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Development of a methodology for the study of polymer wound coatings for application characteristics

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Abstract

This paper reports a research methodology for characterizing wound dressings in order to assess the application properties of medical devices as a whole. Wound dressing was based on grafting polymerization of N-vinyl caprolactam and 2-hydoxyethyl acrylate on polyvinyl alcohol. The obtained copolymer was characterized by FTIR. Cross-linked films of wound dressings were obtained by radiation treatment of the copolymers. The physico-mechemical properties of wound dressings were investigated. Testing included degree of swelling, elastic modulus, tensile strength and elongation at break. The radiation doses of the reaction affected physico-mechanical properties of wound dressings. As the dose of radiation increased, the yield of gel increased, degree of swilling and tensile strength decreased. Also, the results indicated that yield of the crosslinked fraction increases, and the swelling capacity of polymer mesh decreases with increasing 2-hydroxyethyl acrylate content in the graft copolymer

Keywords: wounds, research methodology, degree of swelling, mechanical properties, adhesion to skin.

Introduction

Wounds are different, and each category has its own special reasons for healing. Wound healing is an unsolved therapeutic problem among the medical community and this problem remains relevant due to the severe course of the wound process [1-6]. It is unrealistic to expect that special wound coverings will cover all the characteristics that would meet general needs for wound healing. Functional wound coverings should ensure wound healing with minimal time and cost [7]. In modern medicine, the list of wound coverings is constantly growing. At the moment, there are about 300 names. One of the principles by which you can divide wound coverings into groups is their structural and functional feature. There are the following groups of coverings: film, hydrocolloid, hydrofibres, alginates, collagen, hydrocellular, hydrogel, atraumatic and sorbing coverings [8-10]. The main requirements for formulating wound coatings are the creation of an optimal microenvironment for wound healing, high absorption ability against wound exudate, the ability to prevent the penetration of microorganisms, sufficient permeability to gases, water vapor, elasticity, the absence of pyrogenic, antigenic, toxic, local irritating and allergic actions [11]. An analysis of the literature indicates a continued search for solutions in creating an "ideal wound coating" for treating wounds. Therefore, the assessment of the effectiveness of novel dressings is one of the directions of researchers in this area. The application characteristics of synthetic dressings are determined by the functional activity of the polymer base, the correct choice of the drug and the way it is immobilized into the polymer matrix [12]. Water-soluble poly-N-vinylamides are widely used in medicine, biotechnology, membrane technology, cosmetology, and many other areas. Among these polymers, high-molecular-weight compounds based on N-

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vinylcaprolactam (NVCL) are of special importance due to their availability and valuable physicochemical, chemical, and biological properties [13] Moreover, the properties of the polymer matrix should not reduce the bioavailability of drugs, sorption and desorption properties, gas permeability and mechanical characteristics, i.e. application properties of the medical device as a whole. It is necessary to use modern, objective methods for studying the properties of materials for wound treatment. copolymerization of vinylcaprolactam with representatives of differ- ent classes of vinyl monomers allows changing some properties typical of NVCL homopolymers. Due to a wide range of their useful properties, NVCL and its copolymers are now increasingly applied in medicine as suture materials, wound- and burn-healing dressings, are included in ointments and different medicinal preparations, drug carriers, dietary supplements, *etc* [14-16]. On the other hand, Poly (vinyl alcohol) is a polymer of great interest because of its many desirable characteristics specifically for various pharmaceutical and biomedical applications [17, 18]. PVA is a water-soluble polymer and has a relatively simple chemical structure with a polar hydroxyl groups (‗OH), these highly polar hydroxyl groups tend to form intermolecular and intramolecular hydrogen bonds, improving the integrity of blends accordingly [19, 20]. Due to the fact that there are currently no target standards in the Republic of Kazakhstan for modern wound dressings and coatings, the need to develop a methodology for characterization is becoming obvious and relevant.

The aim of this work is to develop a methodology for the study of the physicochemical properties of wound dressings to assess their performance.

Experimental

Materials

N-vinylcaprolactam (NVCL, 98% purity) and ammonium persulfate (APS) were used without further purification and 2-hydroxyethyl acrylate (HEA, 96% purity) was purified by passing through a column filled with alumina and were purchased from Sigma-Aldrich (USA). Polyvinyl alcohol (PVA) with a molecular weight of M_W ~145,000 and a residual content of acetate groups of 3.013, 98% hydrolyzed, soluble in water when heated to 75 °C, was purchased from Merck (Germany) and used without further purification.

Synthesis of copolymers NVCL with HEA and PVA.

Copolymers of NVCL with HEA and PVA were obtained by the graft copolymerization process. PVA was dissolved in distilled water at 60 °C, after complete dissolution ammonium persulfate, used as the initiator, was added to the initial mixture. Through a dropping funnel, HEA and NVCL were added at a rate of 16 drops/min. Then, the reaction mixture was heated for 3.5 h at 75 °C. At the end of the process, the reaction mixture was cooled to room temperature. Polymer films from synthesized copolymers were prepared by pouring a polymer solution into polyethylene Petri dishes and evaporation of the solvent on air and in a vacuum drying chamber at 30 °C to a constant weight.

Radiation crosslinking of the films was conducted on an industrial electron accelerator ELV-4 with an energy range from 0.8 to 1.5 MeV, with a beam current of accelerated electrons up to 40 mA and maximum power up to 50 kW. After irradiation, the films were placed in distilled water for 24 h, then dried on air and in a vacuum drying chamber at room temperature. The yield of gel fraction (G, %) was calculated by the formula: $G=(m/m_o)\times100\%$, where m is weight of an insoluble film after washing and m is the initial weight of the film.

Wound dressings

Wound dressings were composed of water-soluble PVA-NVCL-HEA copolymers (used as plasticizing agent and stabilizer), agar (used as a thickener), and zinc oxide nanoparticles with antibacterial properties.

Characterization:

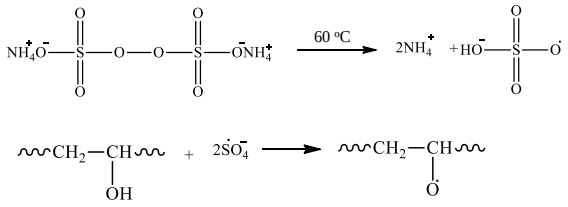
The IR spectra of the initial samples of polymers were recorded on a Nicolet IS10 FT-IR spectrophotometer (Nicolet Instrument Crop.) in the range 4000-800 cm^{-1}. Samples were prepared in the form of tablets with KBr. The kinetics of film swelling was studied by gravimetry. Pre-weighed dry films (square samples 2.5×2.5 cm weighing ~0.05-0.06 g) were placed in distilled water and isotonic 0.9% NaCl solution. The degree of swelling was calculated by the formula: $a=(m-m_o)/m_o$, where m is the weight of swollen film at a certain time point and m_o is the weight of the dry film. The degree of swelling was determined in several parallel experiments and an the mean value was used. The stress-related characteristics of the films were determined on a Zwick Z010 model Universal Testing Machine, tensile testing machine, in tensile mode at a speed of 10 mm/min. The thickness of the films was measured using a Quantum digital caliper Q-ACC-0010. The kinetics of film swelling was studied by gravimetry. Pre-weighed dry films (square samples 2.5×2.5 cm

weighing ~0.05-0.06 g) were placed in distilled water and isotonic 0.9% NaCl solution

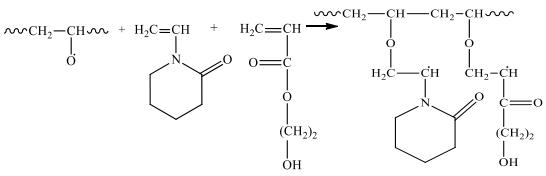
Results and discussion

The grafting polymerization by using $(NH_4)_2S_2O_8$ is shown in Scheme 1. In the initiation step, APS was thermally dissociated into anionic radical SO_4^{-2} [21], which react with OH group of PVA and free radical attached the double bond of NVCL and HEA. The polymerization was terminated when there two radical polymers combined.

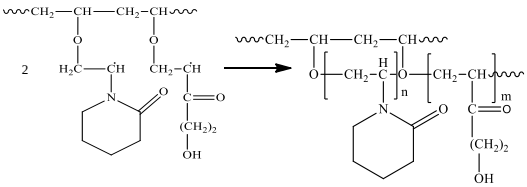
1. Initiation:



2. Propagation



3. Termination



Scheme 1: Mechanism of grafted NVCL and HEA on PVA.

FTIR spectra

The copolymer based on NVCL, HEA and PVA was confirmed by IR spectra of copolymers and PVA. The results obtained as shown in Figure 1. From Figure 1a, for pure PVA, the peaks appearing at 2946, 1264 and 1096 cm^{-1} are attributed to the C–H stretching, C–H bending and C–O stretching bands of PVA, respectively. The band at 3408 cm^{-1} is related to the O-H stretching frequencies of hydroxyl group [22]. The characteristic carbonyl group (C=O) band at 1735 cm^{-1} is related to the residual acetate groups, remaining after the manufacture of PVA from the hydrolysis of polyvinyl acetate [23-25]. New peaks were observed at 1705.8 cm-1 and 1050 cm-1 related to carbonyl group and C – O – C of the NVCL and HEA as shown in Figure 1b.

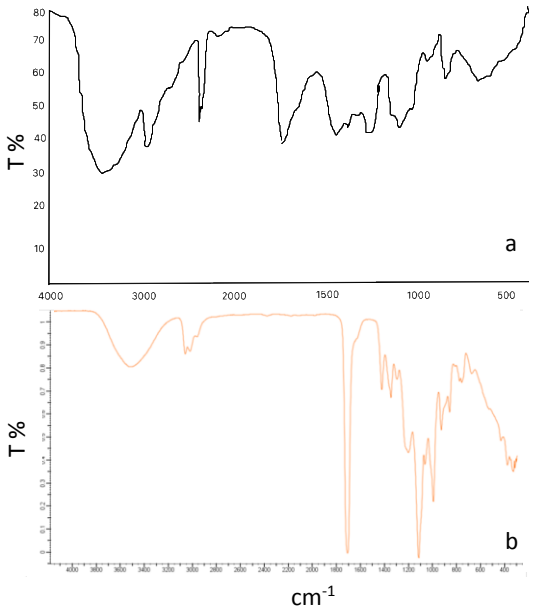


Figure 1. FTIR spectra of (a) Pure PVA; (b) PVA-NVCL-HEA copolymer

Yield of gel

It is known that the main component in wound dressings is the crosslinked polymer matrix whose properties strongly dependent on the degree of crosslinking. Therefore, the determination of the yield of the gel fraction is logical. In this work, *the yield of the gel fraction* was calculated using the equation:

$$\Gamma\% = m_0 \times {}^{100}/_{m_{synthesized}}$$

where m_0 – weight of the dried sample, $m_{synthesized}$ – weight of the synthesized dressing sample. The weight of the dried sample was determined after drying the sample in a vacuum oven until a constant weight.

The yield of the gel fraction depicts the efficiency of crosslinking of polymer molecules, which, in turn, determines the efficiency of immobilization of the antibacterial drug in the hydrogel matrix and its rate of release. Figure 2 presents the data acquired upon studying the yield of sol and gel fractions for hydrogel dressings based on PVA-NVCL-HEA depending on the radiation dose [26]. It was established that the percentage of the gel fraction in the irradiated samples increased with increasing the dose of radiation, especially for samples containing a lower amount of NVCL (Figure 2a): the yield of the gel fraction for samples containing NVCL = 2.71 mol.%, with increasing the dose of radiation from 5 to 25 kGy increased from 9.92 to 15.86%.

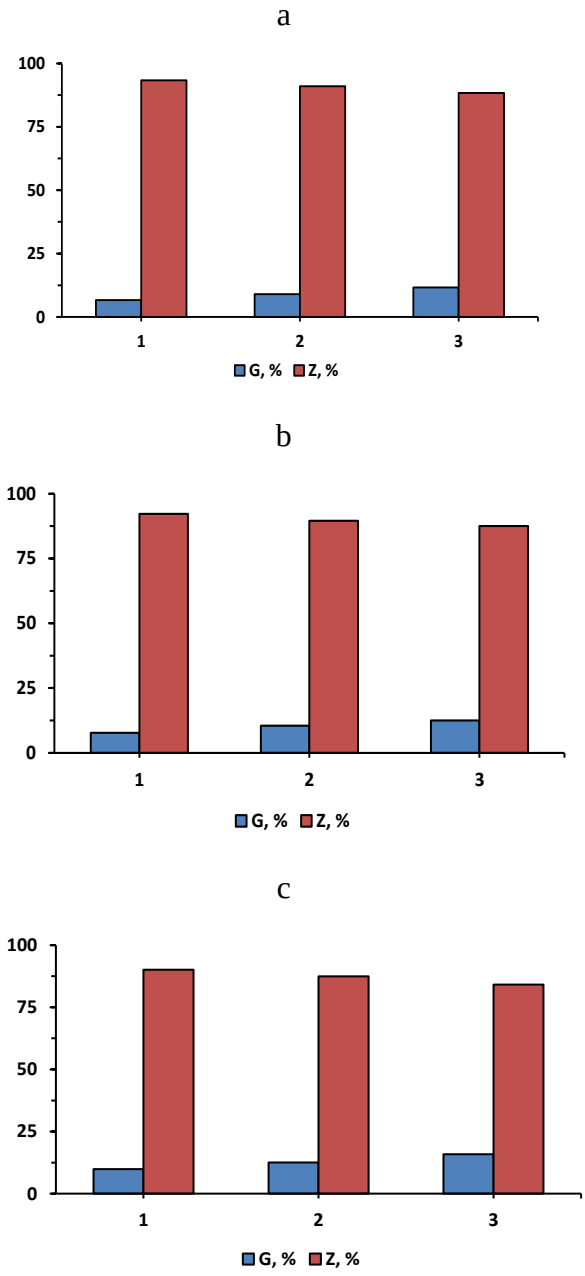


Figure 2. Yield of sol-gel fraction of hydrogel dressings based on [PVA]:[NVCL]:[HEA]= 61.36: 2.71: 35.94 (a); 72.56:10.74:16.69 (b) and 74.18:16.66:9.19 mol.% (c). Dose of irradiation: 5 (1); 15 (2) and 25 kGy (3)

The degree of swelling is one of the most important characteristics of wound dressings and depends on the composition and structure of the hydrogels. Determination of the degree of swelling of wound dressings is used to assess their absorption capacity of fluids and exudates. In this connection, often in the literature this indicator is referred to as the sorption ability of the material.

Figure 3 displays the changes in the sorption ability of PVA-NVCL-HEA based hydrogel samples in various media. The choice of isotonic solution and phosphate buffer is due to a similar composition of solutions with human body fluids.

In addition, the amount of water in hydrogel wound dressing often determined using the following equation:

$$W_w = W_g - W_t/W_g$$

where W_w – weight of water in % relative to the total weight of the sample, W_g – weight of the sample containing water, W_t – weight of the dried sample.

The amount of water in the dressing is an important indicator of the application of wound coatings. Some coatings available on the market, after opening the packaging almost in the first hours of use, lose a large amount of moisture which makes them brittle and as a result unsuitable for further use.

The effectiveness of dressings for treating wounds is largely due to their sorption properties [27]. Extensive wounds produce a significant amount of exudate – up to 0.35 mL/cm^2 per day. Removal of the secreted exudate from the wound surface is necessary to prevent the reverse absorption of toxic decay products of necrotic tissues into the body. At the same time, due to the elimination of Na^+ and K^+ ions, normalization of the osmotic pressure is ensured, therefore reducing the level of damaged tissue. The sorption ability of the wound dressing is dependent on the rate of absorption of exudate and the sorption capacity of the dressing. Sorption capacity is the amount of a substance that is capable of absorbing a sorbent per unit mass [24]. Thus, in this work, the kinetics of sorption of wound dressings based on PVA-NVCL-HEA copolymers prepared at different radiation doses in distilled water, isotonic solution, and phosphate buffer was studied (Figure 3).

The mechanical test of hydrogel dressings is carried out on a tensile testing machine. During the test, parameters such as tensile strength and strain at break are evaluated. Figure 4 depicts one of the examples of specimen preparation of for testing the mechanical properties.

Tensile strength test. In this test, a dumbbell-shaped samples are used with expansion at both ends, a width in the center of the sample from 10 to 15 mm, along

the edges of the sample with a width of up to 30 mm, a length of at least 50 mm. The maximum deviations along the width of the sample should be ±0.2 mm.

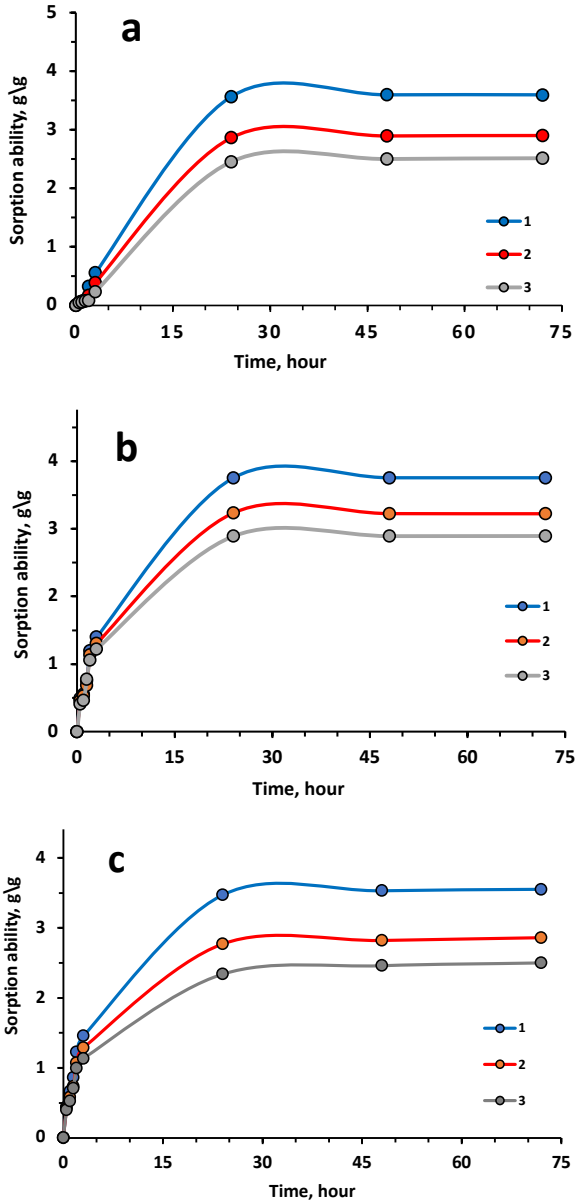


Figure 3. Sorption ability of dressings based on [PVA]:[NVCL]:[HEA] = 61.36: 2.71: 35.94 mol.%. , water (a), isotonic solution (b) and phosphate buffer

The width of the sample should be indicated in the normative and technical documentation for the material. The thickness of the test material is taken as the thickness of the sample. At least five samples are used to test wound dressings. The thickness and width of the samples are measured in three places [28].
From the obtained values, the average means are calculated from which the initial cross section A_0 is then calculated. Tests are performed at 23 ± 2 °C and relative humidity of 50 ± 5%.

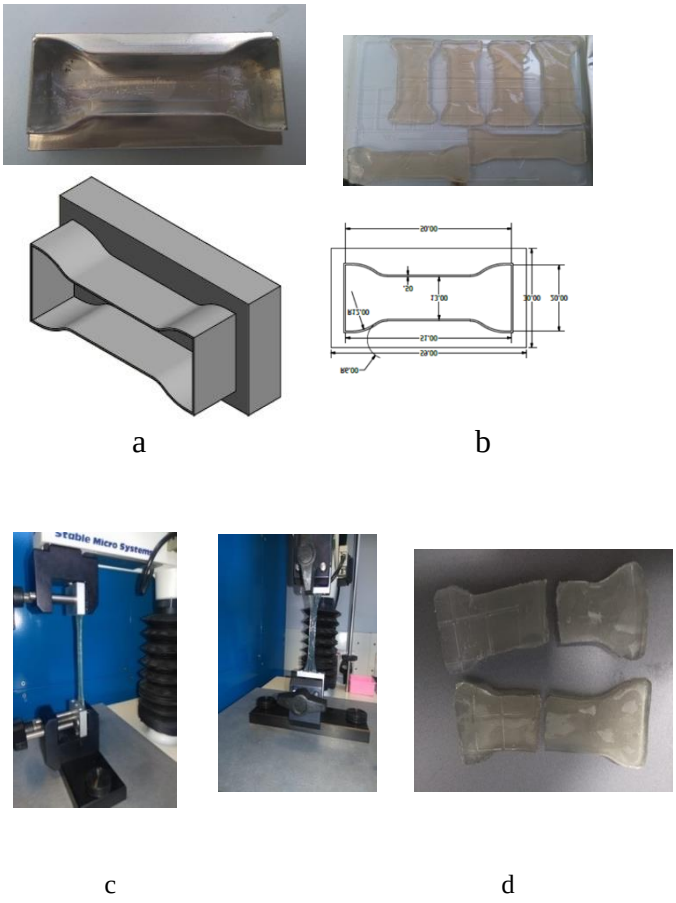


Figure 4 – The mold for cutting samples (a), specimen preparation and dimensions (b), the process of testing hydrogels on a universal tensile testing machine "Texture Analyzer" (c), the type of sample after rupture (d)

In general, the equation for determining the tensile strength of the material as follows:

$$R_p = F_{max}/A_0$$

where F_{max} – load of rupture; A_0 – the initial cross-sectional area of the specimen.

Methods for determining the elastic modulus in strain and compression. Samples are prepared in the form of discs weighing 3 g each with a 2.4 cm diameter, height of 0.7 cm, and surface area of 14 cm^2. The mechanical characteristics of hydrogel

discs are determined on a "Texture Analyzer". For this purpose, five samples of the same composition are used. Tests are carried out using a single compression force on the disc sample. Compression is applied using a metal cylinder with a diameter of the working surface equal to 3.5 cm. The loading speed is 1 mm/min, the compression force is 1 kg, and the compression shutter speed is 10 sec. The experiments are carried out at 24 °C [29-31]. External forces applied to the body cause a change in interatomic distances, which therefore causes a change in the size of the deformable body by Δl in the direction of the force (upon compression – shortening; upon strain – elongation). The relative deformation is equal to the ratio of the absolute deformation Δl to the initial linear size l of the body:

$$\varepsilon = {\Delta l}/{l}$$

The elastic modulus E (Young's modulus) links the elastic deformation and uniaxial stress through a linear relation expressed by Hooke's law:

$$\varepsilon = {\sigma}/{E}$$

While uniaxial strain (compression), the stress is determined using the equation:

$$\sigma = {P}/{A}$$

where P – force applied, A – the area over which the force is distributed or area of the original cross section. Elastic modulus is a measure of the rigidity of the material. Materials with high energy of interatomic bonds are characterized by a large elastic modulus. When conducting compressive strains, diagrams are built by plotting σ values along the ordinate axis and ε values along the abscissa axis. Therefore, according to the acquired data, the effect of the consumption of various components on the deformability of hydrogels is established.

In the course of this work, experiments were conducted to study the physico-mechanical characteristics of hydrogel dressings based on PVA, NVCL and HEA. Comparative studies were performed over relative elongation at break and tensile strength upon strain of hydrogel dressings with different composition of the copolymers. The data presented in Table 1 indicate that with an increase in the acrylate component in the composition of the initial mixture, the physico-mechanical parameters of hydrogels are enhanced.

The increase in tensile strength of hydrogel dressings based on the increase in the content of 2-hydroxyethyl acrylate is explained by, mainly, additional interactions between the functional groups of the polymers, which leads to the appearance of additional crosslinking. An increase in the content of HEA to 16.66 mol.% leads to an increase in tensile strength by 1.5-3 times.

Based on the experimental data depicted in Table 1, it could be concluded that increasing the content of HEA in the polymer base up to 30 wt.% leads to an increase in Young's modulus values by an average of 1.3 times. As mentioned above, interactions between the hydroxyethyl acrylate macromolecules play the role of additional nodes in the structure of the material, which causes an increase in tensile strength of hydrogel dressings.

TABLE. 1. Mechanical properties of the hydrogel dressings based on PVA, NVCL and HEA depending on the composition and dose of irradiation

Copolymer composition [PVA]:[NVCL]:[HEA], mol.%	Dose of irradiation, kGy	Young's modulus, kPa	Tensile strength, Pa	Elongation at break, %
61.36: 2.71: 35.94	5	1.4	366	125.7
	15	2.1	437	120.8
	25	3.6	547	115.2
72.56:10.74:16.69	5	0.9	187	120.6
	15	1.7	286	116.7
	25	2.6	400	115.4
74.18:16.66:9.19	5	1.2	150	112.5
	15	2.0	193	109.6
	25	2.4	218	109.1

Figure 5 presents the effect of the radiation dose on the ultimate tensile strength's values of samples of hydrogel dressings. It was found that with increase in radiation dose, the tensile strengths also increase. Apparently, with an increase in the radiation dose, the degree of crosslinking increases, which in turn, affects to the strength characteristics of the samples. The data acquired are in good agreement with the data on the yield of the gel fraction at different doses of radiation.

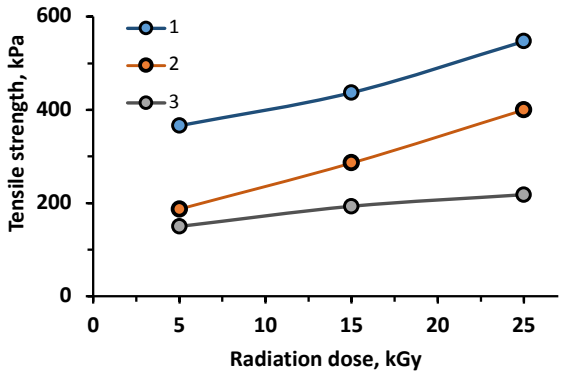


Figure 5: Tensile strength of hydrogel dressings based on [PVA]:[NVCL]:[HEA] mol.% = 61.36: 2.71: 35.94 (1); 72.56:10.74:16.69 (2); 74.18:16.66:9.19 (3) and different radiation dose

Conclusion.

Based on the analysis of the classification of the physicochemical and mechanical properties of wound dressings as well as the synthesized dressings based on PVA-NVCL-HEA, methodologies for determining the physico-mechanical characteristics of hydrogel wound dressings have been developed. These tests include the determination of the tensile strength, hardness, elastic modulus (Young's modulus) under strain and compression, resistance to temperature. The mechanical properties increased with decreasing dose of radiation as well as decreasing ration of HEA in the grafted copolymer. While yield of gel fraction increased with increasing dose of radiation.

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Conflict of interest.

Authors declare no conflict of interest.

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