Chem. Chem. Technol., 2017,
Vol. 11, No. 2, pp. 195–200

Chemistry

PECULIARITIES OF MEDICINAL SUBSTANCE RELEASE UNDER THE CONDITIONS OF INTERFACE DIFFUSION PROCESS AND HYDROLYSIS OF A POLYMERIC MATRIX

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https://doi.org/10.23939/chcht11.02.195

Abstract. Film systems based on chitosan of various molecular weight (334000 Da and 113000 Da) and the antibiotic of an aminoglycoside row (amikacin) have been investigated. The equations of Ritger-Peppas, Hixson-Crowell and Hopfenberg, describing kinetics of medicine release have been analyzed. It is shown that the release of amikacin from films of chitosan acetate under the conditions of interface diffusion processes and dissolution (hydrolysis) of a polymeric matrix is described more correctly by Hopfenberg's equation. It was established that carrying out isothermal annealing is followed by the reduction of values of the kinetic constants characterizing the rate of the release process of medicinal substance from a polymeric matrix.

Keywords: chitosan film, diffusion, enzyme hydrolysis, kinetics.

1. Introduction

In the last decades intensive development and researches of polymeric systems for the controlled release of biologically active compounds [1-7] allowing to eliminate many defects of traditional dosage forms are conducted. Most often such defects increase toxicity and instability of biologically active compounds, uneven rate of their giving, inefficient expense of active components and others. Use of polymeric systems for a controlled release of biologically active compounds gives the chance to systematically and purposefully enter the demanded dose of the medicinal substance (MS). Moreover, using the polymeric form of MS it is possible to vary the time of its release in wide time intervals. Now the attention of researchers is drawn by polysaccharide chitosan as a polymer carrier of medicines. Chitosan possesses a wide range of useful properties among which should be noted biocompatibility with organism fabrics, its biological activity and ability to biodegradation with formation of the nontoxical final products [8-12]. Besides, chitosan easily gives strong and elastic films [13-16], which makes it promising for the creation of protective wound film coverings for treatment, for example, of burnt and surgical wounds. Complexity of the kinetic description of a polymeric matrix system – MS in case of chitosan is caused by the release of medicine which can happen not only *via* the diffusive mechanism, but also due to the process of erosion (dissolution) of a polymeric matrix as the received chitosan matrixes (films) in a salt form are dissolved in water. Besides, it is necessary to consider the fact that chitosan is treated as the biodegraded polymers. For example, it is hydrolized under the influence of enzymes – β- glycosidase that can affect kinetics of MS release from a polymeric matrix.

There is a set of models for the description of kinetics of MS release from polymeric systems. Among them it is possible to note the equation of Ritger-Peppas [17-18], which can be used for the characteristic of medicine release both from swelling up and from not swelling up polymeric matrixes. Also the equation of Hixson-Crowell [19-21] describing kinetics of MS release under the conditions of changing (owing to dissolution) surface areas of a polymeric matrix and the equation of Hopfenberg [22-24] is used very often. It describes the release of MS from the films, which are exposed to the destruction process.

Search of the equation which would correctly describe the release of low-molecular MS from the chitosan films under the conditions of interface in diffusion and dissolution (hydrolysis) processes of a polymeric matrix became the purpose of this work.

2. Experimental

We used the sample of the chitosan (ChT) of Bioprogress production (Russia) received by an alkaline deacetylation of crab chitin (deacetylation degree ~ 84 %) with M_{sd} = 113000. As the medicinal substance (MS) the

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antibiotic of an aminoglycoside row – amikacin sulfate (AM) was used. As an enzyme preparation the hyaluronidase (a trade name of "Liraza" produced by Mikrogen, Moscow) belonging to the β-glycosidase class was used. Concentration of an enzyme preparation was 0.1, 0.2 and 0.3 g/l.

Film samples were prepared by watering the polymer solution in 1% acetic acid on the glass surface to give a film of chitosan acetate. The antibiotic dissolved in a small amount of water (2 ml) was added to ChT solution just before the formation of films. The content of MS in a film was 0.1 mol/mol of ChT. Thickness of films in all experiments was constant and equal to 0.1 mm. Isothermal annealing of the formed film samples was carried out at the temperature of 393 K during certain time.

To study the kinetics of MS release a film sample of 5×5 mm was placed in a cell filled with distilled water or the solution of an enzyme preparation. The antibiotic released in the aqueous phase was recorded spectrophotometrically at the wave length l = 267 nm corresponding to the maximum of absorption of MS in the UV-spectrum. The quantity of ChT released from a film (G_s) to the time t was estimated by calibration dependence. The moment of establishment in the solution of MS constant concentration was considered to be the moment of establishing equilibrium (G_∞).

The kinetics of MS release was described using the following equations:

1) Ritger – Peppas's equation:

$$\frac{G_s}{G_\infty} = Kt^m \qquad (1)$$

where G_s is the quantity of MS released from a polymeric matrix by the time t; G_∞ is the equilibrium quantity of MS released; K is the kinetic constant characterizing the rate of MS release from a polymeric matrix; M is the exponential parameter connected with the mechanism of MS release.

2) The equation offered by Hopfenberg and Katzhendler describes MS release from the films, spheres or infinite cylinders which are exposed to erosion:

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_0 t}{C_0 a_0}\right]^n \qquad (2)$$

where M_t is the quantity of MS released from a polymeric matrix by the time t; M_∞ is the initial quantity of MS entered into a polymeric matrix; k_0 is an erosion rate constant; C_0 is the initial concentration of medicine in a matrix; a_0 is the value of initial radius of the sphere (cylinder) or semi-thickness of a film. The value of an indicator n is accepted to be equal to 1, 2 and 3 for the film, the cylinder and the sphere, respectively.

3) Hixson-Crowell's equation:

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \qquad (3)$$

where Q_t is the quantity of MS which remained in a polymeric matrix by the time t; Q_0 is the initial quantity of MS entered into a polymeric matrix; K_{HC} is the Hixson-Crowell constant.

Mathematical processing of the results was carried out by the method of the smallest squares.

3. Results and Discussion

Earlier, in works [25-26] we studied polymeric film systems based on ChT with a molecular mass of M_{sd} = 334000 Da. The films received from a high-molecular sample of ChT were dissolved in water rather slowly and during the experiment they changed the initial weight no more than by 3–5 % (Fig. 1, *curve* 1). An isothermal annealing which is followed by the process of crosslinking and modification of a polymeric matrix [27-28] leads to a considerable decrease of dissolution rate, and at long times of annealing (about 60 min and more), even to a complete loss of solubility of films of ChT in water. In our case, the used ChT sample, is characterized significantly by smaller molecular weight (M_{sd} = 113000 Da). As a result, at immersion of chitosan films in water, they lose weight quickly enough, owing to dissolution (Fig. 1, *curve* 2). Thus, the main loss of weight happens during the first two hours. After that the rate of dissolution of a film significantly slows down. Moreover, isothermal annealing of films (*curves* 3-5) does not yield basic results: even after 2-hour annealing of a film (*curve* 5), the ChT acetate sample is partially dissolved in water.

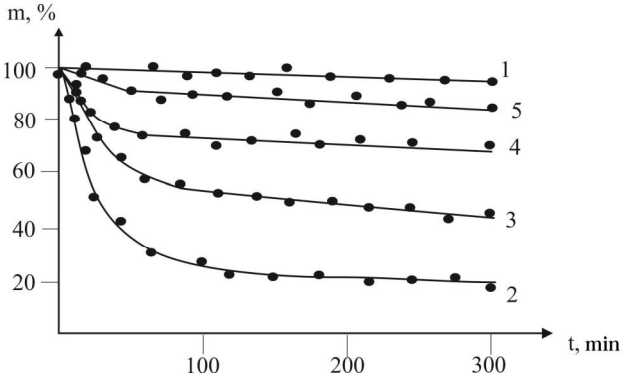

Fig. 1. Curves of mass loss of chitosan films with M_{sd}=334000 Da (1) and M_{sd} = 113000 Da (2-5) without isothermal annealing (1, 2) and with it (3-5) within 30 (3), 60 (4) and 120 (5) min from the time of holding in water

Distinction in solubility of films of different ChT samples finds the reflection in kinetics of MS release from films. Fig. 2 represents experimental data on medicine release – AM into water from ChT acetate films with M_{sd} = 334000 Da (1) and M_{sd} = 113000 Da (2). The

distinction in kinetics of AM release from almost insoluble (*curve* 1) and a soluble (*curve* 2) polymeric matrix is quite significant. In the first case, it is possible to speak about the prolonged release of MS from a film, in the second case we can not speak about it as all MS completely releases during the time comparable to the time of dissolution of a film. According to it, application of Eq. (1) for the description of kinetic regularities of AM release in case of an insoluble and soluble polymeric matrix gives various results (Table 1).

From the data of Table 1 it is clear that the correlation coefficient in case of the use of the dissolved ChT samples with M_{sd} = 113000 Da is less than if we use ChT with M_{sd} = 334000 Da, which is not dissolved during the experiment. However, the case is not in numerical values of correlation coefficient, but in that Ritger-Peppas's equation. It accurately reflects the regularities which are observed under experimental conditions only for ChT with M_{sd} = 334000 Da. In this case the values of kinetic constants K determined by Eq. (1) for the films subjected to isothermal annealing properly reflect the regularities observed in the experiment. The increase in the time of isothermal annealing, which is followed by the decrease of solubility of a polymeric matrix in water leads to the decrease of the MS release rate. When using ChT with M_{sd} = 113000 Da Ritger-Peppas's equation practically does not work.

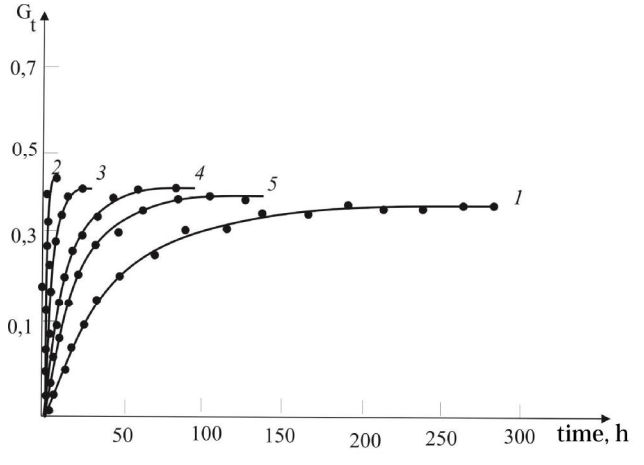

Fig. 2. Kinetic curves of amikacin release into water in coordinates of optical density – time from film system of ChT-AM from ChT acetate films with M_{sd} = 334000 Da (1) and M_{sd} = 113000 Da (2-5), without (1,2) and with (3-5) isothermal annealing within 30 (3), 60 (4) and 120 (5) min

The data on values of kinetic parameters of the AM release from the chitosan films were received when we used Eqs. (2) and (3) (Table 2). From the data of Table 2 we can see that, firstly, both equations give the values of kinetic constants that accurately reflect in the observed experiment the decrease of the MS release rate with the increase in the time of isothermal annealing. However, correlation coefficients in case of using the equation of Hixson-Crowell are lower than if they were used in the equation of Hopfenberg. Obviously, it is connected with the fact that the Hixson-Crowell's model assumes that the rate of MS release is not limited by diffusion, but by the rate of particles dissolution of this medicine.

Secondly, when we use the equation of Hopfenberg, the best coefficient of correlation takes place in the case when the value of the indicator n in Eq. (2) is equal not to 1 (the case of use of films) as it would be possible to expect, but to 3, which corresponds to spherical samples. As the n value in Eq. (2) actually testifies to some possible ways of MS release, the value of n = 1 must mean the fact that MS release from the film in the shortest way takes place migrating through a half of thickness of the film. This will actually occur in the case when the film thickness is only a half more than its width and length. However, in our case, length and width of the film is a half more than its thickness. Thus, it is clear that the MS release is carried out in all three directions, *i.e.* just as it takes place for spherical samples. Besides, it is necessary to consider the fact that AM release, which is carrying out owing to dissolution of a film, occurs from the whole surface area of the film, *i.e.* in three directions (not in one).

Thirdly, Hopfenberg's equation describes both cases such as completely soluble film and partially soluble films, which passed isothermal annealing. The value of kinetic constants testifies that the effect of prolongation of MS release in an annealing consequence is very essential. The kinetic constant of the process of medicinal substance release decreases with the increase of thermal modifying time (k_0 – the value for not annealed film of ChT-AM is equal to $23.2 \cdot 10^{-4}$ min^{-1}, and for the film annealed within 120 min – $0.8 \cdot 10^{-4}$ min^{-1}).

When placing ChT film in the solution of enzyme preparation the MS release takes place not only as the result of MS diffusions from a film and its dissolution, but also as a result of enzyme hydrolysis of a polymeric matrix.

Experimental data on the AM release from a chitosan film in the solution of enzyme preparation are presented in Fig. 3. We can see that the higher is the concentration of the enzyme preparation in the solution, the faster is the AM release from the film, which seems quite logical.

For the quantitative description of the AM release from the films which are exposed to the process of enzyme hydrolysis the equations of Ritger-Peppas and Hopfenberg (Table 3) were analyzed.

Table 1

Value of kinetic parameters in the process of medicinal substance release – amikacin from the chitosan films received with the use of the equation of Ritger-Peppas

M_{sd}, Da	Time of annealing, min	K, min^{-1}	Coefficient of correlation
334000	0	0.045	0.98
	30	0.041	0.98
	60	0.040	0.99
	120	0.039	0.99
113000	0	0.021	0.93
	30	0.062	0.93
	60	0.028	0.94
	120	0.070	0.95

Table 2

Kinetic parameters of the release process of medicinal substance – amikacin – from the chitosan films. The molecular mass of chitosan is 113000

Analyzed system	The equation for analyzing	Value of an indicator n in the equation of Hopfenberg	Kinetic constant of the process, min^{-1}	Coefficient of correlation
ChT-AM	Hopfenberg	1	$k_0 = 4.6 \cdot 10^{-7}$	0.95
		2	$k_0 = 3.2 \cdot 10^{-7}$	0.97
		3	$k_0 = 2.5 \cdot 10^{-7}$	0.98
	Hixson-Crowell	–	$K_{HC} = 14.6 \cdot 10^{-4}$	0.90
ChT-AM, annealing time 30 min	Hopfenberg	1	$k_0 = 2.4 \cdot 10^{-7}$	0.93
		2	$k_0 = 1.6 \cdot 10^{-7}$	0.97
		3	$k_0 = 1.2 \cdot 10^{-7}$	0.98
	Hixson-Crowell	–	$K_{HC} = 4.8 \cdot 10^{-4}$	0.90
ChT-AM, annealing time 60 min	Hopfenberg	1	$k_0 = 1.2 \cdot 10^{-8}$	0.92
		2	$k_0 = 1.1 \cdot 10^{-8}$	0.96
		3	$k_0 = 1.0 \cdot 10^{-8}$	0.96
	Hixson-Crowell	–	$K_{HC} = 3.8 \cdot 10^{-4}$	0.90
ChT-AM, annealing time 120 min	Hopfenberg	1	$k_0 = 1.4 \cdot 10^{-8}$	0.93
		2	$k_0 = 1.2 \cdot 10^{-8}$	0.97
		3	$k_0 = 0.9 \cdot 10^{-8}$	0.98
	Hixson-Crowell	–	$K_{HC} = 0.4 \cdot 10^{-4}$	0.89

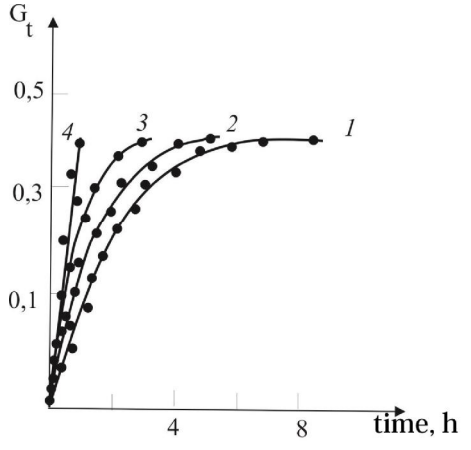

Fig. 3. Kinetic curves of amikacin release in the water environment (1) and in the solution of enzyme preparation (2-4) with concentration of enzyme 0.1 (2), 0.2 (3) and 0.3 (4) g/l in coordinates of optical density – time from film system of ChT-AM. The molecular mass of chitosan is 113000

Table 3

Kinetic parameters of the release process of medicinal substance – amikacin- from the chitosan films. The molecular mass of chitosan is 113000

Analyzing system	The equation for analyze	Concentration of enzyme preparation	Kinetic constant of the process, min^{-1}	Coefficient of correlation
ChT-AM	Ritger-Peppas	0	$K = 0.0214$	0.93
		0.1	$K = 0.073$	0.94
		0.2	$K = 0.083$	0.94
		0.3	$K = 0.098$	0.94
	Hopfenberg	0	$k_0 = 23 \cdot 10^{-4}$	0.98
		0.1	$k_0 = 31 \cdot 10^{-4}$	0.98
		0.2	$k_0 = 61 \cdot 10^{-4}$	0.98
		0.3	$k_0 = 87 \cdot 10^{-4}$	0.98
ChT-AM, annealing time 30 min	Ritger-Peppas	0	$K = 0.062$	0.95
		0.1	$K = 0.077$	0.95
		0.2	$K = 0.176$	0.95
		0.3	$K = 0.208$	0.95
	Hopfenberg	0	$k_0 = 11 \cdot 10^{-4}$	0.97
		0.1	$k_0 = 15 \cdot 10^{-4}$	0.98
		0.2	$k_0 = 30 \cdot 10^{-4}$	0.98
		0.3	$k_0 = 35 \cdot 10^{-4}$	0.98
ChT-AM, annealing time 60 min	Ritger-Peppas	0	$K = 0.028$	0.93
		0.1	$K = 0.089$	0.96
		0.2	$K = 0.129$	0.94
		0.3	$K = 0.196$	0.97
	Hopfenberg	0	$k_0 = 0.9 \cdot 10^{-4}$	0.96
		0.1	$k_0 = 1.0 \cdot 10^{-4}$	0.97
		0.2	$k_0 = 1.5 \cdot 10^{-4}$	0.98
		0.3	$k_0 = 2.3 \cdot 10^{-4}$	0.98
ChT-AM, annealing time 120 min	Ritger-Peppas	0	$K = 0.070$	0.95
		0.1	$K = 0.018$	0.97
		0.2	$K = 0.029$	0.96
		0.3	$K = 0.059$	0.97
	Hopfenberg	0	$k_0 = 0.8 \cdot 10^{-4}$	0.98
		0.1	$k_0 = 0.9 \cdot 10^{-4}$	0.99
		0.2	$k_0 = 1.1 \cdot 10^{-4}$	0.99
		0.3	$k_0 = 1.3 \cdot 10^{-4}$	0.99

The analysis of the data in Table 3 showed that the equation of Hopfenberg is capable to describe the MS release correctly not only in case of dissolution of the polymeric matrix, but also in case of its enzyme hydrolysis. The calculated values of k_0 regularly grow at the increase in concentration of an enzyme preparation and regularly decrease at the increase in time of isothermal annealing. The use of the equation of Ritger-Peppas for the description of kinetics of MS release from the films which are exposed to the process of enzyme hydrolysis not in all cases copes with the task of the correct description of the process. As seen from Table 3, the equation of Ritger-Peppas gives values of K which regularly grow at the increase in concentration of an enzyme preparation that corresponds to the experiment, but not accurately reflect the influence of isothermal annealing of films on kinetic constants of the process.

It is possible to note that the process of isothermal annealing in case of the hydrolyzed films will also lead to a considerable prolongation of the MS release. So, the complete release of MS from an initial film comes within 1 h (at concentration of enzyme preparation of 0.3 g/l), and in case of the film after 2 h of modification – within one day.

The equation of Hopfenberg describes experimental data in an accurate way. It helps to solve the inverted task. The kinetic curve of AM release from the polymer matrix with concentration of enzyme equal to 0.05 g/l (Fig. 4, *curve* 1) was theoretically made on the basis of k dependence on the enzyme. At the same time it was taken an experimental release curve of MS (Fig. 4, *curve* 2,). The analysis of the curves showed that theoretically-made curve fully coincide with the experimental one.

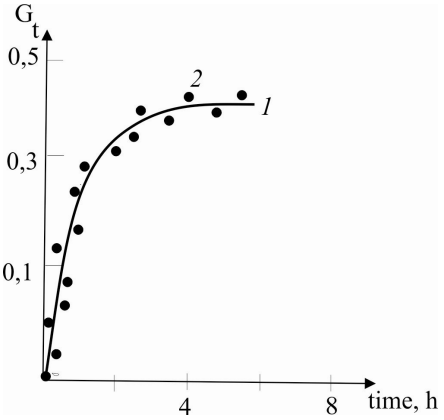

Fig. 4. Kinetic curves of amikacin release in the solution of an enzyme preparation with concentration of enzyme 0.05 g/l in coordinates of optical density – time from film system of ChT-AM for theoretically calculated (1) and experimental (2) curves. The molecular mass of chitosan is 113000

4. Conclusions

Thus, during the work it was established that in case of the use of the polymeric films which are dissolved or exposed to the process of hydrolysis during the experiment, it is more correct to describe kinetics of the MS release from a matrix carrier, using Hopfenberg's equation, than the equations of Ritger-Peppas, and Hixson-Crowell. Obviously, Hopfenberg's equation works most correctly in the conditions of interface of the processes of diffusion and dissolution (hydrolysis).

Acknowledements

The reported study was funded by RFBR according to the research project No. 16-33-00216 mol_a.

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Received: December 17, 2015 / Revised: May 19, 2016 / Accepted: December 07, 2016

ОСОБЛИВОСТІ ВИВІЛЬНЕННЯ ЛІКАРСЬКОЇ РЕЧОВИНИ ЗА УМОВ МІЖФАЗНОГО ДИФУЗІЙНОГО ПРОЦЕСУ І ГІДРОЛІЗУ ПОЛІМЕРНОЇ МАТРИЦІ

Анотація. *Проведені дослідження плівкових систем на основі хітозану з різною молекулярною масою (334000 Da і 113000 Da) і антибіотику аміноглікозидового ряду (амікацин). Проаналізовано рівняння Рітгера-Пеппаса, Гіксона-Кроуелла і Хопфенберга, що описують кінетику вивільнення ліків. Показано, що вивільнення амікацину з ацетатних хітозанових плівок за умов міжфазних дифузійних процесів і розчинення (гідролізу) полімерної матриці більш коректно описується рівнянням Хопфенберга. Встановлено, що ізотермічний відпал супроводжується зменшенням значень кінетичних констант, що характеризують швидкість процесу вивільнення лікарської речовини з полімерної матриці.*

Ключові слова: *хітозанова плівка, дифузія, ферментативний гідроліз, кінетика.*