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# Modification of Polyvinyl Alcohol via Atom Transfer Radical Polymerization for Targeted Drug Delivery Applications

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**Abstract**

In current study,a hydrogel based on biocompatible polymerwas prepared. The functionalization of polyvinyl alcohol (PVA)with epichlorohydrin(ECH) to produce epichlorohydrin-g-polyvinyl alcohol (PVA/ECH) as a suitable macroinitiator for atom transfer radical polymerization (ATRP) reaction was investigated.ThenN-vinyl pyrrolidone (NVP) waspolymerized on the surface of macroinitiatorin presence of CuCl as a catalyst and Pentamethyldiethylenetriamine (PMDETA) as aligand using ATRP to produce PNVP-g-PVA. The synthesized copolymer was characterized by Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC). Also equilibrium swelling was studied in distilled water and indicated the sustained expansion of them. At last, loading capacity and release profiles of ceftriaxone as a model drug from the hydrogel were determined by UV–Vis absorption measurement at $\lambda_{max}$ = 243 nm. In vitro drug release behavior was investigated in three different media (HCl solution: pH=3 and bicarbonate buffer solutions: pH=7 and pH=8).

***Keywords*****:** *Polyvinyl alcohol, N-vinylpyrrolidone, ATRP, Drug delivery systems.*

## Introduction

Controlled drug delivery systems are an effective manner to control the concentration of therapeutic agents in blood and to improve their bioavailability. Such delivery systems offer numerous advantages compared to conventional dosage forms, including improved efficacy, reduced toxicity, and improved patient adoption and convenience [1-3]. Among various systems that can be used, polymers are an important class of materials for a broad array of medical applications, including tissue

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engineering and drug delivery [4-6].

One of the important polymer networks for pharmaceutical application is hydrogels.They are materials which can absorb large quantities of water without dissolving. Also, they are promising for a variety of medical applications due to their high water content and mechanical similarity to natural tissues [7, 8]. The water holding capacity of the hydrogels arise mainly due to the presence of hydrophilic groups such as amino, amide, carboxyl, and hydroxyl groups in the polymer chains. According to Hoffmann, the amount of water presented in a hydrogel may vary from 10% to thousands of times of the weight of the hydrogel [9]. The hydrogels containing PVA with numerous hydroxyl groups present on the backbone have been widely used in the biomedical applications [10-12]. This polymer has been widely explored for numerous applications due to its advantages such as non-toxic, non-carcinogenic, excellent chemical resistance and bioadhesive properties. In addition, PVA has been proven to possess good biocompatibility and is thus a promising material for biomedical applications [13-17]. However, PVA suffers from a number of disadvantages such as its tendency to aggregate, so low process ability [18]. Many efforts have been carried out to overcome these limitations by the chemical modification of PVA. For instance, Gao et al. [19], graft-polymerized sodium 4-styrene sulfonationon the surfaces of cross-linked polyvinyl alcohol for preparation a new oral colon-specific delivery systemwith pH-dependent type and investigated its delivery property. Mahdavinia et al. [20], synthesizedthe magnetic nanocomposite hydrogelbyincorporation of polyvinyl alcohol for targeted drug delivery application.Chang et al. [21], prepared a self-healable chitosan (CS)/polyvinyl alcohol (PVA) hydrogel as an injectabledrug carrier.

The aim of this work is modification of PVA by controlled radical graft polymerization. Radical polymerization is one of the most important methods for modifications of polymers with nearly 50% of synthetic copolymers prepared through radical processes [22]. In particular, atom transfer radical polymerization (ATRP) has been demonstrated to be a versatiletechnique to synthesize well-defined polymers. In this technique a transition metal which was complexed by an appropriate ligand is used as a catalyst for the reaction between analkyl halide initiator and a vinyl monomer. The reaction can be carried out in a variety of solvents and conditions [23-25].

In this work, N-vinylpyrrolidone-graft-polyvinylpyrrolidone/epichlorohydrin (PNVP-g-PVA) hydrogel was synthesized by ATRP method. Epichlorohydrin reacts with the hydroxyl groups of PVA and forms lateral branch with chloride end groups which can be used for ATRP reaction. Then NVP monomer was polymerized on the surface of the macroinitiator in the presence of CuCl and

PMDETA using ATRP method. This resulted hydrogel has potential application foradrug delivery system. The drug released behavior of prepared hydrogelwas investigated in three different media (pH=3, pH=7 and pH=8) using ceftriaxone as the model drug.

## Experimental

*Materials*

The PVA with a molecular weight of 25,000 g/mol, epichlorohydrin (ECH), H2SO4 %98, absolute ethanol (ETOH), acetone, diethylether, sodium hydroxide (NaOH), N-vinyl pyrrolidone, Cu (I) chloride (CuCl), Pentamethyl diethylenetriamine (PMDETA) were purchased from Merck. N-vinylpyrrolidone was dehydrated under vacuum before use and other materials were used as received.

*Equipment*

FT-IR spectra were measured with a Fourier Transform Infrared spectrophotometer (Nexus 670, Thermo Nicolet, USA). The Differential Scanning Calorimetry (DSC) of the prepared samples were determined using the LENSESSTAPT-1000 calorimeter (Germany) by Scanning from the room temperature up to 300 °C with the heating rate of 10°C/min. Furthermore, the UV-Vis. spectrophotometer (T80 – PG Instruments Ltd. UK) was used fordetermination of drug concentration in the drug loading and release study.

*Etherification of PVA with ECH to produce PVA/ECH*

The ethanol (20mL) and ECH (0.42 g, 4.53 mmol) were added in to a 50mL two-necked round-bottom flask equipped with a magnetic stirring bar and reflux condenser. Then H2SO4 98% (0.29 g, 2.95 mmol) was added and the flask was kept under reflux condition for about 3 h. Finally the aqueous solution of PVA (0.1 g. 13.38 mmol in 20 mL water) was added dropwise to the above mentioned solution under continuous reflux condition. The reaction was kept under reflux condition for 24 h. The resultant solution was poured into sufficient acetone and the precipitated was filtrated. The final product was washed with acetone and dried under vacuum at 30°C for 24 h.

*Preparation of PNVP-g-PVA by ATRP method*

In a 50-mL two-necked round-bottom flask equipped with magnetic stirrer bar, reflux condenser and gas inlet and outlet tube, 20 mL of DMF and PVA/ECH (0.2 g, 1.10 mmol) was added and the solution was dispersed by gentle heating for about 1 h. Then PMDETA (0.31 g, 1.78 mmol), CuCl (0.18 g, 1.81 mmol) and NVP (5g, 5ml) were added into the solution. The contents of the flask were degassed for 20 min and then stirred under argon atmosphere at 80°C for 24 h. After this period, the reaction mixture was added to 100 mL diethyl ether to obtain the final product. The product was filtered and washed several times with diethyl

ether and dried under vacuum oven overnight.

*Measure the degree of swelling of the hydrogel*

A tea bag with an average particle size between 40 and 60 mesh (250–420 ml) containing an accurately weighed powdered sample (0.1 ± 0.0001 g) was immersed in distilled water (100 mL) and allowed to soak for 30 h at room temperature. To measure the swelling kinetics or the rate of absorption, after a certain time (t), we took the water absorbed samples from the solution at various time points and the swelling measurements were taken by following the above procedure. Subsequently, the tea bag was suspended in air for 2 min in order to remove the excess fluid in each time [26]. The equilibrated swelling (ES) was calculated twice using the following equation:

$$ES\ (g/g) = (Ws - Wd) / Wd \quad (1)$$

Ws and Wd are the weights of the swollen gel and the dry sample, respectively. Thus, absorbency was calculated as gram of water per gram of hydrogel (g/g).

*Determination of calibration curve*

Maximum wavelength of ceftriaxone was determined byscanning suitable dilutions of stock solutions using UV–Vis spectrophotometer and it was found to be 243 nm. Different concentrations of the ceftriaxone in carbonate buffer (pH=7) were prepared and the absorbance of solutions was measuredat 243 nm. The calibration curve was plotted using concentration against absorbance.

*Drug loading into hydrogel*

Drug loading was performed by a soaking procedure; the samples were immersed in 20mL saturated solution of the ceftriaxone for 3 days at 25°C. After loading, each sample was quickly rinsed with distilled water and dried in vacuum oven at room temperature until constant weight. The loading capacity (LC) was calculated from the difference between the amount of ceftriaxone initially used to prepare the drug loaded copolymer and that of the non-associated ceftriaxone residues divided by the total mass of copolymer.

$$LC\ (\%) = \frac{\text{T a o c fi c is}}{\text{T a o c a}} \quad (2)$$

*Drug release studies*

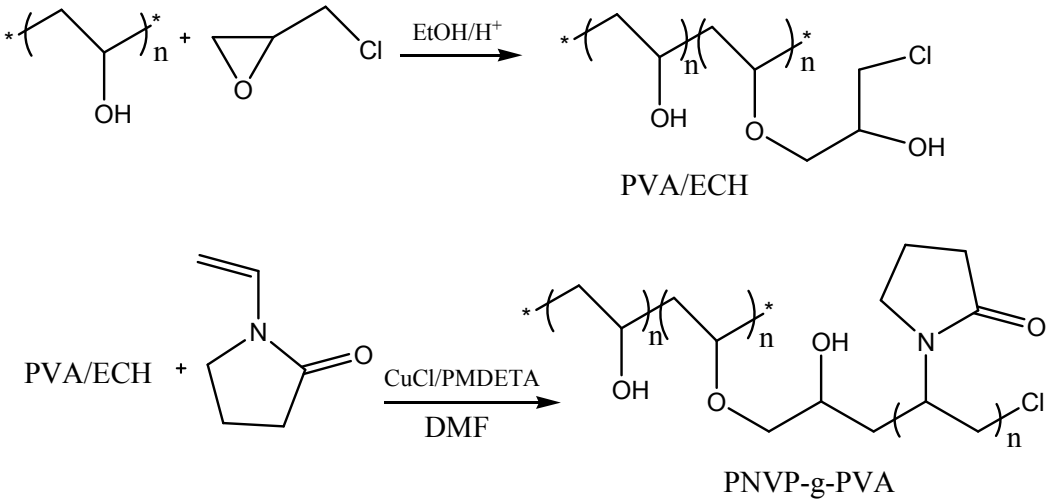
The release of ceftriaxone was determined with UV spectrophotometer at $\lambda_{max}$= 243nm as a function of time. The procedure was as follows: The sample of drug-containing copolymer (50mg) was placed in a dialysis tube in a 100 mL container, containing 50 mL of carbonate-buffered solutions with pH 3, 7, and 8 at 25°C. The in vitro drug release was investigated in the release medium, which was sampled and the

content of the drug in the sample was measured spectrophotometrically at 243 nm. Sampling was carried out in various interval times and after that the sample was poured back into the drug release container. The curve of drug release versus time was calculated from the calibration curve of the drug.

## Results and discussion

*Synthesis and characterization of PNVP-g-PVA*

The PNVP-g-PVAhydrogels was synthesized according to the synthetic route which was depicted in Scheme 1. The hydrogel was prepared by processing in two steps. In the first step, epichlorohydrin reacted with alcohol groups of PVA and generated an ether-bonded chlorohydrin.In this stage, PVA/ECH was prepared as a suitable macroinitiator for ATRP reaction.In the second stage, the polymerization reaction of NVP on the macroinitiator was carried out using ATRP method. For this purpose, the synthesized PVA/ECH underwent the polymerization in the presence of CuCl as catalyst and the PMDETA as ligand. The hydrogel PNVP-g-PVAwas synthesized in this stage.




**Scheme 1.** Synthetic route for preparation of PNVP-g-PVA.

The FT-IR spectra of PVA, PVA/ECH and PNVP-g-PVAare shown in Figure 1.In Figure 1-A, FT-IR spectrum of pure PVA sample is showed. It clearly reveals the major peaks associated with PVA. For instance, it can be observed C–H alkyl stretching band in 2850-2950 $cm^{-1}$ and typical strong hydroxyl bands for free alcohol and hydrogen bonded hydroxyl band in 3250-3650 $cm^{-1}$. Intramolecular and intermolecular hydrogen bonds are expected to occur among PVA chains due to high hydrophilic forces. An important absorption peak was verified at 1100 $cm^{-1}$. This band has been used as an assessment tool of PVA structure because it is a semi crystalline synthetic polymer able to form some domains depending on several process

parameters [27].

The PVA/ECH was identified by Figure 1-B. The absorption bond at 1137cm$^{-1}$ is related to the aliphatic ether. The flat bond at 2500-3500cm$^{-1}$ is related to O-H group and the bond at 2914 cm$^{-1}$ is related to the C-H stretch. The strong absorption bond at 619cm$^{-1}$ is related to the C-Cl groupconfirmsthe ECH immobilization on the PVA. The Spectrum of the PNVP-g-PVAis shown in Figure 1-C.This spectrum showed the characteristic absorption bond around 1683 cm$^{-1}$ is related to carbonyl of amide linkage. A broad peak at 3200–3500 cm$^{-1}$ corresponding to N-H and O-H stretching can be observed from the spectra.It may also be noted that the bands presented in the spectrum of PVA/ECH in 619 cm$^{-1}$ was weaker due to reduction of its concentration in final product respect to growing monomer functions after the ATRP reaction. These results clearly confirm the NVP immobilization on the PVA/ECH.

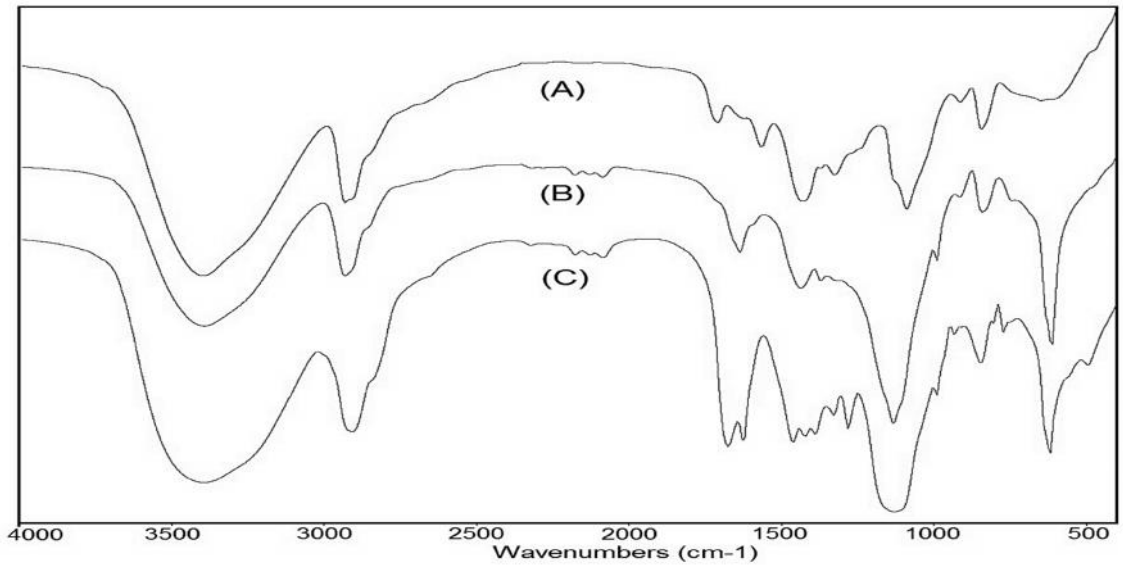



**Figure 1**. The FT-IR spectra of (A) pure PVA (B) PVA/ECH and (C) PNVP-g-PVA.

*Thermogravimetric analysis*

The DSC technique provides information such as glass transition ($T_g$), melting (Tm) and crystallization ($T_c$) temperatures. Figure 2 shows the DSC curves of PVA homopolymer and PNVP-g-PVAin the range of 20°C up to 300°C.The pure PVA (Figure 2-A) displays two endothermic peaks. The first peak at around 100°Ccan be attributed to the loss of absorbed water (moisture) which had the hydrogen bounded with the hydroxyl groups of PVA[28].A sharp endothermic melting transition at 218°C is assigned as Tmdue to the highly crystalline structure of PVA. According to Figure 2-B can be seen four characteristic properties of the PNVP-g-PVA. The first stage can be attributed

to the loss of absorbed water (moisture) which has not been removed in the precedent drying operation. In second stage, glass transition temperature ($T_g$) produced an endothermic peak at 151 °C. The third stage attributed to crystallization temperature ($T_c$=228 °C), which during this stage accrued. The broad peak at 228-293°C due to the degradation point of the grafted groups and followed by the degradation of the copolymer backbone.

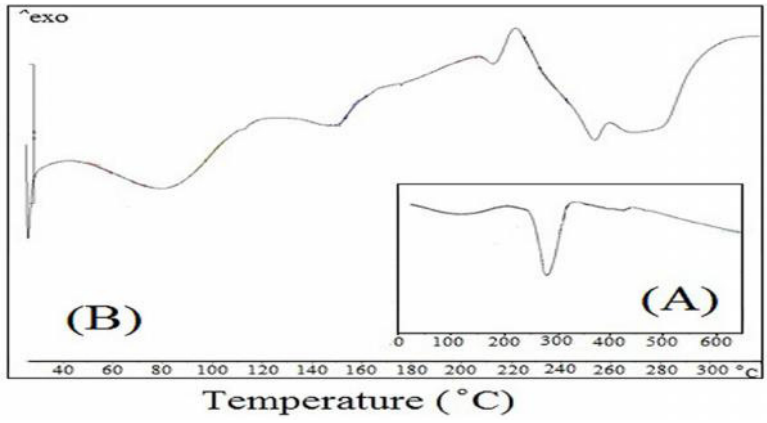



**Figure 2.** The DSC curves of (A) Pure PVA and (B) PNVP-g-PVA.

*Swelling studies*

The most important property of hydrogels is their swelling behavior. The swelling behavior of hydrogel sample in water was studied and the results are shown in Figure 3. The prepared hydrogel, PNVP-g-PVA attained the swelling ratio of 17 according to equation 1. This swelling ratio is related tothehigh interaction of water with hydrophilic part (OH and –CONH–) through hydrogen bonds, thereby leading to higher water uptake capacity.

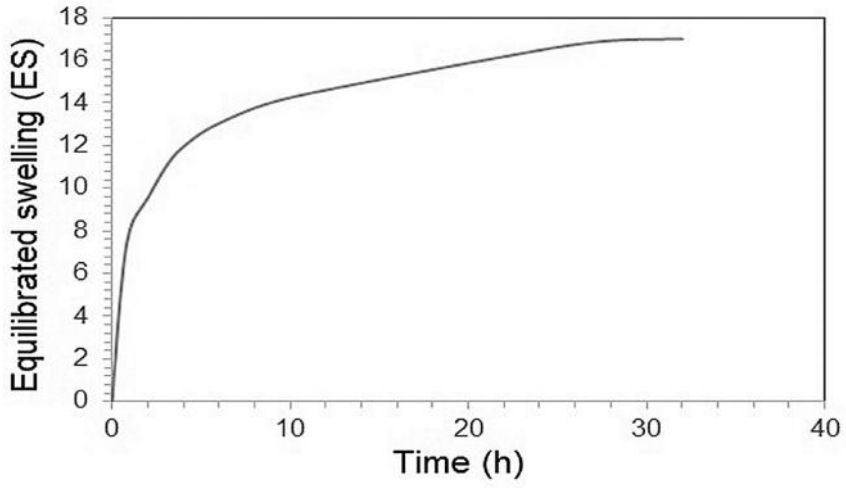



**Figure 3**. Swelling behavior of the PNVP-g-PVA.

*Loading and release behaviors of ceftriaxone from PNVP-g-PVA*

The LC is critical parameters for evaluating the capacity of a selected polymer to entrap the drug. The LC was determined by UV–vis measurements and was calculated 70% for PNVP-g-PVA. This amount of LC was obtained due to intermolecular hydrogen bond that can be formed between the active hydrogen atoms of hydrogel with amine, carbonyl, and carboxylic acid groups of Ceftriaxone and vice versa.

In order to simulate behavior of drug release in the different parts of the body, and evaluation of release behavior on pH of medium, the release of drug from drug loaded hydrogels were investigated in different solutions. The released profile was investigated and plotted in the carbonate buffer solutions at pH 3, 7, and 8 with the ceftriaxone antibiotic as a model drug. Figure 4 shows the drug release profiles form hydrogel. As can be seen, all of the curves show a 'burst' release in the first stage which is attributed to the drug molecules loaded at or near the surface of the particles, and then they are followed by a slower sustained release. The results showed, PNVP-g-PVA has been longer release time for drug at pH 7. This copolymer released total amount of drug within 44h at this pH. On the other hand PNVP-g-PVA released ceftriaxone drug within about 25h in pH= 3 and 8.The drug was released via diffusion through the hydrogel network, also, in acidic and basicmedia, the release was triggered by dissociation of the polymer chains through ionization of the hydroxyl groups of hydrogelwhich resulted in faster release of ceftriaxone in acidic and basic conditions.

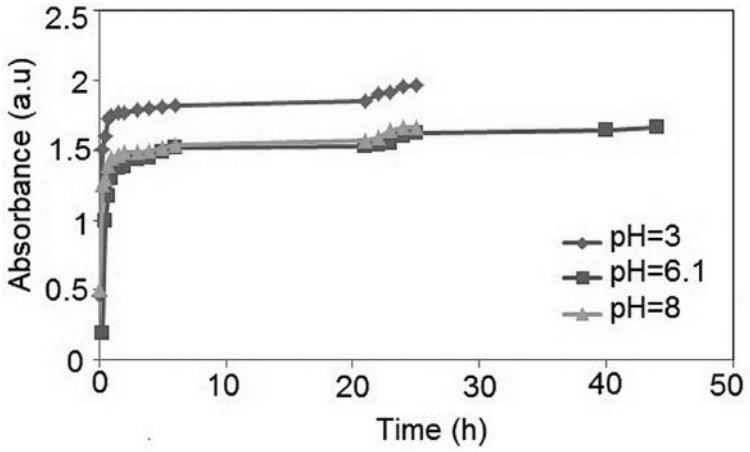



**Figure 4.** Drug release diagram for the PNVP-g-PVA.

## Conclusion

Polyvinyl alcohol was successfully functionalized by epichlorohydrin and then this macroinitiator graftedwithN-vinyl pyrrolidone utilizing the atom transfer radical polymerization (ATRP) technique. The

structure of this copolymer was confirmed by FT-IR andDSC. The swelling measurement of the prepared hydrogel in water showed appreciable swelling capacity.The synthesized hydrogel was investigated for in vitro drug release to reveal its potential use in drug delivery system. These results suggested that PNVP-g-PVAhydrogel would be beneficial for a drug carrier for pharmaceutical applications.

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