2013 International Nuclear Atlantic Conference - INAC 2013
Recife, PE, Brazil, November 24-29, 2013
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: **978-85-99141-05-2**

POLYMER HYDROGELS AS OPTIMIZED DELIVERY SYSTEMS

Jorge G. S. Batista[1], Gustavo H. C. Varca[1], Caroline C. Ferraz[1], Gabriela P. Garrido[1], Bruna M. Diniz[1], Vinícius S. Carvalho[1] and Ademar B. Lugao[1]

Instituto de Pesquisas Energéticas e Nucleares (IPEN / CNEN - SP)
Av. Professor Lineu Prestes 2242
05508-000 São Paulo, SP
jorgegabriel@usp.br

ABSTRACT

Hydrogels are formed by polymers capable of absorbing large quantities of water. They consist of one or more three-dimensionally structured polymer networks formed by macromolecular chains linked by covalent bonds-crosslinks - and physical interactions. The application of hydrogels has been widely studied. Biodegradable synthetic or natural polymers such as chitosan, starch and poly-lactic-co-glycolic acid, have properties that allow the development of biodegradable systems for drug and nutraceutics delivery. This study aimed to develop polymeric hydrogels based on polyvinyl alcohol, polyacrylamide and polyvinylpirrolidone using ionizing radiation in order to develop hydrogels for improved loading and release of compounds. Polymer solutions were solubilized in water and poured into thermoformed packages. After sealing, the material was subjected to ɣ-irradiation at 25kGy. The samples were assayed by means of mechanical properties, gel fraction and swelling degree. Nanostructure characterization was performed using Flory's equation to determine crosslinking density. The systems developed showed swelling degree and adequate mechanical resistance. The nanostructure evaluation showed different results for each system demonstrating the need of choosing the polymer based on the specific properties of each material.

Key words: Hydrogel; Polyvinyl alcohol; Polyvynilpyrrolidone; Polyacrylamide; Ionizing radiation.

1.INTRODUCTION

Currently polymeric materials involve an immense research area, mainly due to their ability to undergo changes in their physical and chemical properties through distinct routes and as a result allow easy processing and control of their final properties.

Drug delivery systems offer advantages over conventional dosage forms, such as high therapeutic efficacy, prolonged, sustained or controlled release of the drug, reduced toxicity, safe administration, and specific targeting [1]. A wide variety of biocompatible polymers, such as polyvinyl alcohol (PVA), polyvynilpyrrolidone (PVP) and polyacrylamide among others, whether obtained from natural or synthetic origin may be applied for the synthesis of drug delivery devices and engineered systems.

Regarding the use of polymers for drug delivery, hydrogels have emerged as a promising option in the development of drug delivery systems. In comparison with other synthetic biomaterials, hydrogels resemble the living tissues in relation to their physical properties due to high water content, softness, firmness and elasticity, among others. Such systems are defined by three-dimensional networks composed by crosslinked polymers of high water content. Additionally, according to HOFFMAN (2002) [2] depending on the chemical composition of the gel, different internal and external stimuli (e.g. pH changes, applying an electric or magnetic field, temperature variations, radiation and ultrasound) may be used to trigger distinct effects such as controlled swelling. Once activated, the release rate of the drug is retained and liberated as a function the polymeric network crosslinks [3]. Moreover, these systems hold the ability to allow diffusion of molecules of different sizes and charges, depending on the degree of crosslinking, porosity and chemical affinity.

Hydrogel interactions with biological tissues has made possible the development of delivery system for oral, nasal, buccal, rectal, ocular, vaginal, and parenteral administration [4]. However, regarding biomedical applications, such as the use of hydrogels as dressings, the selection of the polymer for the synthesis and final properties of the material should be done considered an application based approach. As an example, while some similar characteristics may be shared by distinct types of burns and wounds, each kind of lesion has its own needs and thus frequently requires distinct properties from the material, such as exudate absorption, proteolytic agents, higher permeability, and so on [5].

On this account, this study aimed to develop polymeric hydrogels based on PVA, PAAM and PVP using ionizing radiation in order to develop hydrogels for improved loading and release of compounds and allow proper selection of the polymer based on the final properties and characteristics acquired by the hydrogels from each compound.

The use of ionizing radiation for the synthesis of hydrogels is of great relevance to clinical applications due to the simultaneous crosslinking and sterilization, which leads to the formation of the polymeric matrix and sterilization of the hydrogel inside the final packaging [6].

2. MATERIALS AND METHODS

2.1. Hydrogel Synthesis

The following materials were applied to the synthesis of hydrogel membranes – PVA (325 Celvol®), Anionic polyacrylamide (125 Aguapol®) and polyvinylpyrrolidone (Kollidon K90®); Agar (Technical grade); Polyethylene glycol 400. Reverse osmosis water was used for all experiments.

PVA

PVA was solubilized in water (10%, w/w) under stirring followed by PEG addition (1.5%, w/w) and agar (1%, w/w). The mixture was submitted to autoclaving process and poured into thermoformed packages. After reaching room temperature, the packages were sealed under vacuum, frozen at -20^{o}C and irradiated at 25 kGy by Gammacell irradiator.

PVP

PVP membranes were made by adding PVP (10%, w/w) in water under stirring, further added PEG (1.5%, w/w) and agar (1%, w/w). The process was similar as adopted for the PVA membranes; However no freezing process was performed prior to irradiation.

PAAM

PAAM was dissolved into the water using a mechanical homogenizer at 379 rpm for 4 hours. The solution was cooled for 12 hours at 2-8 ° C (± 2 ° C) and then frozen for 12 hours prior to the lyophilization process. The lyophilized sample (final concentration = 100% PAAM) was fragmented in different sizes and rehydrated with defined water volumes in order to establish different polymer concentrations. The samples were kept frozen at -20 º C (± 2 ° C) for 24 hours and finally exposed to irradiation process at 25kGy. Also 1.5% PEG was added to the formulations as a plasticizer. The polymer concentrations corresponded to 10% (w/w).

2.2. Characterization

The hydrogel membranes were characterized by means of gel fraction, swelling degree, and crosslink density by the Flory equation.

Gel Fraction

The samples were oven dried in stove at 60°C until constant weight and then submitted to extraction using a soxhlet and distilled water as solvent. After 40h the bags were dried and re-weighed until constant weight. The gel fraction was calculated as Eq.(1), using the initial weight of the dry gel (Wi) and the weight of the extracted dry gel (Wd). The gel fraction estimated corresponded to the average of data of 3 analyzed specimens of each formulation.

$$\text{Gel}(\%) = \frac{\text{Wd}}{\text{Wi}} \text{x}100 \qquad (1)$$

Swelling

Hidrogel samples (1 g) were oven dried until they constant weight. After drying, each sample was immersed in beakers containing saline solution (NaCl 0.9%) in triplicate. The samples were weighed at regular intervals until constant weight. The degree of swelling was calculated according to Eq.2, where mi = initial mass of the dry sample and mf = mass of the swollen sample.

$$I\ (\%) = (wf-wi) / wi \times 100 \quad (2)$$

Crosslink density

Crosslinking density was determined using Flory equation (FLORY, 1953) [7]. The following parameters were applied, p= 0,77g.mol^{-1}, v=18 g.mol^{-1}. The parameter μ=0.495 was based on MARK (1999) [8] and χ value was obtained for each sample based in swollen hydrogel data.

$$M_c = \ln (1-\chi)+\chi+\mu\chi^2+p.v/(\chi^{1/3}-0,5\chi) \quad (3)$$

$$q = m / Mc \quad (4)$$

3. RESULTS AND DISCUSSION

All membranes produced were within the acceptable standards with regarding to mechanical properties (data not shown). Specifically, all membranes presented adequate consistency and mechanical resistance. On this account they were considered effective for dressings and other biotechnological application.

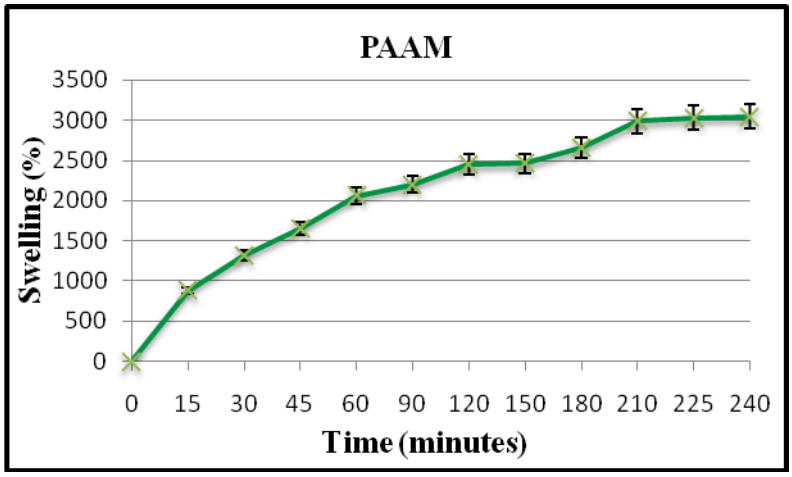

Figure 1. Swelling ratio (%) for PAAM hydrogel membrane

Swelling capacity increased in order of PVA<PVP<PAAM revealing that for exudate absorption purposes, with regard to hydrogels applied as dressings, only PAAM polymer (Maximum swelling 3040.61 ± 182 %) demonstrated high swelling levels (data not shown).

PVA seems to be less affected by water and to hold very low absorption properties (Maximum swelling 42.06 ± 2.77 %) if compared to the other polymers tested (Figures 1, 2 and 3).

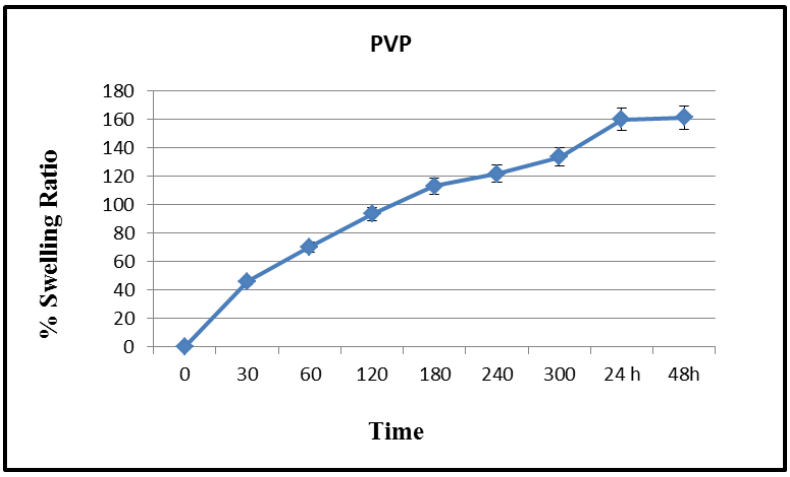

Figure 2. Swelling ratio (%) for PVP hydrogel membrane

PVP presented intermediate levels, although very low swelling levels were registered (Maximum swelling =161.3 ± 4.32). The information suggests that PVA and PVP comprise suitable materials for composing dressings for wounds or burns in cases where there is no exudate formation, and for systems that afford no or minimum swelling or shrinking, such as stents or other materials.

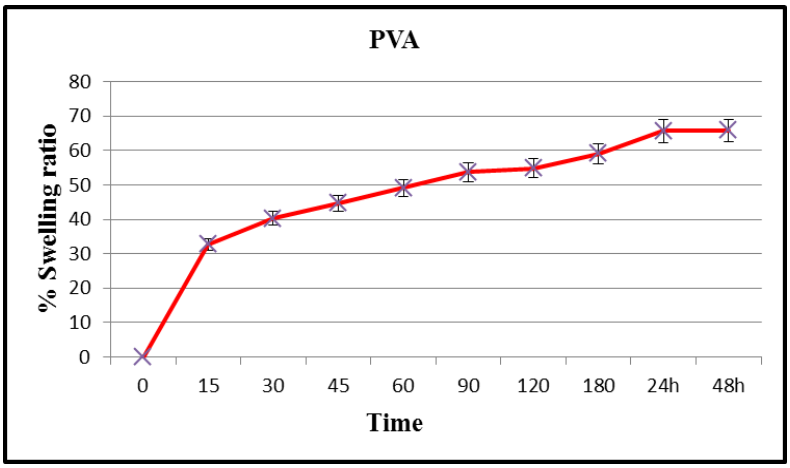

Figure 3. Swelling ratio (%) for PVA hydrogel membrane

Gel fraction measurements (Table 1) revealed that all systems presented intense crosslinking evidenced by high gel fraction levels (>70%). Specifically, PAAM hydrogel presented gel fraction values around 78-90%, PVA 76-82% and PVP 74-80%.

While gel fraction results reveal the exact amount of crosslinked polymer fractions, the crosslinking density measurements provide information as to the pores are formed and its distribuition, as well as the overall distribution of such crosslinks in the matrix, holding a very strong influence over loading and release of drugs or molecules. Regarding this

property, PAAM hydrogels conferred a network with crosslinking density values around 5.00 x 10-2, PVP conferred a network with values of 11.32 x 10-2 and PVA 35.66 x 10-2.

Table 1. Crosslinking density measurements estimated by Flory's equation.

Polymer	**Polymer Concentration**	**Max. Swelling (%)**	**Gel Fraction (%)**	**Crosslinking density (mol/cm^3)**
PVA	**10**	42.06 ± 2.77	76-82	7.59×10^{-3}
PVP	**10**	161.3 ± 4.32	74-80	9.34×10^{-4}
PAAM	**10**	2925 ± 182	78-90	2.57×10^{-4}

3. CONCLUSION

All polymers submit to ionizing irradiation led to hydrogels formation with distinct properties. Swelling ratio decreased as a function of PAAM>PVP>PVA. For exudate or body fluids absorption purposes, only PAAM hydrogels may be used, considering the low swelling ration observed for the other polymers. All polymers held high gel content, above 70% accentuating high crosslinking levels. Crosslinking density measurements revealed networks with distinct pore distribution, decreasing in order of PVA>PVP>PAAM. These data corroborates the swelling profiles, where swelling ratio was inversely proportional to the crosslinking degree. Based on the previous information, concerning loading of large molecules, PAAM seems to be more effective considering that the network originated was not very dense and migth accommodate them properly. PVP and PVA networks presented higher crosslinking density and migth accommodate smaller molecules more efficiently.

ACKNOWLEDGMENTS

The authors would like to thank Pablo Vasquez and Paulo Santos (Radiation Technology Center – IPEN/CNEN-SP) for their kind contribution to the work, CNPQ for the Scholarship.

REFERENCES

1. I. C. Jacobs, N.S. Mason, *Polymer delivery systems concepts, in Polymeric delivery systems: properties and applications*, B.A. Charpentier, Editor, American Chemical Society: Washington, DC. 1993, pp. 1-17.
2. A. S. Hoffman, *Hydrogels for biomedical applications.* Advanced Drug Delivery Reviews. **Vol. n. 54**, p. 3-12, 2002.
3. N. A. Peppas, *et al., Hydrogels in pharmaceutical formulations.* Eur. J. Pharm. Biopharm.**Vol. n.50**, p. 27-46, 2002.
4. P. Gupta, K.Vermani, S. Garg, *Hydrogels: from controlled release to pH-responsive drug delivery.* National Institute of Pharmaceutical. Education and Research. DDT **Vol. n. 7**, No. 10, May 2002.

5. B.D. Ratner, A. S. Hoffman, *Synthetic Hydrogels for Biomedical Applications.* Departments of Chemical Engineering and Bioengineering, University of Washington, Seattle, Wash. Jun. 1976.
6. J.M. Rosiak, J. Olejniczak, *Medical application of radiation formed hydrogels*. Radiat. Phys. Chem.,**Vol. n. 42** (1993), p. 903.
7. P. J. Flory, Principles of Polymer Chemistry, Cornell University, Ithaca, N.Y., 1953
8. J. E. Mark, Polymer Data Handbook, Oxford University Press, New York, 1999. Available in: <http://www.objectplastic.com/2010/03/polymer-data-handbook-james-mark-editor.html>