In-Vitro Release of Ketoprofen Behavior Loaded in Polyvinyl Alcohol / Acrylamide Hydrogels Prepared by Gamma Irradiation

Ghada A. Mahmoud, Dalia E. Hegazy and H. Kamal
National Center for Radiation Research and Technology (NCRRT), P.O. Box 29, Nasr City, Cairo, Egypt.

Received: 25/12/2013 Accepted: 15/1/2014

ABSTRACT

Hydrogels based on various ratios of polyvinyl alcohol (PVA) and acrylamide (AAm) were prepared by gamma radiation. The formed hydrogels were characterized by spectroscopic analysis (FTIR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and swelling studied. It was found that the thermal stability of the hydrogel decreases as the AAm content increases in the hydrogel. The higher the AAm content in the hydrogel, the lower the values of \( T_m \) and \( \Delta H_m \). Ketoprofen was adopted as a model drug to study the adsorption and release behavior of (PVA/AAm) hydrogel. The drug adsorption was decreased by increasing AAm ratio in the hydrogel. From the in vitro drug release study in pH progressive media, the basic medium was showed comparatively the highest release and the (PVA/AAm) hydrogel of composition (70/30) was found to be the highest release one. The mechanism of Ketoprofen release from the (PVA/AAm) matrix was found to be non-Fickian mechanism for all investigated hydrogels at pH 7.

KEY WORDS: hydrogel; Radiation; Ketoprofen; Drug release

INTRODUCTION

Hydrogels are a network of polymer chains that are water-insoluble. Over the decades, hydrogels have been invented for numerous pharmaceutical and biomedical applications (1,2). Hydrogels are inherently soft, hydrophilic, porous, and elastic polymeric systems. The use of polymer hydrogels as biopotential sorbent or carriers for the removal of the model molecules from aqueous solutions or controlled release studies of them has been continued to attract considerable attention in recent years (3-5).

PVA is an important water soluble polymer (1), it is biocompatible and non-toxic. It absorb water, swells easily and it has extensively been used in controlled release applications (6). Therefore, a number of methods have been reported for preparation of PVA hydrogels, including chemical methods using a covalent cross-linking agent (7,8), physical methods (9,10) and radiation methods using \( \gamma \)-radiation (11,12) electron beams (13), or ultraviolet light (14). Radiation polymerization is a useful method for producing hydrogels (15-17). It provides a very clean process, because no initiator and crosslinker need to be added to reaction media (18). Moreover, since the hydrogels are not contaminated with foreign additives, the pore size of hydrogels can be controlled by environmental conditions. AAm based hydrogels are widely used in the drug release systems (19,20). PVA/AAm hydrogels have good physical and mechanical properties in addition to their swelling and drug release capabilities (21).

Ketoprofen, 2-(3-benzoylphenyl)-propionic acid, is an analgesic, antipyretic and a non-steroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis, osteoarthritis and other chronic musculoskeletal conditions (22,23). Conventional dosage forms of this drug, administered orally, three or
four doses per day, have side effects such as peptic ulceration or bleeding and anorexia, and some additional side effects that limit its use. Controlled release of the drug is expected to significantly mitigate these side effects by targeting only the specific organs in the body. Diffusion in polymers is an important mechanism in pharmacy for the controlled release of drugs. Diffusion in polymeric systems is passive, if the driving force is purely a Brownian molecular motion, but diffusion can also be activated by external effects, either by the influence of the release medium by swelling or by the effects of physical forces as electrical, osmotic or convective forces.

In this study, PVA and AAm were chosen to make the hydrogel by gamma irradiation. The structural properties of the (PVA/AAM) hydrogels were characterized by different techniques such as FTIR spectroscopy, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). The swelling properties of the hydrogel were investigated. PVA based hydrogel was used as a drug delivery carriers. The drug delivery will be estimated using Ketoprofen as a model of drug. For this purpose, the effects of AAm content in the hydrogel, initial feed concentrations of drug and pH of medium on the release of Ketoprofen were studied.

MATERIALS AND METHODS

1. Materials

Poly(vinyl alcohol) (PVA; Mw 15,000) was purchased from Aldrich Co. and acrylamide (AAm), obtained from (Merck, Germany) were used as received. Ketoprofen (Sigma chemical Co., USA), structure of the drug is shown below. The other chemicals were reagent grade and used without further purification. The components of the citrate and phosphate buffers were reagent grade and purchased from El-Nasr Co. for Chemical Industries (Egypt) and used as purchased without further purification. Distilled water was used in all experiments.

Chemical structure of ketoprofen

2. Preparation of PVA/AAm Hydrogel

The PVA/AAm hydrogels were synthesized by the free radical polymerization. An aqueous solution of 10% PVA (w/v) was dissolved at 80 °C in water bath with constant stirring for 6 h. After cooling down to room temperature, various compositions of AAm were added to the solution, where, the total concentration was of 20% . The resulting solutions were transferred into the glass tube to irradiate by 60Co gamma source at room temperature with radiation dose 20 kGy. The dose rate of irradiation was 3.065 kGy h-1 after copolymerization, the vials were broken, the formed polymeric cylinder were removed and cut into discs of 2 mm thickness and 5 mm diameter. All samples were washed in excess water to remove the unreacted component then air dried at room temperature.

3. Swelling Measurements

The clean, dried, sample of preweight was soaked in bidistilled water at room temperature for different intervals time durations. The sample was removed and the excess water on the surface was removed by blotting quickly with filter paper and weighed. The swelling ratio was calculated as follows:-

\[
Swelling \ (% ) = \frac{W_s - W_d}{W_d} \times 100 \quad (1)
\]

Where \(W_d\) and \(W_s\) are the masses of dry and wet hydrogel, respectively.
4. Fourier Transform Infrared Spectroscopy (FTIR)

IR spectra of the investigated films were recorded over the range 400–4000 cm\(^{-1}\), using a Mattson 1000, Unicom infrared spectrophotometer (Cambridge, England).

5. Thermogravimetric Analysis (TGA)

Thermogravimetric analysis (TGA) was conducted on a Shimadzu TGA system, Type TGA-50, under nitrogen flow atmosphere of 20 ml/min to prevent thermal oxidation processes of polymer samples. The heating rate was 10\(^\circ\)C/min from ambient up to 500\(^\circ\)C.

6. Differential Scanning Calorimetry (DSC)

DSC measurements were performed using a Shimadzu DSC calorimeter (Kyoto, Japan) equipped with data station. A heating rate of 10 \(^\circ\)C/min was utilized and the scans were carried out under a flowing nitrogen gas at a rate of 20 mL/min.

7. Drug Loading to the Hydrogel

The loading of Ketoprofen drug onto PVA/AAm hydrogels were carried out by swelling equilibrium method. The hydrogels were allowed to swell in the drug solution of known concentration for 24 h at 37\(^\circ\)C and then dried at room temperature. The concentration of rejected solution was measured to calculate the percent entrapment of the drug in the polymer matrix using a Unicam, UV–Vis Spectrometer, Model 1000 at the wavelength 262 nm. The amount of adsorbate per unit mass of adsorbent (qe) was calculated as follows:

\[
q_e (mg/g) = \frac{C_i - C_e}{m}
\]

Where \(C_i\) and \(C_e\) are the initial and equilibrium concentrations of adsorbate solution in mg/ml.

8. In-Vitro Release Studies

In vitro release studies of the drug were performed by placing the pre-weighed hydrogels loaded with Ketoprofen drug in definite volume of releasing medium of buffer at pH 1.5 at 37\(^\circ\)C for 3 h and subsequently in buffer of pH 7 at 37 \(^\circ\)C for 24 h. One milliliter sample was withdrawn on time intervals to follow the release process. The concentration of Ketoprofen drugs was measured. After the complete release; the hydrogels were immersed in pH 3.0 buffer solution and then, 0.1mol/L, HCl for 2 days to remove the remaining drug which may be loaded in the gel system. The total uncertainly for all experiments ranged from 3 to 5%.

RESULTS AND DISCUSSION

The prepared PVA/AAm hydrogels using \(\gamma\)-radiation copolymerization technique as mentioned in the experimental part were then subjected to different characterization techniques; including FT-IR, TGA, DSC and swelling behaviors.

1. FT-IR Analysis

FT-IR spectra of PVA and (PVA/AAm) hydrogels are shown in Figure (1). A broad band appeared around 3348 cm\(^{-1}\) in both cases is attributed to the O-H stretching vibration of the hydroxyl group of PVA. A sharp band at 1094 cm\(^{-1}\) corresponds to the symmetrical stretching C-O-C (in acetyl group) present in the PVA backbone due to the unhydrolyzed acetate groups of poly (vinyl acetate). The asymmetric N-H stretching vibration of the primary amide overlaps with the stretching vibrations O-H.
The aliphatic C-H stretching vibrations appear at 2923 cm\(^{-1}\). A strong band at 1659 cm\(^{-1}\) was observed and can be attributed to the stretching carbonyl (C=O) groups in the carboxamide functional groups of the PVA/AAm hydrogel. The presence of strong bands at 1616 cm\(^{-1}\) corresponding to the asymmetric bending N-H groups\(^{(26, 27)}\). From FT-IR results, it can be concluded that the formation of PVA/AAm copolymer using ionizing radiation was occurred.

\[\text{Figure (1): FT-IR spectra of PVA and PVA/AAm hydrogels.}\]

2. Thermal Stability of the Prepared PVA/AAm Hydrogel

Thermogravimetric analysis (TGA) is considered as the most important method for studying the thermal stability of polymeric materials. It monitors the weight changes in a sample as a function of temperature. The relative thermal stability of the different hydrogels was assessed by comparing the weight change in the temperature range 0 – 600 °C and TGA data is shown in Figure (2) and presented in Table (1). Pure PVA hydrogel shows a stable thermogram up to temperature of 211°C, beyond which a smooth decrease in weight is observed. Whereas PVA/AAm hydrogel shows its famous four degradation steps which due to the loss of associated water, anhydride formation, decarboxylation and backbone degradation, respectively\(^{(28, 29)}\). It can also be noted that, the thermal stability of the prepared PVA/AAm hydrogel decreases as the AAm content increases in the hydrogel. The weight loss for PVA/AAm hydrogel is lower than that of pure PVA hydrogel as shown in Table (1). The copolymer hydrogel (PVA/AAm) of composition (70/30) possesses the highest thermal stability, which is almost similar to that of pure PVA. The analysis of the thermograms shows that the PVA/AAm hydrogels are relatively stable in the temperature range of 100–200 °C, and the degradation of hydrogel is controlled mainly by the composition of the hydrogel.
Table (1): Thermal parameters for PVA/AAm hydrogels at various compositions.

<table>
<thead>
<tr>
<th>PVA/AAm  (wt%)</th>
<th>T_{onset} (°C)</th>
<th>Char residue (%)</th>
<th>T_g (°C)</th>
<th>T_m (°C)</th>
<th>ΔH (J/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/0</td>
<td>211</td>
<td>4.6</td>
<td>79</td>
<td>225</td>
<td>49</td>
</tr>
<tr>
<td>70:30</td>
<td>210</td>
<td>9.3</td>
<td>91</td>
<td>210</td>
<td>45</td>
</tr>
<tr>
<td>50:50</td>
<td>201</td>
<td>10.3</td>
<td>94</td>
<td>206</td>
<td>30</td>
</tr>
<tr>
<td>30/70</td>
<td>200</td>
<td>11.6</td>
<td>99</td>
<td>204</td>
<td>22</td>
</tr>
</tbody>
</table>

* T_m is the Melting temperature
* T_g is the glass transition temperature
* ΔH is the melting enthalpy

Figure (2): TGA thermal diagrams of PVA/AAm hydrogels of various compositions.

3. Thermal Parameters

DSC thermal diagrams of various compositions of PVA/AAm hydrogels were made and shown in Figure (3). The thermal parameters of PVA/AAm hydrogels: T_m, T_g, and ΔH_m, were evaluated and shown in Table (1). Pure PVA hydrogel has exhibited an endothermic peak that corresponds to the T_m at 225 °C. Both T_m and ΔH_m decrease as the percentage of AAm increases in the gel. The higher the AAm content in the hydrogel, the lower the values of T_m and ΔH_m. The decrease in ΔH_m values of PVA/AAm hydrogels compared with the pure PVA can be attributed to the increase in
crosslinking network structure. In addition, the area under the melting peak decreases as the AAm content increases. This indicates a smaller fraction of crystalline phase and a larger fraction of amorphous phase, which may benefit anionic transition. The introducing of AAm into PVA caused changes in the morphological structure in which the crystallinity domains in (PVA/AAm) decreases due to the increase in crosslinking network formation that caused by radiation process. It is well known that, below $T_g$, molecules do not have segmental motion, and some portions of the molecules may not wiggle around, but may only be able to vibrate slightly. The $T_g$ of pure PVA is about 79; by the addition of AAm the $T_g$ is slightly increased. This increase in $T_g$ is due to the increase in crosslinking network structure which decreases the segmental motion and the mobility of the chains.

![DSC thermal diagrams](image)

**Figure (3):** DSC thermal diagrams of (a) PVA, PVA/AAm hydrogels of compositions; (b) 70/30, (c) 50/50 and (d) 30/70.

### 4. Swelling Studies

In order to evaluate the effect of PVA/AAm hydrogel network structure, the swelling behavior of various compositions of PVA/AAm hydrogel as a function of time were carried out and shown in Figure (4). It was found that the swelling capacity of the hydrogels increased with the decrease in AAm content in PVA/AAm hydrogel, i.e. increases PVA content in network structure. This may be due to the increase in crosslinking network structure of PVA/AAm hydrogel with increasing AAm contents in the polymer structure as explained by DSC. Actually the hydrogen bonding due to –OH groups of PVA tends to crystallize the PVA chains through physical cross-linking which due to steric hindrance of the bulky amide groups restricts the chains and decreases the crystallinity of PVA segments.

The effect of swelling medium on the swelling percent of PVA/AAm hydrogel was investigated and shown in Figure (5). The swelling of PVA/AAm hydrogel was carried out in distilled water, pH of 2 and pH of 7 buffers. It can be observed that nearly equal swelling has been observed in distilled water, pH 2 and pH 7 buffers.
Figure (4): Effect of time on the swelling percent of PVA/AAm hydrogels prepared at irradiation dose of 20 kGy at room temperature.

Figure (5): Effect of the swelling medium on the swelling percent of PVA/AAm hydrogels of composition (70/30) that prepared at irradiation dose of 20 kGy at room temperature.

5. Ketoprofen Uptake

Before the investigation of release experiment, the adsorption behavior of various compositions of the prepared PVA/AAm hydrogels towards ketoprofen was investigated. The
Hydrogels were swollen in ketoprofen solution of concentration 100 mg/L at pH 7. The amount of ketoprofen adsorbed into 0.1 gm of PVA/AAm hydrogel was measured and given in Figure (6). It can be seen that the uptake was decreased with increasing the AAm content in the hydrogel. The increase of AAm in the hydrogel results in increasing the crosslinking network structure as confirmed by DSC data. The swelling was found to be decreased by increasing the AAm content in the hydrogel which impedes the interior of ketoprofen drug into the gel.

![Figure (6): Effect of hydrogel composition on the ketoprofen uptake of initial concentration 200 mg/L hydrogels prepared at irradiation dose 20kGy.](image)

6. Release of Ketoprofen

6.1. Effect of pH

The in vitro release of ketoprofen from PVA/AAm hydrogel was investigated at various pH's of medium and shown in Figure (7). It can be seen that the drug release increases with the increase in pH of medium. At low pH, the release of such hydrogel decreases because there is a high H⁺ concentration then H-bond is formed and the migration of drug molecules becomes low. In this case the hydrogel can keep the solute because the texture structure becomes strong. Whatever, the acidic medium is not suitable for releasing process of the drug.
6.2. Effect of Time

Figure (8) shows the drug release behavior of various compositions of PVA/AAm hydrogels as a function of time at pH 7. It can be seen that the release from PVA/AAm hydrogel increases substantially with time up to 500 min and then tends to level off. The amount released depends upon the composition of the hydrogel in the polymer matrix. It was found that the release of ketoprofen increases as the PAAm content decreases in the hydrogel. This is possibly due to the formation of lightly cross-linked PVA/AAm hydrogel given that the cross-linking process in that case takes place between acrylamide and PVA which was confirmed by DSC. Also, increase the AAm content in PVA/AAm hydrogels decreased the swelling capacity; therefore, the diffusion and liberation rate of ketoprofen throughout the polymer matrix was decreased.

The mechanism of transporting the ketoprofen from PVA/AAm hydrogels was analyzed by the Fick’s law\(^ {31} \). The Fick’s law model is expressed as:

\[
F = \frac{W_t}{W_\infty} = k t^n \quad (3)
\]

\[
\ln F = \ln k + n \ln t \quad (4)
\]

where \( n \) is the swelling exponent; \( k \) is the swelling rate front factor; and \( W_t \) and \( W_\infty \) are the drug release by the hydrogel at time \( t \) and the equilibrium time, respectively. A double-log plot of the swelling ratio versus the time provides the value of \( n \), which determines the nature of the solvent diffusion process, that is, Fickian, non-Fickian diffusion kinetics or Super Case II models. When \( n \leq 0.5 \), the mechanism is Fickian type in which the sorption is diffusion controlled. When \( n = 1 \), relaxation control occurs, leading to zero-order release. When the value of \( n \) is between 0.5 and 1, the release follows non-Fickian diffusion, where the system will be diffusion and relaxation controlled. In \( F \) vs. \( \ln t \) graphs are plotted for ketoprofen release from various compositions and shown in Figure (9).
The diffusion exponents ($n$) and diffusion constants ($k$) are calculated from the slopes and intercepts of the lines, respectively, and listed in Table 2. The release of Ketoprofen at pH 7 showed the non-Fickian mechanism for all investigated hydrogels which means the rate of diffusion of drug from the polymer is comparable to rate of polymer chain relaxation. It can be said that, for higher swelling values of the hydrogels, the transport of drug into the hydrogel matrix where the lower polymer relaxation rate resulted in higher diffusion rate $(32)$.

**Figure (8):** Effect of time on the ketoprofen release from various compositions of PVA/AAm hydrogel at pH 7 and initial concentration 100 mg/L

**Figure (9):** Swelling kinetic curve of PVA/AAm hydrogels as $\ln F$ versus $\ln t$. 

37
Table 1: Kinetic parameters of ketoprofen release at various compositions of PVA/AAm hydrogels at pH 7

<table>
<thead>
<tr>
<th>PVA/AAm (%)</th>
<th>n</th>
<th>k</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/70</td>
<td>0.75</td>
<td>0.2853</td>
<td>0.9825</td>
</tr>
<tr>
<td>50/50</td>
<td>0.72</td>
<td>0.4210</td>
<td>0.9770</td>
</tr>
<tr>
<td>70/30</td>
<td>0.76</td>
<td>0.4291</td>
<td>0.9862</td>
</tr>
</tbody>
</table>

6.3. Effect of Feed Concentration

The effect of initial drug concentration on the drug release was investigated and shown in Figure (10). The increase in the initial drug concentration from 50 to 200 mg/L in the swelling medium leads to increase the amount of release of drug. The reason for such result was attributed to the specific bonding of positively charged drug with partially ionized groups of the hydrogel, and the higher free volume available for diffusion.

![Figure (10): Effect of ketoprofen concentration on the release from PVA/AAm (70/30) hydrogel at pH 7.](image)

CONCLUSION

In this study, various compositions of PVA/AAm hydrogel of total concentration 20% was prepared by gamma radiation at irradiation dose of 20 kGy. The thermal stability and swelling percent of the prepared hydrogel decreased as the AAm content increased in the hydrogel. Both \( T_m \) and \( \Delta H_m \) decreased as the percentage of AAm increased in the gel and the PVA/AAm hydrogel of composition (70/30) possesses the highest thermal stability. The release of ketoprofen drug from the PVA/AAm hydrogel was studied and showed that the release of ketoprofen increased as the PAAm content
decreased in the hydrogel. The release of ketoprofen followed a non-Fickian type and the acidic medium is not suitable for releasing process of the drug. The increase in the initial drug concentration leads to increase the amount of ketoprofen releasing. It is suggested that such prepared hydrogel is of practical interest in the field of drug delivery system under control release as it possessed that pH stimuli-responsive character.

REFERENCES

(10) C.M. Hassan, N.A. Peppas, Structure and applications of poly(vinyl alcohol) hydrogels produced by conventional crosslinking or by freezing/thawing methods, Advances in polymer science, 153 (2000) 38.


