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Розроблено модель з використанням бутстреп-методу для оцінки функції розподілу вивільнення лікарського препарату в людському організмі. Показаний приклад застосування методу на препараті Трізіпін-Лонг. Розглянуто випадки з використанням різної кількості випробувань (100, 1000 і 10000). Для дослідження впливу методу інтерполяції проведено порівняльне дослідження емпіричних функцій розподілу кількості препарату, який вивільнився в шлунку, 12-палої кишки і повне вивільнення

Ключові слова: бутстреп-моделювання, сплайн, интерполяция, профіль вивільнення in vivo, Трізіпін-Лонг, функція розподілу

Разработана модель с использованием бутстреп-метода для оценки функции распределения высвобождения лекарственного препарата в человеческом организме. Показан пример применения метода на препарате Тризипин-Лонг. Рассмотрены случаи с использованием разного количества испытаний (100, 1000 и 10000). Для исследования влияния метода интерполяции проведено сравнительное исследование эмпирических функций распределения количества препарата, высвободившегося в желудке, 12-перстной кишке и полное высвобождение

Ключевые слова: бутстреп-моделирование, сплайн, интерполяция, профиль высвобождения in vivo, Тризипин-Лонг, функция распределения

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DEVELOPMENT OF A BOOTSTRAP-MODEL FOR DETERMINING THE RELEASE OF MEDICINAL PREPARATIONS IN THE HUMAN ORGANISM

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1. Introduction

One of the intensively developed directions of contemporary pharmacology is the development of compositions of oral medicines with the assigned profile of the release of medicinal substance in the gastrointestinal tract (GIT), which ensures its optimal effect on the organism. A basis for developing these preparations are experimental studies on the kinetics of dissolution in vitro of finished dosage forms under conditions that imitate the work of GIT. In certain cases, results of studying the kinetics of release can be substituted with studies into bioequivalence. In Ukraine, studies on the kinetics of release are conducted according to the State Pharmacopoeia [1].

A widespread introduction of information technologies contributed to the emergence of a new approach to the creation of preparations with the assigned profile of release, based on the application of mathematical modeling and computer simulation. These models are built based on the results of experimental studies under standard conditions.

Development of models, not linked to particular mechanisms of release and oriented at solving the practical problems of devising medicines is a relevant task.

2. Literature review and problem statement

Contemporary solid dosed forms: tablets, capsules, drops, pills are the complex composite materials, which, in addition to medicine, contain inert fillers, polymeric binders, polymeric matrices and coatings [2]. The therapeutic effect of these forms is predetermined by the release of medicine and its passage into a solution in the liquids of GIT, with subsequent absorption (suction) and passage into blood [3]. Quality and interchangeability of medicines is possible to estimate employing the test "Dissolution". This method is intended for evaluating the kinetics of release of the acting substance from tablets and capsules. At present, in studies into the processes of dissolution and release of medicines, it is possible to isolate the tendencies related to the experimental technique and mathematical modeling of the kinetics of release, examined below.

In the field of experimental technique of measuring the kinetics of release we can highlight two aspects related to the equipment and media. In 2006, the requirements were harmonized on conducting the test "Dissolution" among the pharmacopoeias of the USA, the European and Japanese pharmacopoeias. The use of the following types of apparatuses is allowed: "Revolving basket", "Blade agitator", "Rocking drum", and "Flow-through cell (open and closed system)" [4]. The Pharmacopoeia of Ukraine permitted to use only the two first apparatuses [1].

Apparatuses with a flow-through cell are considered to be more advanced from the point of view of the imitation of dissolution conditions *in vivo* [5]. At present, there is a tendency to use such apparatuses more frequently. For example, when conducting the test "Dissolution" in flow-through devices with nanopowders of the relatively insoluble medicines, the issues of worsening in wettability and adhesion of nanoparticles are removed [6].

As the media for conducting the tests, they traditionally use aqueous buffer solutions at pH 1.2; 4.5 and 6.8, which imitate media in different sections of GIT [4]. Recently, there is a tendency toward employing the so-called biorelevant media. These media are the buffer solutions, which contain a number of specific components of GIT: pepsin, lecithin, bilious acids, etc. [7]. When using the biorelevant media for the relatively insoluble preparations, for example, montelukast sodium, the solubility differs from the buffer solutions [8].

At present, there are three approaches in mathematical modeling of the processes of release [9]. The first of them is the statistical one, which includes exploratory analysis, planning of experiments, multivariate analysis. The use of method of main components with confidence domains deserves considerable attention. For example, employing it made it possible, by the profiles of dissolution, to distinguish three polymorphous modifications of the preparation Furosemide [10].

The second approach includes the use of factors of difference and similarity, which directly use for the comparison of two profiles of dissolution (model- independent approach [9]). The most important is the approach that is based on particular models obtained from certain physical considerations (model-oriented approach [9]). A differential Noyes-Whitney equation serves as a basis for it:

$$\frac{dM}{dt} = K \cdot S \cdot (C_s - C_t), \quad (1)$$

where M is the mass of substance, transferred over time; S is the current surface area of a preparation; K is the velocity constant; C_s is the equilibrium solubility of a preparation; C_t is the concentration of a preparation in moment of time t.

In practice, the most frequently used are the models in the form of algebraic equations, which are derived by solving (1) at various assumptions about the mechanism of release. The following models are most frequently used [9]:

– a zero order model:

$$Q_t = Q_0 + K_0 t, \quad (2)$$

where Q_0, Q_t is the amount of preparation in the solution at the initial moment of time and after time t; K_0 is the dissolution velocity constant;

– a first order model:

$$\frac{dC}{dt} = -Kc; \quad \ln C = \ln C_0 - Kt, \quad (3)$$

where C_0 and C is the concentration of a preparation in the solution at the initial and current moment of time t;

– the Higuchi model (for matrix tablets):

$$Q = A \cdot \sqrt{D(2C - C_s)C_s t} = K \cdot t^{1/2}, \quad (4)$$

where Q is the amount of released medicine in moment of time t per square unit; A is the area of a tablet; C is the initial concentration of a medicine; C_s is the solubility of a medicine in the matrix media; D is the diffusion coefficient of the molecules of a medicinal substance in the matrix;

– the Hixson-Crowell model:

$$W_0^{1/3} - W_t^{1/3} = \kappa t, \quad (5)$$

where W_0 is the initial quantity of a medicine in the pharmaceutical medicinal form; W_t is the remained amount of a medicine in the pharmaceutical medicinal form in moment of time t; κ is the proportionality constant (rate constant);

– the Weibull model:

$$M = M_0 \left[1 - \exp\left(-\frac{(t - T)^b}{a} \right) \right], \quad (6)$$

where a, b, T are the constants, which are determined by "fitting" the experimental data.

At present, widely adapted are the multicomponent tableted forms that contain polymers capable of swelling, of dissolving or degrading. For such objects the more complex models are used in the form of nonlinear algebraic or differential equations. These models consider such factors as the diffusion of a preparation [11], swelling, degradation and the erosion of polymers [12], percolation [13], including with the combined action. In order to calculate using the complicated models, a specialized computer application DDSolver was developed, which contains the library of models, the modules of nonlinear optimization and multidimensional statistical analysis [14]. The use of contemporary cybernetic computer models is described as the alternative for complex mathematical models: artificial neural networks [12], cellular automata in combination with the Monte Carlo method [11].

Thus, at present, there are a large number of developed mathematical models of the release, which differ in the levels of complexity, substantiation and required information, as

well as in the scope of application. This creates the problems of choice for specialists who are engaged in the development of finished dosage forms of medicines. Today there is a need for a unified "working horse" – a computer model, not linked to any particular mechanism of release, which can be utilized for solving practical problems. The latter include, in particular, modeling of a distribution function of the release of a medicine in vivo based on data. The development of such a model is a promising task. Direct measurements of release in vivo in the liquids of GIT are impossible because the dissolved medicine is rapidly sucked through the walls.

3. The aim and tasks of research

The aim of present work is to develop a mathematical model of release, based on experimental data and which makes it possible to model the distribution functions of the release of a medicine in vivo according to data in vitro.

To accomplish the set aim, the following tasks had to be solved:

– to develop a computer model by combining the spline-interpolation and the bootstrap method;

– to investigate properties of the model;

– to illustrate the possibilities of the model on the example of the release of the preparation Trizipin-Long, a prolonged form of the generic analog to the preparation Meldonium.

Table 1

Kinetics of the release of the medicine from the preparation Trizipin Long, mg, in parallel experiments depending on time and pH. Weight of tablets is 1000 mg

pH	Time, h	Numbers of parallel samples					
		1	2	3	4	5	6
1.2	1	42	38	117	45	114	50
	2	106	109	226	114	250	134
	5	242	301	546	314	581	338
	8	515	525	781	525	781	585
	11	728	706	897	701	904	694
	14	830	829	945	836	923	864
4.5	1	148	70	43	67	57	86
	2	322	196	165	204	176	209
	5	683	470	507	542	554	554
	8	859	724	795	755	745	750
	11	936	837	925	857	857	874
	14	963	864	993	888	917	926
6.8	1	77	91	34	86	32	69
	2	216	239	104	217	99	188
	5	568	600	317	565	326	572
	8	702	788	521	771	524	834
	11	808	907	685	867	670	956
	14	902	959	747	913	713	983

4. Materials and methods for examining the release of the preparation Trizipin-Long

4. 1. Examined materials and equipment used in the experiments

As the subject of research we used the medicine "Trizipin Long" (OOO NPF "Mikrokhim", Ukraine), tablets of the prolonged action, 1000 mg, a generic analog to the preparation "Meldonium" or "Mildronate" (Russia, active principle – 2-(2-carboxyethyl)-1,1,1-trimethylhydrazinium).

The test "Dissolution" was conducted in the apparatus Pharma Test PT DT-70 (Germany). The analysis of samples was carried out on the liquid chromatograph SHIMADZU LC-2010 CHT with the UV-detector (Japan). Utilized column – Zorbax 300-SCX 4,6 m×150 mm×5 μm (USA). Mobile phase – 0.05 M solution of KH_2PO_4 at pH=2.5–85 %, acetonitrile – 15 %.

4. 2. Procedure for determining the indicators of properties of the samples

The tablets were tested using the test "Dissolution" in a dissolver by employing a procedure [1], at a temperature of 37±0.5 °C. The stirring device is a blade, 75 r/min. Dissolution medium is aqueous buffer solutions at pH 1.2; 4.5; 6.8. Volume of the medium is 1000 ml

The content of the preparation in the solution was determined by the HPLC method in accordance with [1]. Results of the tests are given in Table 1.

Data represented in Table 1 are used as a basis for numerical simulation in chapter 5.3.

5. Development of a model of the release and its examination

5. 1. Theoretical considerations for developing the model

When developing a model, we took into account the following considerations. The special features of experiments on determining the release are:

– the exhaustive dissolution time whose maximum value (14 hours) matches the mean time of a tablet being in GIT;

– conducting the measurements in series. In the installation they place 5–7 numbered cups with the samples at the same index of medium pH. Next, over the fixed time intervals, the samples are taken from each cup to carry out the analysis [1]. As a result of this experimental technique, each cup with a sample receives its particular set of values at each point of time in a way that is represented in Table 1.

Subsequent processing is typically reduced to the averaging of data for each temporal point. However, data can be examined from another point of view as well. The profile of release for each sample can be considered as a result of the realization of a certain dynamic process, described by time series. In order not to be bound by the physical model of the release, which may appear unknown, here it is proposed to use the interpolation of data. Computer interpolation using the linear or cubic splines can be the most suitable [15]. For the linear spline, adjacent points are connected by the line segments, and each profile is graphically represented as a broken line. For the cubic spline, dependence between the adjacent points is described by a third power polynomial.

Additionally superimposed are the conditions of "smooth seam": equality at the nodal points for the adjacent sections to the right and to the left, as well as for the first and second derivative [15]. As a result, we obtain a smooth function, passing through all nodal points. A value at the intermediate points can be approximately computed from the equation of linear or cubic spline, which are stored in the memory of computer.

To account for the random nature of profiles, it is possible to employ the bootstrap method [16]. The essence of this method consists in the generation out of the initial sample of the new sample of large size and the examination of its statistical characteristics. In order to obtain the current element of the "large" sample, they use the procedure of extraction from the base sample with the return. By applying the Monte Carlo method, they generate the random number of an element of the base sample and the value of this element is assigned to the current element of the "large" sample ("multiplication of samples" or resampling). Based on the large sample, it is possible to numerically build an approximate distribution function, confidence intervals. and other statistical characteristics [16]. The bootstrap method makes it possible to easily and rapidly evaluate statistical characteristics (confidence intervals, dispersion, correlation and so on) for complex models, without the need to rely on the a priori assumptions about the nature of distribution [16]. In recent years, this method has been applied in the medical statistics, for example, when establishing the bioequivalence of medicines based on the clinical and preclinical studies [17–19].

5. 2. The model's algorithm

For the bootstrap-simulation of the profile (more precise, a pseudo-profile) of the release in vitro, we employed the following algorithm:

a) from the set of experimental data (Table 1), at the assigned pH value, we randomly extracted with the return 6 values of the weight of a preparation in the solution that correspond to the sequential temporal points;

b) the obtained pseudo-sample of the values of profile was interpolated by a linear or a cubic spline.

In order to obtain a pseudo-profile of the release in vivo, we applied the following algorithm:

a) at pH 1,2, imitating the release in the stomach:

– we generated a pseudo-profile of dissolution and its spline-interpolation;

– using the spline, we determined the mass of the released preparation in 2 hours after the onset (m_1, mg);

– using the spline, we generated 10–20 intermediate values of the release and placed into the array that contains the values of a profile (of time and the released mass) in vivo;

b) at pH 4.5, imitating the release in the duodenum:

– we generated a pseudo-profile of dissolution and its spline-interpolation;

– using the spline, we computed time t_1, over which m_1 mg of a preparation will be released. This magnitude was accepted as the starting point of the time of the release onset in the duodenum;

– using the spline, we calculated mass m_2 of the preparation, released in 2 hours from the starting point of countdown (period of time in the duodenum), was calculated from spline;

– using the spline, we generated a series out of 10–20 intermediate values of the mass released over 2 hours. The obtained values of time and mass were added to the array of values of the profile in vivo;

c) at pH 6.8, imitating the release in the small intestine:

– we generated a pseudo-profile of dissolution and its spline-interpolation;

– using the spline, we computed time t_2, over which m_2 mg of a preparation will be released. This magnitude was accepted as the starting point of countdown of the release onset in the small intestine;

– using the spline, we calculated mass m_3 of the preparation released in 10 hours from the countdown starting point (period of time in the small intestine);

– using the spline, we generated a series of 100 intermediate values of the mass released over 10 hours. The obtained values of time and mass were added to the array of values of the profile in vivo.

At the last section, it may appear that the release time of m_2 mg of a preparation exceeds 4 hours. Then, in order to find the resulting mass of the released preparation, it will be necessary to use the time that exceeds the use in the experiments (14 hours). In this case, we conducted the extrapolation of this period using the last section.

As a result of calculations according to the algorithm, we obtained the mass of preparation released in GIT and the model of a single profile of the release.

To receive a bootstrap-distribution:

– we reiterated computer experiments employing the algorithm given above for 100–10000 times;

– we generated the arrays of values of the released masses m_1, m_2, m_3 in each test;

– we arranged these arrays by growth;

– we assigned to each ordered value a probability 1/n (n is the number of tests);

– by using the obtained values, we constructed accumulated probabilities and empirical functions of bootstrap-distribution.

The algorithm examined was realized in the programming environment of the applied mathematics package Scilab, developed by Institut national de recherche en informatique et en automatique, France, an analog to the Matlab software, openly distributed in the Internet. This package contains the built-in functions that make it possible to operate with linear and cubic splines.

5. 3. Simulation of the release of the preparation Trizipin-Long

The described algorithm was realized based on data from Table 1 for the simulation of the release of the preparation Trizipin-Long from tablets that contain 1000 mg of the preparation. Fig. 1, 2 show results of the simulation of 100 pseudo-profiles of the release of the preparation in the organism, generated with using the linear and cubic splines. It follows from Fig. 1, 2 that in both cases the qualitative picture is very close. The special features of interpolation by cubic splines are the emergence of negative values in the initial section (Fig. 2). This is so to speak a "price for the smoothness" of splines. In the case of linear splines, this is not observed, but there are fractures at the nodal points.

In order to identify the n number of tests, we conducted the simulation and the construction of a distribution function at n=100, 1000 and 10000. It follows from Fig. 3 that the distribution function, built at 100 tests and approximated using the cubic spline, substantially changes with further increase in the number of tests.

In contrast, an increase in the number of tests from 1000 to 10000 does not practically change the distribution

function. A similar pattern is characteristic as well for the approximation by linear splines. This indicates that conducting 1000 tests is sufficient for obtaining the robust characteristics of bootstrap-simulation.

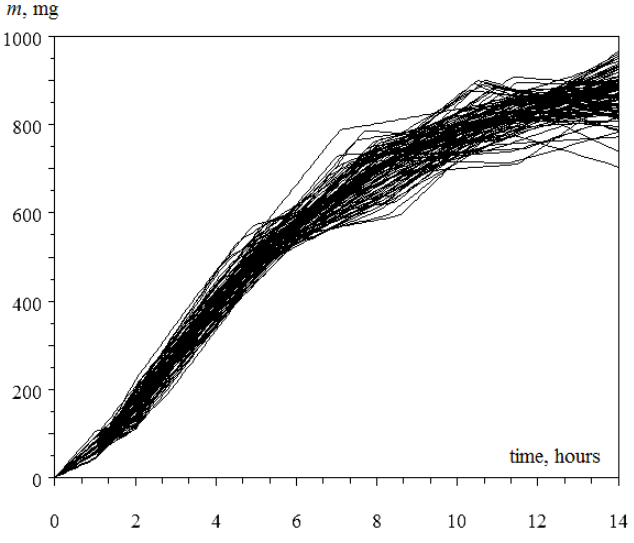

Fig. 1. Bootstrap-simulation of 100 profiles of the release of the preparation Trizipin in vivo using the linear splines

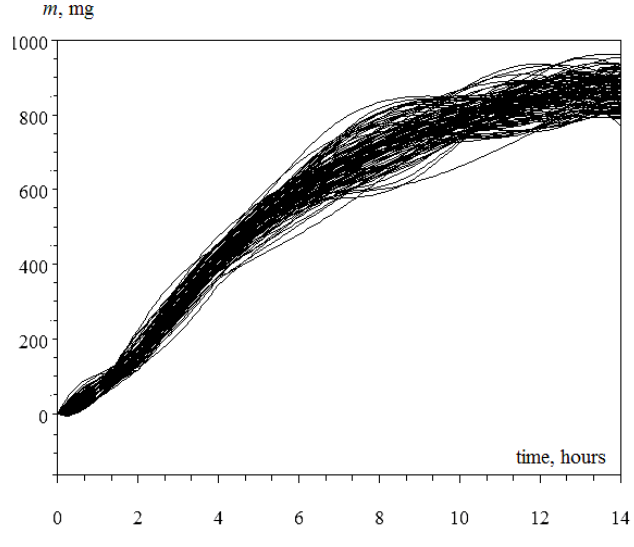

Fig. 2. Bootstrap-simulation of 100 profiles of the release of the preparation Trizipin in vivo using the cubic splines

To investigate the influence of interpolation method, we carried out a comparative study into empirical distribution functions of the amount of preparation released in vivo in 2, 4 and 14 h. Fig. 4 shows that the distribution functions in 2 hours and in 14 hours do not practically depend on the method of interpolation.

Testing by the Lehmann-Rosenblatt criterion, recommended for checking the absolute uniformity of distribution functions [20], revealed the following:

a) distribution functions, obtained using the linear splines and cubic splines at time 2 h and 14 h are uniform at significance level 0.05. This can be interpreted as the equivalence of using both types of splines when applying them to construct the distribution functions;

b) distribution functions at time 4 h prove to be non-uniform, that is, sensitive to the interpolation method, employed during simulation.

A choice of the interpolation method has an effect as well on the mean values of mass of the released preparation. As follows from data in Table 2, at 2 and 14 h, the mean values of released mass for the linear and cubic splines are practically identical. At 4 h, the mean values are noticeably different not only with the low number of tests, but at n=1000 and 10000 as well.

The results obtained testify to the fact that bootstrap-simulation in the initial and final segments of time yields characteristics that do not depend on the interpolation method. In the middle region (the release in the small intestine), results of the simulation depend on the interpolation method.

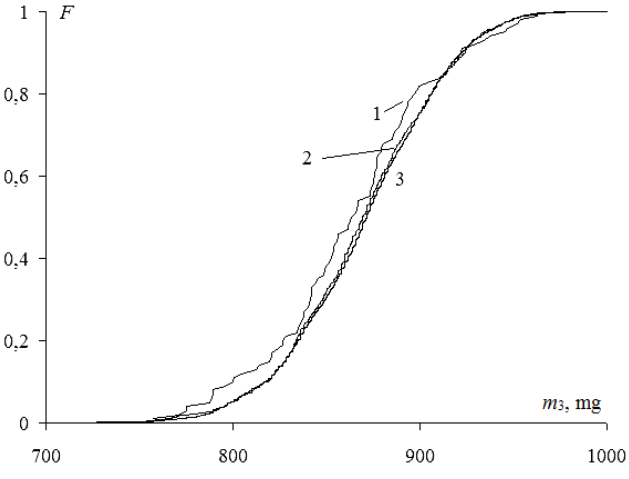

Fig. 3. Distribution functions of the amount of the preparation Trizipin-Long released in vivo over 14 hours. The number of tests: 1 — 100, 2 — 1000, 3 — 10000

Table 2

Mean values of the mass of trizipin released in vivo depending on time, the method of interpolation and the number of tests

n	Method of interpolation	Mean released mass, mg		
		In 2 h	In 4 h	In 14 h
100	Linear	153	389	865
	Cubic	157	413	864
1000	Linear	157	393	872
	Cubic	156	411	869
10000	Linear	156	393	872
	Cubic	156	411	870

The method examined could be used for constructing the confidence interval of predicted value of the release in the organism over the total time of being in GIT. In order to construct a 95 % confidence interval on the curve of a distribution function, it is necessary to highlight the points that match values F=0.025 and F=0.975, which are estimates of the lower and upper bounds of the 95 % confidence interval. According to results of the simulation, confidence interval for n=1000 is (784; 946) mg; for n=10000, it is (788, 946) mg.

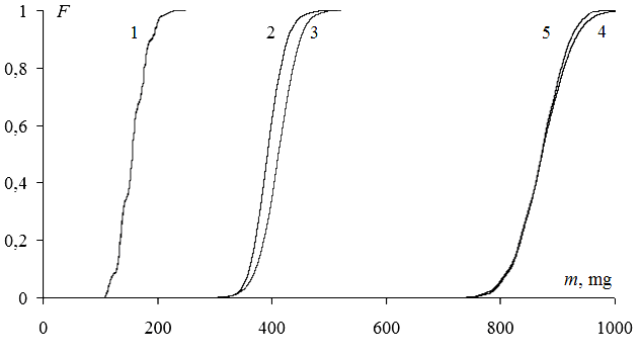

Fig. 4. Distribution function of the mass of Trizipin-Long released in vivo. Interpolation: 1 — in 2 hours, linear and cubic spline; 2 — in 4 hours, linear spline; 3 — in 4 hours, cubic spline; 4 — in 14 hours, linear spline (1); 5 — in 14 hours, cubic spline (2)

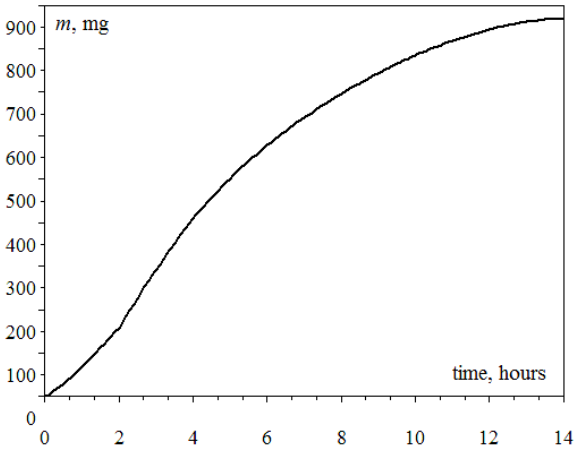

Fig. 5. Mean curve of the release of the preparation Trizipin-Long in vivo

Let us note in conclusion that the approach examined could be used as well to simulate by the mean values of the release according to data in Table 1. For this purpose, a series of splines should be built for the mean values of the release depending on time at different pH. Next, using the algorithm described in 5.1 and the averaged data, to obtain the mean curve of the release of preparation in vitro (Fig. 5).

Judging by curve in Fig. 5, in control points, the release will amount to: in 2 hours – 157 mg, in 4 hours – 410 mg, in 14 hours – 869 mg. This is close to the magnitudes, obtained by the bootstrap-simulation using the spline-interpolation (Table 2). The obtained mean curve (Fig. 4) is a valuable addition to the bootstrap- model. By using this curve, it is possible to compute value of the release in vivo at any point of interval from 0 to 14 hours. In turn, the bootstrap-model makes it possible to estimate the spread of the release relative to the mean curve and to obtain the estimation of confidence interval, especially at the end of the process.

6. Discussion and modeling results

The model examined possesses the following benefits:

– it is not linked to any particular mechanism of the release and physical model related to it;

– it does not contain additional parameters, for example, diffusion coefficient, kinetic characteristics of swelling in polymeric fillers, which are included in the formulation of tablets, etc.;

– obtaining it requires only a set of experimental data, which are received during standard studies into the release of medicines;

These circumstances render the examined model universal and make its use possible for evaluating the release profile of preparations in vivo based on data in vitro. This is important in the course of development of preparations with the assigned profile of the release.

Along with the merits, the model has certain deficiencies. A purely empirical character of the model, the absence of attachment to physical processes do not make it possible to employ it for a detailed study into the mechanisms of the release of medicines from complex modern multicomponent tableted forms.

In further studies, it is planned to investigate the possibility of applying the model considered to solve practical tasks, related to the development of formulations for medicines.

7. Conclusions

1. We developed a bootstrap-model for evaluating the kinetics of the release of medicines in the organism and its computer realization. The model is based on the interpolation of experimental data for the release at pH 1.2; 4.5 and 6.8 by the linear and cubic splines and the use in the simulation of dissolution in the organism by passing the zones with the indicated pH values.

2. The model does not depend on the assumptions about the release mechanism of a preparation and relies on the sets of experimental data on the dissolution kinetics in vitro in different media during maximally possible period of time. The model in question makes it possible to estimate a distribution function, mean profile, spread and confidence interval of the release in vivo in different sections of GIT.

3. We report here an example of using the model for evaluating the release in vivo of the preparation Trizipin-Long based on data in vitro. According to results of computer simulation, mathematical expectation and confidence interval (significance level 0.05) of mass of the released medicine over 14 hours from a tablet that contains 1000 mg of the preparation, are, respectively, 865–872 mg and (784; 946) mg. These magnitudes do not practically vary with an increase in the number of random tests from 1000 to 10000.

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