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Design of sterile mucoadhesive hydrogels for use in drug delivery: Effect of radiation on network structure

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ABSTRACT

Radiation induced graft copolymerization is pure, sterile and additive free method for the synthesis of hydrogels for biomedical applications. In the present work, attempt has been made to prepare the biocompatible, mucoadhesive hydrogels based on natural polysaccharide sterculia gum and polyvinylpyrrolidone (PVP) for use as drug delivery devices. The effect of gamma radiation on swelling and various network parameters of hydrogels such as the polymer volume fraction in the swollen state (ϕ), molecular weight of the polymer chain between two neighboring cross links ($\bar{M}_c$), crosslink density (ρ), and mesh size (ξ) have been studied. Hydrogels have been characterized with scanning electron micrographs (SEMs), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction study (XRD), thermo gravimetric analysis (TGA) and swelling studies. Swelling and mesh size decreased while gel strength and crosslink density increased with increase in radiation dose. The swelling of hydrogels and release of drug ciprofloxacin from drug loaded hydrogels occurred through non-Fickian diffusion mechanism. These hydrogels have been observed to have non-thrombogenic, haemo-compatible and mucoadhesive nature and could be used as mucoadhesive drug delivery system to deliver drug to gastro intestinal tract (GIT) in controlled manner.

1. Introduction

Design of drug delivery system is equally important as the design of new drug molecules. Polymer based drug delivery system, releases the drug in the controlled and sustained manner and eliminates various drawbacks associated with conventional drug delivery systems. Various polymer based drug delivery devices have been developed but special attention has been given to the hydrogels which are hydrophilic and biocompatible in nature. Hydrogels are three dimensional crosslinked networks which are formed through various graft co-polymerization techniques. Hydrogel formation by radiation cross-linking is a pure, sterile, clean and residue-free method [1–3]. Mucoadhesive nature of hydrogels prolongs the contact time between drug delivery device and mucosa. Further, it also increases bio-availability, efficacy and site specificity of the system [4,5].

Hydrogels used in drug delivery applications must have sufficient strength to avoid immediate release of drug due to degradation [6]. The strength of the natural polysaccharide based hydrogels has been improved by combination of the hydrophilic/hydrophobic polymers. The composite polymer matrix of carboxymethyl cellulose (CMC) and polyvinyl pyrrolidone (PVP) have been prepared to improve the strength of CMC [7]. Agar/PVP hydrogel wound dressings have been synthesized by radiation method for sterile temporary skin covers [8]. Irradiation has influenced the crosslink density of the polymer networks which is one of the most important factor that affects gel fraction, water absorption ratio, and mechanical properties of hydrogels [9,10]. Hydrogel film of blends of PVP–CMC has been found to be transparent, flexible and has showed good mechanical and biodegradability properties [11]. In the present work, mucoadhesive hydrogels have been prepared for controlled release of antibiotic drug ciprofloxacin to GIT tract. These hydrogels have been prepared by using biocompatible materials (sterculia gum polysaccharide and PVP) by radiation induced copolymerization method.

Sterculia gum is a natural gum exudate of *Sterculia urens* tree belongs to the family *Sterculiaceae* [12]. It is a complex branched and partially acetylated polysaccharide which consists of glucuronic acid, galacturonic acid, galactose and rhamnose structural units [13]. It is 'Generally Recognized as Safe' in the USA and has been used in food and pharmaceutical applications. When taken at moderate level, it has been reported as nontoxic, non-allergenic,

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non-teratogenic and non-mutagenic. It has also been reported as therapeutic and drug delivery agent [14,15]. Sterculia gum has the special feature of adhering to mucosal surfaces which makes this polysaccharide useful in the development of mucosal patches for release of drug to buccal mucosa [16,17]. PVP is a widely used non-ionic, biocompatible and film forming synthetic polymer which has been used for the mucoadhesive delivery of various active ingredients [18,19]. Consuelo and coworkers [20] have developed mucoadhesive delivery systems by using PVP for trans-mucosal delivery of fentanyl. Ciprofloxacin is a broad spectrum antibiotic and is widely used for infections of GIT tract, urinary tract, lower respiratory tract and for other bacterial infections.

In view of the above, the present study is an attempt to prepare the mucoadhesive biocompatible sterculia gum-PVP hydrogels by radiation crosslinking method for slow release of ciprofloxacin for GIT infections. The polymers have been characterized with SEMs, FTIR, XRD, TGA and swelling studies. The effect of gamma radiation on various network parameters such as the polymer volume fraction in the swollen state (ϕ), molecular weight of the polymer chain between two neighboring cross links ($\bar{M}_c$), crosslink density (ρ), and the corresponding mesh size (ξ) were studied. The gel strength, blood compatibility and mucoadhesion studies of hydrogels were also carried out.

2. Experimental

2.1. Materials and methods

Polyvinyl pyrrolidone, PVP (K 90, molecular weight ~ 360,000) and sterculia gum (karaya gum) were obtained from SIGMA-ALDRICH (USA). Ciprofloxacin HCl was obtained from Ranbaxy Laboratories Limited, India. Irradiation was performed in ^{60}Co gamma irradiator supplied by Board of Radiation and Isotope Technology (BRIT), India.

2.2. Synthesis of ster-cl-PVP hydrogels

Synthesis of hydrogels was carried out by free radial copolymerization reaction in gamma chamber at 1.35 kGy/h dose rate. Reaction was carried out with solution of homogenous mixture of definite concentration of sterculia gum (3.33% w/v) and PVP (3.33% w/v) taken in the aqueous reaction system. Reaction contents were stirred for 3 h at 25 °C temperature and then placed in gamma chamber for specific time. After irradiation, the hydrogels were stirred in distilled water to remove soluble fractions left in the polymer and then polymers were dried in oven at 40 °C until the constant weight was obtained. These polymers were named as ster-*cl*-PVP hydrogels. The optimum radiation dose for the synthesis of hydrogels was determined by varying the dose from 8.1 kGy to 40.5 kGy. Swelling and network parameters of the hydrogels were determined as a function of radiation dose. The hydrogels prepared at optimum reaction conditions were used to study the effect of nature of swelling medium on swelling and drug release.

2.3. Characterizations

The polymers were characterized by scanning electron micrographs (SEMs), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction study (XRD), thermo gravimetric analysis (TGA) and swelling studies. SEMs were taken on FEI SEM Quanta 256, Model D9393 (Singapore). XRD measurements were made using PAN-analytical X'Pert Pro powder diffraction system (The Netherland) operated at 40 kV and 40 mA using the Cu-*K*α radiation. FTIR spectra were recorded in KBr pellets on Nicolet 5700FTIR THERMO (USA). Thermal degradation studies [i.e. thermo gravimetric analysis (TGA), differential thermal analysis (DTA), differential thermogravimetry (DTG)] were carried out on EXSTAR TG/DTA 6300 thermal analyzer. Thermal analysis was carried out under air atmosphere at 10 °C/min heating rate in the temperature range 20–800 °C.

2.4. Swelling and drug release studies

Swelling of the hydrogels was carried out in triplicate by gravimetric method [21]. Release of drug from the drug loaded hydrogels was determined from the calibration curves prepared on the UV Visible Spectrophotometer (Cary 100 Bio, Varian). Procedure for the preparation of buffer solution, calibration curves, drug loading, drug release and preparation of reagents has been discussed elsewhere [21]. Drug release studies were carried out in triplicate. The calibration curves of ciprofloxacin were prepared in distilled water, pH 2.2 buffer and pH 7.4 buffer solution at λ_{max} 276 nm, 277 nm and 271 nm, respectively. The loading of a drug into the hydrogels was carried out by swelling equilibrium method.

2.5. Determination of mechanism of swelling and drug release from polymer matrix

The mechanisms of swelling and drug release have been discussed in detail in our earlier study [21]. Swelling of polymers has been classified into three types of diffusion mechanisms (Fickian diffusion, non-Fickian diffusion and Case II diffusion) on the basis of relative rate of diffusion of water into polymer matrix and rate of polymer chain relaxation. The values of diffusion exponent n and diffusion coefficients have been evaluated using Eqs. (1–4) for the swelling of the polymers and for the release of the drug from the polymers [22–25].

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

$$\frac{M_t}{M_\infty} = 4\left(\frac{D_{it}}{\pi \ell^2}\right)^{0.5} \tag{2}$$

$$D_A = \frac{0.049\ell^2}{t_{1/2}} \tag{3}$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right) \quad \exp\left[\frac{(-\pi^2 D_{Lt})}{\ell^2}\right] \tag{4}$$

where M_t/M_∞ is the fractional release of drug in time t, k *is* the constant characteristic of the drug-polymer system, and n is the diffusion exponent characteristic of the release mechanism. M_t and M_∞ is drug released at time t and at equilibrium, respectively, D_i, D_A and D_L are the initial, average and late diffusion coefficients and l is the thickness (mm) of the sample. $t_{1/2}$ time required for 50% release of drug. To investigate the parameters of release kinetics of drug from the drug loaded hydrogels, Eq. (5) was used.

$$\frac{t}{C_t} = \alpha + \beta t \tag{5}$$

here C_t is the amount of drug released at time t, $\beta = 1/C_{max}$ is the inverse of the maximum amount of released drug, $\alpha = 1/(C_{max})^2\, k_{rel} = 1/r_o$ is the inverse of the initial release rate, and k_{rel} is the constant of the kinetic of release [26].

2.6. Determination of network parameters

The most important parameters used to characterize network structure are the polymer volume fraction in the swollen state (ϕ), molecular weight of the polymer chain between two neighboring cross links ($\bar{M}_c$), Flory–Huggins interaction parameter (χ), crosslink density (ρ), and the corresponding mesh size (ξ). One of the most