yield arabinose, galactose, rhamnose and glucuronic acid (FAO, 1999; Phillips, 1998; Idris, Williams, & Phillips, 1998). GA is a water soluble gum and forms solutions over a wide range of concentrations without becoming highly viscous (Cozic, Picton, Garda, Marlhoux, & Cerf, 2009). GA is a non-digestible food ingredient that has found many applications in the food and pharmaceutical industries. GA has strong antioxidant properties, and a major mechanism for the induction of renal or hepatic toxicities is the generation of free radicals (Ali, Ziada, & Blunden, 2009). Recently, it has been reported that gum acacia extract is haemostatic, non-haemolytic, and antibacterial in nature (Bhatnagar, Parwani, Sharma, Ganguli, & Bhatnagar, 2013).

* Corresponding author.
E-mail address: baljitsinghhpu@yahoo.com (B. Singh).

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Carbopol is a mucoadhesive poly(acrylic acid) polymer which has been used in gel formation for transdermal drug delivery applications (Jana, Manna, Nayak, Sen, & Basu, 2014). On the other hand, poly(NVP) polymer is a water soluble, hydrophilic polymer and has been used in wound dressings materials. It has been found cytocompatible for human dermal fibroblasts and has significantly increased fibroblast viability (Shahbuddin, Bullock, MacNeil, & Rimmer, 2014). Poly(NVP) addition in the composite polymer matrix improved the blood compatibility of the biomaterials (Wetzels & Koole, 1999).

2. Materials and methods

2.1. Materials

Gum acacia (GA), carbopol 940 (CP) [Loba Chemie Pvt. Ltd., Mumbai-India], and N-Vinylpyrollidone (NVP) [Merck Specialities Pvt. Ltd., Mumbai, India] were used as materials for the synthesis of polymers. Ammonium persulphate (APS) [Qualigens Fine Chemicals, Mumbai-India] was used as initiator, N,N-methylenebisacrylamide (NN-MBA) [Acros organics, New Jersey-USA] was used as crosslinker and glycerol [S.D. Fine Chemical Ltd., Mumbai-India] was used as plasticizer for the synthesis of these polymer films. Moxifloxacin [Lifestar Pharma Pvt. Ltd., New Delhi, India] was used as model drug to study the release profile of the drug from polymer matrix.

2.2. Synthesis of hydrogels

Synthesis of polymers was carried out by free radical graft copolymerization method, where the grafting of polymer chains occurs on backbone, the acacia gum. Grafting of vinylic monomer in the presence of crosslinker form the three dimensional network. Reaction mixture, containing definite concentration of GA (5% w/v) and carbopol (2% w/v), was hydrated and stirred at 100 rpm with overhead stirrer for definite time period (6 h) at 25 °C. Then solution of definite concentration of NVP (28.15×10^{-2} mol L^{-1}), APS (5.48×10^{-3} mol L^{-1}), NN-MBA (8.10×10^{-3} mol L^{-1}), and glycerol (0.27 mol L^{-1}) was added and reaction mixture was again stirred for definite time period (6 h). Then the cross-linked polymer matrix was obtained by solution casting method. It was then washed in distilled water and dried in oven till constant weight was obtained. These dried polymers were named as gum acacia-*cl*-(carbopol-*co*-polyNVP) [GACVP] polymers/hydrogels. The optimum reaction parameters for the synthesis of hydrogels were determined by varying the [NVP] from 9.4 to 46.9×10^{-2} mol L^{-1} and [carbopol] from 1.0 to 3.0%. Optimization of reaction parameters, for the synthesis of hydrogels was determined on the basis of swelling of hydrogels and the reaction condition of maximum swelling of hydrogels in distilled water after 24 h at 37 °C was taken as optimum condition for further synthesis of hydrogels. Optimum conditions were obtained as [NVP] = 28.2×10^{-2} mol L^{-1} and [carbopol] = 2.0% (w/v).

2.3. Characterization

Characterization of polymers was carried out by using different instrument which include ^{13}C solid state nuclear magnetic resonance (NMR) spectroscopy [Jeol Resonance ECX-400], Fourier transform infrared (FTIR) spectroscopy [Nicolet 5700 FTIR THERMO (USA)], elemental analysis [Thermo Finnigan, Italy], scanning electron micrography (SEMs) [FEI Quanta 200F, The Netherlands], atomic force microscopy (AFM) [NT-MDT, Russia], cryo scanning electron microscopy (cryo-SEM) [Jeol – JSM 7600, Japan], X-ray diffraction study (XRD) [Bruker D8, USA], thermo gravimetric analysis (TGA) [EXSTAR TG/DTA 6300 thermal analyzer (Japan)], differential scanning calorimetry (DSC) [NETZSCH DSC 204 (USA)] and swelling studies (Singh & Sharma, 2009).

2.4. Evaluation of wound fluid absorption and drug release mechanism

Diffusion mechanisms for swelling and drug release from the polymer matrix have been evaluated by using Ritger and Peppas (1987a, 1987b) power law expression ($M_t/M_\infty = kt^n$). where M_t/M_∞ is the fractional swelling/drug release in time t, 'k' is the constant and 'n' is the diffusion exponent characteristic of the swelling or release mechanism. M_t and M_∞ are the swelling/drug release at time 't' and at equilibrium respectively. Wound fluid absorption studies were carried out by gravimetric method.

2.5. Drug loading and drug release studies

Drug loading of moxifloxacin into the hydrogel films was carried out by swelling equilibrium method and drug release profile from drug loaded hydrogels was determined in different mediums from calibration curves prepared on UV–vis spectrophotometry (Singh & Sharma, 2009). The maximum loading was 78 ± 0.71% in the polymer matrix. *In vitro* release studies of the drug were carried out by keeping the drug loaded hydrogel films of constant loading in releasing medium at 37 °C. The amount of drug released was measured using a UV visible spectrophotometer in pH2.2 buffer (λ_{max} 295 nm), phasphate buffer saline (PBS) (λ_{max} 288 nm), and simulated wound fluid [SWF] (λ_{max} 288 nm) after every 30 min up to 300 min in each case and then after 24 h. To find out best fit model for the release profile of moxifloxacin, different release models (*i.e.*, zero order, first order, Higuchi square root law, Korsmeyer-Peppas, and Hixson-Crowell cube root models) were applied (Shoaib, Tazeen, Merchant, & Yousuf, 2006; Sullad, Manjeshwar, & Aminabhavi, 2010).

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 volumetric flask. The pH of simulated wound fluid was observed 8.0 ± 0.2

2.6. Determination of network structural parameters

The control of the hydrogel network structure allows for the proper design of hydrogel dressings, diffusion of bioactive molecules and migration of cells through the network (Hoffman, 2012). Some important network parameters used to assess crosslinked network structure of hydrogel have been determined which include polymer volume fraction in the swollen state (ϕ), molecular weight between two neighboring cross-links ($\overline{M}_c$), Flory-Huggins interaction parameter (χ), cross-link density (ρ), and mesh size (ξ). Swelling of polymer in distilled water was used to evaluate $\overline{M}_c$ by the Flory-Rehner Eq. (i) (Aithal, Aminabhavi, & Cassidy, 1990; Bajpai & Singh, 2006; Lira et al., 2009).

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

The volume fraction, ϕ of the polymer in the swollen state was calculated by using Eq. (ii).

$$\phi = \left[\left(\frac{d_p}{d_s} \right) \left(\frac{w_\infty - w_o}{w_o} \right) + 1 \right]^{-1} \quad \text{(ii)}$$

Where d_p and d_s are densities of polymer and solvent (g/cm^3) respectively; w_o and w_∞ are respectively, the weight of polymer before and after 24 h swelling. Flory-Huggins interaction parameter (χ) was calculated experimentally from the temperature coefficient