

EFFECT OF DIFFERENT PLASTICIZERS ON POLY(*N*-VINYL-2-PYRROLIDONE) HYDROGELS CROSS-LINKED BY RADIATION

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ABSTRACT

The use of hydrogel membranes usually demands polymers capable of forming films with high elastic and flexible properties besides having high water absorption. In terms of improvements of polymer plasticity, addition of special plasticizers to polymers can do it with promising results, although within limits of concentrations. The objective of this study was to evaluate the different effects of poly(ethylene glycol) (PEG) and glycerol as plasticizers on hydrogel membranes synthesized from poly(*N*-vinyl-2-pyrrolidone) (PVP) as the main polymer in aqueous polymeric solutions. For that, hydrogels of PVP/agar/PEG, PVP/agar/glycerol and without agar or plasticizer were simultaneously synthesized and sterilized by irradiation of mixtures of such products in aqueous solutions, using gamma-rays from a ^{60}Co source at a dose of 25 kGy. The results based on gel fraction, swelling in water, and some mechanical tests suggest that the degree of PVP cross-linking prevailed over the greater hydrophilicity of glycerol compared to that of PEG with regard to the degree of swelling of the hydrogels.

1. INTRODUCTION

Hydrogels are three-dimensional networks formed from hydrophilic homopolymers, copolymers, or macromers (preformed macromolecular chains) cross-linked to form insoluble polymer matrices. Cross-linking of such polymer systems can be carried out physically (by hydrogen bondings, electrostatic interactions, hydrophobic interactions, others), occurring without forming effective covalent bonds; or chemically, with formation of effective covalent bonds. In this case, cross-linkers and catalyst usually are utilized to perform the cross-linking or this can be induced by means of a physical process, for example, temperature, uv radiation, ionizing radiations such as X-rays, electron beam (EB), γ -rays. Applications of hydrogels are numerous, which might be listed in this work. Maybe the most successful and promising is their use in the fields of medicine and pharmacy [1].

In many cases a single polymer alone cannot attend divergent demands in controlled drug release in terms of both properties and performance [2]. In other applications, such a drawback may also exist. However, if it is blended with one or more different polymers could be a simple alternative, most the times economically advantageous with attainment of a novel material showing sometimes synergistic properties [3] from its components.

PVP is a very hydrophilic polymer, biocompatible, and has quite low toxicity. Its use as a synthetic blood plasma comes from World War II [4]. Throughout decades this polymer has been utilized in numerous applications in medicine, pharmacy, biotechnology, food and cosmetics industries, others.

Mixtures or blends of PVP-agar -PEG-water and PVP-agar-glycerol-water have been used in hydrogel preparation [5] for diverse applications. Agar is a natural polysaccharide of some species of marine macroalgae [6] and is widely used in the food industry, in cosmetics, and for microbiology. Applications include use as a thickener, gelling agent, binding agent, suspension agent, and as a stabilizer. It has been used in preparation of one-component and blend hydrogels as matrices for drug release [7]. Lower-molecular weight PEGs and glycerol are well-known plasticizers for various natural and synthetic polymers, for example, chitosan [8], poly(vinyl alcohol) (PVA) , PVP [9], others.

Incorporation of a plasticizer in a given polymer mainly aims to lower the glass transition temperature (T_g) of this. Plasticizing makes the polymer a material with some improvements or adjustments in terms of its original physical properties (film formation, higher elasticity and elongation at the rupture, more softness, etc.) and enables it more diversified applications.

In this approach, we are taking into account only the external plasticizing of the polymer PVP, which also could be plasticized internally via copolymerization during its polymerization process or by grafting, branching, others [10], what would become a more challenging task.

PEG and glycerol have been used in hydrogels based on PVP. They physicochemically act as plasticizers on PVP and still increase its hydrophilicity once they have highly hydrophilic

polar OH groups capable of interacting either with water or polar groups of the polymer, in this case ternary amide groups of PVP, through hydrogen bondings. Action of plasticizers — almost the times short-chain molecules chemically compatible with a determined polymer — are very similar to that of water, which is a polar solvent and also a natural plasticizer for numerous polymers with which is chemically compatible. The plasticizers are incorporated among the polymer chains, promoting disentanglements as well as raising the intermolecular distances of them, diminishing their interchain interactions, therefore facilitating the macromolecules' mobility. In addition, a plasticized polymer rheologically becomes more plastic and flexible, more sensitive to thermal and mechanical events. This can be technically confirmed by thermal or mechanical tests for a same plasticized and non-plasticized polymer.

Interactions between polymer chains and plasticizers can be accomplished by hydrogen bondings, Van der Waals interactions, diverse others, as well. Of such interactions, hydrogen bondings play a relevant role. Polymers containing ternary amide groups, such as poly(*N*-vinyl-2-pyrrolidone) (PVP), are potentially good proton acceptors due to the basic nature of these functional groups. These structures favor hydrogen bonding interactions. At the same time, short-chain poly(ethylene glycol) (PEG) and glycerol (propane-1,2,3-triol, IUPAC) carry two proton-donating hydroxyl groups at their chain ends. According to most citations in literature, PVP is an amorphous linear homopolymer, whereas PEG is also a linear homopolymer but capable of forming a crystalline phase. The third component of a PVP–agar–glycerol blend is a low-molecular weight volatile liquid, very soluble in water, and quite hygroscopic (therefore, in terms of its concentration, much attention must be paid to its use as a polymer plasticizer) [11].

PVP-based hydrogels have been object of study, especially in the last five decades. PVP has aroused interest in being used as hydrogel owing to possess many favorable inherent characteristics for this end. The polymer is totally soluble in water up to very high concentrations, even at room temperature, besides being soluble in other polar and non-polar solvents as well as biocompatible and practically atoxic. Therefore, physical and chemical hydrogels from PVP are easily attainable in a large range of concentrations (commonly from 2 % to 20 % by weight) in aqueous solutions.

As cited initially, various methods are applied to production of hydrogels. Ionizing radiation has long been recognized as a very suitable tool for formation of hydrogels, and shows many advantages owing to be a simple, efficient, clean and environment-friendly process. It compulsorily has no need of addition of initiators, cross-linkers or catalysts to accomplish the cross-linking, and the majority of these substances use to be very toxic [12]. Furthermore, ionizing radiation usually allows combining the synthesis and sterilization in a single technological step, thus reducing costs and production time [13].

Cross-linking induced by ionizing radiation is caused by the mutual recombination of polymeric radicals or macroradicals. When an aqueous polymer solution is submitted to the radiation, this directly can act on the polymer chains by breaking these on their backbones, mainly on C-C bonds, or abstracting H atoms from their backbones or moieties more susceptible to scission. The recombination of the free macroradicals formed leads to the cross-linking of the polymer system by means of covalent bonds. [14]. Ionizing radiation also acts on water or other solvents of polymeric systems, generating a lot of distinct radiolysis products. Water radiolysis occurs forming, for example, diverse products such as hydrogen atom (H•), radical hydroxyl (OH•), and many others. Hydroxyl radicals are very reactive and promote abstraction of H atoms of the polymer chains, generating more free macroradicals and, consequently, enhancing the cross-linking. Many authors call this cross-linking enhancement as caused by the indirect action of the radiation as shown in Fig. 1.

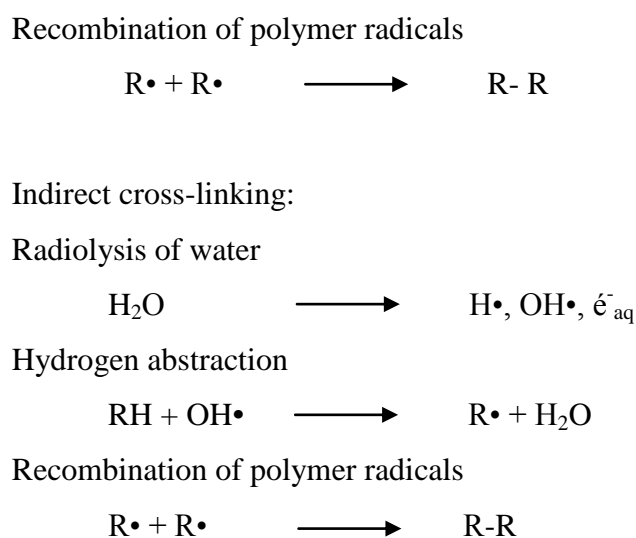


Figure 1. Main water radiolysis products acting on indirect cross-linking of polymers, from Darwis [15].

The aim of this work was the characterization of PVP hydrogels obtained from aqueous solutions of PVP-agar-PEG and PVP-agar-glycerol containing different concentrations of the reagents, and irradiated by γ -rays, followed by evaluation of the effect of the plasticizers PEG and glycerol on the hydrogel membranes. The characterization made use of several tests: gel fraction, swelling in water, and some mechanical properties.

2. MATERIALS AND METHODS

2.1. Materials

Poly(*N*-vinyl -2-pyrrolidone) (PVP K90) from BASF (Germany); PEG 300 and glycerol from Oxiteno; agar n. 1 from Oxoid. As solvent, reverse-osmosis water (ROW) was utilized. All these materials were used without further purification.

2.2. Preparation of hydrogels

The mixtures of PVP-agar-PEG-water and PVP-agar-glycerol-water were prepared using conventional methods: weighing of each component previously; sequential addition of PVP, agar, PEG or glycerol into water (ROW) contained in a glass recipient kept on heating bath (glycerin) and under mechanical stirring (manually with aid of a glass rode). Temperature was regulated to 90°C since dissolution of agar is far less immediate than that of PVP. After ca. 1 h transparent solutions were gotten and cooled to room temperature (ca. 20°C), next bubbled with N₂ to remove dissolved O₂, submitted to vacuum for bubble elimination, thereafter poured in thermoformed molds and sealed for irradiation. The hydrogels were then obtained by irradiation onto these sealed molds from a ⁶⁰Co γ -rays' source at a dose of 25 kGy and a dose rate of 1.67 kGyh⁻¹. Composition of the obtained hydrogels is shown in Table 1, and preparation scheme in Fig. 2.

Table 1. Formulations of hydrogel samples (% by weight)

Samples	A (%)	B (%)	C (%)	D (%)	E (%)	F (%)
PVP K90	4.0	4.0	4.0	20.0	20.0	20.0
PEG 300	-	5.0	-	-	5.0	-
Glycerol	-	-	5.0	-	-	5.0
Agar	1.5	1.5	1.5	-	-	-
H₂O (ROW)	94.5	89.5	89.5	80.0	75.0	75.0

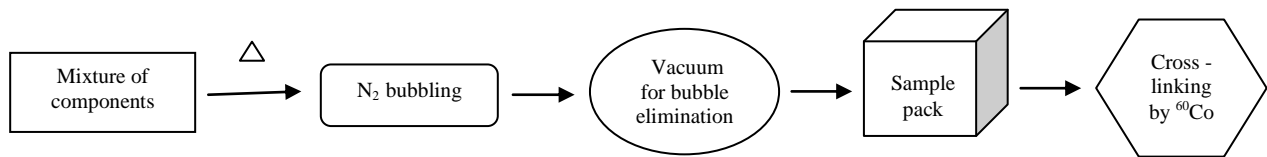


Figure 2 – Scheme of preparation of the PVP-based hydrogels.

2.2.1 – Gel Fraction

To obtain the gel fraction, the sol part was extracted from the γ -irradiated sample previously dried and packed in stainless steel screen (500 mesh) immersed in reverse-osmosis water (ROW) and kept in an autoclave at 121°C for 2 h. Next, the samples were dried until constant weight, and the % gel fraction was calculated according to Equation 1:

$$\text{Gel fraction (\%)} = \frac{W_d}{W_i} \times 100 \quad (1)$$

where W_i and W_d are the dry weight of the dried sample before and after extraction, respectively. The final result of the gel fraction for each sample was taken as the numerical average of the results of its corresponding specimens tested.

2.2.2. Swelling in water

Five specimens with ca. 20 mm x 24 mm x 2 mm sizes (each of ca. 1.7 g) of a sample of each formulation were immersed in 100 mL of reverse-osmosis water (ROW) during 20 min in the first hour, at 30 min in the second hour and at intervals of 1 h during the 6 subsequent hours, being each specimen rapidly dried in a soft filter paper for weighing and return to water. Afterwards, they were kept immersed for evaluation 24 h, 48 h, 72 h, and 96 h, i.e. until the swelling stabilization or swelling balance, making the same procedures of drying and weighing. The tests were performed at a temperature of 30°C, and the degrees of swelling were calculated by Equation 2:

$$\text{Swelling (\%)} = \frac{W_s - W_d}{W_d} \times 100 \quad (2)$$

where W_d is the initial dried sample weight and W_s is the weight of sample after swelling. The final result of the swelling degree for each sample was taken as the numerical average of the results of its corresponding specimens tested.

2.2.3. Mechanical properties

Tensile stress at rupture (σ_R) and elongation at rupture (ε_R) of the hydrogel membranes were measured on a TA.XT *Plus* Texture Analyzer from Stable Micron Systems, equipped with a 50 kg load cell and in according to ASTM D882-95 [16], using rectangular specimens with 100 mm x 24 mm sizes cross-linked in thermoformed packages. The matrices were stretched at a deformation rate of 0.833 mm.s⁻¹ (samples A, B and C) and 8.33 mm.s⁻¹ (samples D, E and F) as recommended by the standard. The speed pretest adopted was of 2.0 mm.s⁻¹ and the trigger force defined as 5 g. A minimum of 5 specimens from each sample was prepared. Before testing they were conditioned for 6 h at 20°C and relative humidity of 65%; afterwards, tested at these conditions. Tensile stress at rupture was calculated on the basis of the area of the transversal section of each sample; elongation on the basis of deformation of the sample in relation to the percentage of its initial length ($L_o = 60$ mm) according to Equation 3:

$$\text{Elongation at rupture (\%)} = \frac{L_b - L_o}{L_o} \times 100 \quad (3)$$

where L_b and L_o are final length at rupture and initial length, respectively. All final results were calculated basing on the numerical average of the results of each set of specimens.

3. Results and discussion

3.1. Gel fraction

In this test, some hydrogels rendered a high content of gel (A, D, E and F), indicating a high cross-linking among the polymeric molecules. However, the hydrogels B and C obtained showed results of low cross-linking. The comparative results are shown in in Fig. 3.

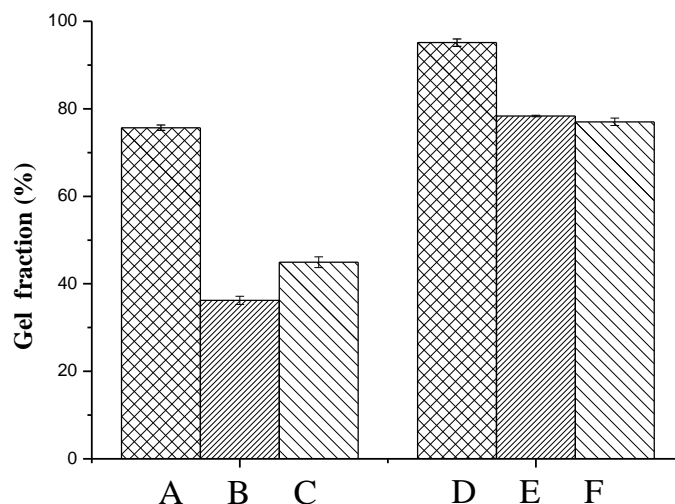


Figure 3. Results of gel fraction of hydrogels cross-linked at 25 kGy, room temperature and common atmosphere. Samples A, B, and C prepared with 4.0 % of PVP; D, E, and F prepared with 20.0 % of PVP.

In general, both plasticizers influenced on a decrease the density cross-linking of the hydrogels. Such a fact also was reported by Ajii *et al* in experiments on PVP hydrogels plasticized with PEG [5] and by D'Ericco *et al* [17] studying PVP hydrogels plasticized with glycerol. The results obtained from tests of gel fraction (Table 2) showed 36% for hydrogel membrane B and ca. 45 % for hydrogel membrane C, indicating a greater amount of soluble fraction for the hydrogels prepared with PEG. For membranes E and F, prepared with PEG and 5% of glycerol, respectively, the results were ca.78% for membrane E and ca.77% for membrane F, indicating that there was no meaningful difference between the cross-linking densities of these two hydrogels.

3.2 Swelling in water

In relation to the swelling curves of the 4.0 % PVP samples (Fig. 4a), sample A (PVP/ agar, without any plasticizer) showed to have high degree of cross-linking (high gel fraction, ca. 76 % as a result of both cross-linked polymers probably) and consequent low degree of swelling (only ca. 20 %).

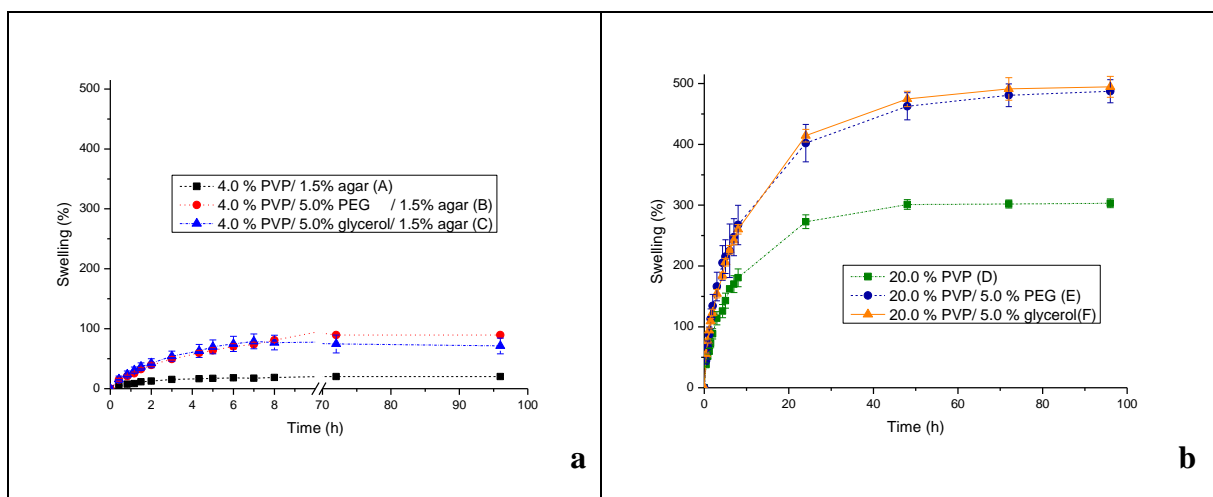


Figure 4. Kinetics of swelling of the hydrogels cross-linked at 25 kGy, room temperature and common atmosphere. (4a) samples A, B, and C were prepared with 4.0 % of PVP; (4b) samples D, E, and F prepared with 20.0% of PVP.

It also exhibited a very regular swelling curve that leveled off since 8 h of immersion of the hydrogel in water. Sample B (PVP/agar/PEG) curve showed a profile of high and relatively regular swelling throughout the 96 h. The swelling curve profile of the sample C showed rather dispersed results, probably influenced by glycerol acting as a scavenger suppressing action of radical OH from water radiolysis [18, 19]. This scavenger action of glycerol leads to a diminution of free macroradical formation and, consequently, lowers the degree of cross-linking of both polymers (PVP and agar), besides increasing the fluidity of these. Interestingly, the swelling results of sample B and C (lower than 50 %) are coherent with those of their gel fractions, (ca. 36 % and ca. 45 %, respectively) among those of all samples tested, nevertheless they are not negligible. A very inhomogeneous cross-linking density presumed for the polymer system of sample C may be the main factor responsible for such high discrepancies on its degree of swelling and gel fraction.

In summary, in the 4.0 % PVP samples the amounts of the plasticizers were extremely high — higher than that of the main polymer studied, i.e. a ratio of 1.25:1 for plasticizer PEG or glycerol and PVP in the mixture, taken as dry weight —, what can cause accentuated deviations on cross-linking densities of the hydrogels influenced by the scavenging effect of glycerol allied to the solvent effect of both plasticizers and that of water on the hydrophilic polymer system.

Regarding the swelling curves of the 20.0 % PVP samples, PVP plasticized with 5.0 % of PEG (E) and PVP plasticized with 5.0 % of glycerol (F) (Fig. 4b), their swelling curve profiles are very close, indicating a similar behavior of both samples in this event, besides showing much higher degrees of welling (ca. 484 %) whether compared with those of the 4.0% PVP samples. Their gel fractions (Fig. 3) also were very close (ca. 78% and 77%, respectively) and high, which could be attributed to the cross-linking formation caused by the closer proximity of PVP molecules at higher concentrations [20]. Furthermore, the deviations in their swelling curves and gel fractions were small. This is a very interesting fact, for the concentration of the plasticizer in relation to that of the polymer being plasticized (in this case, a 20:100 ratio in dry weight for PEG or glycerol and the main polymer PVP, respectively, taken as dry weight) already signalizes a certain optimization in the plasticizer concentration. Addition of plasticizers to polymeric systems is a subject matter that deserves thorough studies searching for the best concentration of their plasticizing action on such systems. These are not even simple, and evaluation and interpretation of their structures after cross-linked under ionizing radiations can be rather complex.

Concerning the sample of pure 20.0 % of PVP (D), absence of hydrophilic plasticizer influenced on its higher gel fraction (ca. 95 %, Fig. 3) and a lower degree of swelling (Fig. 4b) of the three 20.0 % PVP samples tested.

3.3. Mechanical properties

Figure 5 shows the curves of tensile stress at rupture (σ_R , in MPa) versus elongation at rupture (ϵ_R , in %) obtained on tensile tests with very varied profiles for hydrogel samples A, B, C, D, E, and F. It is complemented with the data registered in Table 2.

Ductile behavior of the membranes prepared with 4.0 % of PVP (samples A, B, and C) is observed. The curves suggest that such a behavior can be explained by greater amount of water present in the 4.0% PVP, taking into account that water entrapped in these systems also acts as a strong plasticizer. The hydrogel membranes prepared with 4.0 % of PVP and 1.5 % agar without any plasticizer (Fig. 5a) showed a high tensile stress and low elongation at rupture, besides presenting to be fragile due to their high degree of cross-linking in the polymer blend; those of 4.0 % of PVP, 1.5 % of agar and 5 % of glycerol (Fig. 5c) exhibited

more irregular profiles, and only 4 curves of 14 specimens of this sample tested were obtained.

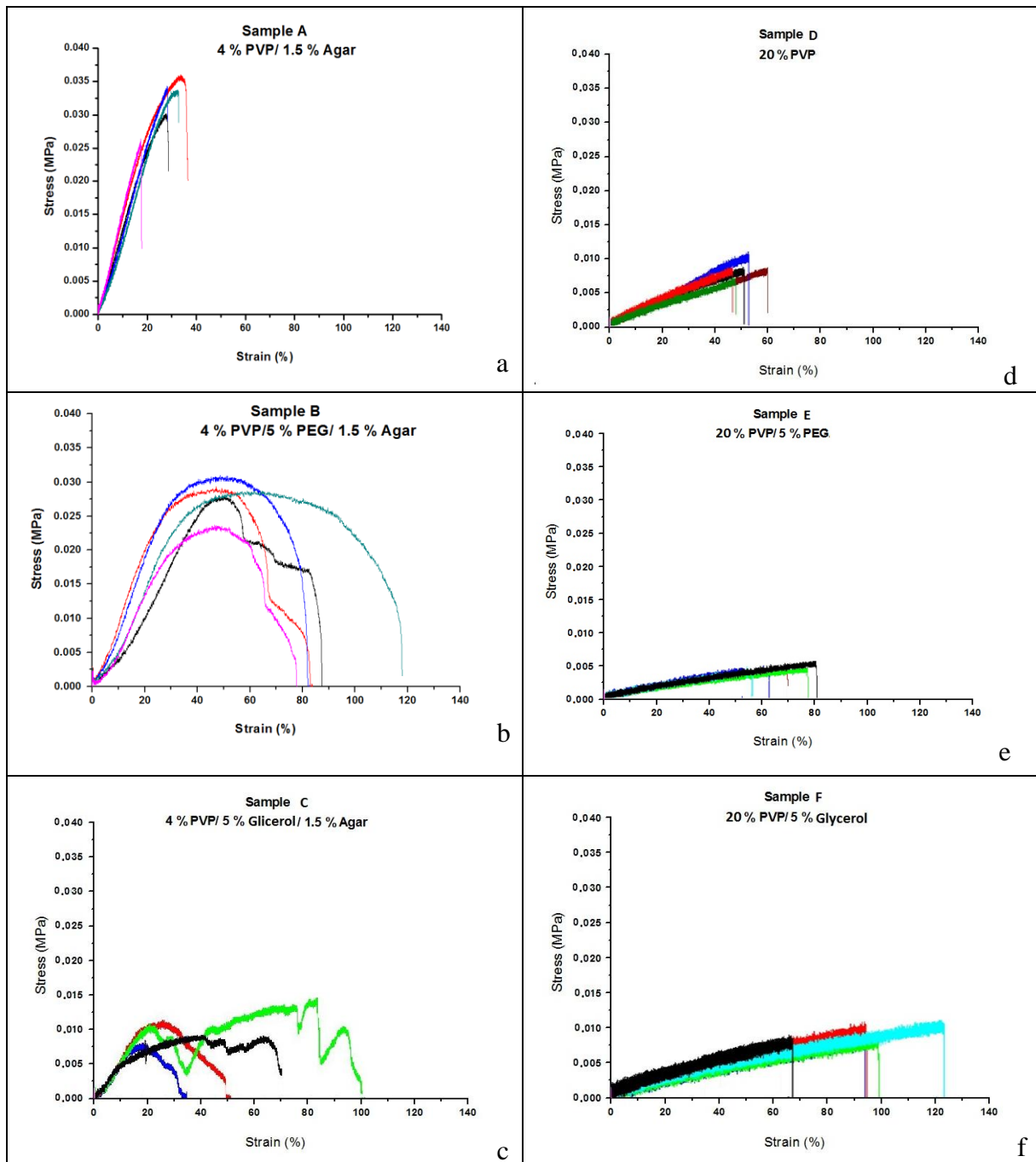


Fig. 5 – Stress x strain curves obtained in tensile tests for the hydrogel membranes with 4.0 % of PVP (samples A, B, and C) and 20.0 % PVP (samples D, E, and F).

It is possible to observe abrupt changes in stress values, indicating partial disruption in the specimens, followed by further increase of the stress values. Maybe the stress results would have reached values much higher than those that partially rupture membranes of low

consistence. The membranes prepared with PEG as the plasticizer (Fig. 5b, 4.0 % of PVP, 1.5 % of agar, 5 % of PEG and Fig. 5e, 20.0 % of PVP, 5.0 % of PEG) also presented to be fragile, but it was possible to get five curves with a smaller number of specimens of these samples. In this case, the curves of Fig. 5b showed different profiles, as well, and the specimens were subjected to partial rupture during the trials like that observed in the membrane plasticized with glycerol (5c).

The average stress results and elongation at rupture obtained with specimens of the samples analyzed are present in Table 2.

Table 2. Results of average tensile stress at rupture (σ_R) and elongation at rupture (ϵ_R) obtained from graphics in tensile tests of diverse PVP hydrogels studied.

Sample	σ_R (MPa)	ϵ_R (%)
A	0.0323 ± 0.0043	28.38 ± 6.69
B	0.0278 ± 0.0026	88.71 ± 16.50
C	0.0106 ± 0.0030	69.86 ± 31.70
D	0.0085 ± 0.0021	52.21 ± 5.33
E	0.0047 ± 0.0010	66.34 ± 15.66
F	0.0049 ± 0.0008	99.23 ± 20.37

For the membranes prepared with hydrogels containing 20.0 % of PVP, the results of tensile stress and elongation at rupture tests were influenced by the increase of the polymer concentration as well as a higher cross-linking. Their networks probably have a more homogeneous cross-linking density in these systems if compared with those obtained with the 4.0 % PVP hydrogels. In this second situation, the results of the tensile stress and elongation at rupture of the non-plasticized samples were larger and smaller, respectively, than those of the plasticized samples with PEG or glycerol. However, for the membranes prepared with 20.0 % of PVP plasticized with PEG (5e) and glycerol (5f) their tensile stress results were very close, whereas the average elongation at rupture of the membranes containing glycerol was ca. 50 % larger than that of the membranes without plasticizer (5d) or plasticized with PEG (5e).

In summary, an increase of the degree of cross-linking raises the tensile stress of the membrane and diminishes its elongation at rupture, and vice-versa. Addition of PEG or glycerol as plasticizers in to these PVP polymeric systems generally leads to a decrease in tensile stress and an increase of elongation at rupture of the hydrogels within the conditions at which they were tested.

CONCLUSIONS

As expected, the hydrogel membranes plasticized with glycerol and PEG were more flexible and more capable of swelling than those without plasticizer (A and D) which presented low cohesion regardless of the concentration of the main polymer (PVP).

Sample A, although containing a relatively low concentration of PVP (4.0%) and 1.5% of agar, displayed results with the highest tensile stress and the lowest elongation at rupture among all the samples tested. Probably, cross-linked agar in this blend contributed to these results since the amount of agar is meaningful in relation to PVP, i.e. ca. 27% in the blend, besides not undergoing influence of plasticizers on its cross-linking. This also demonstrated the feasibility of getting low-concentration stable hydrogels by ionizing radiation.

Hydrogel C, prepared with 4.0 % of PVP, 1.5 % agar, and 5.0 % of glycerol, presented to be a low-consistence gel of difficult handling, on the contrary for hydrogels B, E, and F.

Despite the relatively low concentration of the polymers in hydrogel B, with 4.0 % of PVP, 5.0 % of PEG, and 1.5 % of agar, it presented a high tensile stress, ductile behavior, whereas hydrogel F with high concentration of the polymer (20% of PVP, 5.0 % of glycerol) exhibited higher elongation and swelling despite its fragile behavior.

In addition, the results suggest that the degree of PVP cross-linking prevailed over the greater hydrophilicity of glycerol compared to that of PEG with regard to the degree of swelling of the hydrogels.

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