Hydrogel wound dressing preparation at laboratory scale by using electron beam and gamma radiation

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Abstract

The present work describes the preparation of hydrogel based on cross-linked networks of poly (*N*-vinylpirrolidone), PVP, with polyethyleneglicol and agar with 90% water and PVP nancomposites with a synthetic nanoclay, Laponite XLG, for use as burn dressings. These systems were obtained in two ways: using gamma Co-60 and electron beam radiation. The gelation obtained dose was $D_g = 1.72$ kGy. The elastic modulus of hydrogel was independent of the method of irradiation. It was 0.39 MPa for the hydrogel irradiated with gamma Co-60 and 0.38 MPa for electron beam irradiation. The elastic modulus of the nanocomposite membrane was 1.25 MPa, three times higher. These results indicate that the PVP/Laponite XLG nanocomposite hydrogel membrane is the best choice for wound dressing applications due to its high water sorption capacity and its superior mechanical properties.

Key words: *hydrogels, PVP, burns, gamma radiation, electron beams, cabalt 60*

Preparación de apósitos de membranas de hidrogeles a escala de laboratorio mediante haz de electrones y radiación gamma

Resumen

En el presente trabajo se describe la preparación de hidrogeles basados en redes entrecruzadas de poli (*N*-vinilpirrolidona), PVP con polietilenglicol, agar y un 90% de agua, y nanocomposites de PVP con una nanoarcilla sintética, la Laponita XLG para su empleo como apósito para quemaduras. Estos sistemas se obtuvieron por dos vías: radiación gamma de Co-60 y haz de electrones. La dosis de gelificación obtenida fue de $D_g = 1.72$ kGy. El módulo elástico de los hidrogeles resultó independiente del método de irradiación, siendo igual a 0.39 MPa para el irradiado con Co-60 y 0.38 MPa para el irradiado con haz de electrones. El módulo elástico de la membrana de nanocomposite fue 3 veces superior, 1.25 MPa. Estos resultados muestran que los hidrogeles de nanocomposites de PVP/Laponita XLG resultan superiores para su aplicación en el tratamiento de quemaduras, por su alta capacidad de sorción de agua y sus mejores propiedades mecánicas.

Palabras clave: *hidrogeles, PVP, quemaduras, radiación gamma, haces electrónicos, cobalto 60*

Introduction

Hydrogels are essentially highly hydrophilic three dimensional polymer networks that swellsignificantly in water but do not dissolve. The cross-link density of the network regulates the magnitude of water sorption and the mechanical properties of hydrogels [1]. Hydrogelsexhibit very smooth surfaces and mechanical properties similar to those of human tissues. Therefore these materials find numerous applications in biomedicine [2]. Particular interest has received in the last decade the use of hydrogels as dressings for managing wounds and burns.

It has been stressed that and ideal wound dressing must fulfill the following conditions: create and keep the moist environment, protect the wound from secondary infections, adsorb fluids and exudates, prevent the wound desiccation and stimulate growth factors; the wound dressing has to be elastic, non-antigenic and biocompatible. Many of these conditions are fulfilled by hydrogels. Therefore hydrogels prepared from synthetic polymers (poly (ethylene glycol), poly (vinylpyrrolidone), poly (propylene glycol), polyurethane) [2-4] as well as from polymers of natural origin (xanthan, methyl cellulose, carboxymethyl cellulose, alginate, hyaluronan) [2, 5-8] have been proposed as wound managing aids. Hydrogel wound dressings can be found in the market the trade name of Vigilon, Ivalon, Aqua gel, Kik gel, among others [9].

Ionizing radiation has been recognized as a suitable tool for the formation of polymer hydrogels. The advantages of ionizing radiation in hydrogel preparation are: easy process control, possibility of combining hydrogel formation and sterilization simultaneously, no need to add any chemical initiators [10]. In consequence the obtained hydrogel membranes are ready to use.

Poly(N-vinyl-2-pyrrolidone) (PVP)-based hydrogels, produced by radiation-induced cross-linking and simultaneous sterilization, have been applied successfully as local dressings in wounds, such as burns, skin ulcerations, bedsores and skin grafts. The production process of these hydrogels by using radiation was developed by Rosiak [11]. The process involves radiation cross-linking and sterilization in a single step to produce theready to use hydrogel wound dressing. The methodentails the use of a hydrophilic polymer component, like poly(vinyl pyrrolidone) (7-10%) along with agar-agar (1-2%) or another polysaccharide with would act as antioxidant, a biocompatible humectante.g.polyethylene glycol (1-2%) and across-linkingpromoter, e.g. ethylene glycol dimethacrylate, triethylene glycol dimethacrylate, N,N′-methylene-bis-acrylamide [2]. Similar procedures are commonly used for the production of wound dressings using gamma radiation [10, 12-14].

Hydrogels, particularly highly swollen ones, usually possess poor mechanical properties. Therefore, it is sometimes desired to improve the mechanical properties of hydrogels by the use of reinforcing materials. In recent years, the preparation of polymer/filler nanocomposites usinga synthetic clay (mostly layered silicates) as a transparent filler has attracted considerable interest for its reinforcing ability. The most commonly used layered silicates for the preparation of polymer/inorganic clay nanocomposites are montmorillonite, hectorite, and saponite [15]. Synthetic clay is an inexpensive, transparent, environmentally benign, nanoparticulate material with unique mechanical and rheological properties. Another benefit of synthetic clay is that it can be produced with high enough purity for critical manufacturing applications [16]. Synthetic clay has been used as reinforcing additive for epoxy resins, polyamides, polystyrene, polyurethane, polypropylene, polyesters, etc. These nanocomposites demonstrate improvements in tensileproperties, gas barrier action, thermal stability and flameretardation [17].

Polymer/inorganic clay nanocomposites are classified in three different groups, namely (1) intercalated nanocomposites, for which insertion of polymer chains into a layered silicate structure occurs in a crystallographically regular fashion, with a repeat distance of few nanometers, regardless of polymer-to-clay ratio, (2) flocculated nanocomposites, for which intercalated and stacked silicate layers flocculate to some extent, and (3) exfoliated nanocomposites, for which the individual silicate layers are separated in the polymer matrix by average distances that depend only on the clay loading [18].

Haraguchi, et. al. [19] studied the mechanical behavior of temperature-sensitive nanocomposite hydrogels-consisting of poly(N-isopropylacrylamide) (polyNIPA) and clay, reporting he first observation of a retractive mechanical force as a result of a coil–globular transition of polyNIPA chains. More recently, Thomas et al. [20] useda synthetic layered silicate from the Laponite family to prepare clay-cross-linked polyNIPA gels for cation-binding and separation. They used a kind of hectorite, Laponite RD, which is a synthetic layered silicate clay that is in the form of disk-like nanoparticles with a diameter of 25 nm and a thickness of 0.9 nm. When polymerized with NIPA and initiator, the particles form bonds with several NIPA chains and thereby the particles serve as the cross-links in the gel network. The particles also have numerous negative charges on their faces, which present binding sites for cations. These nanocomposite hydrogels resulted efficient materials for separation and ion exchangeowing to the strong binding affinity of certain cations for the anionic surfaces of the clay nanoparticles within the gel matrix. Kokabi, et. al. [21] prepared nanocomposite hydrogelwound dressings based on poly(vinyl alcohol) (PVA) and organically modified montmorillonite (OMONT) clay by the cyclic freezing–thawing method. They report that adding 10 wt-% of OMONT to PVA hydrogel, the tensile modulus of hydrogel shows an increase of 27%. After evaluating other essential properties of these materials such as swelling, their ability in transmission of water vapor and resistance to microbe penetration they concluded that the quantity of clay was the key factor to obtain nanocomposite hydrogels with desirable properties for wound dressing applications.

In the present work, polymer–clay nanocomposite hydrogels based on poly (vinylpyrrolidone), PEG and Laponite XLG were prepared by cross-linking usingelectron beam and gamma radiation in order to obtain an applicable nanocomposite hydrogel wound dressing for external usage. The nanocomposite hydrogel were characterized in terms of mechanical properties.

The PVP hydrogel wound dressing clinical test has been successfully finished. The government approval for clinical use had been given by CECMED with the register permission No. 1006013.

Materials and Methods

Materials

Polyvinylpyrrolidone (PVP) with an average molecular weight of 1.2 x 106 g/mol was purchased from Kollidone, BASF. Agar bacteriological, Lot No. 3000180 was obtained from Life Technologies (Scotland) and poly (ethylene glycol) (PEG) purchased from Aldrich. Laponite XLG Lot 06-234 from ROCKWOOD was used without purification. Double distilled water was always used.

Irradiation facilities

A linear accelerator ELU-6E (Electronika–Moscow) was used and is shown in Figure 1. It provides pulsed electron beam for basic radiation studies as well as for technological applications. With two independent easily switchable modulators LINAC can generate:

Single pulses of 8 MeV electrons with duration times equal to 2.5, 5, 10, 20 ns and peak current ca 12 A.

Single pulses of 5 MeV electrons with duration time variable from 0.5 to 4.5 μs and peak current 1 A.

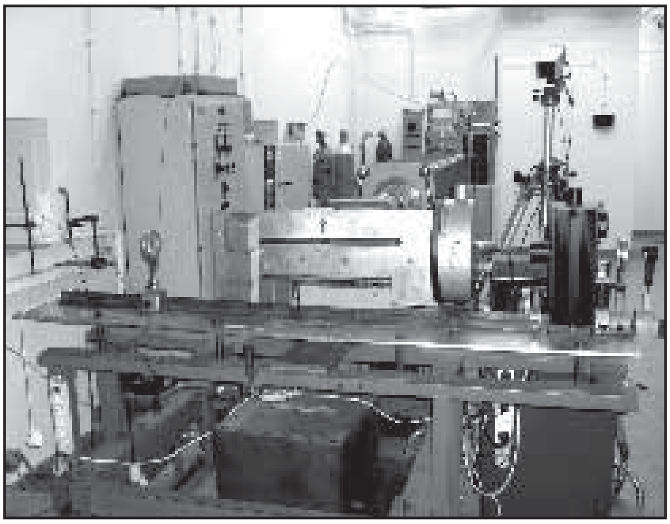

Figure 1. Linear accelerator ELU-6E

For technological irradiation pulses produced with repetition 10-200 Hz can be scanned across a 40 cm long exit window.

EB irradiation was performed with the average dose rate 9.0 kGy/min determined by calorimetry.

A critical decision when designing an electron beam treatment process is the choice of the irradiation topology, namely horizontal or vertical irradiation [22]. A horizontal irradiation arrangement was used in the present study based on its easy validation (Figure 2).

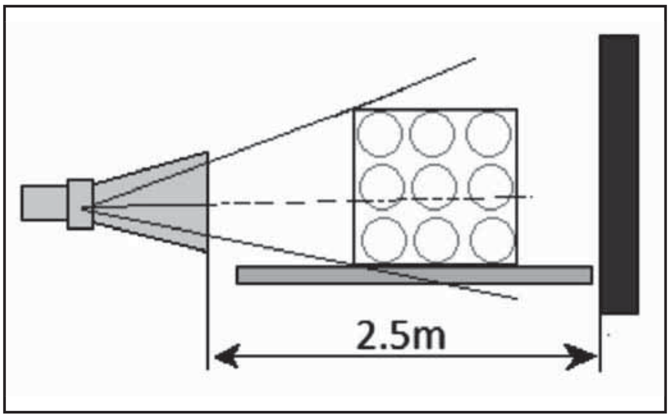

Figure 2. Horizontal beam line topology used for PVP hydrogel wound dressing membranes electron beam irradiation

The electron beam irradiation facility was calibrated by using a water calorimeter located at the distance of 2.5 m from the beam output window all the involved elements were positioned on the same horizontal surface, see Figure 3. A single side irradiation was considered during the hydrogel membranes irradiation; from the point that in case of a double sided irradiation choicea simple turning mechanism is required.

A cobalt 60, self shielding irradiation chamber ISOGAMMA-LL Co from Hungary with dose rate 7.6 kGy/h according to Fricke dosimetry was used for γ-irradiation.

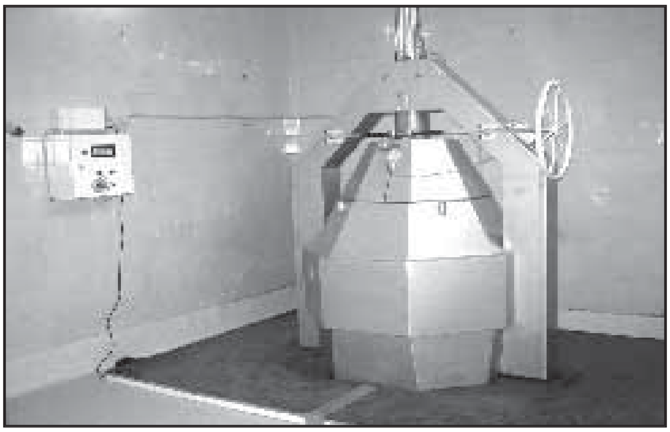

Figure 3. Cobalt 60 irradiation facility ISOGAMMA-LL Co

Preparation of hydrogel membranes at laboratory scale

The laboratory scale preparation of the hydrogel dressing carried out following the method developed by Rosiak [11, 23] according to the following steps. Aqueous solutions of PVP (7.0 wt/v-%), PEG (1.5 wt/v-%) and agar (1.0 wt/v-%), were mixed and heated at 50-60 °C until homogeneity. The solution was poured in 50-100 diameter moulds. The moulds were packed inside envelopes of polyethylene films and irradiated. Irradiation of samples was carried out using electron beam irradiation or γ-irradiation.

Laponite loaded hydrogels were prepared following the same procedure, by adding Laponite XLG to the PVP solution before irradiation. The laponite concentration in the solution was 0.01 wt-%.

Characterization

Determination of the radiation chemical yield value by sol-gel analysis

The gel fractions were calculated as the ratio of the weight of dried gel to the initial weight of the polymer for a given radiation dose. Gelation dose (D_g) and ratio radiation chemical yields of chain scission to cross-linking yields (p_0/q_0) where p_0 and q_0 are degradation and cross-linking density, respectively, were determined. The ratio p_0/q_0 was calculated by the Charlesby-Rosiak method [24], with the aid of the computer program Gel Sol 95 [23]; this program calculates the gelation dose D_g, the virtual dose Dv and the ratio of radiation chemical yields of chain scission to cross-linking, p0/q0, by using the Charlesby-Rosiak equation [24].

$$s + \sqrt{s} = \frac{p_0}{q_0} + \left(2 - \frac{p_0}{q_0}\right)(D_v + D_g)/(D_v + D)$$

where s is the soluble fraction for a given radiation dose D.

FTIR spectral analysis

FTIR spectra were obtained with KBr discs and recorded in the spectral range from 4000 to 500 cm^{-1} by using a Nicolet AVATAR 330 Fourier-Transform Infrared Spectrophotometer (Nicolet Instrument Corp., Madison, WI). Spectra were obtained with a resolution of 2 cm^{-1} and were averaged over 100 scans. Samples were thoroughly dried and ground with KBr and discs were prepared by compression under vacuum.

Mechanical analysis

Mechanical properties of PVP membranes were evaluated with a Zwick BZ2.5/TN1S universal testing machine (Zwick GmbH & Co. KG, Ulm, Germany). Samples were prepared in cylindrical specimens of 10 cm diameter and 1.0 cm height. The upper load limit was fixed at 1 kN with a crosshead speed of 5 mm min^{-1}. The compressive modulus was determined from the slope of the initial part of the stress-strain curve.

Results and Discussion

The radiation technology employed in the present work is ideal for obtaining wound dressing hydrogel membranes because the cross-linked hydrogel network is generated and sterilized in a single technological process. This way the product obtained does not require additional operations and is ready to use. The process is schematically shown in Figure 4.

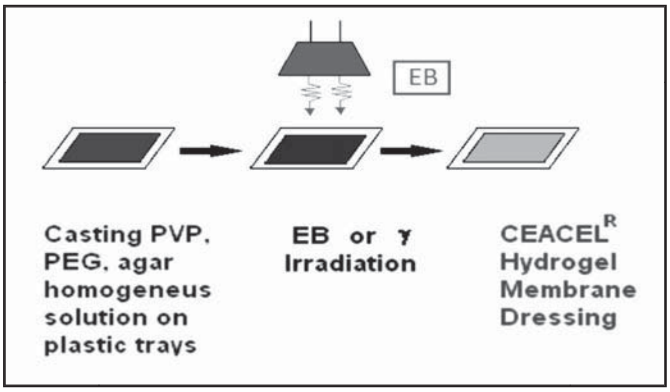

Figure 4. Electron beam and gamma irradiation process for PVP hydrogel wound dressing preparation

Electron beam irradiation hydrogel dressing process

In an electron beam treatment process the machine should be focused, and scanned by electric or magnetic field to create a suitable irradiation area and increase the efficiency of the irradiation process [25]. A useful magnitude to determine the necessary electron energy is the product of the density (ρ) and penetration length (X) usually called standardized depth Z = ρX. If ρis measured in g/cm^3 and X in cm then Z has the unity g/cm^2.

In the present study the irradiated hydrogel dressing membranes,prepared by means of EBwere obtained as 0.3-4.0 mm thick sheets with energy deposition from 1.5 to 2.0 MeV cm^2/g. Figure 5 shows the calculated depth dose curves for energy deposition corresponding to 1,7 MeV cm^2/g on the standardized 3-5 g/cm^2depth. The black dotted line corresponds to the energy of 5 MeV, while the red corresponds to the energy of 8 MeV, respectively.

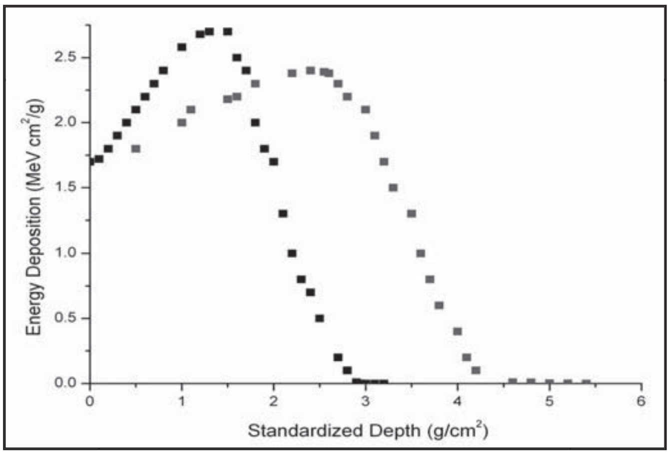

Figure 5. Depth dose distribution, for 5 to 8 MeV electrons

The aqueous solution of PVP, PEG and agar used for the preparation of hydrogels was a clear, almost transparent homogeneous liquid. When irradiating with the cobalt 60 facility the hydrogels dressings obtained were also transparent and came out as fully sterile 3-4 mm thick sheets. Hydrogels dressings were flexible and did not dissolve in hot water but showed high sorption capacity. They were easy to handle and pleasant in touch.

Hydrogel membranes dressingswere also prepared in laboratory batches from 1000 mL initial polymer solutions each, producing 60 or 42 circular membranes per batch with diameters ∅ = 50 mm, or ∅ = 100 mm, respectively. These hydrogel dressings have a 90 wt-% water content. They come out in individual fully sterile packets as shown in Figure 6 for samples irradiated with Co-60 at 25 kGy.

The physical and mechanical characteristics of the finally obtained hydrogel membrane depend on a number of factors such as the PVP molecular weight and concentration, the additives used and the radiation absorbed dose. In particular, the PVP concentration and the rheological behavior of the starting polymer solution

Figure 6. Hydrogel membranes dressing batch of PVP, Agar, PEG, and 90% of Water. Disc shape with size ∅ =100 mm, and ∅ =50 mm Irradiated with Electron Beam and Cobalt 60 irradiation facility at 25 kG, at the laboratory scale

can influence the resultant hydrogels properties. We have found that in order to obtain hydrogels with adequate characteristics for wound dressings PVP concentrations should be greater than 5 wt %. At these concentrations PVP solutions exhibit a pseudoplastic behavior.

Preparation of membranes with nanoaditive

Ahigh purity grade inorganic synthetic clay (hectorite: Laponite XLG),with empirical formula Na$_{0,7}$+ [(Si$_8$Mg$_{5,5}$Li$_{0,3}$)O$_{20}$(OH)$_4$]$^{-0,7}$ was used as nanoaditive. Laponite XLG is a layered silicate with low heavy metals content. In dry form the nanoclayparticles are stacked together in the form of tactoid columns which are readily hydrated [24].

In the present study a transparent dispersion of nanoclay with the rest of additives was achieved, and after irradiation uniform hydrogels were obtained (Figure 7).

Figure 7. PVPHydrogel membranes with 0.01% Laponite XLG irradiated with EB at 25 kGy

Taking in to account the Laponitebehavior on water solutions, care has to be taken during preparation to obtain uniform reacting solutions, in order to avoid the formation of residual heterogeneities. These heterogeneities can result from insufficient exfoliation of clay aggregates or presence of bubbles, which could affect the polymer solution homogeneity to achieve transparent mixture with Laponite XLG. After irradiation the obtained hydrogel dressings, behaved reologically as a viscoelastic cross-linked structure in the range of compositions tested.

Sol Gel Analysis

When PVP is irradiated in water solution with ionizing radiation such as γ-rays or fast electrons, most of the energy is absorbed by water. Ionization of water molecules leads to the formation of hydrated electrons, hydroxyl radicals and hydrogen atoms [26]. Hydroxyl radicals have been shown to be the main species responsible for reactivity transfer from water to polymer. They abstract hydrogen atoms from PVP macromolecules, producingpolymer radicals. These macroradicals recombine, and if they are located in different chains, give rise to new macromolecules. If the amount of these new macromolecules is sufficiently great, a gel like material is obtained by intermolecular cross-linking as shown Figure 8.

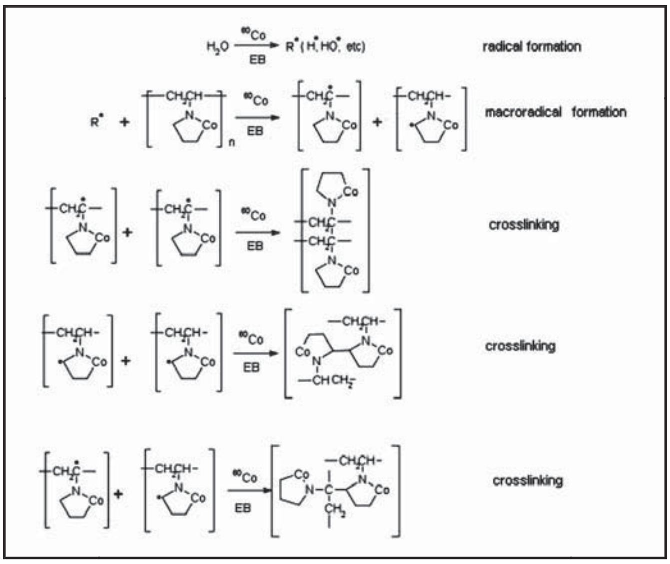

Figure 8. Possible cross-linking reaction mechanisms of PVP hydrogel formation

For the formation of cross-linked macromolecules, the presence of two radicals on neighboring chains and their subsequent combination is required. In the proposed mechanism the two radicals are combined themselves or with each other.

Figure 9 shows the gel content of cross-linked PVP chains formed as a function of the absorbed radiation dose.

As it can be seen the gel content increases from approximately 43% to about 97% with an increase of the absorbed dose from 8 kGy to 40 kGy. Ajji, et. al. [13] reported a high gelation percent in PVP membranes in the absence of PEG, and a gelation decrease with increasing the PEG concentration. They explainedthat PEG plays a role of plasticizer and also acts as a radical scavenger. In the present work the PEG concentration used was only 1.5%, which is close to the value used by Ajji, at absorbed dose of 25 kGy when producing hydrogel wound dressings using gamma radiation [13].

In Figure 10 are presented the results of sol-gel analysis obtained in the present work for the radiation cross-linking of PVP. The data for the sol-gel analysis were obtained from the gravimetric determination of sol fraction after a given irradiation dose. With the values of s and D, it is possible to estimate the cross-linking parameters with the use of a freely available computer program [27]. The values obtained are $p_0/q_0 = 0$, $D_v = 0.71$ and $D_g = 1.72$. This value of D_g is in good agreement with the value reported for PVP hydrogels by Benamer, et. al. [28]. The ratio $p_0/q_0 = 0$ indicates that cross-linking of PVP chains was the only occurring process during irradiation.

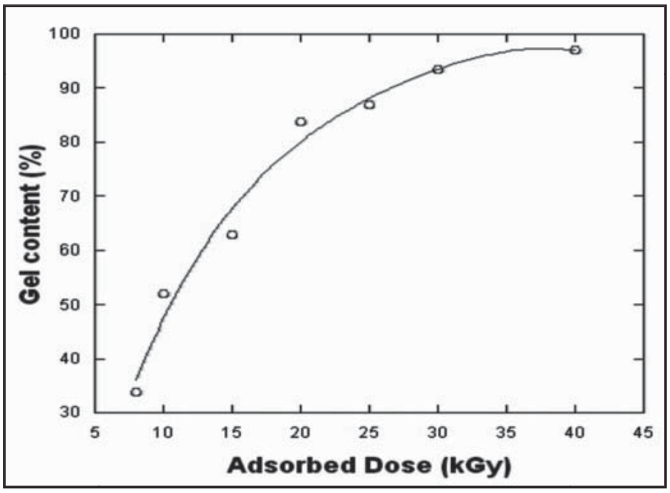

Figure 9. Effect of absorbed dose on PVP gel content

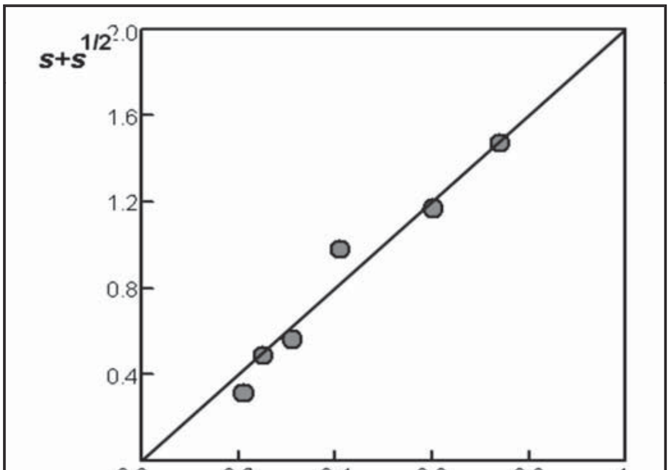

Figure 10. Sol-gel data of plotted in co-ordinates corresponding to Charlesby-Rosiak equation for PVP hydrogel membranes irradiated with EB at different absorbed dose

Olejniaczak, et. al. [29] reported p_0/q_0 values for gamma irradiation of PVP in aqueous solution of 0.22 in aerated solution and zero, from argon saturated solution and N_2O. Lugao, et. al. [10] reported a value close to 0.25 for aerated solution. They explain this difference by the long irradiation periods involved in UV-cross-linking and also the possible interference of degradation products. As it can be seen in figure 10, the obtained results fit to the straight line with good correlation as predicted by the Charlesby-Rosiak equation.

FTIR Spectroscopy

FTIR spectra of radiation cross-linked PVP, PVP loaded with 0.5% Laponite XLG and Laponite XLG are shown in Figure 11. The spectrum of pure PVP shows the characteristic absorption bands at 2948-2875 cm-1, CH and CH_2 stretching; 1759-1649 cm^{-1}, non-hydrogen bonded νC=O; 1492,1459,1419 and 1371 cm^{-1}, CH deformation of cyclic CH_2. A strong absorption band can be seen at 3390 cm^{-1}, which is due to OH stretching [14]. In the FTIR spectrum of Laponite XLG (empirical formula: $Na_{0,7}+[(Si_8Mg_{5,5}Li0,_3)O_{20}(OH)_4]^{0,7-}$) one can observe a broad band at 1044-952 cm^{-1}, Si-O stretching vibration and Mg-OH vibration, and 650 cm^{-1}, Si-O-Mg vibration. As expected, in the FTIR of PVP/Laponite XLGnanocomposite hydrogel, the main characteristic bands of both components were present.

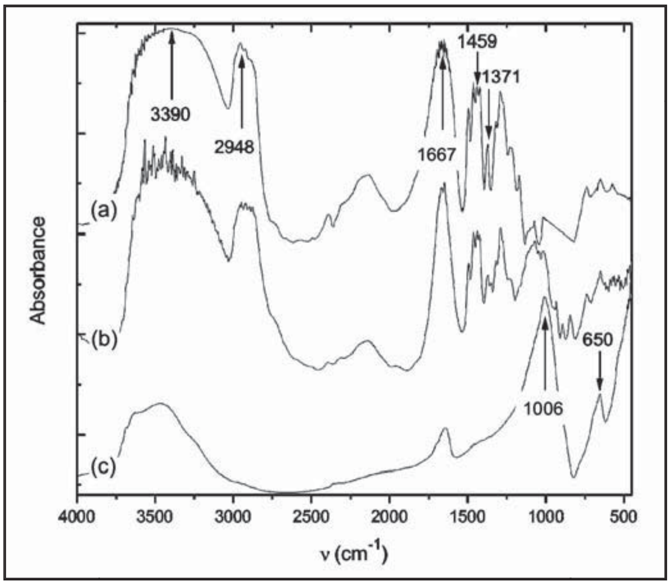

Figure 11. Infrared spectra of (a) pure PVP; (b) PVP xerogel membrane with 0.5% of Laponite XLG irradiated with EB at 25 kGy; (c) Laponite XLG

Mechanical analysis

As mentioned before, the main interest in the preparation of nanocomposites is to achieve materials with better mechanical properties. The mixing process of Laponite XLG with PVP hydrogel solutionprovoke the diffusion of the polymer chains into the basal space of the silicate layers of the organoclay creating strong interfacial interactions. Therefore it is expected that the nanocomposite hydrogel could bear higher external loads than the pure hydrogel.

The stress-strain curves obtained for the hydrogels prepared by EB and Co-60 irradiation procedures and the PVP nanocompositehydrogel membrane with 1% Laponite are shown in Figure 12. The resultant elastic mudulii evaluated from the initial slope of the curves were 1.25 MPa for the nanocomposite membrane, 0.39 MPa for the Co-60 irradiated and 0.38 MPa for the EB irradiated PVP hydrogel membranes.

These results indicate that that the irradiation method had almost no influence on the elastic modulus of PVP hydrogels, although Co-60 irradiation seems to have produced a somewhat stronger hydrogel as reflected by the higher area under the stress-strain curve. The higher value of elastic modulus for the nanocomposite hydrogel is undoubtly due to the presence of nanoclay, which results in a more entangled structure in compare with pure gel. This is a significant result because an increase in swelling ratio is usually accompanied by a decrease in shear modulus for non-composite gels [30].

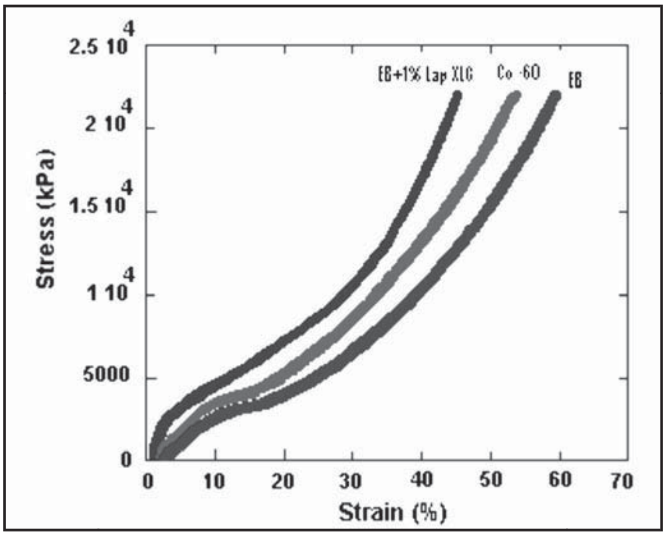

Figure 12. The stress-strain curves for the PVP hydrogel membranes irradiated with EB and with Co-60 irradiation facilities at 25 kGy

Figure 13 shows the elastic modulus of PVP hydrogel wound dressing as a function of the laponite XLG concentration. As can be seen the elastic modulus increases with increasing laponite concentration from 0.01 to 1.0%. This behaviour may be due to the intercalation of the polymerchains into the galleries of the clay layers, whichleads to the suppression of the mobility of thecopolymer segments near the interface and reinforce the network. Because of the improvement on the mechanical properties, the new membrane could be candidate for wound dressing under stresses.

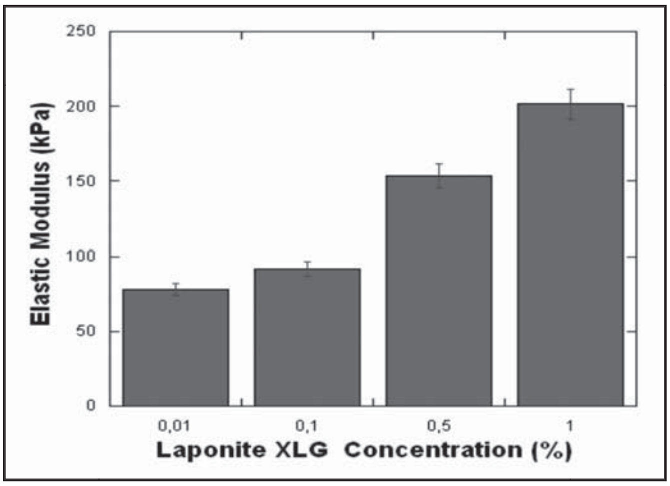

Figure 13. Elastic modulus of the PVP membrane dressing with respect to the laponite XLG concentration, irradiated with EB at 25 kGy

Estimated scale up developmentof CEACEL® wound dressing

After the positive results obtained at laboratory scaleit was decided to propose the production of a these PVP hydrogel membranes in larger scale, under the trade name CEACEL®. In order to determine technical viability for the pilot and industrial scale manufacture, the basic irradiation facility capacities such as irradiator activity or energy, raw material quantity and control parameters such as temperature, total production required for satisfying medical needswere estimated.

Subsequently, the obtained wound dressings should be subjected to physical and mechanical analysis in order to establish the product specifications.

Taking into account the existing manufacturing facilities for industrial and pilot trial studies, a general simplified diagram is proposed, to achieve the large scale production of CEACEL®. It is presented in Figure 14.

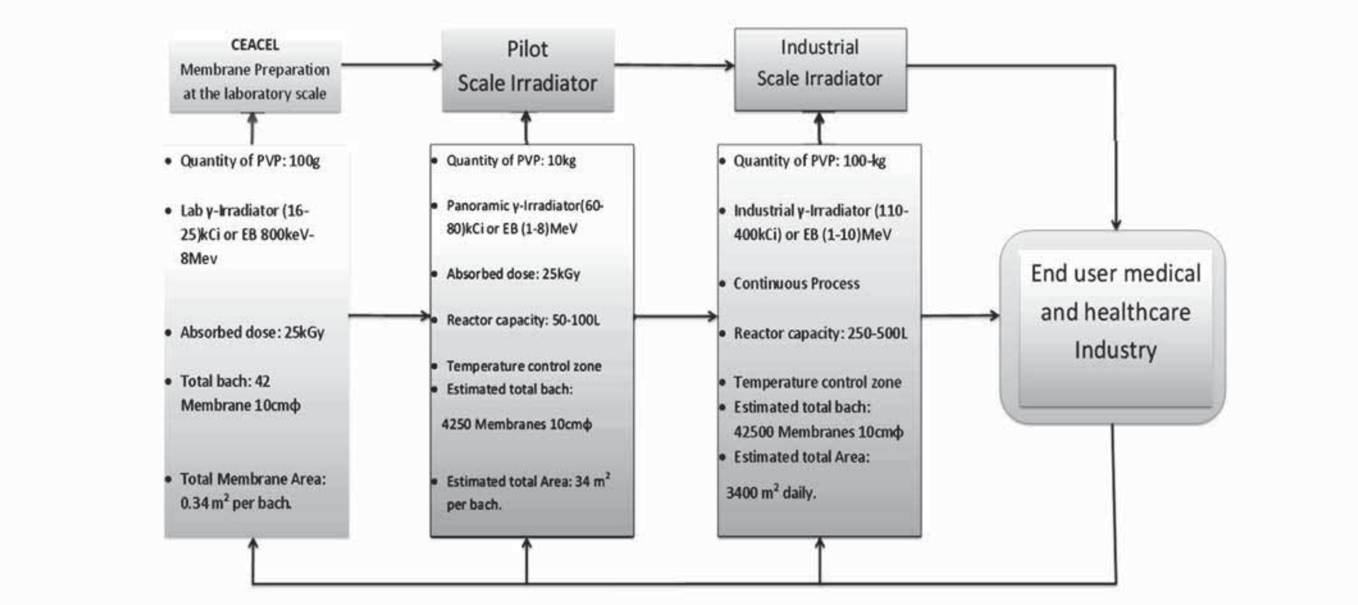

Figure 14. Estimated scale up development cycle for hydrogel CEACEL® wound dressing

Conclusions

Polyvinyl pyrrolydone hydrogel membranes and nanocomposite PVP hydrogel composites with Laponite XLG nanoclaywere prepared at laboratory scale by electron beam and Co-60 gammairradiation at 25 kGy, The elastic modulus of pure PVP hydrogels were almost independent of the irradiation procedure, but it was three times bigger for the nanocomposite hydrogel with 1.0% Laponite XLG. Therefore, the addition of Laponite XLG to PVP hydrogel will provideit with better elasticity. These results indicate that the nanocomposite hydrogel is the best choice for wound dressing applications due to its superior mechanical properties. On the basis of these results industrial and pilot trial studies for achieving a large scale production of the hydrogel dressing CEACEL® are proposed.

Acknowledgements

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