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Analysis of the swelling kinetic in hydrogels gelled by radiation and by thermal cycling

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ABSTRACT

Hydrogels are cross-linked polymer networks, which are of interest in biomedical applications such as drug delivery system. To achieve successful results in this kind of application it is essential to understand the diffusion mechanisms which are generated in the hydrogel during the swelling process. For this reason, this work consists in carrying out an analysis of the swelling kinetics in hydrogels elaborated through gamma radiation and the combination of gamma radiation with thermal cycling processes. The hydrogels were synthesized using biocompatible polymers irradiating their solution at different doses. A swelling test was performed and the diffusion coefficient and the diffusional exponent were calculated, making an analysis of the kind of diffusion mechanism in the hydrogel matrix. This test showed that the higher radiation absorbed used to get the gels, the lower the swelling percentage, as well as the diffusion coefficient of the water molecules in the hydrogel. The results of the kinetic analysis showed an anomalous diffusion mechanism for the gels obtained at 25 kGy. For those gels of 30 kGy, the diffusion was Fickian. Finally since those gels of 35 kGy was not possible to classify it according to the Fick's law of diffusion. Furthermore, we could observe that the hydrogels that had been obtained by thermal cycling and by irradiation had higher swelling percentages compared to those that were only cross-linked by irradiation. This analysis allowed us to understand the intrinsic behavior of the polymer / solvent mesh system at different doses and under two different crosslinking conditions.

Keywords: **hydrogel, radiation, thermal cycling, swelling, crosslinking.**

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1. INTRODUCTION

Hydrogels are described as cross-linked polymer networks that constitute three-dimensional structures able to modify their volume in the presence of water due to capillary forces phenomena, osmosis and molecular interactions between the polymer and the solvent [1]. In general, hydrogels have mechanical properties similar to elastomeric materials, however under certain temperatures they express viscoelastic characteristics [2].These materials have excellent biocompatibility properties, for this reason they are of great interest in biomedical applications such as in the construction of contact lenses, scaffolds for cell growth, wounds dressings and drugs delivery [3].

According to the nature of the chemical bonds that make up the network, the hydrogels can be classified as physical or chemical gels. The first have weak bonds such as hydrogen bonds, Van der Waals forces or ionic interaction, and they are reversible when they subjected to high temperatures [4]. The chemical hydrogels consist of strong covalent bonds whose rupture leads to the degradation of the gel, they are non-reversible. The physical gels are elaborated by the freezing/heating process while the chemical gels are generated by ionic initiators, ultraviolet light, redox systems or by ionizing radiation [1, 5].

One of the mentioned applications with great potential and progress in recent years is the use of hydrogels for drugs delivery whose release is the result of a diffusion mechanism governed by the swelling that occurs in the polymeric material [6]. This process involves two actions that happen simultaneously, one of which is the absorption of water or biological fluid by the polymer matrix and the other is the drug release. When the water enters the hydrophilic matrix, the hydrogel in the vitreous state swells and its glass transition temperature can reach values lower than the surrounding medium temperature. In this way, the gel passes to an elastomeric state in which a relaxation of its polymer chains occurs which generates a network expansion [6, 7]. In this condition, the solute diffuses outwards and the process will be controlled by the diffusion coefficient of the water and the active ingredient in the hydrogel, the swelling percentage and the gel mesh size and the relaxation rate of the polymeric chains [8]. Therefore, it is of fundamental importance to understand the diffusion mechanism that is generated in the hydrogel during the swelling process as well as to evaluate the modifications that the cross-linking can generate in the process.

The kinetics of release of the active principle has been analyzed by several models that are based on the solve of the Fick's diffusion equation [9].The mathematical theory of this equation for isotropic substances is based on the fact that the mass transfer velocity that diffuses through area unit of a section is proportional to the concentration gradient that is measured normal to said section.

In 1986 Peppas and Ritger introduced a simple exponential equation as expressed in Equation 1 that describes the diffusion mechanism of a polymeric system taking into account the geometry of the device, which can be flat, cylindrical or spherical and also consider the possible non-uniformity in the size of the solute [10]. Currently this equation is widely used in the kinetic analysis of the drugs delivery in polymeric matrices as well as in the study of the swelling mechanisms of hydrogels [9, 11, 12].

$$Ms = Kt^n \tag{1}$$

Where n is the diffusional exponent, k is a constant that depends on the diffusion coefficient and the material thickness, t is the time and Ms is equivalent to $H\ (i)$ shown in the following Equation 2 that is calculated according to the swelling equation in function of time, where i is the amount of data acquired.

$$H(i) = ((w(i)-w0)/w0)*100= Kt^n \tag{2}$$

Here, $w\ (i)$ is the weight increased at one time t_i and $w0$ is the weight of the xerogel (dehydrated hydrogel).

Equation 2 is applied to the natural logarithm and Equation 3 is obtained, which corresponds to the equation of a straight line.

$$ln(H(i)) = ln(k)+ (n*ln(t)) \tag{3}$$

The diffusional exponent n is obtained as the curve slope of ln $(H\ (i))$ as a function of $ln\ (t(i))$.

The analysis of the diffusional exponent for a planar geometry allows us to evaluate the kind of diffusion mechanisms that are representative in hydrogels [13].

• Fickian diffusion (FD): it is the most common kind of diffusion that follows Fick's law; in this case the diffusion rate is much lower than the relaxation of the gel matrix. In this kind of mechanism the diffusional exponent takes the value of 0.5 [11].

• Case II diffusion (CII): it is also called Diffusion; here the transport mechanism is controlled only by the diffusion which is faster in comparison with the relaxation processes of the polymeric network. The diffusional exponent obtained when the system presents this kind of diffusion is 1 [13].

• Non-Fickian diffusion (DNF): this kind of diffusion also called anomalous arises from the simultaneous and comparable contribution of the diffusion phenomenon of the bioactive agent molecules and the relaxation of the polymer chains. The value of the diffusional exponent is between 0.5 and 1 [12].

In this work we carried out a swelling test in hydrogels of polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA) cross-linked with gamma radiation and thermal cycling process in order to evaluate and compare the diffusion kinetics of the water molecules in the hydrogels matrix with the aim of understanding the transport mechanisms that are generated during the swelling process for a future application in drugs delivery.

2. MATERIALS AND METHODS

PVP k90 polymers (Mw 1000-1500 kDa) of Solkem and 99% hydrolyzed PVA (Mw 70-1000kDa) of Sigma Aldrich were used. A polymeric solution was prepared by using 5 g of PVA and 5 g PVP per 100 ml of deionized water at 90 °C with stirring for 2 hours. The solution was placed in the molds inside multilaminated bags. Subsequently, half of the solution was subjected to a thermal cycling process of 24 hours freezing at -20 ºC +/- 1 ºC and 24 hours of heating at room temperature. Then, all the samples were irradiated for Co-60 plant at three different radiation absorbed doses: 25 kGy, 30 kGy and 35 kGy and with a dose rate of 7.5 $kGyh^{-1}$.

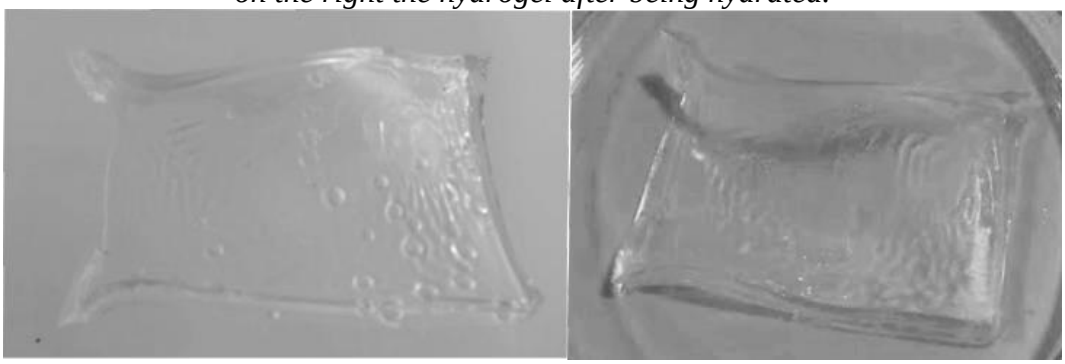
The resulting hydrogels were evaluated by a swelling test according to ASTM 570. In this test, the hydrogels were taken to xerogel in an oven (Lindberg-B-242424-EG model) at 50 ° C for 24 hours. Then, the samples were placed in a container with sterile distilled water and weight measurements

were made each 30 min in the first hour, then each 8 hour until 48 hours at 25 °C. With the obtained data, the swelling percentage, the diffusion coefficient and the diffusional exponent were calculated. The diffusion coefficient was calculated as the slope of the first segment of the increased weight curve of the hydrogels as a function of the square time root specified in the same standard under which the swelling test is performed.

3. RESULTS

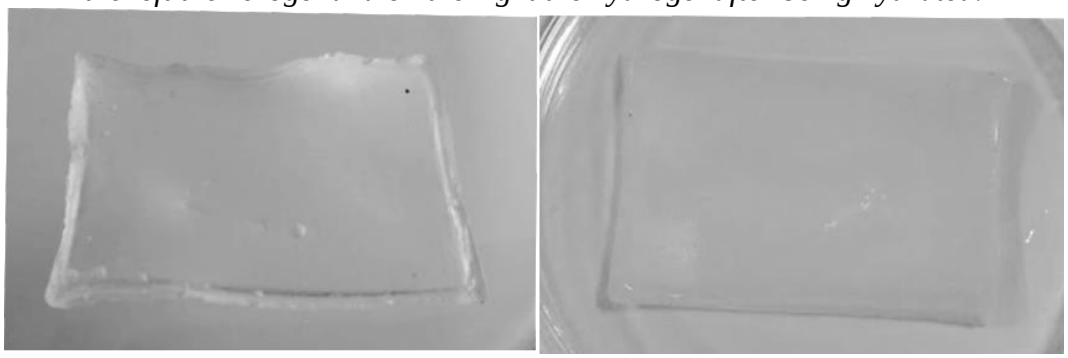
For each irradiation dose, four hydrogels were produced which were obtained only by gamma radiation (R) and another four were obtained by the combination of thermal cycling and radiation (TR). In Figure 1 the R xerogel is shown on the left and the same gel hydrated after 48 hours on the right.

Figure 1: *Hydrogels cross-linked only with gamma radiation at 35 kGy. On the left the xerogel and on the right the hydrogel after being hydrated.*



While in Figure 2 the xerogel TR is seen to the left and to the right the same swollen hydrogel after 48 hours.

Figure 2: *Hydrogels cross-linked only with thermal cycling and gamma radiation at 35 kGy. On the left the xerogel and on the right the hydrogel after being hydrated.*

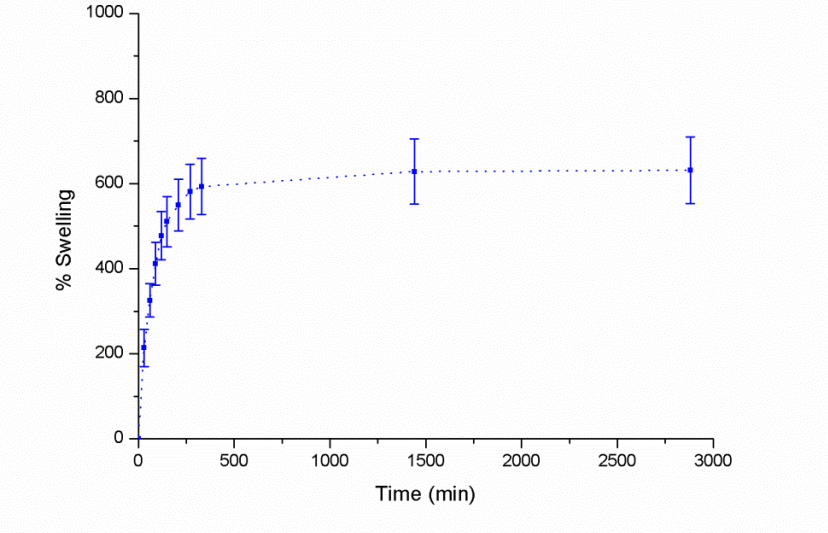


Below are the results of the swelling test.

3.1. Swelling of irradiated hydrogels at 25 kGy

The Figure 3 shows the swelling percentage of the R hydrogels as a function of time. At 48 hours equivalent to 2880 min the hydrogel reaches a swelling of 631.46% +/- 78.57%.

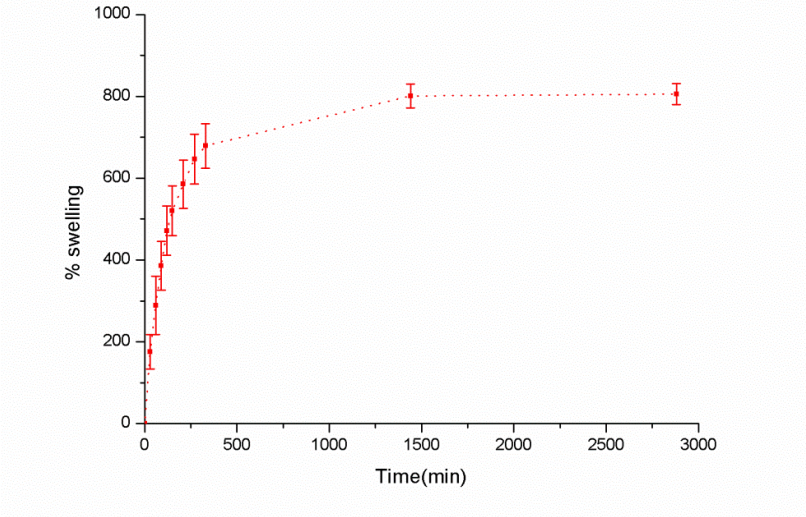
Figure 3: *Swelling percentage of the R hydrogels at 25 kGy.*



The diffusion coefficient obtained was 0.41 +/- 0.023 and the diffusional exponent was 0.60.

The Figure 4 shows the swelling percentage of the TR hydrogels as a function of time. In this case, the swelling percentage at 48 hours resulted in 805.00 % +/- 25.99 %, the diffusion coefficient obtained was 0.43 +/- 0.028 and the diffusional exponent was 0.71.

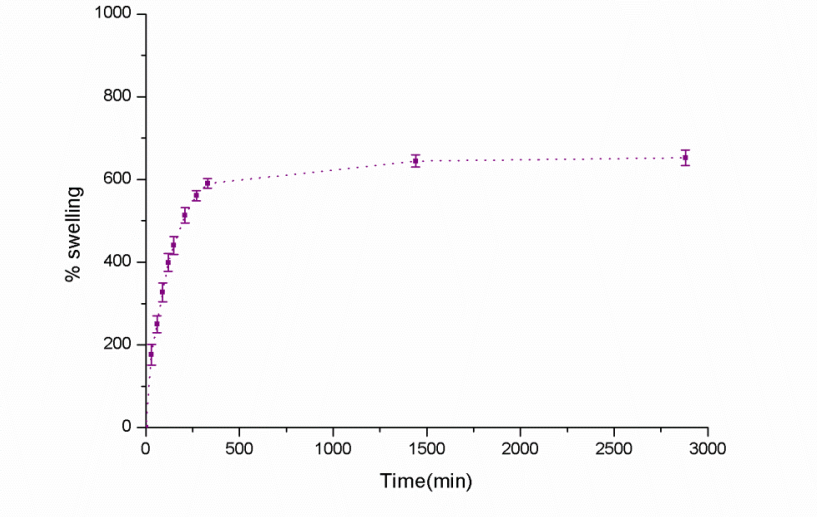
Figure 4: *Swelling percentage of the TR hydrogels at 25 kGy.*



3.2. Swelling of irradiated hydrogels at 30 kGy

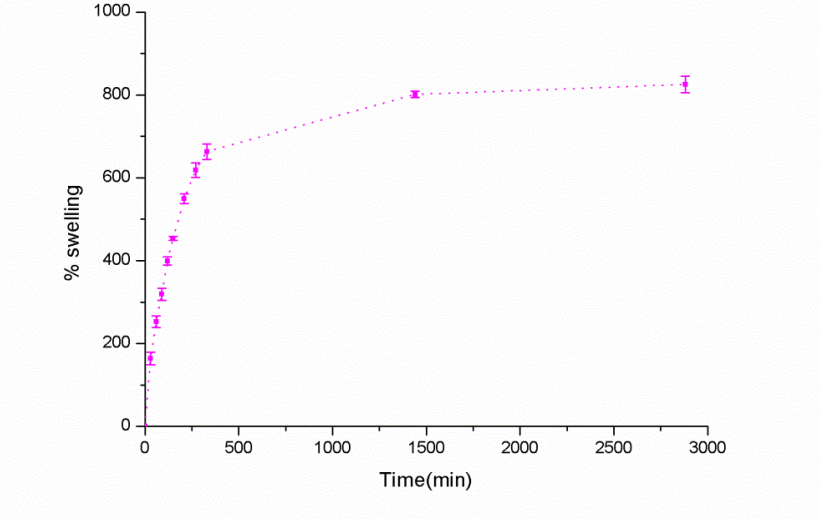
The Figure 5 shows the swelling percentage of the R hydrogels as a function of time. The swelling at 48 hours was 652.46% +/- 18.69%, the diffusion coefficient obtained was 0.32 +/- 0.0015 and the diffusional exponent was 0.50.

Figure 5: *Swelling percentage of the R hydrogels at 30 kGy.*



The Figure 6 shows the swelling percentage of the TR hydrogels as a function of time. At 48 hours the swelling obtained was 825.26% +/- 19.62%. The diffusion coefficient was 0.33 +/- 0.016 and the diffusional exponent obtained was 0.60.

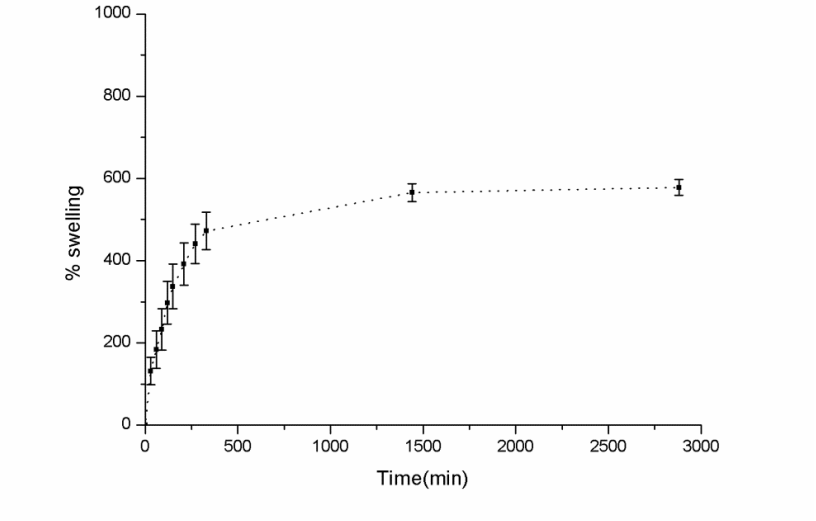
Figure 6: *Swelling percentage of the TR hydrogels at 30 kGy.*



3.3. Swelling of irradiated hydrogels at 35 kGy

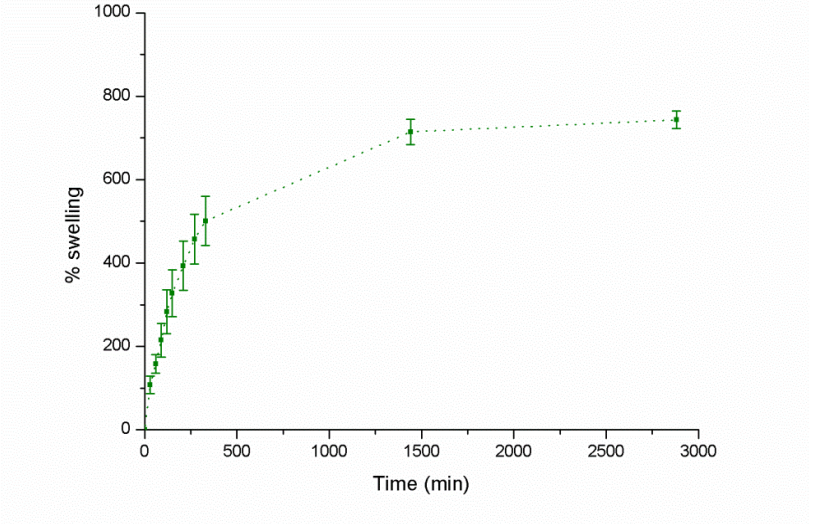
The Figure 7 shows the swelling percentage of the R hydrogels as a function of time. At 48 hours the saturation percentage was 578.16% +/- 19.24%, the diffusion coefficient was 0.24 + - / 0.0047 while the diffusional exponent was 0.47.

Figure 7: *Swelling percentage of the R hydrogels at 35 kGy.*



The Figure 8 shows the swelling percentage of the TR hydrogels as a function of time. The swelling reached at 48 hours was 743.50% +/- 20.98%, the calculated diffusion coefficient was 0.27 +/- 0.020 and the diffusional exponent was 0.49.

Figure 8: *Swelling percentage of the TR hydrogels at 35 kGy.*



For comparative purposes, the data obtained in the swelling tests were shown in the following Table 1 in such a way that the results can be visualized with greater clarity.

Table 1: Results obtained in the swelling test

	Swelling test parameters							
Dose (kGy)	**%S-TR**	**D-TR**	**n-TR**	**DM-TR**	**%S-R**	**D-R**	**n-R**	**DM-R**
25	805	0.43	0.71	DNF	631.46	0.41	0.60	DNF
30	825.26	0.33	0.61	DNF	652.42	0.32	0.50	FD
35	743.50	0.27	0.49	-	578.16	0.24	0.47	NA

%S: Swelling percentage, D: Diffusion coefficient, n: Diffusional exponent, DM: Diffusion Mechanism, NA: non-apply, DF : Fickian diffusion, DNF: Non-Fickian diffusion.

The swelling percentage of cross-linked TR hydrogels at 25 kGy and 30 kGy present a difference of less than 2.5 %, however at 35 kGy the reduction in swelling becomes greater, reaching 9.90 % compared to those obtained at 30 kGy.

In the case of the R, the swelling percentage of the irradiated hydrogels at 25 kGy and 30 kGy present a difference of less than 3.5 %. While at 35 kGy the swelling is reduced by 11.4 % compared to those obtained at 30 kGy. It is evident that in both cases TR and R the increase of the dose to 35 kGy reduced the swelling percentage of the gels, this may be possible due to the fact that the increase in the energy absorbed during the synthesis process of the hydrogels induced to the formation of covalent bonds that contribute to reduce the free volume of the polymer mesh with the subsequent decrease in absorption capacity. The swelling of the TR hydrogels exceeds by 21.5 % +/- 0.64 % the swelling of the R hydrogels, this may be possible because the TR hydrogels have hydrogen bonding bonds that were generated during the temperature cycle and that have the ability to promote water retention since they allow the exposure of the hydrophilic functional groups present mainly in the PVA [12, 14].

The results of the diffusion coefficient indicate that as the radiation absorbed dose increases the diffusion capacity of the water molecules is reduced which is closely linked to the crosslinking degree derived from the absorbed dose [15].

The values obtained from the diffusional exponent of the R hydrogels show that at 25 kGy the diffusion behavior of the water molecules tends to be anomalous, this implies that the water diffusion rate is assimilated to the relaxation rate of the polymer chains. However, when the dose increases to 30 kGy the water molecules have a greater difficulty to diffuse, therefore, the diffusion rate is lower compared with the relaxation rate of the polymer chains. At 35 kGy the transport

mechanism presents a greater limitation generated by the higher cross-linking degree, therefore it is not possible to classify it according to the Fick diffusion law.

In the case of irradiated TR hydrogels at doses of 25 kGy and 30 kGy, the diffusion mechanism turns out to be anomalous since it is within the established range according to the literature [13], however it is important to clarify that the diffusional exponent at 25 kGy is superior to at 30 kGy and approaches the case II mechanism in which the water molecules diffusion is much greater than the relaxation rate of the polymer chains. At 35 kGy despite the fact that the diffusional exponent value indicates that it is not classifiable according to the ranges of the literature [13], it can be considered that it presents a Fickian diffusion mechanism due to the proximity to the value considered in said methodology.

4. DISCUSSION

As it was observed in the results, at higher absorbed dose the swelling kinetics parameters such as the swelling percentage, the diffusion coefficient and the diffusional exponent are reduced, so it could be said that they present certain dependence with it. In addition, the introduction of weak bonds in the hydrogels mesh due to the thermal cycling process modified these parameters, increasing their values with respect to those gels that were only irradiated. This is an advantage when evaluating a control process that allows drugs to be administered effectively.

The parameters that allow to evaluate the swelling kinetics have been widely used in the study of the release of active principles of polymeric meshes since there is an intrinsic correlation between the swelling capacity of these materials and the transport mechanisms that are generated in the release of active principles [6]. The use of the semi-empirical equation for the analysis of the diffusion mechanisms turns out to be appropriate since it simplifies the classification process, nevertheless it is necessary to consider the boundary conditions and the experimentation system [10].

Currently the systems that allow the storage and controlled release of drugs are in controversy since in most cases the control in the drug desorption is limited [16]. Attempts to improve this situation have led to look for intelligent polymeric materials including hydrogels that can modify

their capacity for swelling or desorption according to environmental conditions such as temperature or pH [17]. The disadvantage of these systems is that upon reaching the threshold temperature the release of the drug is not controlled and can generate toxic levels for the organism.

The hydrogels with active ingredient are often used to dressing wounds, particularly for burns. An ideal dressing should have the following characteristics: to absorb exudates from superficial wounds, to maintain moisture in the wound, to allow gas exchange, to provide thermal insulation, to prevent the entry and growth of bacteria, to reduce necrosis on the wound surface, to be biocompatible, non-toxic or allergenic, to facilitate the growth and regeneration of healthy tissue [18].

There are some research works in which hydrogels are developed in combination with active ingredients to be used as wound dressings. Arredondo et al. [19] developed a matrix of PVA hydrogel combined with Silver Sulfadiazine (SP) for the control of sepsis in dermal wounds. This group used the thermal cycling technique to achieve a physical gelling of the material but they did not performed a diffusion assay. Alves de Oliveira et al. [20] used N-methyl glucamine as an active ingredient in PVP hydrogels, PVA and clays synthesized with gamma radiation at 25 kGy for the treatment of leishmaniasis wounds, the results of preclinical studies showed a reduction of wounds in treated patients with the hydrogel with respect to the control group, however, they did not make any type of assay of the drug's diffusion mechanism. Other research groups such as Gao et al. [21] used electron beam radiation as a tool for the synthesis of hydrogels from PVA loaded with SP dissolved in ammonium solution to test its antimicrobial efficacy in Escherichia Coli and Staphylococci Aureus. They observed that as the concentration of SP in the hydrogel increased, the inhibition halo in the culture plate also increased, this shows that the bactericidal action can be controlled by the concentration of the drug. In this work, once again, a conclusion of the control in the release of the drug is reached without carrying out any study of the diffusion mechanism. In general, in these studies there is no control of the diffusion of the drug, it is only known that it is spreading since they verify its treatment capacity. Despite this, they cannot assure that at some point the drug can be released, saturating the system and generating overdose. For this reason, we believe that it is necessary to carry out a diffusion assay, to know the transport mechanisms that govern the movement of water into and out of the hydrogel in order to know the behavior of the polymeric

mesh and to predict the behavior of different active principles to a possible application in controlled drug release.

5. CONCLUSION

In this work, two synthesis methods for the production of hydrogels were carried out. One of them was to use only ionizing radiation as a crosslinking element and the other was based on the combination of irradiation with a thermal cycling process. The results of the swelling test showed that the hydrogels water absorption percentages as well as the diffusion coefficient of these molecules in the polymeric mesh are closely related to the irradiation dose. In the particular case of swelling we also observe that the presence of weak bonds in the system can generate an increase in the absorption capacity of the hydrogel. We also observed that the diffusion mechanism of water molecules in hydrogels is a parameter that can be controlled by the dose absorbed during the synthesis process of the itself and by the amount of thermal cycling to which they could be subjected. The analysis of the swelling kinetics of the obtained hydrogels allowed us to know the intrinsic behavior of the polymeric / solvent mesh system at different irradiation doses. This would allow us to predict in the future the transport mechanism of any other molecule that can be incorporated in hydrogels as an active ingredient for a possible application in drug delivery.

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