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APPLICATION OF KINETIC RESULTS OF DOXORUBICIN RELEASE FROM POLYACRYLIC ACID-BASED HYDROGEL TO HIGUCHI, KORSMEYER-PEPPAS, HIXON-CROWELL EQUATIONS

Sh. Z. Tapdiqov*[1,2], D. B. Taghiyev[2]

[1]*«OilGasScientificResearchProject» Institute, SOCAR, Baku, Azerbaijan*

[2]*Institute of Catalysis and Inorganic Chemistry named after Acad. M. Nagiyev, Ministry of Science and Education of the Republic of Azerbaijan, Baku, Azerbaijan*

A B S T R A C T

In the study, the release processes of doxorubicin immobilized in the pH-sensitive water-swellable hydrogel sample obtained from the crosslinking of polyacrylic acid with an average molecular weight of 230 kDa with 10% (mass) N,N'-methylene-bis-acrylamide were investigated. The immobilization of doxorubicin on the water-swelling polyacrylic acid-based hydrogel was carried out by the sorption method. The immobilization was monitored for 24 hours and continued until the equilibrium concentration of the drug in the medium was reached. It was found that the immobilization of doxorubicin on the polyacrylic acid-based gel occurs through non-covalent chemical interactions, including hydrogen bonding, electrostatic forces, and hydrophobic interactions. It has been shown that the immobilized organic substance, localized both inside and on the surface of the gel, retains its physicochemical properties for an extended period of time. The controlled release process was studied in a buffer medium of pH=7, which is close to the small intestine medium. The drug release was quantitatively characterized as a function of time. The kinetic data of the release were fitted to various kinetic equations such as zero order, first order, Higuchi square root law, Korsmeyer-Peppas and Hixson-Crowell cube root. It was found that the release of doxorubicin occurs by a non-Fickian diffusion mechanism and the direction of release fits well with the Higuchi model. Thus, the effective viscosity of polyacrylic acid and its ability to complex with metal ions to form gel systems provide the basis for its use in the preparation of materials for isolation formation water and sand protection in oil and gas industry applications.

Keywords: polyacrylic acid; hydrogel; immobilization; controlled release; kinetic models.

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Introduction

It is known that the oral use of physiological active substances such as antibiotics, enzymes, alkaloids, etc., in their free form, cannot maintain therapeutic concentrations in the body over extended periods. As a result, the affected area, such as inflammation or injury, cannot be effectively treated [1, 2]. The limited efficacy of such drug preparations is associated with their rapid distribution through the bloodstream and subsequent metabolism. To maintain therapeutic effect, it becomes necessary to frequently use the drug or take doses 2-3 times higher than the therapeutic amount [3, 4]. This, in turn, negatively affects the function of other tissues, causes adverse reactions, and sometimes leads to their dysfunction and the development of other chronic diseases [5, 6].

To overcome this problem, it is required that drug preparations maintain therapeutic concentrations in the blood for extended periods. To this end, gels based on natural and synthetic polymers, as well as their combinations with metal nanoparticles, have been developed as carriers, coatings, thin ultrafilms, and other advanced biomaterials [7-9]. Such polymers, biosystems [10], and gel-forming systems can be used not only in medicine [11] but also in the oil and gas industry [12], as additives in cement [13], and as surfactants [14]. These materials allow for the effective delivery of an immobilized active drug to the required area, while ensuring controlled release to maintain the therapeutic concentration [15]. Of course, it is crucial that the hydrogel behaves properly in the presence of irritating factors in the medium. As a result, the synthesized hydrogel is pre-designed according to the characteristics of the working medium and is characterized as pH-sensitive [16], temperature-sensitive [17], ion-strength-sensitive [18], and responsive to electric fields [19].

Hydrogels are three-dimensional materials created by the cross-linking of linear natural and synthetic polymers with bifunctional small-molecule compounds [20, 21]. Due to their ability to expand and contrast in volume depending on the medium conditions and absorb a certain amount of

**E-mail:* shamo.z.tapdiqov@socar.az

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water molecules, hydrogels exhibit biocompatibility, allowing them to behave like tissue [22]. This property ensures the controlled release of drug preparations immobilized on the volume and surface of the gels.

The non-toxicity, hydrophilicity, mucoadhesiveness, and the tendency of polyacrylic acid (PAA) to form complexes with pharmaceutical reagents make hydrogels based on it suitable as matrices for the effective delivery of drugs [23, 24]. Analysis of research studies shows that after the immobilization of drug preparations, the main problem is the mechanism of their release from the hydrogel [25, 26]. These results ensure the controlled and prolonged release of the drug. From this perspective, the kinetic studies of the release of the model drug, doxorubicin antibiotic, from the pH-sensitive hydrogel, made by cross-linking PAA with N,N'-methylenebisacrylamide (MBAA) and, were conducted in the research work.

Materials and methods

Polyacrylic acid (fig. 1a) was chemically pure (97-98%) and was obtained from Merck, with an average molecular weight of 230 kDa. The cross-linking reagent MBAA (fig. 1b) was also chemically pure and was sourced from Fluka. The model drug used, doxorubicin hydrochloride (fig. 1c), was a pharmaceutical product with 99% purity, coded ATX L01DB01, manufactured by TEVA Pharmaceutical Industries (Israel) for pharmacological research. It has a molar mass of 579.98 g/mol, was water-soluble, and was an organic substance in the form of a red-pink crystalline powder.

The cross-linking of PAA with MBAA, gel purification, and immobilization of the drug preparation were carried out according to the methodology in [21].

The amount of doxorubicin antibiotic in solution and its immobilization using the simple adsorption method were calculated based on precisely prepared solutions, following the methodology described in [8], and determined using a calibration graph. The optical densities of the solutions were measured at 510 nm using a Specord UV-Vis device (Carl Zeiss), and the linearity range was determined. For doxorubicin concentrations of 0.00056, 0.0016, 0.0031, 0.0044, 0.0056, 0.0066, 0.0076, 0.0085, and 0.0174 mg/L, the corresponding optical densities (A, adsorption, absorption) were 0.002, 0.005, 0.011, 0.015, 0.047, 0.060, 0.132, 0.169, and 0.339, respectively. A linear relationship was maintained in the concentration range of 0.002-0.132 mg/L for the antibiotic.

Result and discussion

The process of cross-linking PAA with MBAA, the swelling degree of the obtained gel structure, the spectral study of the cross-linking process, and the swelling and sorption kinetics in different mediums were studied in detail in [21]. During the research, the optimal swelling degree of the PAA form obtained, when absorbed with doxorubicin, and the subsequent release of the immobilized drug in a pH=7 medium at 37 °C were studied. Kinetic data regarding the release were analyzed using various mathematical equations, providing preliminary information on the release mechanism. Although the release procedure was also studied in acidic and alkaline mediums, considering the complexity of the mathematical models and the fact that the primary site of drug release in the body is the intestinal medium, the study was conducted in a neutral medium.

Initially, the time-dependent release of doxorubicin from the PAA-based hydrogel was studied (fig. 2). It was determined that the release process occurs in two phases: a rapid release phase and an equilibrium phase (relatively

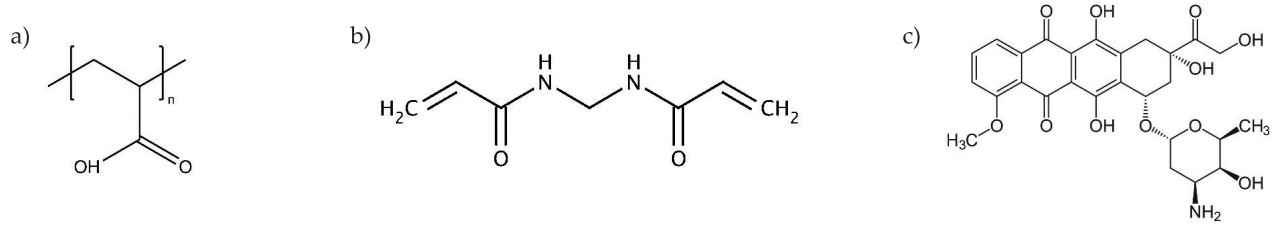

Fig. 1. The chemical molecule formula of polyacrylic acid, MBAA and doxorubicine

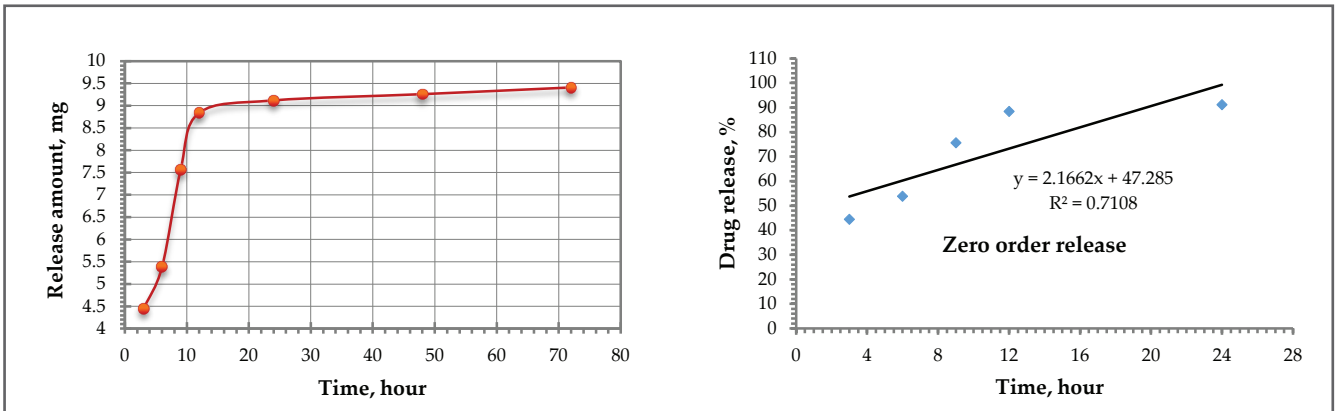

Fig. 2. Kinetics of doxorubicin release from PAA-based hydrogel as a function of time and Zero-order release dependency, T=37 °C, V=15 mL, 11-12 mg/100 mg drug/gel

controlled release). Specifically, during the first 10-12 hours, the release of the drug into the medium occurs suddenly. During this time, the gel releases 85-90 % of the drug it contains. The release, based on a diffusion process, shows more linearity in this phase [27]. In subsequent phases, the release reaches an equilibrium state, where a balance was established between the concentration of the drug in the medium and the drug present in the gel's pores. If the concentration of doxorubicin in the medium decreases, the drug will again diffuse from the gel into the medium. By applying various kinetic equations [28] dependencies to the amount of drug released over time, useful information about the release mechanism was obtained.

Initially, the results were applied to the *zero-order release kinetic model*, and the release constants were calculated. According to this model, the drug release from the carrier occurs freely and is independent of the drug concentration in the medium. Its simple form is expressed by the following equation:

$$Q = Q_0 + K_{0t}$$

here, Q represents the amount of drug released or dissolved. Q_0 was the initial amount of drug in the medium, which is usually considered to be zero. K_0 was the kinetic constant for zero-order release. When applying the model, the time-dependent release of the drug, expressed as a percentage or in mg, is plotted (fig. 2). If the points in the time-dependent plot fall on a straight line, the model is validated. This type of release is ideal for a single-dose drug form and results in minimal fluctuations in the drug's plasma levels [29]. This type of release is mainly associated with transdermal systems, tablets, poorly soluble drugs, and coated forms. As seen, the R^2 value was 0.7108, which does not match the expected behavior for the mentioned systems.

First-Order Kinetic Release – The results were also tested using the first-order kinetic release model, and the release rate constants were calculated. The first-order kinetic equation expresses the dependence of the drug release rate on the concentration (fig. 3) and is determined by the following equation:

$$LogC_t = LogC_0 - \frac{Kt}{2.303}$$

where, K is the first-order release constant, expressed in terms of the inverse of time. C_0 is the initial concentration of the drug, in mg/L, and C_t is the concentration at time t. The equation predicts the first-order dependence of the concentration gradient (C_0-C_t) between the static liquid layer adjacent to the solid surface and the bulk liquid. The dependency graph was plotted based on the time-dependent logarithm of the remaining drug amount in the matrix, as Log%. According to this kinetic model, water-soluble drugs were released from the matrix pores, and the release rate was proportional to the amount of drug present in the matrix over a given time. A regression coefficient of 0.6626 indicates that the PAA-based hydrogel was not favorable for use in such systems.

Higuchi model – In general, the first mathematical model for determining the release mechanism of drugs from matrix systems was proposed by Higuchi in 1963 [30]. This model was applied to study the release of water-soluble or poorly soluble drugs incorporated into semi-solid and solid matrices. The model is expressed by the following mathematical equation:

$$Q = A[D(2C - C_s)\cdot C_s \cdot t]^{1/2} \text{ or } Q = Kt^{1/2}$$

here, Q represents the amount of drug released from the unit A surface at time t, in mg. C is the initial concentration of the drug, in mg/mL, C_s is the concentration of the drug dissolved in the medium, and D is the diffusion coefficient (which characterizes the diffusion of drug molecules in the matrix). The simplified Higuchi model expresses the release of drugs from insoluble matrices as a dependence on the square root of time based on Fickian's diffusion equation (fig. 3). As seen, with R^2=0.9882, this suggests that the PAA-based hydrogel can provide an ideal release for controlled release of doxorubicin from such systems.

Hixon-Crowell cube root law kinetic release model

The cube root law was first proposed by Hixon and Crowell [31] to express the rate of drug dissolution in the medium, normalized for the reduction of the surface area of the solid over time. The Hixon-Crowell cube root law describes the release in systems where changes occur in the surface area or diameter of particles or tablets. The assumption is that if the matrix's form does not change while the active component in the drug form is being released, the surface area of the matrix decreases by two-thirds of its original weight. This relationship was used by Hixon-Crowell in deriving the cube root law. By applying the immersion condi-

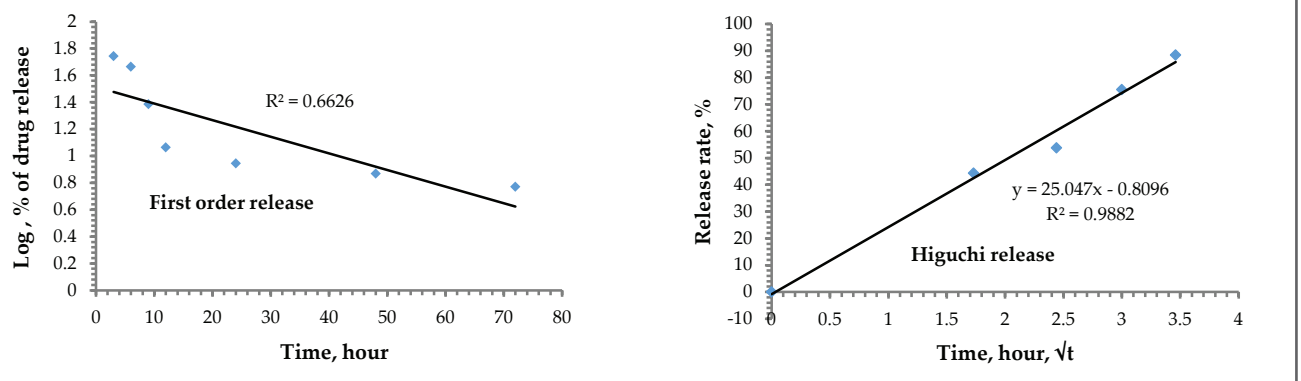

Fig. 3. First- Order and Higuchi mathematical model dependencies for the release of doxorubicin from pH-sensitive PAA-based hydrogel, T=37 °C, V=15 mL, 11-12 mg/100 mg drug/gel

tions, the cube root law can be written as follows:

$$Q_t^{\frac{1}{3}} = Q_0^{\frac{1}{3}} - K_{HC}t \quad \text{or} \quad Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = K_{HC}t$$

Q_t – the amount of drug remaining at time t, in mg; Q_0 – the initial mass of the solid at t=0, in mg. K_{HC} is the dissolution (release) rate constant and indicates the surface-to-volume incorporation. If equilibrium is not reached and the geometric dimensions of the drug form decrease proportionally over time, the cube root of the remaining drug amount should show a linear relationship with time (fig. 4). According to this model, it can be assumed that the release rate is limited by the dissolution rate of the drug rather than by diffusion. This model is used to determine the release mechanism in tablets and erodible polymer matrices. In this case, the regression coefficient of 0.8295 indicates that the PAA-based hydrogel may not be particularly suitable for such pharmacological formulations, or that there is only partial compatibility.

Korsmeyer-Peppas model – Korsmeyer and others proposed a simple equation describing the release of drug substances from polymer systems [32]. Korsmeyer and Peppas developed an empirical equation to analyze both Fickian and non-Fickian release from swellable and non-swellable gels and materials. To determine the mechanism of drug release, the data for the first 60% of the release were checked using the Korsmeyer-Peppas model (fig. 4). The equation is mathematically expressed as follows:

$$\frac{M_t}{M_\alpha} = Kt^n$$

Here, M_t/M_α is the fraction of the drug released at time t. K is the release constant, which reflects the structure and geometric characteristics of the delivery system. n was the release exponent, which indicates the drug's delivery mechanism through the polymer. The value of n can be used to characterize different release mechanisms. It has been determined that, in this case, the R^2 value of 0.7631 indicates a lower degree of fit.

Based on the values of R^2, the closest fit occurs in the Higuchi release model. Considering that this model allows the determination of the release mechanism of water-soluble or poorly soluble drugs from semi-solid matrix systems, it is confirmed that the diffusion of doxorubicin from the swollen PAA-based hydrogel occurs through this mechanism [33, 34]. By applying the equation $Q=Kt^{1/2}$, the release constant (K) was determined from the slope of the linear plot, and it was found to be K=6.472. The high value of K suggests that the creation of oral pharmaceutical forms is more favorable. From these results, it can be concluded that the pH-sensitive gel obtained by crosslinking 10% (w/w) PAA with MBAA can be used to prepare drug formulations of anthracycline antibiotics that were suitable for oral delivery.

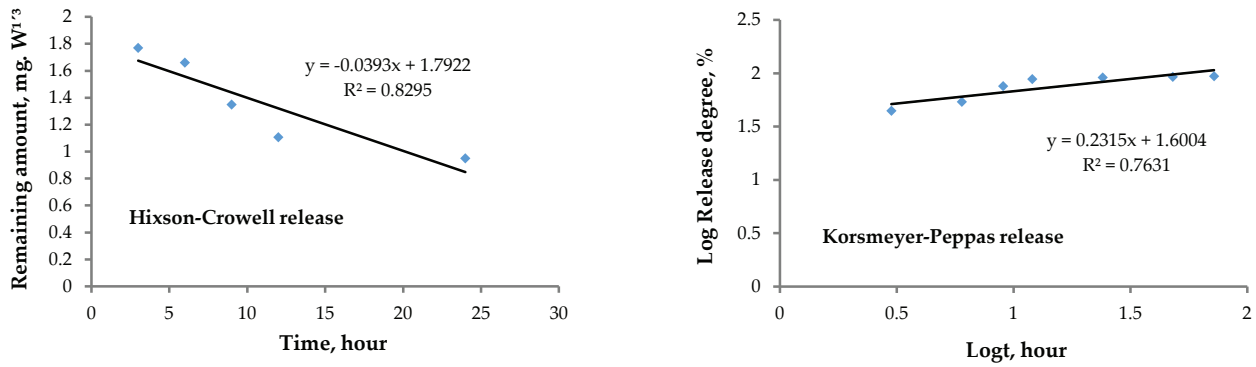

Fig. 4. The release of doxorubicin from pH-sensitive PAA-based hydrogel following Hixon-Crowell and Korsmeyer-Peppas mathematical model areas of linear dependency, T=37 °C, V=15 mL

Conclusions

1. The material obtained by treatment polyacrylic acid with an organic crosslinking reagent, N,N'-methylenebisacrylamide, at a 10% weight ratio using ultraviolet radiation, with a molecular weight of 230 kDa, can be used as a depo for the controlled delivery and release of certain drugs, such as anthracycline antibiotics.
2. The prepared polymer-based matrix, which immobilizes the model drug doxorubicin, could maintain its chemical and biological activity for a long period, and the drug diffusion does not occur until hydration takes place.
3. The long-term release of doxorubicin from the polyacrylic acid-based gel matrix occurs via a Fickian diffusion mechanism, which ensures its stable release in pH=7 mediums. In this regard, the gel matrix can be used to prepare swelling pharmacological formulations for the treatment of certain diseases.
4. Such gel forming polymer systems can be used not only in biotechnology, but also in the oil and gas industry as a specific component of isolating compositions for the purpose of preventation of sand and formation water in the downhole zone.

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