

RADIATION-INDUCED CROSSLINKING OF POLY(VINYL ALCOHOL)-POLYETHYLENE GLYCOL COMPLEXES FOR APPLICATION AS HYDROGEL WOUND DRESSINGS

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Abstract

Impact of pulsed electron beam irradiation conditions and component composition on physical properties of radiation crosslinked hydrogels based on poly(vinyl alcohol)-polyethylene glycol (PVA-PEG) complex has been investigated in terms of wound dressing applications. A significant influence of electron beam density and sample temperature during irradiation on crosslinking processes has been obtained experimentally. Results have been analyzed using the term «optimal crosslinking dose» D_{oc} , which is more convenient to use if it necessary to evaluate hydrogel crosslinking quality as wound dressings. Thus, essential dependencies D_{oc} on the sample temperature, electron beam density (dose rate) and PVA/PEG mass fraction have been explored.

Keywords: radiation crosslinking, hydrogel wound dressing, poly(vinyl alcohol), polyethylene glycol, optimal crosslinking dose.

Introduction

Prospects of using radiation crosslinked hydrogels as bandages for sores and burns treatment are widely known and discussed in particular in the authors earlier paper [1]. For medical purposes are relevant physical, chemical and biological properties such as:

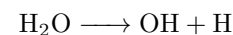
- high water content – for efficient pain relief by cooling the wound, creating a moist environment at the wound surface and for adhesion prevention;
- great absorption ability – for sorption and further removal of wound physiological secretions;
- proper water solutions and oxygen diffusion rate – for drug delivery from an outer surface of dressing;
- extreme sterility;
- impermeability to microorganisms;
- non-toxicity and biological compatibility;
- nice mechanical strength and elasticity – to cover the wound comfortably in extreme conditions.

All these conditions can be satisfied by correct selection of polymer composition, irradiation conditions and dose. This factors will be discussed in the present paper.

1. Crosslinking process

Radiation crosslinking occurs as a result of interaction of radical (which is part of one polymer macromolecule) with an atom of other macromolecule. Ionizing radiation creates radicals in hydrated polymer systems by two main mechanisms:

- 1) direct interaction of high-energy particles with polymer macromolecule atoms and resulting ionization;
- 2) radiation interaction with water molecules, which leads to radiolysis, ionization and dissociation into free (movable) radicals. Mainly it is



Movable radicals chemically interact with the polymer, creating bonds in its structure [2]. For example, the hydroxyl group OH can capture hydrogen atom H from the C–H polymer bond to form a water molecule H_2O , leaving carbon atom dangling bond in the polymer chain. Created by this mechanism radicals form crosslinks with other areas of same polymer macromolecule or with other macromolecules.

In hydrogels that have been studied number of water molecules is one order of magnitude greater than number of all other molecules. Therefore H_2O molecules are the main absorber of high-energy radiation. Hence, the second mechanism of polymer crosslinking should be considered as major.

Some of the hydrogen atoms formed in the process of water radiolysis combine in H_2 molecules, forming gas bubbles 0.2 – 2.0 mm scale in samples volume. Their size and concentration correlate with irradiation dose.

2. Materials and methods

Poly(vinyl alcohol) (average value of the dynamic viscosity of a 4% solution = 8000 Pa·s; average value of the acetate groups content = 1%) as base polymer and polyethylene glycol (average molar mass = 6000 g/mol) as auxiliary polymer have been used for aqueous solutions preparation. After production of solution with

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desirable polymer mass fraction it has been packed and sealed into polyethylene bags. Then bags have been placed between two coupled thin metal plates which provide formation of the homogeneous layer of solution (2 – 3 mm thick) in a flexible package. In this case plane of the plates and sample is perpendicular to the electron beam generated by linear electron accelerator which works in impulse mode. The electron accelerator that provides $E_e = 4 \text{ MeV}$ particle energy, $4 \mu\text{s}$ pulse duration and 4 ms pulse period has been used.

The dose values given in this work are obviously inflated in comparison, for example, with paper [3] because of usage of metal plates for sample fixation. An electron beam has high enough energy to pass through the plate, but the equivalent crosslinking dose is much greater in this case. In conditions of direct irradiation, it is real to obtain an order of magnitude smaller dose values.

Monitoring of the current density in the electron beam and integral irradiation dose was performed by Faraday cylinder method. Hydrogel temperature measurement during irradiation has been carried out using differential thermocouple Chromel/Alumel.

3. Results and discussion

3.1. «Optimal crosslinking dose» term and its dependence on the component composition of polymer system

Tensile strength and elongation at break are ones of the most important hydrogel characteristics, as it has been mentioned. Experimental data obtained by different research groups indicates the presence of non-monotonic dependence between hydrogel mechanical parameters and irradiation dose [1, 3, 4, 5]. According to these researches, for each polymer system configuration there is a certain dose interval wherein samples mechanical characteristics reach a peak. Therefore, in our opinion, in the context of hydrogels application as wound dressings, it is more convenient to define the term «optimal crosslinking dose» – one of the dose values at which the peak of mechanical properties is reached – instead of making radiation chemical yield calculations, gel fraction or gelation dose measurement. Usually length of the optimal doses interval is 3 – 5 kGy, so usage of such parameter is fairly accurate. Furthermore, considering that

- in case of insufficient irradiation dose – sample sticks to the package, smears and it is not able to maintain its shape under the little pressure;
- in case of abundant irradiation dose – sample strengthens, starts to give off the water and pulls back from the package surface (presumably, the accumulation of radiation induced crosslinks constricts formed 3D structure insomuch that hydrogel is not able to hold off a whole volume of the solvent [6]);

transition point between two of this states is clearly noticeable without any measurements, and it is the same dose point at which peak of hydrogel mechanical properties is reached.

It is clear that for different polymer systems and even for different component mass fractions optimal crosslinking dose should be different.

Dependence of the gelation dose of the polymer concentration (curve shapes) from papers [2, 7] is evidence of the fact that optimal crosslinking dose is quite correct value for experiment preforming: optimal crosslinking dose D_{oc} dependence of PVA mass fraction displayed the same curve shape (Fig. 1).

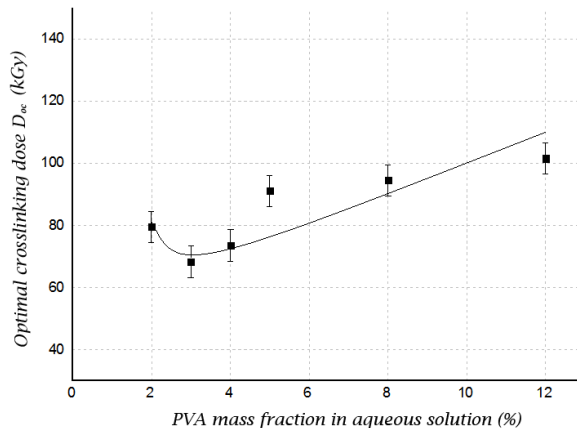


Fig. 1. Optimal crosslinking dose as a function of PVA mass fraction in aqueous solution (experiment carried out at the constant dose rate $J = 0.35 \frac{\mu\text{A}}{\text{cm}^2}$)

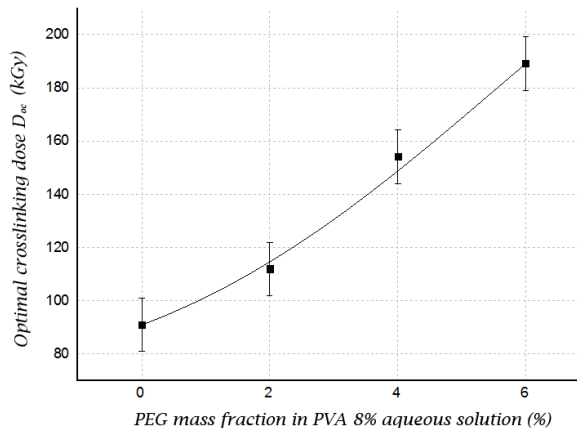


Fig. 2. Optimal crosslinking dose as a function of PEG mass fraction in PVA 8% aqueous solution (experiment carried out at the constant dose rate $J = 0.35 \frac{\mu\text{A}}{\text{cm}^2}$)

Thus, optimal crosslinking dose noticeably depends on the polymer mass fraction. For high PVA mass fraction because of high solution viscosity intermolecular crosslinking prevails and because of low macroradicals mobility there are relatively high D_{oc} values. This values can be reduced by mass fraction decrease, i.e. by macroradicals mobility increasing. Upon further mass fraction reducing number of radiation-produced solvent radicals increases, however probability of ineffective intramolecular combination increases as well [7].

For the auxiliary polymer – PEG – $D_{oc}(\text{massfraction})$ dependence has a form as shown on Fig. 2.

It is clear that the PEG addition in base solution causes optimal crosslinking dose escalation. Bearing in mind Fig. 1 this result was anticipated.

Nevertheless, the presence of PEG in solution at low PEG/PVA ratios leads to considerable tensile strength and elongation at break increasing. Apparently occurs PEG-PVA network formation which overlaps with PVA-PVA network.

3.2. Optimal crosslinking dose dependence on the dose rate

It was found that for each hydrogel composition optimal crosslinking dose depends on the electron beam density (dose rate). In particular, Fig. 3 shows the dependence of this parameter for the two hydrogel types.

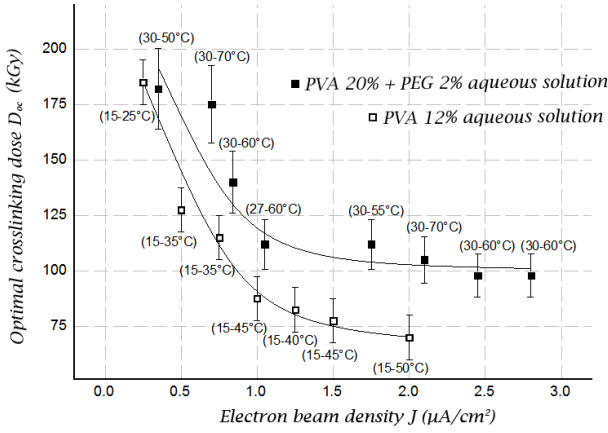


Fig. 3. Optimal crosslinking dose as a function of integral (average over 1 second) pulsed electron beam density (dose rate). Pulse duration = 4 μs . Initial and final samples temperature displayed next to each data point

Optimal crosslinking dose reduction by half is seen for two polymer compositions at about the same initial samples temperature. This means that creation of approximately equal crosslinks number at high dose rate requires twice less electron irradiation than at low dose rate. In other words, radiation crosslinking efficiency is directly proportional to the dose rate.

This can be explained as follows: increasing electron beam density (dose rate) leads to a higher average concentration of intermediate products (radicals), and thus leads to increasing the number of reactions in which they take parts. In the case of pulsed irradiation this may be related to the ratio between the radicals lifetime and impulses/intervals between impulses duration (Fig. 4).

Number of crosslinks is proportional to stationary concentration of radicals R_{st} which sets up as result of radicals formation and recombination (or passivation,

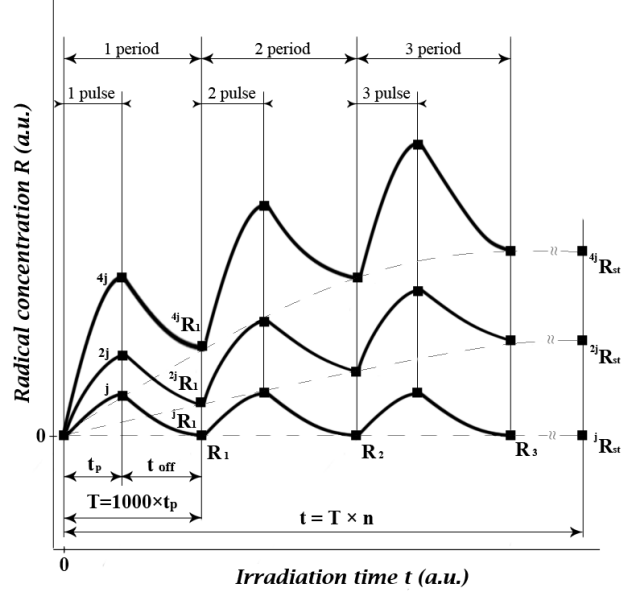


Fig. 4. Radical concentration R in polymer solution during the first three periods of pulsed electron irradiation with beam density = J , $2J$ and $4J$. Pulse duration t_p , interval between pulses t_{off}

including formation of crosslinks) processes equilibrium. In the absence of passivation additives in the investigated doses interval we may assume that all radicals are used for the crosslinks formation.

During the electron pulse t_p (in experiment $t_p=4\mu\text{s}$) occurs radical formation with speed λ_R and its extinction as a result of crosslinks formation. Radicals accumulation process time constant denoted as τ_1 . Exponential decrease of radicals concentration R (as result of crosslinks formation) occurs in a time between pulses $t_{off} \approx 1000 t_p$. Radicals reduction process time constant (i.e. radicals lifetime) denoted as τ_2 . As a result, the R time dependence has a saw-like shape (Fig. 4).

One can see that in case of $\tau_2 \ll t_{off}$ and low pulse density J radicals concentration R may drop to 0 before the start of next pulse. In case of increasing pulse density (with the same value τ_2) to $2J$ or $4J$ residual concentration of radicals which did not recombine before the next pulse is rising: ${}^J R_1 < {}^{2J} R_1 < {}^{4J} R_1$. So, during further pulses residual concentration of radicals (for $2J$ and $4J$) increases. The minimal radicals concentration for the period (dashed line in Fig. 4) increases faster at higher density. Eventually, stationary concentration R_{st} is established, and it is proportional to the pulsed beam density (dose rate).

Radiation crosslinking process can be represented as formation of a couple: radical which is part of a polymer molecule with another molecule atom. Then the kinetics of crosslinks accumulation can be written as:

$$\begin{cases} \frac{dR}{dt} = \lambda_R - \chi_{Rx} \cdot R \cdot N_x \\ \frac{dZ}{dt} = \chi_{Rx} \cdot R \cdot N_x \end{cases} \quad (1)$$

where:

N_x – stands for concentration of such atoms,
 R – for radicals concentration,

Z – for crosslinks concentration,
 λ_R – for radicals generation rate,
 χ_{Rx} – for cross section of interaction between radicals and polymer atoms.

The initial radicals accumulation rate $\frac{dR}{dt}|_{t \rightarrow 0}$ depends on the radiation intensity (dose rate). Over the time radicals concentration stationary value R_{st} is setting up as a result of the generation and passivation processes balance during crosslinks formation. R_{st} value correlates with the pulsed beam density as well. R stationarity means: $\frac{dR}{dt} = 0$, so first equation of system (1) turns into:

$$\chi_{Rx} \cdot R_{st} \cdot N_x = \lambda_R \quad (2)$$

Substituting it in the second equation of system (1) we obtain:

$$\frac{dZ}{dt} = \lambda_R \quad (3)$$

The solution of this equation is an expression:

$$Z(t) = \lambda_R \cdot t \quad (4)$$

That means that crosslinks accumulation occurs proportionally to irradiation time and therefore to irradiation dose.

Considering that

$$\frac{dZ}{dD} = \frac{1}{J} \cdot \frac{dZ}{dt} \quad (5)$$

where:

D – absorbed dose,

$J = \frac{dD}{dt}$ – pulsed beam density (dose rate),

we obtain:

$$\frac{dZ}{dD} = \frac{\lambda_R}{J} \quad (6)$$

However $\lambda_R \sim J$ by definition. Therefore, crosslinks formation efficiency $\frac{dZ}{dD}$ should not depend on the radiation intensity. As well as inversely proportional to it optimal crosslinking dose $D_{oc} \sim \frac{dD}{dZ}$.

However, finally, approximation of the experimental data showed at Fig. 3 provides dependence $D_{oc} \sim \frac{1}{J}$, which means $\frac{dZ}{dD} \sim J$, which means that crosslinking efficiency is still proportional to the radiation intensity (pulsed beam density or dose rate).

3.3. Optimal crosslinking dose dependence on the initial samples temperature

Crosslinking efficiency dependence on the initial samples temperature has been investigated. Fig. 5 illustrates experimental dependence of the optimal crosslinking dose on the samples temperature. A significant D_{oc} decrease with temperature decreasing is evident. Under considered $k_B T$ change (from high to low values) a considerable increase of gel viscosity occurs, which means dipole interaction between the polymer macromolecules impact enhancing. Dipole interaction leads to distance decrease and spatial location structuring between macromolecules. In our opinion, this could substantially increase the probability of intermolecular and intramolecular crosslinks establishing and therefore – to be the cause of D_{oc} reduction.

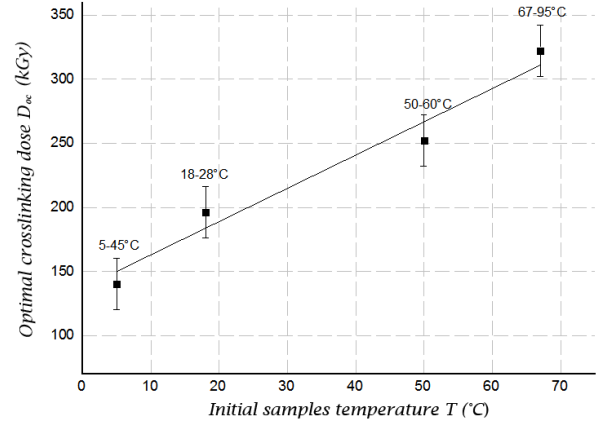


Fig. 5. Optimal crosslinking dose as a function of initial samples temperature (experiment carried out at the constant dose rate $J = 0.35 \frac{\mu A}{cm^2}$)

Initial and final samples temperature are displayed at Fig. 3 next to each data point because of the fact that in case of high electron beam density values ($J > 1.5 \frac{\mu A}{cm^2}$) occurs matter-of-course sample heating. And because of the fact that crosslinking efficiency is in direct ratio to the dose rate and in inverse ratio to the sample temperature, gradual $D_{oc}(J)$ dependencies turn to a constant value may be described as this two factors rivalry.

Conclusions

Aforementioned experiments demonstrated significant dose rate, samples temperature and polymer mass fraction influence on the crosslinking efficiency. This dependencies may be used to optimize hydrogel wound dressings manufacturing.

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