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DESİGNİNG POLY-N-VİNYLPYRROLİDONE BASED HYDROGEL AND APPLİED HİGUCHİ, KORSMEYER-PEPPAS, HİXSON-CROWELL KİNETİC MODELS FOR CONTROLLED RELEASE OF DOXORUBİCİN

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The paper deals with water swollen and pH environment-sensitive hydrogels by means of stitching of poly-N-vinylpyrrolidone with average molecular weight 10 kDa and N,N`- methylene-bis-acrylamide by 1-20% (mass). Hydrogel`s swelling degree and kinetics and their structures were characterized by FTIR, NMR, SEM and TGA methods. Also, some mechanical, biocompatible and mucoadhesive properties of hydrogels were determined. Besides, hydrogels were immobilized by means of doxorubicin as a model preparation and various mathematical models of zero and first order, as well as laws of Korsmeyer -Peppas and Hixson-Crowell were applied to its release profile. Note that the drug proceeded in line with non-Fickian diffusion mechanism while the releaee profile is best fitted with the Higuchi square root model.

Keywords: *poly-N-vinylpyrrolidone, gel, drug, controlled release, kinetic model, Higuchi, Non-Fickian*
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Introduction

As is known, antibiotics, enzymes, alkaloids as well as physiological active compounds cannot provide long-term therapeutic concentrations in the organism. As a result, the area of inflammation or trauma cannot be effectively cured. The effect of the drugs is due to their short-term distribution and metabolism in the bloodstream.

In order to control the effect of treatment, it is necessary to take the drug more often or 2-3 times the therapeutic dose. But this can lead to adverse complications in other tissues , sometimes violate their functions and led to other chronic diseases[1-3].

To overcome this drawback, it is necessary to maintain a therapeutic concentration of drugs in the blood for a long time.. For this purpose efforts were made to prepare natural and synthetic compounds-based hydrogel, as well as carriers arising from their combination with metal nanoparticles, coatings, ultra-thin films, etc. and improved biomaterials. This led to the effective delivery of the active drug immobilized in a pre-structured composition to the desired area and at the same time controlled release to provide a therapeutic limit. It is important that the hydrogel acts against environmental irritants. As a result, the synthesized hydrogel is pre-designed taking into account the nature of the working medium and is characterized as hydrogels sensitive to pH, temperature, ionic strength, and electric field [4-6]. Hydrogels are three-dimensional materials, which created by crosslinking linear natural and synthetic polymers with bifunctional low molecular weight compounds. The ability of hydrogels to expand and tighten in volume depending on environmental influences and behave like tissue, absorbing a certain number of water molecules, leads to biocompatibility. This property provides a controlled release of immobilized drugs by volume and surface of the gels. The non-toxicity of poly-N-vinylpyrrolidone (PVP), its hydrophilicity, mucoadhesiveness and the tendency to form complexes with drugs make it possible to use

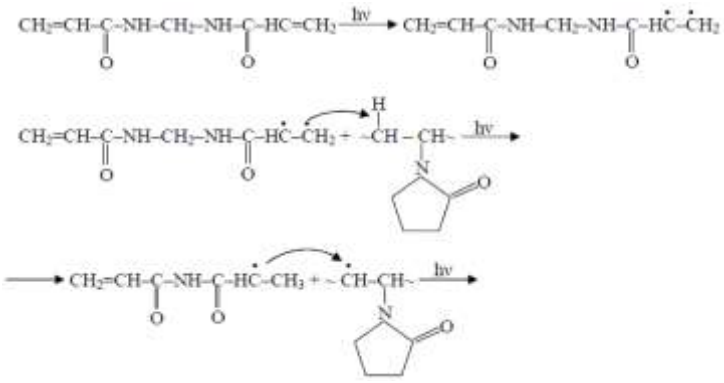
this hydrogel as a matrix for the efficient transport of drugs [7-9]. An analysis of the studies shows that the main problem after the immobilization of drugs lies in the mechanism of their separation from the hydrogel. These results provide a controlled and sustained release of the drug. From this point of view, the pH-sensitive hydrogel was synthesized by the interaction of PVPr with N, N'-methylene-bis-acrylamide (MBAA); besides, kinetic studies of the separation of antibiotic doxorubicin from the hydrogel as a model drug were carried out.

Experimental part

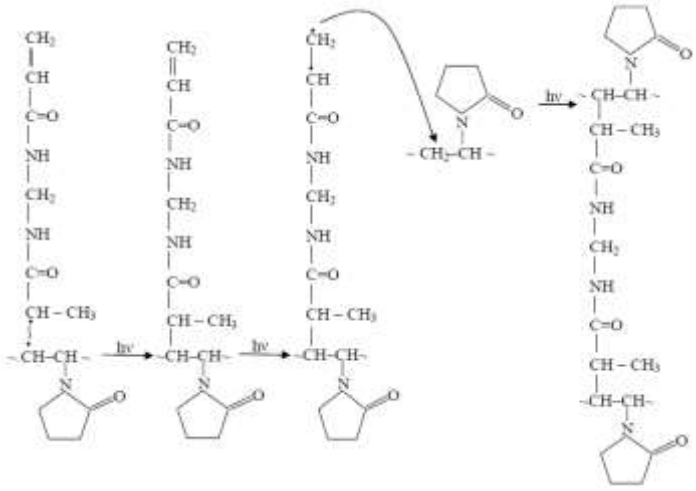
The chemically pure Poly-N-vinylpyrrolidone with average molecular weight of 10 kDa and cross-linking reagent - N, N`-methylene-bis-acrylamide were received from Fluka. Doxorubicin-Na used as a model drug is manufactured by TEVA Pharmaceutical Industry (Israel) under the code name ATX L01DB01 with a purity of 98% for pharmacological studies. Note that compounds such as a CH_3COOH, NH_4OH, CH_3COONH_4, HCl and KOH used to prepare buffer solutions, were chemically pure for chemical analysis. The structures were confirmed through the use of IR spectroscopy with Fourier transformation (Nicolet 5700FTIR THERMO) within the range of 4000 and 400 cm^{-1}. The ^{13}C NMR analysis of the samples was carried out on a BRUKER DSX-300 spectrometer and thermal analysis on a TQA EXSTAR TG / DTA 6300 instrument with a heating rate of 100 ° C / min and at atmospheric pressure within the range of 25-2000° C. A degree of hydrogel swelling was determined by the gravimetric method. The process of separating Na-doxorubicin from a hydrogel as a model preparation was studied in distilled water and buffer solutions with a pH of 2.2 and a pH of 7.4 [10, 11]. All the studies were carried out three times. Both, mechanism of hydrogel swelling and mechanism of drug release from the drug-loaded hydrogels were determined by using equation ($M_t/M_\infty=ktn$) provided by Ritger and Peppas [12,13]. Here, the ratio of M_t / M_∞ was the fractional swelling/separation of the drug at time t; k was constant for the drug-polymer system, and n was the diffusion rate of the swelling/separation mechanism. Different parameters of release kinetics of drugs from drug-loaded hydrogels were determined. Maximum amount of separation and initial amount were calculated by the equation $t/C_t = \alpha + \beta_t$. Here, $\boldsymbol{C_t}$ is the amount of drug released at time $\boldsymbol{t}$, $\boldsymbol{\beta=1/C_{max}}$ is the inverse of the maximum amount of released drug, $\boldsymbol{\alpha=1/(C_{max})^2}$, $\boldsymbol{k_{rel}=1/r_o}$ is the inverse of the initial release rate, and $\boldsymbol{k_{rel}}$ is the constant of the release kinetics [9]. To find out the mechanism of drug release from hydrogels, the data was treated in different mathematical models, i.e. zero order, first order, Higuchi square root law, Korsmeyer-Peppas model, and Hixson-Crowell cube root [14].

Results and discussion

The mechanism of the PVPr formation process, the structure of starting materials and the embedded polymer were identified using IR and NMR spectroscopy. In the IR spectrum of PVPr, absorption bands of 1430, 1230, 1638, and 3345 cm^{-1} frequencies to comply with functional groups > CH_2, -CH, > C = O, were observed and in the IR spectrum of the constructed polymer a decrease in the intensity of the absorption band > CH_2 observed. On the contrary, a characteristic peak of the -CH_3 group was observed in the spectrum. According to these results, it can be assumed that the construction of homopolymer took place according to the following chemical mechanism [15].



The cross-linking reaction occurring radical chain reaction and hydrogel obtained recombination of macroradicals. We can show the chemical structure of hydrogel as following according to NMR and FTIR analysis of initial and final productions.



The SEM images of hydrogel showed a porous structure with rough surface morphology. Also, porous structure provides more channels for water to diffuse out of swelled polymers and control the diffusion of the entrapped water-soluble drugs. With that consideration, as amount of MBAA increased, the size of porous one decreased, and the swelling degree began to get a low value. The 10% mass amount of cross-linking reagent characterized optimal swelling degree (180-200%) that was suitable for the immobilization of drugs. According to x-ray diffraction analysis, polymers exhibited a wide intensity spectrum characteristic of amorphous substances in the spectrum. In hydrogels, crystallinity increases by 5-15%. This results in a gentle peak narrowing. According to the TQA analysis, hydrogels loss up to 8.2-11% of their mass up to 1000 °C due to the separation of water molecules bound by hydrogen bonds on the surface or near internal volumes. Thermochemical destruction of hydrogels (weight loss 80-83%) occurrs after 150^0 C.

It was shown that the swelling of hydrogels, i.e. diffusion of solvent molecules occurs according to the non-Fickian mechanism. According to this mechanism, the diffusion rate of the solvent can be compared with the relaxation of polymer macromolecules. Solvent molecules increase the mobility of the polymer chain from glassy to swollen rubber. In a hydrogel sample, an increase in the amount of cross-linking material is characterized by an increase in swelling at first quickly and at an optimal rate for a short period of time, after which stabilization or a slight decrease is observed. The swelling rate in a 0.9% NaCl solution is less than the swelling rate in a distillation medium. This decrease in the swelling rate is due to the load protection effect of the leading cations, which reduces the osmotic pressure between water and gel.

Note that mechanical properties of hydrogels are very important for drug delivery pharmaceutical applications and protection of sensitive therapeutic reagents to be delivered to specific regions in the drug delivery system. The desired mechanical property of the hydrogels can be achieved by adjusting the cross-linking degree. Rise in the degree of cross-linking of the system results in a stronger gel. The mechanical property could be harmonious with a swelling degree of gel. Experiments found that optimal swelling degree and strong mechanical property for 10 kDa PVPr was 8-10% mass value of MBAA. Note that mucoadhesive and absorption properties of the hydrogel by the mucous membrane of the intestinal was investigated. The maximum force of adhesion was observed for the adhesion of PVPr-10MBAA hydrogel with the intestinal mucus membrane for 300-second contact time. This might be due to the ionic interaction of gel with the membrane. A little difference for swelling degree of gel was apparent in acidic and alkaline medium. This was due to the same degree of dissociation of functional groups in the hydrogel content at a wide interval of buffer solutions. The drug released was higher in pH 2.2 buffer than pH 7.4 buffer solution and distillation water medium.

That was due to better solubility of doxorubicin in pH=2.2. The swelling of hydrogels was nearly the same in both pH 2.2 and pH 7.4 buffer and, hence, the drug release in the present case was solubility controlled. The release of the drug occurred through a non-Fickian diffusion mechanism and the rate of diffusion was higher during the earlier stages of drug release (Tab.1).

Table 1. Kinetic parameters of doxorubicin release from drug-loaded PVPr - 10% MBAA-based hydrogel, n-diffusion exponent, k-gel characteristic constant, and different diffusion coefficients.

Release medium	diffusion exponent, n	gel characteristic constant, $k\times10^3$	Maximum amount of released drug, C_{max}(mgL^{-1})	Constant of the kinetic of release, $k_{rel}\times10^5$ (S^{-n})	Initial release rate, $r_0\times10^2$ (mgL^{-1}s^{-1})	Diffusion coefficients (cm^2/min)		
						Initial, $D_i\times10^5$	Average, $D_a\times10^5$	Late time, $D_l\times10^5$
pH=2.2 buffer	0.682	17.754	451.34	89.27	178.74	24.752	15.118	22.437
Dest. water	0.678	18.134	250.61	153.82	103.41	21.236	14.790	20.862
pH=7.4 buffer	0.698	16.057	392.72	81.73	144.55	26.218	14.017	24.261

The kinetic parameters indicated that the maximum amount of drug (Cmax) has been released in a pH 2.2 buffer solution. It has also been found that drug release from hydrogel has obeyed all kinetic models (R2 > 0.97) and best fitted in the Higuchi square root model with the highest value of the regression coefficient (R2) (Tab.2).

Table 2. Kinetic interpretation of doxorubicine release from PVPr-10MBAA based hydrogel.

Release medium	Zero order [R^2], k_0 (min^{-1})	First order [R^2], k_1 (min^{-1})	Higuichi [R^2], k_H (min$^{-1/2}$)	Korsmeyer-Peppas [R^2], k_{KP} (min^{-n})	Hixon-Crovell [R^2], k_{HC} (min$^{-1/3}$)
pH=2.2 buffer	0.9658	0.9824	0.9946	0.9958	0.9943
Dest. water	0.9724	0.9946	0.9956	0.9932	0.9983
pH=7.4 buffer	0.9817	0.9712	0.9972	0.9947	0.9981

According to the Higuchi square root model, the separation of a drug from a hydrogel is directly proportional to the square root of time. The separation model was described by

the Higuchi model where a part of the loaded drug was first separated, so that these layers had a weakened bond with the drug molecules while the interaction was intense. The drug in the inner layers of the next polymer matrix started to be released upon dissolution and diffusion [16-17].

In hydrophilic polymer-based drug delivery systems, the drug release is controlled by the inward flux of water molecules and resultant swelling of the polymer matrix, which are referred to as swelling-controlled drug delivery systems. In these systems, the drugs are initially dissolved or dispersed in the glassy polymers. Upon contact with biological fluids, the hydrogels begin to swell and two distinct phases can be observed in the polymer; the inner glassy phase and the swollen rubbery phase. The drug molecules are able to diffuse out of the rubbery phase of the polymer. Clearly, the drug release from the drug-loaded polymers is controlled by the velocity and position of the glasserubbery interface, since no drug diffuses out of the glassy region of the polymer. A very important phenomenon of macromolecular relaxation takes place at the glasserubbery interface and significantly affects the drug release [18]. According to kinetic results hydrogel - cross-linking of PVPr with 10% (mass) MBAA could use as depo for addresses delivery and control release of antibiotics and protein, and treatment of local infections.

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POLİ-N-VİNİLPİRROLİDON ƏSASLI HİDROGELİN DİZAYNI VƏ DORKSORUBİSİNİN NƏZARƏTLİ AYRILMASINA HİQUÇİ, KORSMEYER-PEPPAS, HİKSON-KROVELL KİNETİK MODELLƏRİNİN TƏTBİQİ

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Tədqiqat işində orta molekul kütləsi 10 kDa olan poli-N-vinilpirrolidonun N,N`-metilen-bis-akrilamidlə 1-20% (kütlə) tikilməsindən mühitin pH-na həssas, suda şişə bilən hidrogellər sintez edilmişdir. Hidrogellərin şişmə dərəcəsi və kinetikası, eləcə də onların struktur quruluşları İQ, NMR, SEM, TQA üsulları ilə xarakterizə edilmişdir. Həmçinin hidrogellərin bəzi mexaniki, biouyğunluq və mukoadgeziv xassələri öyrənilmişdir. Bundan savayı model dərman kimi doksorubisinin hidrogellərə yüklədilməsi həyata keçirlmiş və sıfır, birinci tərtib, Hiquçi kvadrat kök qanunu, Korsmeyer-Peppas və Hikson-Krovell kub kök müxtəlif kinetik modelləri ayrılmanın profili üçün tətbiq edilmişdir. Dərmanın ayrılması qeyri-Fikian diffuziya mexanizmi ilə baş verir və ayrılmanın istiqaməti yaxşı halda Hiquçi kök sahə modelinə uyğun gəlir.

Açar sözlər: *poli-N-vinilpirrolidon, N,N`-metilen-bis-akrilamid, gel, doksorubisin, Hiquçi, Korsmeyer-Peppas və Hikson-Krovell kinetik modelləri.*

РАЗРАБОТКА ГИДРОГЕЛЯ НА ОСНОВЕ ПОЛИ-N-ВИНИЛПИРРОЛИДОНА И ПРИМЕНЕНИЕ КИНЕТИЧЕСКИХ МОДЕЛЕЙ ХИКУЧИ, КОРСМЕЙЕРА-ПЕППАСА, ХИКСОНА-КРОВЕЛЛА ДЛЯ КОНТРОЛИРУЕМОГО ВЫДЕЛЕНИЯ ДОКСОРУБИЦИНА

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Синтезированы набухающие в воде и чувствительные к pH среды гидрогели путем сшивания поли-N-винилпирролидона со средней молекулярной массой 10 кДа и N,N`-метилен-бис-акриламида (1-20%). Степень и кинетика набухания гидрогелей, а также их структуры были определены

методами ИК, ЯМР, СЭМ, ТГА. Также были изучены некоторые механические, биосовместимые и мукоадгезивные свойства гидрогелей. Кроме того, осуществлена иммобилизация гидрогелей доксорубицином в качестве модельного препарата и к профилю его выделения применены различные математические модели – нулевого и первого порядков, закон Хикучи, Корсмейера-Пеппаса и Хиксона-Кровелла. Высвобождение лекарственного средства происходило по нефиковскому механизму диффузии, а профиль высвобождения лучше всего соответствует модели Хигучи.

Ключевые слова: *поли-N-винилпирролидон, N,N`-метилен-бис-акриламид, гель, доксорубицин, закон Хикучи, Корсмейера-Пеппаса и Хиксона-Кровелла*