J Pharm Biopharm Res, 2019, 1(1): 1−14
DOI: 10.25082/JPBR.2019.01.001

RESEARCH ARTICLE

Functionalization of carbopol with NVP for designing antibiotic drug loaded hydrogel dressings for better wound management

Baljit Singh* Abhishek Dhiman

Abstract: In the present work an attempt has been made to design the antibiotic drug loaded carbopol-poly(NVP) based hydrogel wound dressings for better wound care. The polymer films were characterized by SEM-EDX, AFM, FTIR, ^{13}CNMR, TGA/DTA/DTG, DSC, and swelling studies. Besides drug release, various biomedical properties (*viz.* blood compatibility, mucoadhesion, oxygen permeability, water vapour transmission rate, microbial penetration, tensile strength, bursting strength, resilience, stress relaxation, and folding endurance) have also been studied. The polymer films have been observed to be biocompatible, permeable to oxygen and water vapour and have absorbed simulated wound fluid 11.37±0.31g/g of polymer film. The drug release profile followed the Case-II diffusion mechanism and release profile best fitted in Hixson-Crowell's kinetic models. Mechanical properties results showed that the polymer film had 0.65±0.12 Nmm^{-2} tensile strength, 119.38±14.26% elongationand 25.49±0.72% resilience.

Keywords: drug delivery, 1-Vinyl-2-pyrollidone, hydrogel, wound dressing

1 Introduction

The concept of wound treatment always focuses on reducing the risk caused by wound itself, minimizing potential environmental complications and enhancing proper regeneration and reestablishment of the wounded skin tissue.[1] Infected skin that is left untreated may delay healing and even lead to death.[1,2]Recently, a wide range of wound dressings are available in market, but hydrogel is a material of choice for designing dressings for better wound management.Hydrogel dressings are more successful in clinical results as compared to the conventional wound dressings. Hydrogel wound dressings containing antibiotic drugs have been used against wound infections.[3]In order to maximise the effectiveness of antibiotics for longer periods, slow and sustained release of antibiotics is very important. These drug loaded hydrogel dressings have been found to be instrumental in achieving successful and long lasting healing effects from antibiotic loaded wound dressings.[4]

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of biological fluids. These are closely related to the natural living tissue, more than any other class of synthetic biomaterials due to their high water content, porosity and soft consistency.[5]They can be made from a wide range of biocompatible materials. They can provide moist healing environment, and slow drug delivery at wound site.[6] Hydrogels are capable of promoting the autolytic debridement of necrotic tissues and are usually more efficient at drying wounds with few exudates.[7] A great advantage of hydrogel dressings is that they are usually applied and removed without interfering with the wound bed. In addition, these dressings are flexible, non-antigenic, and permeable to water, oxygen and metabolites.[8]

In view of the above, it is reasonable to assume that a antibiotic drug (moxifloxacin) loaded hydrogel dressings composed of carbopol-poly(NVP) would provide the slow release of antibiotic drug locally in a controlled manner besideproviding moistwound for improving wound healing. Poly(NVP) is a water solublehydrophilic biocompatiblepolymer.[9,10] Its hydrogel films have been applied as local dressings.[11] These hydrogel dressings can act as a barrier against bacterial penetration.[12] It is one of the most frequently used material in biomedical applications due to their biocompatibility with living tissues and extremely low cytotoxicity.[13,14]Inclusion of poly(NVP) in the composite hydrogels can improve swelling and other biomedical proper-

Received: January 7, 2019 **Accepted:** January 21, 2019 **Published:** January 25, 2019

***Correspondence to**: Baljit Singh, Department of Chemistry, Himachal Pradesh University, Shimla, 171005, India; Email: baljitsinghhpu@yahoo.com

Citation: Singh B and Dhiman A. Functionalization of carbopol with NVP for designing antibiotic drug loaded hydrogel dressings for better wound management. *J Pharm Biopharm Res*, 2019, **1**(1):1−14

ties.[9,15] On the other hand, carbopol is a hydrophilic, non-toxic, biocompatible, bioadhesive and non-irritant polymer.[16,17]It has been used in drug delivery systems for buccal, transdermal,[18] ocular, rectal, vaginal,[19] nasal[20] and wound dressing applications.[21]

2 Experimental

2.1 Materials used

1-Vinyl-2-pyrollidone (NVP) [MerckSpecialities Pvt. Ltd. Mumbai-India], carbopol (CP) [Loba Chemie Pvt. Ltd., Mumbai-India], N,N-methylenebisacrylamide (NN-MBA) [Acros organics, New Jersey-USA], ammonium persulphate (APS) [Qualigens Fine Chemicals, Mumbai-India], glycerol, [S.D. Fine Chemical Ltd., Mumbai, India], and moxifloxacin HCl [Lifestar Pharma Pvt. Ltd.], New Delhi, India] were used as received.

2.2 Synthesis of CP-cl-poly(NVP) polymers

Synthesis of the polymers was carried out by chemically induced free radical copolymerization method using APS as initiator and NN-MBA as cross-linker. Polymer reaction was carried out with solution of definite concentration of CP [2.0% (w/v)], taken in beaker. This solution was prepared by stirring at 100 rpm for definite time after 12 hours hydration. To this homogenous content, solutions of a definite concentration of [NVP] = 28.15×10^2 mol/L, [NN-MBA] = 8.10×10^3 mol/L, glycerol = 0.27 mol/L and [APS] = 5.48×10^3 mol/L were added, and the reaction mixture was again stirred. The reaction content was stirred for total 12 hours at 25 °C. The reaction mixture was then transferred to the petri dish which was placed in hot air oven maintained at 55 °C to get the cross-linked polymer. The polymer films were formed by solution casting method. The cross-linked polymer formed was washed with distilled water and ethanol to remove the soluble fractions left in the polymer. Then it was dried in an oven maintained at 40 °C till constant weight was obtained. This cross-linked polymer was named as CP-*cl*-poly(NVP) polymer.

2.3 Characterization

The polymers were characterized by scanning electronmicrography (SEMs), energy dispersion X-ray analysis (EDX), atomic force microscopy (AFM), Fourier transform infrared (FTIR) spectroscopy, ^{13}C nuclear magnetic resonance (NMR) spectroscopy, X-ray diffraction study (XRD), thermo gravimetric analysis (TGA), differential scanning calorimetry (DSC) and swelling studies. SEM-EDX analysis was done on FEI Quanta 200 F (The Netherlands). AFM (NTEGRA, NT-MDT, Russia) of polymer film was done in 5 m^2 areas, in semi-contact mode. FTIR of polymer was recorded on Perkin Elmer-Spectrum RX-I (USA). The solid state ^{13}C NMR of polymer was carried out using JEOL RESONANCE ECX 400 solid state NMR spectrometer operating at a magnetic field of 9.3 T and at a frequency of 100 MHz for carbons. X-ray diffractogram were obtained using a Bruker D8 Advance diffractometer (USA), operating at 40 kV with Cu-K radiation.TGA of polymer was done using EXSTAR TG/DTA 6300 thermal analyzer (Japan), at a scan rate of 10 °C/min. DSC thermogram of polymer was recorded with NETZSCH DSC 204 (USA) in temperature range 25-500 °C at a scan rate of 10 °C/min.

2.4 Swelling Studies

Swelling studies of the polymers were carried out in different mediums for 24 hours, by gravimetric method.[22]

2.5 Drug release studies

Initially the drug loading into hydrogels was carried out by the swelling equilibrium method.[22] Release profile of moxifloxacin HCl from drug loaded polymer samples was carried out in simulated wound fluid (SWF) and release was determined from the standard curve made on Cary 100 Bio, Varian, UV visible spectrophotometer at λ_{max} (288nm). Drug release mechanism was evaluated by using power law expression given by Ritger and Peppas.[23,24] Different kinetic models (*i.e.* zero order, first order, Higuchi square root law, Korsmeyer-Peppas and Hixson-Crowell cube root model) were applied to drug release profileto determine the best fit model for the release of drug from the drug loaded polymers.[25,26]

2.6 Blood compatibility

As a preliminary investigation, the in vitro biocompatibility was determined on the basis of thrombogenicity and hemolysis assessment. Thrombogenicity of CP-*cl*-poly(NVP) polymer was carried out using a gravimetric method.[27] The positive and negative control was taken as glass beaker with absence of sample and glass beaker with absence of sample and blood respectively.[28] The thrombose percentage is calculated as follow:

$$\text{Thrombogenicity (\%)} = \frac{\text{Mass of test sample - Mass of negative control}}{\text{Mass of positive control - Mass of negative control}} \times 100 \quad (1)$$

The haemoglobin released by haemolysis was measured by the optical densities (OD) of the supernatants at 540 nm using a UV-visible spectrophotometer. The

percentage of haemolyis (%) was calculated as follows:

$$\text{Haemolysis (\%)} = \frac{\text{OD of sample - OD of negative control}}{\text{OD of positive control - OD of negative control}} \times 100 \quad (2)$$

2.7 Mucoadhesion studies

Mucoadhesive property of the polymer was investigated by using texture analyzer (TA-XT, Stable Micro Systems, UK) equipped with a 5 kg load cell and a mucoadhesive holder. The maximum force required to separate the probe from the goat mucosa (*i.e.* maximum detachment force, F_{max}) and distance travelled by film before detachment could be directly recorded in the instrument.

2.8 Oxygen permeability

Permeability of synthesized polymer towards O_2 has been evaluated by using Winkler's method.[29] The test flasks were placed in an open environment for 24 h.[3] The collected water samples were then analyzed for dissolved oxygen according to Winkler's method.[29]

2.9 Water vapour transmission rate

WVTR of polymer film was determined gravimetrically using desiccant method.[30] All the vials were then placed in desiccator, containing saturated solution of NaCl at 37 °C (Relative humidity ∼75%).[31] These vials were weighed after every 24 hours up to eight days and WVTR (g/m^2/day) was calculated using following equation.[31]

$$WVTR = \left(\frac{\Delta w}{\Delta t}\right) \times \frac{24}{A} \quad (3)$$

In this equation (Δw/Δt) is the slope of the plot 'w' *vs* 't', where 'w' is the weight gain (g) along the specified time period, 't' (h) and A is the effective transfer area (m^2).

2.10 Microbial penetration

In the present study, microbial penetration test was performed for polymer film to check their capacity, to prevent secondary infection. The polymeric film (thickness = 1 mm) was placed on top of the test tubes (test area: 1.3±0.03 cm^2) containing 5ml of sterile nutrient broth (2.5% w/v) (Merck Specilities Pvt. Ltd. Mumbai-India) and was sealed to test microbial penetration through them. Before test, polymeric films, nutrient broth and glass test tubes were sterilized in autoclave at 121 °C, 15l bs pressure for 20 minutes. The negative control was the closed test tube with an airtight cap preventing any kind of microbial penetration, while the positive control was the open test tube having no barrier for microbes. The test tubes were placed in an open environment and observed for 30 days period. Permeability for micro-organisms was evaluated by observing microbial growth (in term of turbidity) in test tubes. Any visual turbidity of the nutrient broth was considered as sign of microbial contamination.

2.11 Mechanical properties

In order to access the mechanical strength of the polymer film, some important mechanical tests such as, tensile strength, burst strength, resilience, relaxation, and folding endurance have been performed.

2.11.1 Tensile Strength

Tensile strength of polymeric film was studied using texture analyzer (TA-XT, Stable Micro Systems, UK) equipped with 50 kg load cell.

2.11.2 Bursting strength

Bursting strength of polymeric film was studied using texture analyzer (TA-XT, Stable Micro Systems, UK) equipped with 50 kg load cell. The force (N) and distance (mm) at break point were recorded.

2.11.3 Resilience

Resilience is measurement of how well a sample recovers from deformation. Resilience of polymeric film was studied using texture analyzer (TA-XT, Stable Micro Systems, UK) equipped with 50 kg load cell. Resilience was calculated by using following equation.

$$\text{Resilience (\%)} = \frac{A_2}{A_1} \times 100 \quad (4)$$

where A_2 is the work returned by the sample as compressive strain is removed (known as recoverable work) andA1 is work required for compression.

2.11.4 Stress relaxation test

Stress relaxation of polymeric film was studied using texture analyzer (TA-XT, Stable Micro Systems, UK) equipped with 50 kg load cell. Stress relaxation was evaluated in terms of retained force (%) which was calculated by the following equation.

$$\text{Retained force (\%)} = \frac{\text{Relaxed force}}{\text{Force at targate distance}} \times 100 \quad (5)$$

2.11.5 Folding endurance

The flexibility of the film was accessed from the determination of the folding endurance of film. During folding endurance test, polymer film of thickness 1 mm, length 30 mm and breath 30 mm was repeatedly folded

and de-folded at the same place until it breaks. The number of repeated folding and de-folding at the same place without breaking or cracking gives the value of folding endurance.[32]

3 Result and discussion

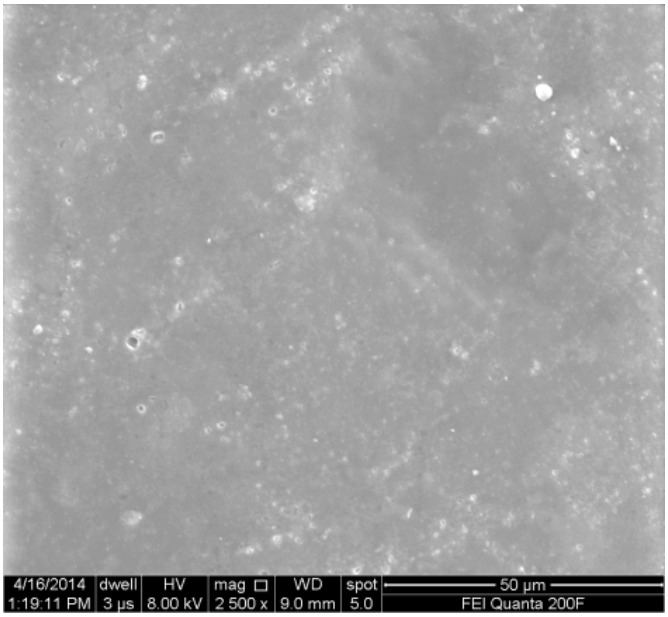
3.1 Characterization

A photograph of CP-*cl*-poly(NVP) polymer film was showed transparent nature of the wound dressing (Figure 1(a)) which helps in monitoring of the wound healing progress wound exudates accumulation without removal of wound dressing.[33] Generally transparent wound dressings are preferred for partial-thickness wounds with moderate exudation. SEM image ofCP-*cl*-poly(NVP)polymer film is given in Figure 1(b). This image showed less degree of heterogeneity in the polymer surface which indicating the high degree of miscibility of polymeric contents. Further, the average surface roughness (S_a) was 14.26 nm and root mean square roughness (S_q) was 18.59 nm from the AFM image of CP-cl-poly(NVP) polymer film (Figure 1(c)). Recently, AFM has been implemented as a surface characterization technique in biomaterial research and it is very helpful for the determination and verification of morphological features of polymer film. AFM particularly permits non-destructive imaging of surfaces on a molecular scale.[34] Being more hydrophilic poly(NVP) is more miscible in CP and it increases surface hydrophilicity of the crosslinked polymer. A more hydrophilic surface and high water content in the hydrogel leads to less surface roughness.[35] It has also been reported that grafting of NVP on polymers can make the surface smoother.[36,37] In another research Kennedy and co-workers (2009) have reported that polymer grafted with NVP give smooth surface in comparison to acrylic acid grafted polymers.

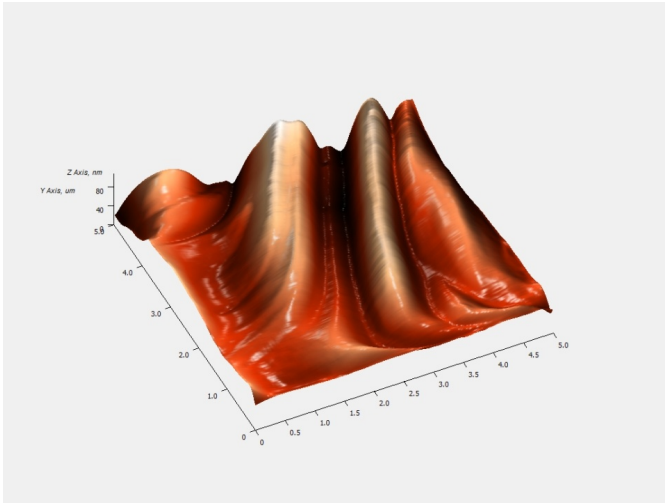
Results of EDX analysis of CP and CP-*cl*-poly(NVP) polymers indicating the incorporation of poly(NVP) in the crosslinked polymer in the form of additional peak of nitrogen which is correlated to the presence of poly(NVP) and cross linker NNMBA in the polymer film (Figure 2).

FTIR spectra of CP and CP-*cl*-poly(NVP) polymer are presented in Figure 3. In case of CP, a broad band at 3116.4 cm^{-1} (due to O-H stretching), a band at 2961.4 cm^{-1} (due to C-H stretching), a sharp intense band at 1714.1 cm^{-1} (due to C=O stretching), at 1454.4 cm^{-1} (due to C-H bending), at 1413.5 cm^{-1} (due to O-H in plane bending), and at 1247.4 (due to C-O stretching) have been observed. Beside, absorption band at 1171.4 cm^{-1} due to C-O-C stretching was observed which has proved ethereal crosslonking in CP. Some less intense

(a)



(b)



(c)

Figure 1. (a) Photograph, (b) SEM image, and (c) AFM image of CP-*cl*-poly(NVP) polymer film

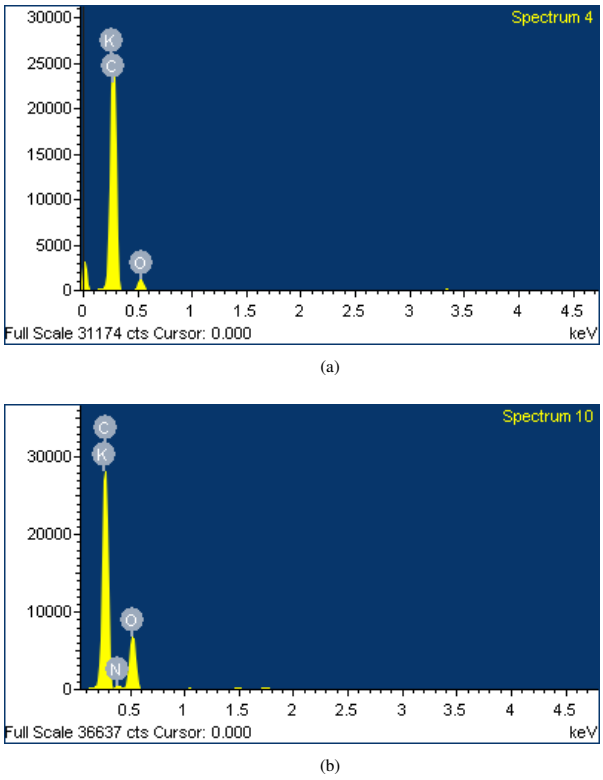


Figure 2. Elemental analysis results of (a) CP and (b) CP-*cl*-poly(NVP) polymer

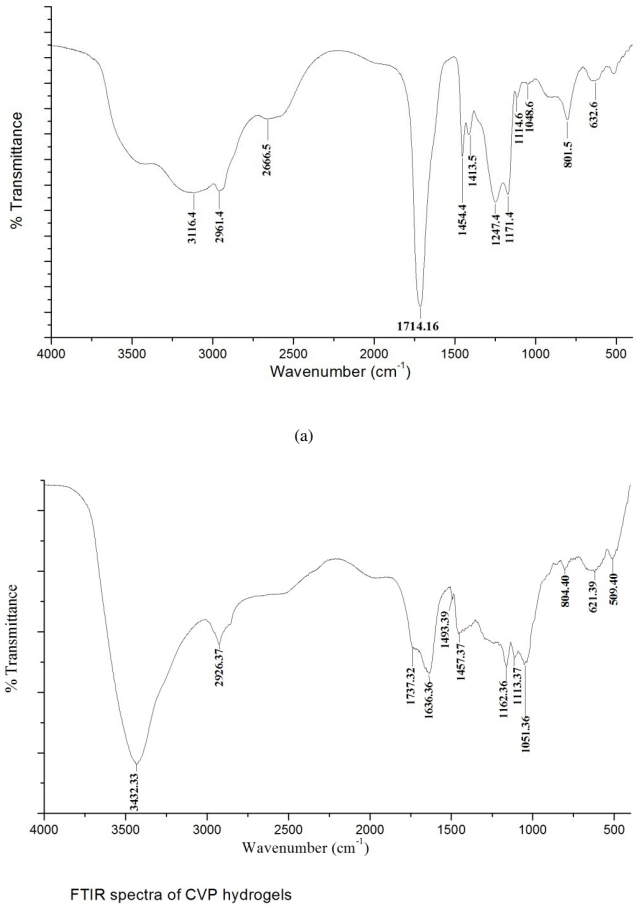


Figure 3. FTIR spectra of (a) CP and (b) CP-*cl*-poly(NVP) polymer

bands at 1114.6 and 1048.6 cm^{-1} (due to O-H deformations), along with a sharp band at 801.5 cm^{-1} due to =C-H out of plane bending vibrations have been observed. This band at 801.5 cm^{-1} is characteristic of CP 940, which appears due to the presence of crosslinker (allyl ether of pentaerythrol) in carpool 940.[38–40] In case of CP-*cl*-poly(NVP) polymera broad band around 3432.33 cm^{-1} (due to O-H), a band at 2926.37 cm^{-1} (due to C-H stretching), at 1737.32 cm^{-1} (C=O stretching of CP), at 1636.36 cm^{-1} (C=O stretching of polyNVP), at 1457.37 cm^{-1} (ring CH_2 wagging, ring C-N stretching of polyNVP), at 1162.36 (C-O-C stretching in CP and ring CH_2 twist of polyNVP). Some less intense bands at 1113.37 and 1051.36 cm^{-1} (due to O-H deformations) have been observed.[39–41]

^{13}C NMR spectra of CP and CP-*cl*-poly(NVP) polymer are presented in Figure 4. In case of CPan intense splitted peak at 183.49, 179.90 ppm [due to carbon ofcarbonyl groups] and another intense but broad peak at 42.57 ppm [due to methylene (-$\underline{C}H_2$-CH-) and methine (-CH_2-$\underline{C}H$-) groups of acrylic chains] has been observed.[38,42] The signal due to methylene and methine carbons overlapped to give a single broad peak at 42.57 ppm. In case of CP-*cl*-poly(NVP) polymer, the chemical shift peak at 178.44 ppm [due to carbonyl (C=O) carbons of poly(NVP) and CP] was observed. Broad peak along with some adjacent smaller peaks was observed, due to different environments of carbonyl carbon in the major constituents. Some peaks at 43.43 ppm [due to CP main chain carbons (-$\underline{C}H$-), vinylic carbons (-$\underline{C}H$-N<) and ring carbons (-$\underline{C}H_2$-N) of poly (NVP)]. This peak represents the polymerization of N-vinyl 2-pyrrolidone to poly (N-vinyl 2-pyrrolidone). The absence of characteristic peak of NVP around δ=94.0 and 129.0 ppm for sp^2 hybridized carbon atoms (CH_2=CH-) indicate the involvement of double bond in grafting and cross-linking during polymerization reaction. Chemical shift peaks at 31.97 ppm [due to ring carbons of NVP (O=C-$\underline{C}H_2$-CH_2-) and18.90 ppm [due to ring carbons of NVP -CH_2-$\underline{C}H_2$-CH_2)] were also observed.[38,43,44] Besides, sharp peaks at 73.50 ppm and 63.94 ppm can be attributed to formation of some new cross links during polymerization reaction.

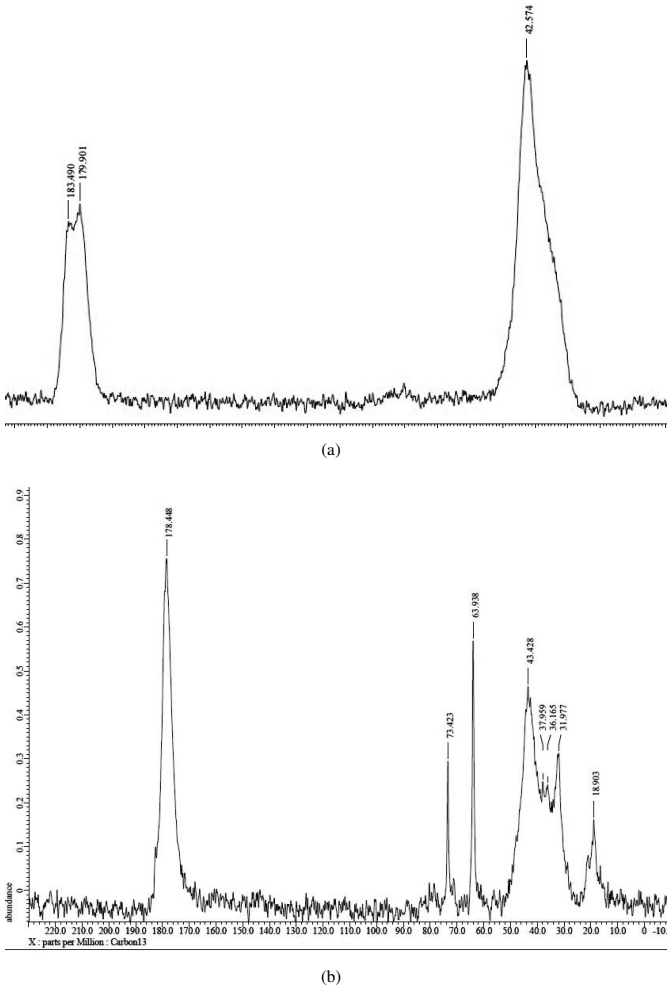


Figure 4. ^{13}CNMR spectra of (a) CP and (b) CP-*cl*-poly(NVP) polymer

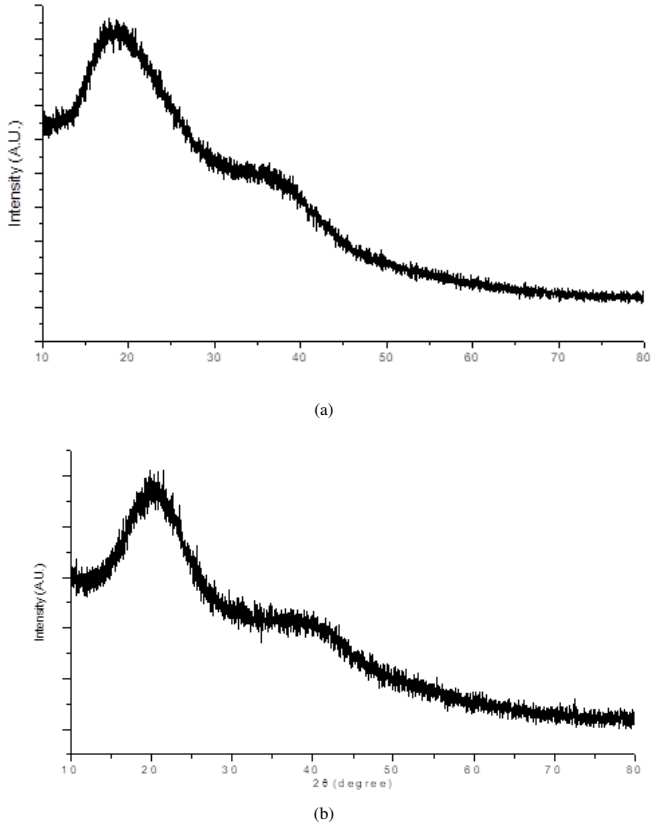


Figure 5. XRD of (a) CP and (b) CP-*cl*-poly(NVP) polymer

XRD spectra of CP and CP-*cl*-poly(NVP) polymer are presented in Figure 5. In case of CP there is no crystalline region in its X-ray diffractogram, indicating completely amorphous nature of CP.[45] XRD spectra of CP-*cl*-poly(NVP) polymer also showed no crystalline region in its polymer sample. Process of cross-linking and grafting may have hindered formation of any regular pattern in polymeric samples.

TGA, DTA and DTG of CP and CP-*cl*-poly(NVP) polymer are presented in Figure 6. In each case weight loss due to entrapped moisture has been ignored and initial decomposition temperature (IDT) has been taken as the temperature where actual degradation of material started. In case of CP, initial 7.59% weight loss occurred up to 100 °C, which indicates that CP has 7.59% bounded water. Kanis and co-workers (2000) have observed about 5% weight loss upto 150 °C due to bounded water. Ignoring the initial weight loss due to free and bounded water, two stages decomposition was observed in CP. In the present case, first stage started at 198.99 °C (residue left = 88.78%) and second stage started at 396.86 °C (residue left = 31.92%). IDT and final decomposition temperature (FDT) have been observed 199 °C and 462 °C (residue left = 5.29%) respectively. Early degradation after 199 °C can be attributed to the formation of formation of cyclic structures (anhydrides) associated with loss of water loss of water. Final decomposition of CP after 396.86 °C onwards occuredat a very high rate, due to decarboxylation, formation of unsaturated structures, depolymerisation of the residual polymer and and complete degradation of polymer forming gaseous products.[46–48]In case of CP-*cl*-poly(NVP)initial 4.30% weight loss occurred upto 100 °C, which indicates that CP-*cl*-poly (NVP) polymer has 4.30% bounded water. Three stage decomposition observed in the case of crosslinked polymer. In the present case, first stage started at 152.95 °C (residue left = 91.25%), second stage started at 315.64 °C (residue left = 71.29%) and third stage started at 439.24 °C (residue left = 26.17%). IDT and FDT have been observed 157 °C and 527 °C (residue left = 0.05%) respectively.

TGA curves show that thermal degradation of cross-

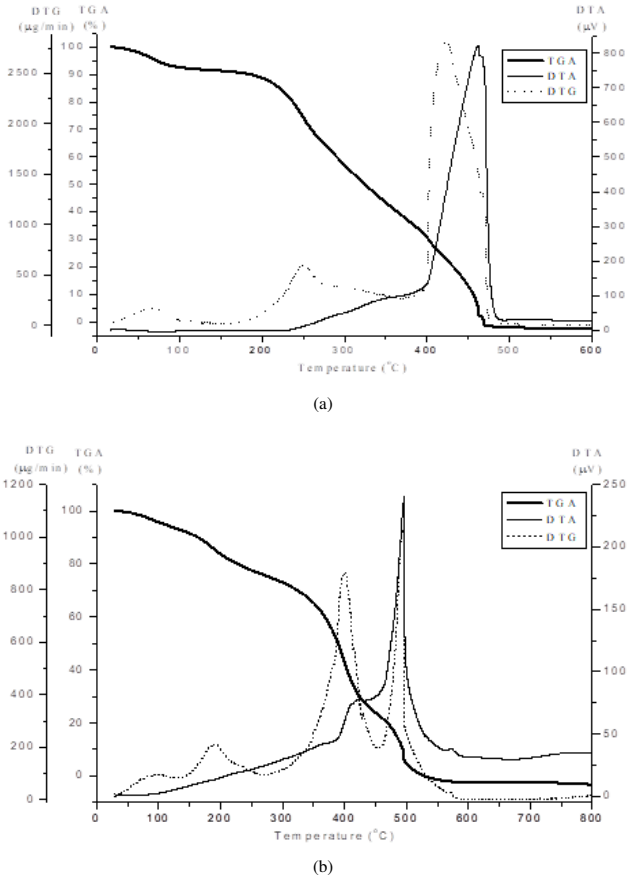


Figure 6. TGA/DTA/DTG curves of (a) CP and (b) CP-*cl*-poly(NVP) polymer

linked hydrogel was slow in comparison to CP, indicating more interactions in cross-linked polymer. 50% weight loss occurred at 325 °C and 390 °C for CP and CP-*cl*-poly(NVP) polymer respectively, indicating that crosslinked polymeric filmsto be more thermally stable than CP. Thermal degradation of the hydrogels was slow and gradual in comparison to CP, as no sudden weight loss has been observed. Increase in thermal stability of cross-linked hydrogels can be attributed to crosslinking and grafting reactions.[49] Besides the strong interaction between carboxyl of CP and carbonyl group of polyNVP may be one factor for enhanced thermal stability.[50]

DTG analysis was studied as a function of rate of weight loss (μg/min) with increase in temperature. In case of CP, two peaks at 251 °C (590 μg/min) and 424 °C (2810 μg/min) have been observed. In case of CP-*cl*-poly(NVP) polymer three stage degradation has been observed, where first stage is associated with very slow degradation rate with a peak at 190 °C (211 μg/min), second stage degradation showed DTG peak at 400 °C (870 μg/min), third peak at 493 °C (1030 μg/min). Results of DTG support the TGA, as relatively slow degradation rate was observed in cross-linked polymer matrices in comparison to CP. It is important to mention here that temperature at which maximum degradation rate was observed shifted from 424 °C to 493 °C on going from CP to cross-linked polymer. The results of thermal degradation thus confirm the conclusion that cross linking and grafting has occurred which has improved thermal stability of CP-*cl*-poly(NVP) polymer in comparison to CP.

DSC curves of CP and CP-*cl*-poly(NVP) polymer are presented in Figure 7. In case of CP two endothermic peaks, at 61.0 and 228.7 °C, were observed, with a heat of fusion 122.6 and 248.7 J/g respectively. The initial endotherm can be due to the evaporation of unbound water in the polymer and the latter can be attributed to the loss of water due to formation of anhydrides in CP.[51] Glass transition temperature (T_g) for CP has been observed in the temperature range 128.5-135.1 °C (ΔCp = 0.574 J/g K). Gómez-Carracedo *et al.* (2004) have reported that various grades of CPs show T_g in the range 130-140 °C. CP-*cl*-poly(NVP) polymer showed quite different DSC thermo gram in comparison to CP. Two endothermic peaks have been observed at 89.3 °C and 221.9 °C. The first endotherm with a heat of fusion 89.74 J/g, can be attributed to the evaporation of unbound water in the cross-linked polymer and second endotherm (108.6 J/g) can be due to anhydride formation in the polymer.[52]

3.2 Swelling studies

The swelling polymers was determined in simulated wound fluid (pH = 8), phosphate buffer saline and pH 2.2 buffer to evaluate the effect of nature of swelling medium on network structure of hydrogels (Table 1). Swelling was observed more in SWF (1137.35±31.21%) as compared to swelling in pH 2.2 buffer (287.49±23.47%) and PBS (1100.04±12.25%). pH sensitivity of the hydrogel can be attributed to the presence of CP in the polymer matrix and in alkaline solution, partially ionization of carboxylic groups develop internal ion osmotic pressure due to electrostatic repulsion and swelling of hydrogels.[53] On the other hand, at lower pH solution, the hydrogen-bonding interactions leading to generation of additional physical crosslinking. So, the electrostatic repulsion due to COO- groups is restricted, and the polymeric network tends to shrink.[54]The swelling of polymers was observed less in 0.9% NaCl solution (355.04±5.88%) as compared to distilled water (1198.78±34.30%).Increase in salt concentration shielded the electrostatic repulsion between charged groups, causing decrease of hydrogel swelling.[45] Swelling of hydrogels increased with increase in temperature of swelling medium. At higher

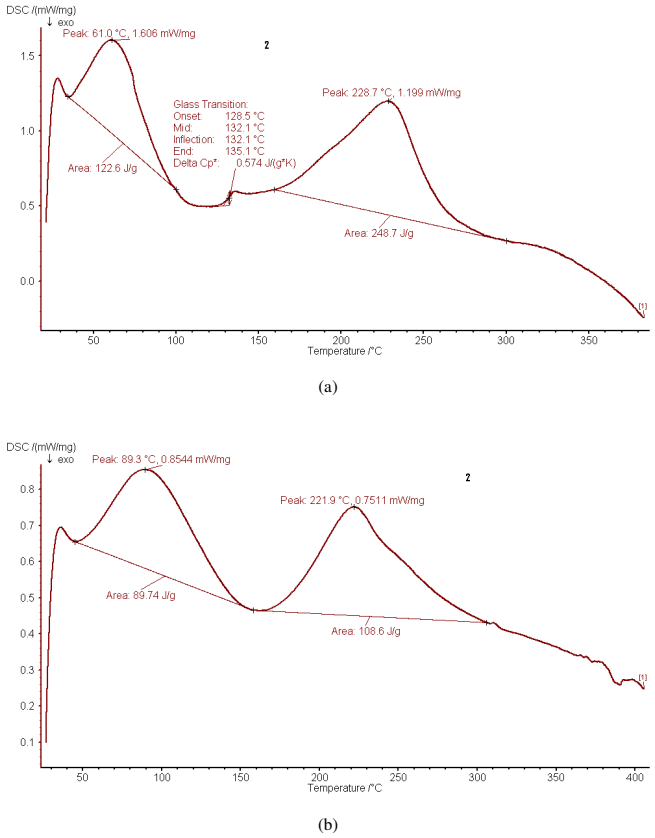


Figure 7. DSC curves of (a) CP and (b) CP-*cl*-poly(NVP) polymer

temperature the chain mobility increases which facilitates the network expansion and leads to increase in swelling of hydrogel[55](Table 1).

Overall, these hydrogel wound dressing showed high wound fluid absorption capacity and one gram of hydrogel film has taken 11.37±0.31 g of simulated wound fluid. Moist wound bed has been widely accepted as the most ideal environment for effective wound healing.[56] The accumulation of wound exudates often causes maceration and bacterial overgrowth in the wound site.

Table 1. Results of swelling for CP-*cl*-poly(NVP) hydrogels

Sr. No.	Parameter	Swelling after 24 hrs (%)
	Effect of swelling medium	
1.	pH 2.2 buffer	287.49±23.47
2.	Phosphate buffered saline (pH 7.4)	1100.04±12.25
3.	Simulated wound fluid (pH 8.0)	1137.35±31.21
4.	Distilled water	1198.78±34.30
5.	0.9% Sodium chloride solution	355.04±5.88
	Effect of temperature	
6.	27°C	1127.93±52.65
7.	37°C	1198.78±34.30
8.	47°C	1264.31±54.51

3.3 Drug release profile

Release profile of moxifloxacin from drug loaded CP-*cl*-poly(NVP) hydrogels was evaluated in simulated wound fluid (SWF) and results are shown in Figure 8 and Table 2. The release profile of entrapped drug showed slow and sustained release in SWF. No significant burst release was observed and considerable amount of drug release was observed after every half an hour, which can help in maintaining constant drug concentration at the wound site for a long time. The high surface area and porous structure of the hydrogels enabled the drugs to diffuse into the aqueous medium. Penetration of solvent led to formation of micro-cavities which cause the drug migration into solvent.[57] Diffusion exponent and various diffusion coefficients for the release of drug from the drug loaded polymers have been calculated and results have been presented in Table 2. The release of moxifloxacin from hydrogels occurred through Case-II diffusion mechanism. Case II diffusion mechanism occurs when rate of diffusion is very rapid as compared to the rate of relaxation of polymeric chains (relaxation controlled transport).The values of initial and late time diffusion coefficients were found comparable. The *in vitro* drug release data from CP-*cl*-poly(NVP) hydrogels in different releasing mediums were evaluated kinetically using various important mathematical models like zero order, first order, Higuchi, KorsmeyerPeppas, and Hixson-Crowell models. When the respective R^2 were compared, it was found that it followed best by Hixson-Crowell's model with highest values of regression coefficient. Hixson-Crowell's model applies to such pharmaceutical dosages, where the dissolution occurs in planes that are parallel to the drug surface if the dosage dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.[58]

3.4 Blood compatibility

Hemolysis, defined as the release of hemoglobin into plasma due to damage of erythrocytes membranes, is directly related to blood compatibility of material. Direct contact hemolytic assay is considered to be reliable method for measuring blood biocompatibility of biomaterials. Results of hemolysis test for CP-*cl*-poly(NVP) polymer have shown (3.97±0.72)% haemolysis classifying it as non-haemolytic material. These hydrogels can be regarded as safe for wound applications. Li *et al.* have reported increase in blood compatibility on grafting with NVP.[59] Moreover, Blood compatibility of these crosslinked polymer can be attributed to its constituting materials poly(NVP) and CP, which are highly hydrophilic and biocompatible in nature.[13,60] These re-

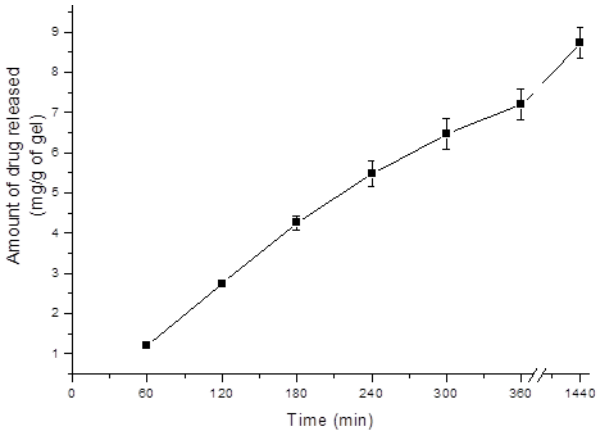


Figure 8. Release profile of moxifloxacin hydrochloride from drug loaded CP-*cl*-poly(NVP) hydrogels, in simulated wound fluid at 37 °C

sults revealed the hemocompatibility of hydrogel dressings, which indicates material will not alter the integrity of the blood during *in-vivo* application.During thrombogenicity test, weight of the clot formed with hydrogels was slightly less (0.31±0.02 g) in comparison to blood without hydrogels (0.34±0.05 g). These results indicate that 91.39±7.44% thrombogenicity was observed in the presence of CP-*cl*-poly(NVP) polymer, classifying the material as non-thrombogenic (Table 3).

3.5 Mucoadhesion studies

The results of mucoadhesion studies for CP-*cl*-poly(NVP) polymer are presented in Table 3. Maximum detachment force (F_{max}) required for detachment of hydrogels from mucosal surface was 79.98±8.16 mN. Bioadhesive properties in the present case can be attributed to synergistic mucoadhesive effect of poly(NVP) and CP. CP and poly (NVP) are known to improve mucoadhesive properties of the biomaterials.[61,62] Carboxylic groups of CP are capable of forming strong hydrogen bonds with oligosaccharide chains present in mucins leading to adhesion.[62] Mucoadhesion is desirable for a topical wound dressing as it will help the dressing to retain its position with less chances of dislocation from the wound site. Mucoadhesive polymers are widely explored for developing novel drug delivery systems. The close contact between a delivery system and the absorbing cell layer will improve both efficiency and effectiveness of the mucoadhesive system. Interaction of a polymeric system with these mucus glycoproteins is the major reason for the mucoadhesion phenomenon. Inter-penetration and inter-diffusion of polymeric chains with the mucus lining is one among the important steps in determining the bioadhesive interactions. Specific non-covalent interactions between the functional groups in the polymers and the mucus glycoproteins further reinforce these interactions.[63]

Table 2. Results of diffusion exponent 'n', gel characteristic constant 'k', various diffusion coefficients, and correlation coefficients of different models for release profile of moxifloxacin hydrochloride from drug loaded CP-*cl*-poly(NVP) hydrogels, in simulated wound fluid at 37 °C

Diffusion exponent 'n'		1.013
Gel characteristic constant 'k'×10^2		0.233
Correlation coefficient (R^2)		0.985
Diffusion coefficients (cm^2/min):	Initial D_i×10^6	7.73
	Average D_A×10^6	2.41
	Late Time D_L×10^6	5.4
Zero Order Model:	R^2	0.977
	k_0 ×10^2 (min^{-1})	0.23
First Order Model:	R^2	0.99
	k_1×10^2 (min^{-1})	0.533
Higuchian Model:	R^2	0.997
	k_H ×10^2 ($min^{-1/2}$)	6.28
Korsmeyer-Peppas Model:	R^2	0.985
	k_{KP}×10^2(min^{-n})	0.233
Hixson–Crowell's Model:	R^2	0.999
	k_{HC} ×10^2 ($min^{-1/3}$)	0.132

3.6 Oxygen permeability

The results of oxygen permeability are presented in Table 3. In the present case, the airtight flask (negative control) and opened flask (positive control) had dissolved oxygen values of 4.95±0.07 mg/L and 7.4±0.0 mg/L, respectively, whereas flasks covered CP-*cl*-poly(NVP)polymer film had dissolved oxygen values of 6.43±0.05 mg/L. The results show that CP-*cl*-poly(NVP) polymer film has shown considerable permeability to oxygen. Similar results have been reported in literature.[64] These results can be attributed to hydrophilicity of hydrogel films as observed in swelling studies. Hydrophilicity of the material results in water plasticization effect that will lead to polymer chain relaxation, increase in pore size and hence improved gaseous permeability.[65,66] Gaseous permeability especially for oxygen is a crucial factor for proper wound healing. On one side oxygen is necessary for regeneration of damaged tissue, while on the other side wound hypoxia leads to impaired wound healing. All result suggested that sufficient oxygen was able to penetrate through the polymeric network of crosslinked films. Oxygen availability is suitable for tissue homoeostasis, energy production, cell membrane maintenance, mitochondrial function, and cellular repair.[64]

Table 3. Results of biomedical properties of ofCP-*cl*-poly(NVP) hydrogels

Thrombogenicity	**Weight of blood clot (g)**	**Thrombose (%)**	**Inference**
	0.31±0.02	91.39±7.44	Non-thrombogenic
Haemolysis	OD at λ_{max} = 540 nm	Haemolytic Index (%)	Inference
	0.23±0.03	3.97±0.72	Non-haemolytic
Mucoadhesion[a]	Maximum detachment force F_{max} (mN)	Work of adhesion, W_{ad} (mN.mm)	Detachment distance (mm)
	79.98±8.16	32.40±4.34	5.19±0.55
Tensile strength[b]	Breaking force (N)	Tensile strength ($N.mm^{-2}$)	Elongation at break (%)
	13.19±2.41	0.65±0.12	119.38±14.26
Burst strength[c]	Dimension of film (cm^2)	Bursting strength (N)	Distance at burst (mm)
	3×3	8.25±0.31	15.30±1.65
Resilience[d]	Dimension of film (cm^2)	Force at target distance (g)	Resilience (%)
	3×3	154.70±29.89	25.49±0.72
Relaxation[e]	Force at target distance (N)	Relaxed force (N)	Retained force (%)
	0.54±0.09	0.23±0.02	43.56±2.69
O_2 permeability	Thickness of polymer(mm)	O_2 in test flask (mg/L)	Inference
	1.0	6.43±0.05	Permeable
Water vapour	Thickness of polymer (mm)	WVTR ($g/m^2/day$)	Inference
permeability	1.0	400.00±13.90	Permeable
Microbial penetration	Time (days)	Positive control (turbidity)	Polymeric films and negative control (turbidity)
	1	No	No
	2	Light	No
	14	Clear	No
	30	Complete	No

[a] (Contact time = 60 s, Return distance =15.0 mm, Applied force = 0.10 N, Trigger force = 0.029 N, Test speed = 0.10 mm/s, Pre test speed = 0.50 mm/s, Post test speed = 0.10 mm/s)

[b] (Trigger force = 0.029N, Test speed = 2.00 mm/s, Pre test speed = 0.20 mm/s, Post test speed = 10 mm/s)

[c] (Distance = 15.0 mm, Trigger force = 0.049 N, Test speed = 1.0 mm/s, Pre test speed = 2.0 mm/s, Post test speed = 10 mm/s)

[d] (Distance = 2.0 mm, Trigger force = 0.049 N, Test speed = 0.5 mm/s, Pre test speed = 1.0 mm/s, Post test speed = 0.5 mm/s)

[e] (Distance = 2.0 mm, Trigger force = 0.049 N, Test speed = 0.5 mm/s, Pre test speed = 1.0 mm/s, Post test speed = 10 mm/s)

3.7 Water vapour transmission rate

Parallel to oxygen permeability, evaluation of water vapour transmittance through the films is also necessary. WVTR for CP-*cl*-poly(NVP) films was 400.00±13.90 $g/m^2/day$, and for open vial it was 4192.38±106.29 $g/m^2/day$. However in case of sealed vial no water vapor transmittance was observed indicating CP-*cl*-poly(NVP) films were permeable to water vapors, but to a very less extent in comparison to open vial. Excess evaporation from the wound leads to wound dehydration and complete sealing leads to collection of wound exudates, both results in delayed wound healing. Intermediate WVTR for CP-*cl*-poly(NVP) hydrogels will help to maintain moist wound healing environment without collection of wound exudates.

3.8 Microbial penetration

Microbial penetration test was carried out for a month period and it was found that no microbial contamination occurred in open environment in case of nutrient broth sealed with CP-*cl*-poly(NVP) hydrogel films, while high turbidity in the open test tube was observed as a result of microbial contamination (Table 3). This test highlights that these hydrogel films could be considered as a good barrier against the microbes to prevent any secondary infection during wound healing. Similar results have been reported in literature.[56] The goal of wound therapy is to keep the wound microorganism content as low as possible in order to prevent infection and accordingly to stimulate the repair process. The hydrogel has the potential to mimic the extracellular matrix, which may lead to the tissue regeneration necessary for wound healing. In designing a matrix which promotes wound healing, it is important to provide an adequate antimicrobial protection. Hydrogel dressings are considered as a good barrier against microbes and this is important, especially for protecting the wound from further infection and accelerating the healing of the wound.[56]

3.9 Mechanical Properties

The results of mechanical properties (viz. tensile strength, burst strength, resilience, stress relaxation and folding endurance) of the CP-*cl*-poly(NVP) polymer film are given in Table 3. The polymers showed tensile strength (0.65±0.12 Nmm^{-2}) and elongation at break (119.38±14.26%). Tensile strength represented to the maximum tension that a material can withstand without tearing, while elongation at break was used to evaluate the malleability of materials. A crosslinked network im-

parts greater tensile strength and a more malleability to the hydrogels.[3] The considerable tensile strength are the results of long polymeric chains and interpenetrating network present in the polymeric film. Results of burst strength test revealed that 8.25±0.31 N force was required to burst the polymer film with a ball probe (P/5s) and distance at burst (15.30±1.65 mm) was shown by the polymer, indicating high mechanical strength. In stress relaxation test, when a constant strain (2 mm) was applied for 30 second (F_{max}=0.54±0.09 N) on 1 mm thick polymeric films, 0.23±0.02 N force was relaxed/retained by the polymer.

So, stress relaxation test shows 43.56±2.69% force was retained by the polymer sample indicting viscoelastic behaviour of the polymer film. The folding endurance was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good film properties. These polymer films did not show any cracks even after folding for more than 300 times. Folding Endurance test results reveal that these hydrogels were flexible and suitable for wound dressing applications. High flexibility can be attributed to high hydrophilicity of the hydrogels and glycerol, the biocompatible plasticizer.[65] Resilience is evaluated from of work returned by the sample when it is strained upto a distance (2 mm in present case). 25.49±0.72% resilience of the polymers was observed, indicating slight elastic character of the polymer film. Resilience and elongation values are measure for elasticity of a material, and in the present case the polymer film has shown high values for elongation and was resilient upto an extent, displaying elastic nature of the material.[66] Hence, the mechanical parameters obtained for the CP-*cl*-poly(NVP) polymer film indicate that it meets the requirements for a potential wound dressing material. Compromised mechanical properties of hydrogels often limit the scope of their applications.

4 Conclusion

From the forgone discussion it can be concluded that modification of CP with poly(NVP) was successfully carried out by free radical polymerization. The polymer was obtained in the form of a transparent flexible film. SEM and AFM studies demonstrate small degree of heterogeneity of the surface of the polymer film. The hydrogels showed high simulated wound fluid absorption and hydrogel dressings were found non-hemolytic, non-thrombogenic, oxygen permeable and water vapour permeable. In addition these hydrogels were transparent which will allow monitoring wound healing progress. Moxifloxacin released was observed in controlled manner from drug loaded hydrogels. Drug release from hydrogels occurred through Case-II diffusion mechanism and best fitted in Hixson-Crowell's model. Since the polymers were transparent, real time monitoring of wound healing is possible. These polymer films displayed high mechanical strength and flexibility. Overall the preliminary investigation suggested that CP-*cl*-poly(NVP) hydrogel films can act as potential candidate for wound dressing applications.

References

[1] Chandika P, Ko SC, Jung WK. Marine-derived biological macromolecule-based biomaterials for wound healing and skin tissue regeneration. Int J Biolog Macromol, 2015, **77**: 24-35. https://doi.org/10.1016/j.ijbiomac.2015.02.050

[2] Percival SL, Emanuel C, Cutting KF, *et al*. Microbiology of the skin and the role of biofilms in infection. Int Wound J, 2012, **9**: 14-32. https://doi.org/10.1111/j.1742-481X.2011.00836.x

[3] Jiang Q, Wang J, Tang R, *et al*. Hypromellose succinate-crosslinked chitosan hydrogel films for potential wound dressing.Int J Biolog Macromo, 2016, **l91**: 85-91. https://doi.org/10.1016/j.ijbiomac.2016.05.077

[4] Tavakoli J, Tang Y. Honey/PVA hybrid wound dressings with controlled release of antibiotics: Structuralphysico-mechanical and *in vitro* biomedical studies. Materials Science and Engineering, 2017, **C77**: 318-325. https://doi.org/10.1016/j.msec.2017.03.272

[5] Caló E, Khutoryanskiy VV. Biomedicalapplications of hydrogels: A review of patents and commercial products Eur Polym J, 2015, **65**:252-267. https://doi.org/10.1016/j.eurpolymj.2014.11.024

[6] Slaughter BV, Khurshid SS, Fisher OZ, *et al*. Hydrogels in regenerative medicine. Adv Mater, 2009, **21**: 3307-3329. https://doi.org/10.1002/adma.200802106

[7] Moura LI, Dias AM, Carvalho E, *et al*.Recent advances on the development of wound dressings for diabetic foot ulcer treatment-a review. Acta biomaterialia, 2013, **9**: 7093-7114. https://doi.org/10.1016/j.actbio.2013.03.033

[8] Lloyd LL, Kennedy JF, Methacanon P, *et al*. Carbohydrate polymers as wound management aids. Carbohydr Polym, 1998, **37**: 315-322. https://doi.org/10.1016/S0144-8617(98)00077-0

[9] Song J, Yu R, Wang L, *et al*. Poly (N-vinylpyrrolidone)-grafted poly (N-isopropylacrylamide) copolymers: synthesis characterization and rapid deswelling and reswelling behavior of hydrogels. Polymer, 2011, **52**: 2340-2350. https://doi.org/10.1016/j.polymer.2011.03.038

[10] Telford AM, James M, Meagher L, *et al*. Thermally crosslinked PNVP films as antifouling coatings for biomedical applications. ACS Appl Mater Interfaces, 2010, **2**: 2399-2408. https://doi.org/10.1021/am100406j

[11] Shahbuddin M, Bullock AJ, MacNeil S, *et al*. Glucomannan-poly (N-vinyl pyrrolidinone) bicomponent hydrogels for wound healing. J Mater Chem, 2014, **B2**: 727-738. https://doi.org/10.1039/C3TB21640C

[12] Zheng A, Xue Y, Wei D, *et al*. Synthesis and characterization of antimicrobial polyvinyl pyrrolidone hydrogel as wound dressing. Soft Mater, 2014, **12**: 179-187. https://doi.org/10.1080/1539445X.2013.831357

[13] Smith LE, Rimmer S, MacNeil S. Examination of the effects of poly (N-vinylpyrrolidinone) hydrogels in direct and indirect contact with cells. Biomaterials, 2006, **27**: 2806-2812. https://doi.org/10.1016/j.biomaterials.2005.12.018

[14] Wan LS, Xu ZK, Huang XJ, *et al*. Hemocompatibility of Poly (acrylonitrilecoNvinyl2pyrrolidone): Swelling Behavior and Water States. Macromol Biosci, 2005, **5**: 229-236. https://doi.org/10.1002/mabi.200400157

[15] Bajpai SK, Pathak V, Soni B, et al. CNWs loaded poly (SA) hydrogels: effect of high concentration of CNWs on water uptake and mechanical properties. Carbohydr Polym, 2014, **106**: 351-358. https://doi.org/10.1016/j.carbpol.2014.02.069

[16] Islam MT, Rodriguez-Hornedo N, Ciotti S, *et al*. Rheological characterization of topical carbomer gels neutralized to different pH. Pharma Res, 2004, **21**: 1192-1199.

[17] Sahoo S, Pani NR, Sahoo SK. Microemulsion based topical hydrogel of sertaconazole: Formulationcharacterization and evaluation.Colloids SurfB Biointerfaces, 2014, **120**: 193-199. https://doi.org/10.1016/j.colsurfb.2014.05.022

[18] Jana S, Manna S, Nayak AK, *et al*. CP gel containing chitosan-egg albumin nanoparticles for transdermal aceclofenac delivery. Colloids Surf B Biointerfaces, 2014, **114**: 36-44. https://doi.org/10.1016/j.colsurfb.2013.09.045

[19] Wang Y, Lee CH. Characterization of a female controlled drug delivery system for microbicides. Contraception, 2002, **66**(4): 281-287. https://doi.org/10.1016/S0010-7824(02)00354-2

[20] Jaiswal M, Kumar A, Sharma S. Nanoemulsions loaded CP? 934 based gel for intranasal delivery of neuroprotective Centella asiatica extract: invitro and exvivo permeation study. J Pharma Invest, 2016, **46**: 79-89. https://doi.org/10.1007/s40005-016-0228-1

[21] Silva JP ,Dhall S, Garcia M, *et al*. Improved burn wound healing by the antimicrobial peptide LLKKK18 released from conjugates with dextrin embedded in a CP gel. Acta Biomater, 2015, **26**: 249-262. https://doi.org/10.1016/j.actbio.2015.07.043

[22] Singh B, Sharma N. Mechanistic implication for cross-linking in sterculia-based hydrogels and their use in GIT drug delivery.Biomacromolecules, 2009, **10**: 2515-2532. https://doi.org/10.1021/bm9004645

[23] Ritger PL, Peppas NA. A simple equation for description of solute release I, Fickian and non-Fickian release from non-swellable devices in the form of slabsspherescylinders or discs. J Control Rel, 1987, **5**:23-36. https://doi.org/10.1016/0168-3659(87)90034-4

[24] Ritger PL, Peppas NA. A simple equation for description of solute release II, Fickian and anomalous release from swellable devices. J Control Release, 1987, **5**: 37-42. https://doi.org/10.1016/0168-3659(87)90035-6

[25] Dash S, Murthy PN, Nath L, *et al*. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm, 2010, **67**: 217-223.

[26] Sullad AG, Manjeshwar LS, Aminabhavi TM. Novel pH-sensitive hydrogels prepared from the blends of poly (vinyl alcohol) with acrylic acid-graft-guar gum matrixes for isoniazid delivery. Ind Eng Chem Res, 2010, **49**: 7323-7329. https://doi.org/10.1021/ie100389v

[27] Imai Y, Nose Y. A new method for evalution of antithrombogenicity of materials. J Biomed Mater Res, 1972, **6**: 165-172. https://doi.org/10.1002/jbm.820060305

[28] Ferreira P, Pereira R, Coelho JFJ, *et al*. Modification of the biopolymer castor oil with free isocyanate groups to be applied as bioadhesive. Int J Biolog Macromol, 2007, **40**: 144-152. https://doi.org/10.1016/j.ijbiomac.2006.06.023

[29] Winkler LW. Die bestimmung des im wasser gel?sten sauerstoffes,Berichte der deutschen chemischen Gesellschaft, 1888, **21**: 2843-2854. https://doi.org/10.1002/cber.188802102122

[30] Chamb iHNM, Grosso CRF. Mechanical and water vapor permeability properties of biodegradables films based on methylcelluloseglucomannanpectin and gelatin. Food Sci Technol, 2011, **31**: 739-746. https://doi.org/10.1590/S0101-20612011000300029

[31] Greenspan L. Humidity fixed points of binary saturated aqueous solutions. J Res Natl Bur Stand, 1977, *81*: 89-96. https://doi.org/10.6028/jres.081A.011

[32] Wu P, Fisher AC, Foo PP, *et al*. In vitro assessment of water vapour transmission of synthetic wound dressings. Biomaterials, 1995, **16**: 171-175. https://doi.org/10.1016/0142-9612(95)92114-L

[33] Bajpai SK, Saggu SS. Insulin release behaviour of Poly(methacrylamideco Nvinyl2pyrrolidonecoitaconic acid) Hydrogel: An Interesting Probe, Part II. J Macromol Sci A, 2007, **44**: 153-157. https://doi.org/10.1080/10601320601030707

[34] Pal K, Banthia AK, Majumdar DK. Preparation of transparent starch based hydrogel membrane with potential application as wound dressing. Trends Biomater Artif Organs, 2006, **20**: 59-67.

[35] Wei Y, Xie R ,Lin Y, *et al*. Structure formation in pH-sensitive hydrogels composed of sodium caseinate and NO-carboxymethyl chitosan. Int JBiolog Macromol, 2016, **89**: 353-359. https://doi.org/10.1016/j.ijbiomac.2016.04.081

[36] Pramanick AK, Gupta S, Mishra T, *et al*. Topographical heterogeneity in transparent PVA hydrogels studied by AFM,Mater Sci Eng C, 2012, **32**: 222-227. https://doi.org/10.1016/j.msec.2011.10.022

[37] Ahuja M, Thakur K, Kumar A. Amylopectin-g-poly (N-vinyl-2-pyrrolidone): Synthesischaracterization and in vitro release behaviour.Carbohydr Polym, 2014, **108**: 127-134. https://doi.org/10.1016/j.carbpol.2014.03.007

[38] Du J, Liu X, Liu W, *et al*. One-step preparation of vinyl-functionalized material surfaces: a versatile platform for surface modification. Sci China Chem, 2014, **57**: 654-660. https://doi.org/10.1007/s11426-014-5067-1

[39] Patel MM, Smart JD, Nevell TG, *et al*. Mucin/poly (acrylic acid) interactions: a spectroscopic investigation of mucoadhesion. Biomacromolecules, 2003, **4**: 1184-1190. https://doi.org/10.1021/bm034028p

[40] Capra RH, Baruzzi AM, Quinzani LM, *et al*. Rheologicaldielectric and diffusion analysis of mucin/CP matrices used in amperometric biosensors Sens Actuators B Chem, 2007, **124**: 466-476. https://doi.org/10.1016/j.snb.2007.01.022

[41] Szakonyi G, Zelkó R. CP?-crospovidone interpolymer complex for pH-dependent desloratadine release. J Pharma Biomed Anal, 2016, **123**: 141-146. https://doi.org/10.1016/j.jpba.2016.02.012

[42] Zhu X, Lu P, Chen W, *et al*. Studies of UV crosslinked poly (N-vinylpyrrolidone) hydrogels by FTIRRaman and solid-state NMR spectroscopies.Polymer, 2010, **51**: 3054-3063.

[43] Tanodekaew S, Prasitsilp M, Swasdison S, *et al*. Preparation of acrylic grafted chitin for wound dressing application. Biomaterials, 2004, **25**: 1453-1460. https://doi.org/10.1016/j.biomaterials.2003.08.020

[44] Jin S, Gu J, Shi Y, *et al*. Preparation and electrical sensitive behavior of poly (N-vinylpyrrolidone-co-acrylic acid) hydrogel with flexible chain nature. Eur Polym J, 2013, **49**: 1871-1880. https://doi.org/10.1016/j.eurpolymj.2013.04.022

[45] Liu S, Luo W, Huang H. Characterization and behavior of composite hydrogel prepared from bamboo shoot cellulose and -cyclodextrin. IntJBiolog Macromol, 2016, **89**: 527-534. https://doi.org/10.1016/j.ijbiomac.2016.05.023

[46] Loh GOK, Tan YTF, Pe KK. Hydrophilic polymer solubilization on norfloxacin solubility in preparation of solid dispersion.Powder Technol, 2014, **256**: 462-469. https://doi.org/10.1016/j.powtec.2014.01.089

[47] Bentez-Guerrero M, López-Beceiro J, Sánchez-Jimnez PE, *et al*. Comparison of thermal behavior of natural and hot-washed sisal fibers based on their main components: Cellulosexylan and lignin, TG-FTIR analysis of volatile products. Thermochimica Acta, 2014, **581**: 70-86. https://doi.org/10.1016/j.tca.2014.02.013

[48] Verma SK, Pandey VS, Behari MYK. Gellan gum-g-N-vinyl-2-pyrrolidone: Synthesisswellingmetal ion uptake and flocculation behavior. Int J Biolog Macromol, 2015, **72**: 1292-1300. https://doi.org/10.1016/j.ijbiomac.2014.10.036

[49] Chun MK, Bhusal P, Choi HK. Application of CP/PVP interpolymer complex to prepare mucoadhesive floating granule.Arch Pharmacal Res, 2013, **36**: 745-751.

[50] Lin SY ,Yu HL. Thermal stability of methacrylic acid copolymers of Eudragits LSand L30D and the acrylic acid polymer of CP. J Polym Sci A, 1999, **37**: 2061-2067. https://doi.org/10.1002/(SICI)1099-0518(19990701)37:13⟨2061::AID-POLA20⟩3.0.CO;2-Y

[51] Lee WF, Chiang WH. Swelling and drugrelease behaviour of the poly (AAcoNvinyl pyrrolidone)/chitosan interpenetrating polymer network hydrogels. J Appl Polym Sci, 2004, **91**: 2135-2142. https://doi.org/10.1002/app.13353

[52] Shah R, Saha N, Saha P. Influence of temperaturepH and simulated biological solutions on swelling and structural properties of biomineralized (CaCO3) PVPCMC hydrogel. Prog Biomater, 2015, **4**: 123-136. https://doi.org/10.1007/s40204-015-0043-1

[53] Singh R, Singh D. Radiation synthesis of PVP/alginate hydrogel containing nanosilver as wound dressing. J Mater Sci Mater Med, 2012, **23**: 2649-2658. https://doi.org/10.1007/s10856-012-4730-3

[54] Jain GK, Pathan SA, Akhter S, *et al*. Mechanistic study of hydrolytic erosion and drug release behaviour of PLGA nanoparticles: Influence of chitosan. Polym Degrad Stab, 2010, **95**: 2360-2366.

[55] Tally M, Atassi Y. Synthesis and characterization of pH-sensitive superabsorbent hydrogels based on sodium alginate-g-poly (acrylic acid-co-acrylamide) obtained via an anionic surfactant micelle templating under microwave irradiation. Polym, Bulletin, 2016, **1**: 26. https://doi.org/10.1007/s00289-016-1649-8

[56] Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharma Sci1, 2001, **3**: 123-133. https://doi.org/10.1016/S0928-0987(01)00095-1

[57] Tang C, Yin L, Yu J, *et al*. Swelling behavior and biocompatibility of CPcontaining superporous hydrogel composites.J Appl Polym Sci, 2007, **104**: 2785-2791. https://doi.org/10.1002/app.25930

[58] Malik S, Kumar A, Ahuja M. Synthesis of gum kondagogug-poly (N-vinyl-2-pyrrolidone) and its evaluation as a mucoadhesive polymer.Int J Biolog Macromol, 2012, **51**: 756-762. https://doi.org/10.1016/j.ijbiomac.2012.07.009

[59] L R, Wang H, Wang W, *et al*. Simultaneous radiation induced graft polymerization of N-vinyl-2-pyrrolidone onto polypropylene non-woven fabric for improvement of blood compatibility. Rad Phys Chem,2013, **88**: 65-69. https://doi.org/10.1016/j.radphyschem.2013.03.013

[60] Hall DJ, Khutoryanskaya OV, Khutoryanskiy VV. Developing synthetic mucosa-mimetic hydrogels to replace animal experimentation in characterisation of mucoadhesive drug delivery systems. Soft Matter, 2011, **7**: 9620-9623. https://doi.org/10.1039/c1sm05929g

[61] Sajeesh S, Sharma CP. Mucoadhesive hydrogel microparticles based on poly (methacrylic acid-vinyl pyrrolidone)-chitosan for oral drug delivery. Drug Deliv, 2011, **18**:227-235. https://doi.org/10.3109/10717544.2010.528067

[62] Zhang D, Zhou W, Wei B, *et al*. Carboxyl-modified poly(vinyl alcohol)-crosslinked chitosan hydrogel films for potential wound dressing. Carbohydr Polym, 2015, **125**: 189-199. https://doi.org/10.1016/j.carbpol.2015.02.034

[63] Dias AMA, Rey-Rico A, Oliveira RA, *et al*. Wound dressings loaded with an anti-inflammatory juca (Libidibia ferrea) extract using supercritical carbon dioxide technology. J Supercrit Fluids, 2013, **74**: 34-45. https://doi.org/10.1016/j.supflu.2012.12.007

[64] Wittaya-areekul S, Prahsarn C. Development and in vitro evaluation of chitosanpolysaccharides composite wound dressings. Int JPharma, 2006, **313**: 123-128. https://doi.org/10.1016/j.ijpharm.2006.01.027

[65] Chen Q, Liang S, Thouas GA. Elastomeric biomaterials for tissue engineering. Prog Polym Sci, 2013, **38**: 584-671. https://doi.org/10.1016/j.progpolymsci.2012.05.003

[66] Borde A, Larsson M, Odelberg Y, *et al*. Increased water transport in PDMS silicone films by addition of excipients. Acta Biomater, 2012, **8**: 579-588. https://doi.org/10.1016/j.actbio.2011.09.022