Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: <http://www.curipms.umlub.pl/>

Role of stable hydrogen isotope variations in water for drug dissolution managing

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ARTICLE INFO

Received 02 October 2019

Accepted 12 November 2019

Keywords:

kinetics dissolving,
laser diffraction spectroscopy,
deuterium depleted water
(ddw),
kinetic isotope effect (KIEs),
water clusters,
antibacterial,
neuroprotective drugs.

ABSTRACT

In the present work, we provide the results of defining by utilizing Laser diffraction spectroscopy, the kinetic isotopic effect of solvent and constant of dissolution rate κ , s^{-1} of an active pharmaceutical ingredient (API) in water with a different content of a stable 2H isotope on the basis of the laws of first-order kinetics. This approach is based on the analysis of the light scattering profile that occurs when the particles of the dispersion phase in the aquatic environment are covered with a collimated laser beam. For the first time, the dependence of the rate of dissolution is demonstrated not only on the properties of the pharmaceutical substance itself (water solubility mg/ml, octanol–water partition coefficient $\log P_{oct/water}$, topological polar surface area, Abraham solvation parameters, the lattice type), but also on the properties of the solvent, depending on the content of stable hydrogen isotope. We show that the rate constant of dissolution of a sparingly hydrophobic substance moxifloxacin hydrochloride (MF · HCl) in the Mili-Q water is: $k=1.20\pm0.14\cdot10^{-2} s^{-1}$ at 293.15 K, while in deuterium depleted water, it is $k=4.24\pm0.4\cdot10^{-2} s^{-1}$. Consequently, we have established the development of the normal kinetic isotopic effect ($kH/kD > 1$) of the solvent. This effect can be explained both by the positions of the difference in the vibrational energy of zero levels in the initial and transition states, and from the position of water clusters giving volumetric effects of solvation, depending on the ratio D/H. The study of kinetic isotopic effects is a method that gives an indication of the mechanism of reactions and the nature of the transition state. The effect of increasing the dissolution of the API, as a function of the D/H ratio, we have discovered, can be used in the chemical and pharmaceutical industries in the study of API properties and in the drug production through improvement in soluble and pharmacokinetic characteristics.

INTRODUCTION

Since the discovery and release of a heavy hydrogen isotope in 1932, thanks, among other things, to the works of Harold Clayton Urey [1], based on differences in physical and chemical properties (protium) and (deuterium), a period of isotopic research began with the use of labeled atoms and the introduction of "heavy" substances into the industry. Deuterated polymers, inorganic deuterides, metal deuterides and alloy deuterides have been the hot topics studied in military and energy fields [2-4]. Deuterium offers a subtle, but sometimes powerful, medicinal chemistry tool that has

received little attention to date in the context of new drugs [5]. There was a separate direction in the medical industry, connected with deuteration API. It was shown [6] that deuteration is a tool useful for optimization of metabolic stability and toxicity of drugs. Selective replacement of hydrogen with deuterium leads to increased bond strength that in turn increases the biological half-life and thus the metabolic stability of the drug [7-8]. At the same time, there are significant changes in pharmacokinetics and reaction rates, as well as in the changes in the ways of metabolism within the Cytochrome P450 superfamily [9]. From a clinical point of view, this can lead to increased efficiency and reduced side effects of pharmacotherapy [10]. The first deuterated drug, now approved by the U.S. Food and Drug Administration,

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is Deutetrabenazine (brand name Austedo®). This belongs to the drug class of VMAT2 inhibitors [11,12]. Deuterated drugs are better tolerated, have less effects on the metabolism, less side effects associated with high concentration of the API [13].

Chemical deuteration significantly increases the efficiency of fluorescence for the oxazine dyes in deuterated solutions. This effect results from a combination of both intrinsic effects, as well as the substantial contribution from altered fluorophore-solvent interactions [14].

Water with modified isotopic composition of hydrogen, for example, deuterated/heavy water, also found its application in nuclear installations for scattering of slow neutrons [15,16]. The use of deuterated water as a solvent for validation of the API by NMR spectroscopy is shown [17]. The selectivity of NMR spectroscopy authenticity method for nuclei was greater if D₂O was used as the solvent. The work [18] has demonstrated a large solvent isotope effect (KIE = 12.0±1.5 at 298 K) of allylindium iodide solvolysis in H₂O and D₂O. Compared at the same temperature, D₂ gas is more soluble in water than H₂ gas, showing a “normal” isotope effect [19].

Differences in physical properties of water ¹H₂O and ²H₂O cause abnormally high natural variations of the isotopic composition: ¹H₂¹⁶O, ¹H₂¹⁷O, ¹H₂¹⁸O, ¹HD¹⁶O, ¹HD¹⁷O, ¹HD¹⁸O, D₂¹⁶O, D₂¹⁷O, D₂¹⁸O [20-21]. According to the SMOW-V standard, the content of stable isotopes in natural water is D/H_{SMOW} = (155.76±0.05) · 10⁻⁶ [23]. Isotopic compositions of reactants affect the rates of chemical and biochemical reactions. Usually it is assumed that heavy stable isotope enrichment leads to progressively slower reactions. Yet the effect of stable isotopes may be nonlinear, as exemplified by the “isotopic resonance” phenomenon [24].

Solubility is one the most important physicochemical properties in various stages of drug discovery and development [25]. Low solubility in water and low bioavailability are limiting factors in oral delivery of lipophilic drugs – about 85% of the best-selling drugs in the U.S. and Europe are taken orally [26]. According to [27], more than 40% of all drug candidates are classified as practically insoluble in water, consequently, they do not pass the stage of preclinical studies. In the pharmaceutical industry, various approaches are used to increase the solubility of APIs: micronization, modification of the crystal structure, salt formation, preparation of solid dispersions, self-nanoemulsifying drug delivery system, mechanochemical synthesis and others [28-30]. In recent studies it was found that the physicochemical and biological properties of API aqueous solutions – the mutarotation rates, the angle of optical rotation, the lifetime of the cell biosensor are dependent on the D/H ratios [31-34].

In this study, we proposed a novel approach to enhancing the poorly soluble drugs solubilization characteristics of different chemical and pharmacological classes, based on the stable hydrogen isotope variations in water as assessed by the Laser Diffraction Spectroscopy method.

Background

In Pharmacopoeia regulation, the “Solubility” test consists in the visual estimation of solubility of the API and excipients at a fixed temperature until the achievement

of thermodynamic equilibrium comes about [35]. According to USP, the standard test is to add a measured amount of solvent to a very fine powder sample and shake continuously for 10 minutes at a temperature of (20±2)°C. The observation is made after cooling the solution to room temperature and vigorous shaking for 1-2 minutes: the sample is considered dissolved if observation of the solution passing through a tube does not detect its particles. The approximate solubility of a compendial substance is indicated by one of the following descriptive terms given in [36]. As regulation of test for solubility comes down to visual assessment and approximate solubility of API, we developed a technique of kinetic assessment of dissolution by Laser Diffraction Spectroscopy. The method is based on registering the light scattering indicatrix in time for the electromagnetic radiation to interact with the particles of the dispersed phase. The result of a sample dispersion decrease over the time is based upon changes in the angular distribution of the scattering intensity (Low-Angle Laser Light Scattering, LALLS): $\pi d/\lambda$, where λ – the wavelength of the electromagnetic radiation, d – particle size [37]. Mathematically, Laser Obscuration (LO) may be presented by the following form:

$$LO = 1 - I/I_0 \cdot 100\% \quad (1)$$

where, I is the light intensity measured by the detector while the particle is inside the measurement cell, I_0 is the light intensity measured by the detector without the particle in the measurement cell (Figure 1).

Figure 1. Optical set-up of kinetic dissolution

The LALLS method was first USP introduced in 2002 and intended for API, pharmaceutical excipients and finished drug product quality control in terms of «Particle size analysis by laser diffraction». The method is based on the ISO standards 13320:2009 [38]. The use of the method as regulated for granulometry as an instrument for studying the dissolution of the API gave us the opportunity to carry out kinetic analysis with the calculation of the rate of dissolution constant $k(c^{-1})$.

Effects of Isotopic Substitution on Physical and Chemical Properties of H₂O

Water with modified isotopic composition of hydrogen has distinctive physical and chemical properties – the substitution of hydrogen atoms in H₂O with deuterium causes significant changes in the properties of the solution [39]. However, a clear description of the effects of isotopic

substitution at low contents of deuterium (deuterium depleted water/ddw, light water) is still lacking and of considerable scientific interest. In this work, we show that water with a low content of heavy hydrogen also has distinctive physical and chemical properties. A comparison of various properties of D₂O, H₂O and ddw are given in Table 1.

Table 1. Physical and chemical properties of H₂O (water with natural content of stable hydrogen isotope), D₂O and deuterium depleted water [40,41]

Properties	Values		
	deuterium depleted water	Water with natural content of stable hydrogen isotope	D ₂ O 99.9%
Melting point, T _f , °C (101.325 kPa)	-1.5	0	3.82
Surface-tension values σ^* , mN·m ⁻¹ * $\sigma = V_r/2nR$ (ρ/n), where V is the volume of liquid corresponding to n -drops released from the stalagmometer with the radius of the tube R ; ρ is the fluid density ** Properties data retrieved at 20±0,05°C	75.172	72.860	67.800
Kinematic viscosity, mm ² /s	0.987	1.012	1.274
Maximum density* (saturated liquid), g·cm ⁻³ *Properties data retrieved at 25±0,05°C	0.9969	0.9982	1.1042
D_r – self-diffusion coefficient*, 10 ⁹ , m ² s ⁻¹ ; * collective movements	0.63	0.46	0.52
Spin-spin relaxation time * T_2 , s * time constant characterizing the signal decay	0.35	2.000	–
Volume concentration of water clusters*, vc (%) * data refer to Light Scattering method	0.20	1.00	0.18
laser obscuration/light scattering* ($\lambda = 632.8$ nm) * data refer to the Light Scattering method	0.003	0.02	0.005

Experimental data show the importance of the content of a heavy hydrogen isotope for measuring not only physical constants in water samples with isotope variations, but also the chemical properties of the resulting solutions [42,43].

2. Experimental

2.1 Water specimens

The dissolution kinetics of APIs were investigated in two water solvents: deionized high-ohmic water (> 18 MΩ·cm⁻¹) received by means of pyrogenous distilled water purification employing the Milli-Q system (Millipore U.K.) with natural content of stable hydrogen isotope. Water, deuterium depleted (≤1, ppm Deuterium oxide) was obtained by means of liquid hydrogen low temperature vacuum rectification. Chemical Purity – 99.5% of H₂O (Merck, Darmstadt, Germany). The deuterium concentration was determined by using the mass-spectrometry method and the Multipass laser absorption spectrometry method (LWIA24d instrument - produced by Los Gatos Research).

2.2. Active Pharmaceutical Ingredients

We utilized the ingredients of two pharmaceutical and chemical groups: topiramate – a sulphate fructopyranose derivative, neuroprotective agent and anticonvulsant that is a powder intended for the manufacture of non-sterile dosage forms (Xian Bodigard Pharmaceutical Co., Ltd., China); moxifloxacin hydrochloride – an antibacterial agent (Second Pharma Co., Ltd., Shaoxing Shi, Zhejiang Sheng, China) (Figure 2) [44-46].

Figure 2. Chemical structures and systematic names of active pharmaceutical ingredients

2.3. Particle sizes

As the scattering indicatrix changes due to the relationship with $\pi d/\lambda$, the rate of dissolution is proportional to the surface of the solid and inversely proportional to the diameter of the particles. We, therefore, have carried out an API particle size analysis utilizing the laser diffraction technique, according to the pharmacopoeia requirements (Figure 3).

Figure 3. Laser granulometry distribution of the particle size (diameter of an equivalent sphere) in suspensions of topiramate (a) and moxifloxacin hydrochloride (b)

The substance topiramate is polydisperse and bimodal with a diameter of 20 and 120 μm. The particle diameter of moxifloxacin corresponds to a modal value with a diameter of 120 μm.

RESULTS AND DISCUSSION

Kinetics of Drug Dissolution

The kinetic involved in the dissolving of drugs were investigated by utilizing a Particle Sizer (Malvern Instruments, Malvern, UK) based on light scattering indicatrix registration in time. A 30 second background measurement was made prior to adding the examined disperse system to account for electrical background and scattering from the optics and 'clean' dispersant. Water with different contents of the heavy isotope of was used as a background. A capacity cell manufactured of quartz glass was used; the necessary quantity for the measurement of the sample material was 3 ml. The capacity cell equipped with the actuator helped to keep the particles in suspension in the process of their measurement and prevented their agglomeration; the speed of the actuator was regulated manually.

Laser diffraction spectroscopy is based on the analysis of the intensity of angular dispersion of the monochromatic electromagnetic plane wave on particles of suspended material. Three repeated measurements were made on each aliquot, using a 30 second measurement time that is equivalent to 30,000 individual light scattering measurements [47]. The measurement of Laser Obscuration Time (LOT) was started while adding water to the cell and continued with 10 s intervals until the complete solubility of the substance which was recorded up to the end of change in the time of the examined laser obscuration parameter.

Dissolution rate in Mili-Q water with natural stable hydrogen isotope content

The exponential dependence of LOT values in the course of various pharmaceutical and chemical groups of powder substances dissolution is shown in Figure 4.

Figure 4. The dependence of the laser obscuration time values while dissolving the drug substance of topiramate (a) and moxifloxacin hydrochloride (b) in the Mili-Q with natural stable hydrogen isotope content ($n=5$, $p=0.95$)

The kinetics of API's dissolution in Mili-Q water are a two-step process: a sharp decrease in the recorded LOT parameter of the test substance powder from the onset of dissolution (first stage) is replaced by a gradual decrease in the laser obscuration value to reach the plateau (second stage). We had fixed it as a complete dissolution of the substance. **The first stage is the speed – determining.**

The rate of dissolution of substances in water is associated with both the thickness of the diffusion layer and the concentration gradient. The heterogeneous dissolution process of API is limited by diffusion, adsorption, and desorption according to Fick's law and the dissolution of the Nernst-Shchukarev equation:

$$dC/dt = kS (C_{\text{saturated}} - C_t) \quad (2)$$

$$k = DS/\delta V \quad (3)$$

The process of the API crystals dissolution in water becomes quite obvious: the dissolution rate is higher at the beginning of the process, when the difference in magnitude ($C_{\text{saturated}} - C_t$) is maximized within the diffusion layer, and then gradually reduced to a plateau.

If we assume that the change in the concentration of one of the reagents — the solvent in the process of dissolution can be neglected, then the general order of the kinetic equation is equal to unity and the reaction proceeding in such conditions is of the pseudo-first order [48].

$$V = -dC/dt = kC \quad (4)$$

The final expressions are given by:

$$k = 1/t \ln C_0/C \quad (5)$$

$$C = C_0 e^{-kt} \quad (6)$$

And to be satisfied are: $C=C_0$ at $t=0$.

Equation 6 proves an exponential decrease in the time of the concentration of one of the reagents. According to a technique based on the method of laser light diffraction, this means a decrease in laser dimming, which depends on the dispersion of the medium.

We calculated the values of the constant dissolution rate of log-linearizing of equation 6:

$$y = a + bx \quad (7)$$

$$k = -\text{tg}\alpha \quad (8)$$

$$\text{tg}\alpha = -d \text{ laser obscuration}/dt \quad (9)$$

The reaction rate constant is determined by the coefficient b of the equation 7 of a straight line, as the tangent of the angle of inclination to the abscissa axis in Figure 5.

Figure 5. The dependence of the natural logarithm of laser obscuration values of topiramate (a) and moxifloxacin hydrochloride (b) dissolving in the water with natural stable hydrogen isotope content, plotted versus t, s ($n=5$, $p=0.95$)

Dissolution rate in Water, deuterium depleted

The analysis of exponential curves dissolution kinetics of the powder of poorly soluble drugs in deuterium depleted water, when compared with that in normal water, allowed identifying differences such as that dissolution is twice as fast as in the Mili-Q water with natural content of in linear (a, b) and semi-logarithmic (c, d) coordinates (Figure 6).

The results in Figs. 4 and 6 indicate that the dissolution of poorly soluble drugs increases with decreases in the stable hydrogen isotope content in water, both for the neuroprotective and antibacterial drug substances. The higher dissolution rate of poorly soluble drugs in the ddw indicates that the D/H ratio plays a significant role in the dissolution.

Kinetic isotope effect (KIE) for solvent. Elements of statistical analysis

The study of the API's dissolution kinetics showed the development of a normal kinetic isotope effect when the condition is: $k_H/k_D > 1$. Validation of the analytical method for determining the dissolution rate of the API by laser diffraction spectroscopy was carried out via repeatability and intermediate precision parameters. For the

statistical analysis of graphic data we applied the software package of OriginLab Corporation (USA).

Figure 6. The dependence of laser obscuration values while dissolving the drug substance of topiramate (a, c) and moxifloxacin hydrochloride (b, d) in water, deuterium depleted in linear and semi-logarithmic coordinates, plotted versus t, s ($n=5, p=0.95$)

The repeatability of the technique was evaluated with identical conditions on the same subjects within a short period of time (Table 2) [49].

Table 2. Evaluation of the rate constant of poorly soluble drugs dissolution in water with stable hydrogen isotope variations with the observed kinetic isotope effect (KIE) ($n=5, p=0.95$)

Sample	$(\bar{k} \pm SD) \cdot 10^2, s^{-1}$		$\Delta \bar{k} \cdot 10^2$ tp, $f = 2,78, P=0,95$ $n=5, f=4$		kH/kD
Topiramate	water with natural stable hydrogen isotope content	water, deuterium depleted	water with natural stable hydrogen isotope content	water, deuterium depleted	1.1
	1.70 ± 0.11	1.90 ± 0.04	0.14	0.05	
Moxifloxacin Hydrochloride (MF · HCl)	1.20 ± 0.14	4.24 ± 0.2	0.17	0.25	3.5

Reproducibility (intermediate precision) as an expression of the proximity of the results between the series of measurements has been evaluated when testing in the laboratory on identical samples of the same series of API on different days ($n=25, P=0,95$). The calculated values of relative standard deviation/coefficient of variation RSD, % ($CV=(S/K) \times 100\%$) reveal the suitability of the developed analytical method with the use of laser diffraction spectroscopy method: $RSD_{topiramate/ddw} = 2.1\%$; $RSD_{topiramate/mili-q} = 5.8\%$; $RSD_{MF \cdot HCl/ddw} = 4.7\%$; $RSD_{MF \cdot HCl/mili-q} = 7\%$.

The observed KIE by the solvent for substances of different classes (see Table 2) can be explained from the position of the difference in zero energies of the bonds of isotope molecules. At the same time, the curves of the potential energy of the C-H connection are identical with the C-D communication curves, that is, the classical energy of activation for the reactions of such molecules can be considered the same [50]. The difference in reaction speeds is due to the difference in the vibrational energy of zero levels in the initial and transition states [51]. Since zero energy is

associated with the frequency of oscillation of the coupling by the expression:

$$E^0 = \frac{1}{2} \sum h\nu_i \quad 10$$

And the frequency of oscillation is represented by the expression:

$$\nu_i = \frac{1}{2} \pi \sqrt{f/m^*} \quad 11$$

where: $m(D) = 1:2$, then the zero energy for the connection with deuterium in is less than for the connection with the protium, because the true activation energy is determined by the ratio:

$$E^a = E + E_{\text{activated complex}} - E^0 \quad 12$$

Therefore, the activation energy of the link break with the proton will be less than with the deuterium.

As follows from the work on the theoretical and experimental studies of KIE [52,53], the change in the reaction rate in isotopic substitution is possible when the communication is broken at the limiting stage of the reaction. The concept of API dissolution on the example of $MX \cdot HCl$ in water with isotopic variations is presented in Figure 7.

*The Transition-state Theory (TST) developed in 1935 by H. Eyring and Polanyi allows characterizing the kinetic dissolution process in terms of the enthalpy and entropy of activation

Figure 7. Solubility scheme of a drug in water with stable hydrogen isotope variations so as to form an activated complex [54]

According to the concept proposed in [55,56], the ratio of velocity constants is influenced by the process of interaction with the solvent containing isotopic molecules. This interaction leads to varying degrees of polarization and hydration of reactive bonds, which is reflected in the size of the kinetic isotope effect. In addition, for hydrogen atoms, there is the possibility of a non-classical passage of the energy barrier ("tunnel"-effect) [57].

In investigating the solvation effects at 298.15, the authors of [58] have compiled a wide variety of experimental data in order to explore the differences in solvation effects for various electrolyte and nonelectrolyte molecules between H_2O and D_2O . Assessment of these differences consists of comparing the transfer properties, defined as:

$$\Delta Y^0 = \bar{Y}_{D_2O} - \bar{Y}_{H_2O} \quad (13)$$

where Y is the partial molar property of the solution. These differences represent the change in solvation energy upon transfer from H_2O to D_2O . The general idea behind the standard Gibbs energy of transfer is that it represents the difference in work done against the cohesive forces of the solvents to create a cavity where the molecule will be placed. This appears to make sense, as water with D_2O

contents is considered a more “structured” solvent at room temperature [59].

We assume that in ddw water, the hydration process (Fig. 7 stages 2) by molecular HOH is considerably facilitated in contrast to that by molecular deuterium stabilized water clusters in Mili-Q water containing a mixture water isotopologues: $^1\text{H}_2\text{O}$; ^1HDO ; D_2O and others [60]. Usually, the replacement of the protium for deuterium leads to a decrease in the reaction rate by 3-8 times [61]. In our case, the removal of deuterium from the dissolution medium led to an increase in the dissolution rate of $\text{MX} \cdot \text{HCl}$ by 3.5 times.

Drug Dissolution Managing

The difference in deuterium depleted water dissolution between the topiramate and the $\text{MF} \cdot \text{HCl}$ (showed in Table 2) also increases with their property's differences, such as, solubility, octanol–water partition coefficient log and the lattice type. It has previously been shown that the D/H ratio is more significant for lipophilicity and sparingly/slightly soluble drugs substances [62].

Probably, the physicochemical properties of the soluble substance, including solubility, pH, pKa and lipophilicity, which determine the main mechanisms of intake and distribution of *in vivo*, play an important role in the acceleration of dissolution (Table 3) [63]. It is known that the absorption process through the intestinal epithelial membrane depends on the lipophilicity of the drug and the nature of distribution and penetration through biological barriers depends on its solubility.

Table 3. Some physicochemical properties of drug substances of different pharmacological and chemical classes [64].

Active Pharmaceutical Substance	pKa	pH
Gentamicin	12.55	3.5-5.5
Taurin	1.5	1.4-5.6
Topiramate	11.09	6.3
Caffeine	14	6.9
Moxifloxacin	5.7	3.9-4.6
Furosemid	4.25	8.0
Dexamethason	12.4	7.5-10.5
Diazepam	3	6.2-6.9
Verapamil	9.68	4.1-6.0

To explain the observed kinetic isotope effect during drug dissolution, we ranked the log P values for substances of different pharmacological and chemical classes in order of their water solubility increase based on reference data (Figure 8) [65].

Based on this two-dimensional diagram, we can predict the biggest kinetic isotopic effect for the substances occupying the upper left area of the diagram – characterized by hydrophobic properties and by being poorly soluble in water. As a result, the conducted studies make it possible to evaluate the important role of stable hydrogen isotope variations in water for correcting/managing the dissolution characteristics of drug substances.

Figure 8. One-to-one correspondences: log P oct/wat – solubility (mg/ml) for substances of different pharmacological and chemical classes

According to the results obtained, an increase of the API's dissolution occurs when the water solvent is deuterium depleted and this leads to the development of the normal kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} > 1$) of poorly soluble drug dissolution. These results indicate a decrease in the transit time of the activated complex that is directly linked with the hydration of the API by HOH, HOD or D_2O molecules. The contribution of molecular water clusters to the kinetics of the formation and disintegration of the API hydrates by protium and deuterium molecules is shown. Consequently, the solvent can be considered as a “means of management” of the properties and processes of dissolution.

CONCLUSIONS

Considering that deuterium depleted water is a safe and accessible (as opposed to heavy water) water solvent, the results of the research will have practical application in the management of the rate of dissolution of substances in water, for example, in chemical and pharmaceutical industries in the study of API properties and in the drugs manufacture with improved solubility and pharmacokinetic characteristics.

Taking into account the previously obtained results on the rate of moxifloxacin degradation in organic solvents [66-68], we propose the unique analytical approach that is offered, consisting of an increase in speed of dissolution of slightly soluble and hydrophobic substances on the basis of variation in the isotope composition of water.

Furthermore, a technique for the kinetic evaluation of the API dissolution by Laser diffraction spectroscopy analyzer has been developed. The technique can be applied to improve and supplement the existing Pharmacopoeial solubility test.

ACKNOWLEDGEMENT

The publication has been prepared with the support of the “RUDN University Program 5-100”.

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