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RELEASE KINETICS OF TRAMADOL HYDROCHLORIDE FROM SOLID DRUG FORMULATIONS

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The aim of this paper is to present the use of a reaction and a dissolution kinetic approach for evaluating the dissolution profile of a drug. As model substances, two controlled-release formulations (with different type of matrix) with tramadol hydrochloride were chosen. Release kinetics of tramadol hydrochloride was studied at isothermal conditions (37 °C) and at different pH values for media used for dissolution. The dissolution profiles obtained by using HPLC with UV detection were fitted by the first-order kinetic model, Korsmeyer–Peppas, Higuchi, and Weibull models. The main results of regression analysis were the determination of the first-order release rate constant (k_1), the release exponent (n) from Korsmeyer–Peppas model, Higuchi constant (K_H), and the parameters of Weibull model (b, λ).

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Introduction

Many important areas of chemical kinetics including reactions involving gases, solutions, and solids have been described over the past decades but an application of basic principles of chemical kinetics in pharmaceutical technology is relatively new. An important element in drug development is *in vitro* dissolution test [1]. During the dissolution test, the released amount of drug as a function of time — the dissolution profile — is observed. Quantitative evaluation of the drug dissolution profile allows to analyze the dissolution mechanism and to describe the drug release from pharmaceutical formulations using mathematical, statistical or kinetic models. Kinetic analysis of the dissolution data is important not only for explanation of the drug release mechanism, but it also enables a comparison of pharmacokinetic properties of various drug formulations with the same active substance and its contribution to the drug development.

Description and Modelling of Dissolution Profiles

Models based on the principles of chemical kinetics together with physical diffusion models are the most commonly used for evaluation and description of the processes of active substances released from various drug formulations [2-4].

The principal rules for the evaluation of drug release kinetics were established by Noyes and Whitney in 1897 [5]. In the Noyes–Whitney equation, the dissolution process corresponds to a first order reaction. The Noyes–Whitney equation was modified by Brunner *et al*. by incorporating the area of the dissolution surface (or diffusion layer, respectively [6,7]). Brunner and Nernst applied Fick's law of diffusion to define a relationship between the constant K_1 in the modified Noyes–Whitney equation and the diffusion coefficient K_D of the solute [4-6]. Nernst and Brunner assumed that the process at the surface proceeds much faster than the transport process and that a linear concentration gradient is limited by the layer of solution adhering to solid surface [6-8].

Active substance release from dosage forms that do not disaggregate and release the drug independently on time can be described by zero-order kinetic model [9-11]. Rate of the drug dissolution from dosage forms is constant and being equal to the zero-order rate constant k_0.

Application of the first-order model [2,8-11] to drug dissolution studies was first proposed by Gibaldi and Feldman [12] and later also by Wagner [13]. This model is usually used for description of the drug release from pharmaceutical dosage forms containing water-soluble drugs in porous matrices (where the release rate is determined mainly by solubility of the active substance). The first order kinetics is usually expressed by the equation

$$A_{t(l)} = A_0 e^{-k_1 t} \quad (1)$$

where $A_{t(l)}$ is the released amount of drug in time t, A_0 is the initial amount of drug and k_1 is the first order release rate constant. Higher order kinetic models have much lower practical application because it is often difficult to prove the physical legitimity for their use.

Theoretical models for description of the release of water soluble and low soluble drugs incorporated in semi-solid and solid matrixes were proposed by Higuchi [14,15]. Conclusions of his studies can, in a general way, be expressed by the equation

$$A_{t(l)} = k_H \sqrt{t} \quad (2)$$

known as the simplified Higuchi model [2]. In Eq. (2), K_H is the Higuchi dissolution constant and $A_{t(l)}$ is the amount of drug released in time t. Higuchi described the drug release as a diffusion process based on the Fick's law and Eq. (2) applies to the description of the drug dissolution from several types of CRDSs, such as the transdermal systems [16] or matrix tablets with water soluble drugs [17-20].

For description of the dissolution processes, where the release mechanism is not well-known yet or, in the case, when more than one type of release phenomena could be involved, Korsmeyer–Peppas model was proposed [21,22]. In general form, this model can be expressed by the equation

$$A_{t(l)} = A_0 a t^n \quad (3)$$

or by the logarithmic form

$$\ln A_{t(l)} = \ln A_0 + \ln a + n \ln t \quad (4)$$

where A_0 is the initial amount of the drug in the solid drug formulation (representing the maximum releasable amount of drug A_∞), a being constant incorporating structural and geometric characteristics of the dosage form and, finally, n is the release exponent indicating the release mechanism of the drug. The constant a is often denoted as the release rate constant [8]. The release exponent and interpretation of the diffusion release mechanism are both discussed in [2,8, 21,22].

Furthermore, an empiric Weibull model adapted to the dissolution process [2,23] can then be expressed by the equation

$$A_{t(l)} = A_0 \left(1 - e^{-\lambda (t - T_i)^b}\right) \quad (5)$$

where λ represents the reciprocal value of time scale of the process, T_i represents the location parameter defining the lag time before the onset of the dissolution (in most cases being zero) and *b* describes the shape of the dissolution curve progression. Because the Weibull model is empiric (and there is no kinetic fundament), it reveals some drawbacks having thus been the subject of critisism [32,33]. To compare the dissolution profiles of two drug formulations, the model dependent methods (curve fitting), statistic analysis, and model independent methods can be chosen [2,8,24-30].

As mentioned above, the aim of this paper is to present the use of reaction kinetics axioms in order to evaluate the drug dissolution profile. Description of this drug dissolution profile by using of suitable kinetic model allows us to obtain the proper kinetic parameters, such as the release rate constant k_1 (for the first order kinetic model, Eq. (11)), the maximum amount of active substance A_0 (Eqs (4), (5), and (11) that can be released, the release exponent *n* (Korsmeyer–Peppas, Eq. (4)), reciprocal value of the time scale of the process λ, and the shape parameter *b* (Weibull, Eq. (5)) or Higuchi dissolution constant K_H (Eq. (2)). Using all these parameters, it is possible to quantitatively describe the dissolution behaviour of a drug formulation.

Experimental

Material and Methods

For preparation of standard tramadol hydrochloride (TH) solution and dissolution media, redistilled water and chemicals of analytical grade (Lach - Ner s.r.o., Neratovice, the Czech Republic) were used throughout the experimental work. Tramadol hydrochloride reference standard (European Pharmacopoeia (EP) Reference Standard, Sigma-Aldrich) was used for all measurements as the standard of the active substance. The active substance standard solutions were prepared by dissolving of 20 mg TH reference standard in 100 ml of an appropriate dissolution medium. Acetonitrile (for HPLC, ≥ 99.9%, Sigma-Aldrich) and trifluoracetic acid (for HPLC, ≥ 99 %, Sigma-Aldrich) were used for HPLC determination of TH. All studied excipients were purchased from Sigma-Aldrich.

In Vitro Dissolution Studies

In vitro dissolution studies were performed with two commercially formulated TH tablets marketed in the Czech Republic — the original drug formulation F1 (Tramal Retard Tablety 200 mg, Grünenthal GmbH, Aachen, Germany) and a generic form F2 (Tralgit SR 200, ZENTIVA, a. s., Bratislava, Slovak Republic).

Both commercial drugs contained 200 mg of TH in each tablet. Formulation F1 (original drug) represented hydrophilic matrix based on microcrystalline cellulose and hypromellos, whereas the formulation F2 (generic form) had lipophilic matrix based on glycerol dibehenate.

Dissolution profiles were studied in two different dissolution media (pH 1.2 and 7). All the tests were carried out 24 hours in the paddle apparatus (Sotax AT 7 Smart, Switzerland) at a stirring rate of 125 rpm in accordance with recommendations of Czech Pharmacopoeia 2009 [31] and the U.S. Pharmacopoeia [1]. Temperature was maintained at 37 ± 0.5 °C. One tablet containing 200 mg of TH was transferred into a dissolution vessel with 900 ml of the dissolution medium. At pre-determined time periods, 3 ml of the dissolution medium was automatically withdrawn and replaced with the same volume of fresh medium. Consecutively, the sample was filtrated and TH concentration determined using HPLC with spectrophotometrical detection. Each experiment (with six tablets) was performed in six replicates and the mean values of the released amount of TH were calculated and expressed together with the corresponding standard deviations.

All experimental data were mathematically processed and statistically evaluated by means of the"Graph Pad Prism" and "Origin 9 Pro" computer programmes. The coefficient of determination (R^2) and the residual sum of squares (*RSS*) were used for comparison of the kinetic models used. The respective statistical significance was evaluated by using Student *t*-test for unpaired samples, at a significance level of $P < 0.05$.

The Dissolution Media Preparation

All the dissolution media were prepared in accordance with [34], with the recommendations of the Czech [31] and the U.S. Pharmacopoeia standards [1]. Preparation of a typical dissolution medium (pH 1.2) had been as follows: 250 ml 0.2 M NaCl was mixed with 425 ml 0.1 M HCl and the solution diluted to 1000 ml with redistilled water when the pH value being adjusted with HCl if necessary. Preparation of dissolution medium (pH 7) had then been made in the following way: 29 ml 1 M sodium dihydrogen phosphate and 50 ml 0.5 M disodium hydrogen phosphate were mixed and filled up with redistilled water to 1000 ml, the pH value checked using pH meter and adjusted with 0.1 M NaOH or 0.1 M HCl if needed. The pH value of all prepared dissolution media was measured by pH glass electrode calibrated using commercially available calibration buffers (Sigma Aldrich).

Determination of TH Using HPLC

High-performance liquid chromatography analyses were performed again in accordance with the Czech [31] and the U.S. Pharmacopoeia standards [1]. An Ecom HPLC system (Ecom Prague, the Czech Republic) was used consisting of a system controller, high pressure pump Beta, degaser, injector and a UV VIS detector Safir. Chromatographic data were analyzed and stored using "Data Apex Clarity" software. The column used for separation of the dissolution products was a C18 column ("Kromsil 60 Silica", 250 × 4.6 mm × 7 μm; Ecom Prague, the Czech Republic). Mobile phase was prepared according to the Czech Pharmacopoeia 2009 [31] when using trifluoracetic acid and water (2 ml CF_3COOH + 998 ml H_2O) and mixing with acetonitrile (70:30, v/v). Each sample was measured at a wavelength of 271 nm (recommended by the Czech Pharmacopoeia 2009 for the determination of TH). An isocratic method was applied with a flow rate of 1 ml min^{-1} and column temperature of 37 °C.

Results and Discussion

The release of TH from the original drug (F1) and the generic form (F2) was studied by using of the dissolution study *in vitro* in two dissolution media under conditions set correspondingly to those in the gastrointestinal tract. During the dissolution test, the released amount of TH as a function of time was observed and these experimental data evaluated by the regression analysis.

In order to study the release kinetics of TH from the studied formulations, the dissolution profiles obtained from dissolution tests were fitted by Higuchi (Eq. (2)), Korsmeyer–Peppas (Eq. (4)), Weibull (Eq. (5)) and the first order kinetic model. For doing this, equation for the first order kinetics (Eq. (1)) had to be adapted because it was necessary to distinguish between the drug amount in the solid form $A_{t(s)}$ and an amount in the dissolution medium $A_{t(l)}$.

The release of the drug from CRDSs which follows first order kinetics can be expressed by the exponential equation

$$A_{t(s)} = A_0 e^{-k_1 t} \tag{6}$$

where $A_{t(s)}$ is the amount of drug in solid formulation in time t, A_0 is the initial amount of the drug in solid formulation (maximally releasable amount of the drug) and k_1 is the first order rate constant expressed in units of $time^{-1}$.

The time dependence of the released amount of drug $A_{t(l)}$ can then be obtained from equation

$$A_{t(l)} = A_0\left(1 - e^{-k_1 t}\right) \tag{7}$$

being used for evaluating the dissolution profiles obtained by the first order model.

The untransformed dissolution profiles of hydrophilic matrix tablet F1 and lipophilic matrix tablet F2 fitted by the first order model (Eq. (7)) and Weibull model (Eq. (5)) are shown in Fig. 1. Linearisation by Korsmeyer–Peppas model (Eq. (4)) and Higuchi model (Eq. (2)) is presented in Figs 2 and 3. Finally, the results from regression analysis are summarised in Tables I and II.

Table I Regression analysis of F1 dissolution profiles

pH	Model	Parameter ± *SD*	R^2
1.2	$A_{t(l)} = A_0\,[1 - \exp(-k_1 t)]$	$k_1 = 5.56\times10^{-3} \pm 8.87\times10^{-5}$ min^{-1} $A_0 = 101.8 \pm 0.4$ %	0.9955
	$\ln A_{t(l)} = \ln A_0 + \ln a + n \ln t$	$n = 0.52 \pm 0.01$	0.9796
	$A_{t(l)} = k_H\sqrt{t}$	$K_H = 4.08 \pm 0.14$	0.9662
	$A_{t(l)} = A_0\,[1 - \exp(-\lambda t^b)]$	$\lambda = 5.52\times10^{-3} \pm 9.1\times10^{-5}$ $b = 0.95 \pm 0.02$ $A_0 = 102.3 \pm 0.4$	0.9959
7	$A_{t(l)} = A_0\,[1 - \exp(-k_1 t)]$	$k_1 = 5.27\times10^{-3} \pm 7.7\times10^{-5}$ min^{-1} $A_0 = 94.4 \pm 0.3$ %	0.9963
	$\ln A_{t(l)} = \ln A_0 + \ln a + n \ln t$	$n = 0.55 \pm 0.02$	0.9611
	$A_{t(l)} = k_H\sqrt{t}$	$K_H = 3.87 \pm 0.06$	0.9937
	$A_{t(l)} = A_0\,[1 - \exp(-\lambda t^b)]$	$\lambda = 5.13\times10^{-3} \pm 6.1\times10^{-5}$ $b = 0.90 \pm 0.013$ $A_0 = 95.6 \pm 0.3$	0.9983

For both value of pH, the dissolution profiles of F1 and F2 are formed by smooth exponential curves with a high-release rate in the beginning of the dissolution process (Fig. 1). High release rate of the active substance in the initial stage of the dissolution process can be explained by the surface erosion and the starting disaggregation of the matrix tablet (F1 and F2), formation of the gel layer around the tablet core (F1) and also by a high solubility of TH in aqueous solutions. Hydrophilic matrix of the F1 formulation contains hypromellose. It is known that hypromellose (HPMC) is stable over a wide pH range 3-11 [35]; however, the release rate of active substance from such hydrophilic matrix with HPMC is affected by changing pH due to the penetration of water and swelling. Release of the active substance from matrix tablet containing hydrophilic polymers is also influenced by diffusion.

When *in vitro* studies are performed, the diffusion rate is in relation with transport of the drug from dosage matrix into the dissolution medium and the resultant pH and composition correspond both to the specific part of gastrointes-

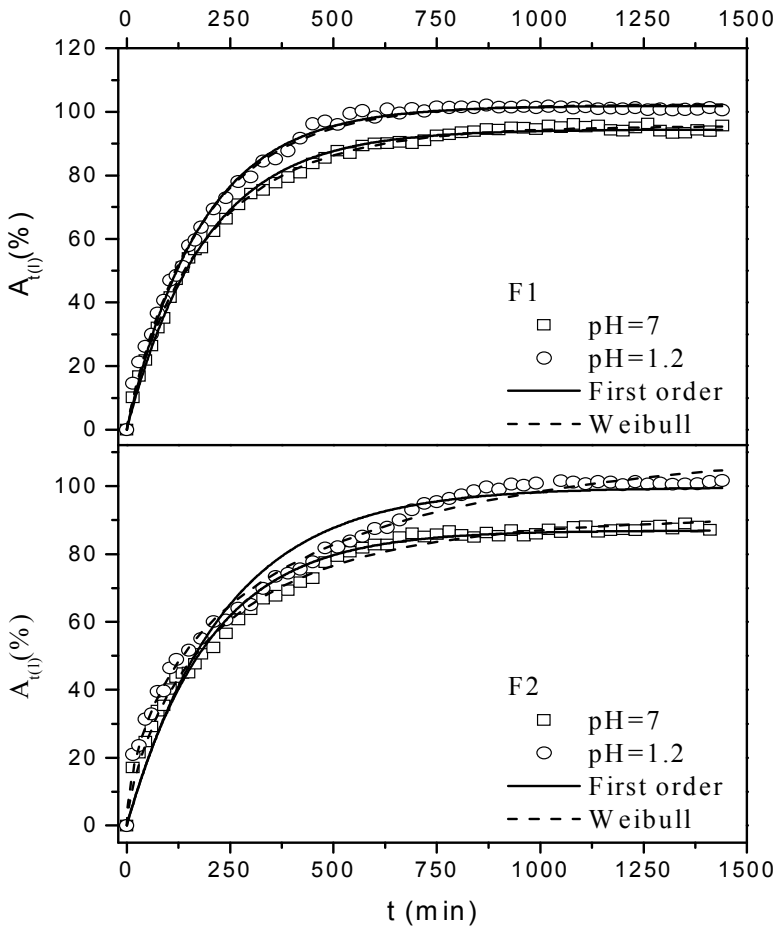

Fig. 1 Nonlinear approximation of F1 and F2 dissolution profiles (with the first order and Weibull model). F1 – hydrophilic matrix tablet, F2 – lipophilic matrix tablet, dissolution medium pH 1.2 (circle) and pH 7 (square), temperature 37 °C, dissolution time 24 hours, paddle apparatus at a stirring rate of 125 rpm, the first order fit (line), Weibull model fit (dash)

tinal tract. The driving force of this process is a concentration gradient. At the beginning of dissolution, the concentration gradient is high, thus corresponding to a high value of the release rate. The slope of the initial part of the dissolution profile determines then the release rate [35].

Based on the experiments performed, it was confirmed that the dissolution profile of F1 formulation follows the first order kinetic model and Weibull model with high value of R^2. Similarly high values of R^2 for the first order kinetic model and Weibull model have also been found for both dissolution media (Table I). When the shape parameter b in Eq. (5) is equal to one, the Weibull empiric model corresponds to the first order kinetic model (Eq. (7)) and the parameter λ in Eq. (5) corresponds to the first order release rate constant k_1. As can be seen in Table I, the shape parameter b is equal to 0.95 (pH = 1.2) and 0.90 (pH = 7), which corresponds to the fact that the dissolution process of F1 formulation can be considered to obey the first order kinetics.

Table II Regression analysis of F2 dissolution profiles

pH	Model	Parameter ± *SD*	R^2
1.2	$A_{t(l)} = A_0 [1 - \exp(-k_1 t)]$	$k_1 = 4.24\times10^{-3} \pm 2.3\times10^{-4}$ min^{-1} $A_0 = 99.6 \pm 1.3$ %	0.9534
	$\ln A_{t(l)} = \ln A_0 + \ln a + n \ln t$	$n = 0.40 \pm 0.01$	0.9924
	$A_{t(l)} = k_H\sqrt{t}$	$K_H = 3.16 \pm 0.06$	0.9911
	$A_{t(l)} = A_0 [1 - \exp(-\lambda t^b)]$	$\lambda = 3.00\times10^{-3} \pm 2.5\times10^{-4}$ $b = 0.63 \pm 0.02$ $A_0 = 114.4 \pm 2.9$	0.9925
7	$A_{t(l)} = A_0 [1 - \exp(-k_1 t)]$	$k_1 = 4.96\times10^{-3} \pm 1.7\times10^{-4}$ min^{-1} $A_0 = 87.0 \pm 0.7$ %	0.9782
	$\ln A_{t(l)} = \ln A_0 + \ln a + n \ln t$	$n = 0.44 \pm 0.01$	0.9953
	$A_{t(l)} = k_H\sqrt{t}$	$K_H = 3.16 \pm 0.05$	0.9921
	$A_{t(l)} = A_0 [1 - \exp(-\lambda t^b)]$	$\lambda = 4.49\times10^{-3} \pm 1.6\times10^{-4}$ $b = 0.75 \pm 0.02$ $A_0 = 91.1 \pm 0.9$	0.9925

Dissolution profile of the F2 formulation (with lipophilic matrix) follows the Weibull model with high value of R^2 in both dissolution media (with R^2 = 0.9925 for both pH values), but it has been found that the shape parametr b is equal to 0.62 ± 0.02 (pH = 1.2) or 0.75 ± 0.02 (pH = 7). It implies that the Weibull kinetic model does not correspond to the Eq. (7) and the dissolution process of F2 formulation does not fulfil the first order kinetic model. This was also confirmed by the fit to the untransformed experimental data by the first order kinetic model (Eq. (7)) and, consequently, by the results of regression analysis. For the first order kinetic model, lower values of R^2 in comparison with Weibull model were found. The respective fit of the dissolution profile for F2 by Eqs (5) and (7) is presented in Fig. 1. The kinetic parameters are summarised in Table II.

As presented in Figs 2 and 3, the *in-vitro* release profiles of TH from the investigated formulations F1 and F2 were linearized by Higuchi model (Eq. (2)) and, to confirm the diffusion mechanism, the data were fitted to the Korsmeyer–Peppas model (Eq. (4)). For evaluation of the dissolution kinetics and the determination of kinetic parameters, only the first 12 hours of the dissolution profiles were used [8]. The release exponent n indicating the drug release mechanism was determined for both formulations in both dissolution media (Tables I and II); again, when using linear regression.

For hydrophilic formulation F1, the release exponents n = 0.52 ± 0.01 (for pH = 1,2) and n = 0.55 ± 0.02 (pH = 7) were obtained from Eq. (4) indicating the Fickian diffusion. This fact was proved by the linearization of the dissolution pro-

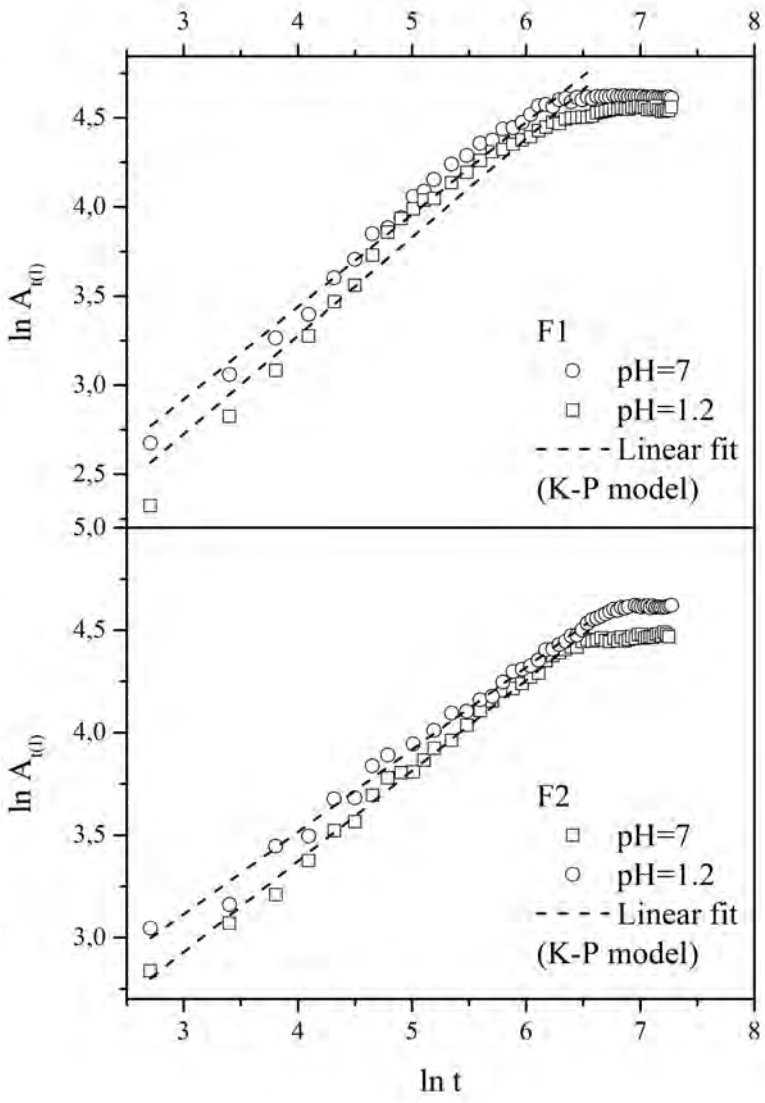

Fig. 2 Linear fit (Korsmeyer-Peppas model) of F1 and F2 dissolution profile. F1 – hydrophilic matrix tablet, F2 – lipophilic matrix tablet, dissolution medium pH 1.2 (circle) and pH 7 (square), temperature 37 °C, dissolution time 24 h, paddle apparatus at a stirring rate of 125 rpm, Korsmeyer–Peppas model fit (dash)

file of F1 by Higuchi model (Eq. (2)), where the release rate is a function of time $t^{0.5}$. The results of regression analysis are also gathered in Table I. For lipophilic F2 formulation, the release exponents $n = 0.40 \pm 0.01$ (for pH = 1.2) and $n = 0.44 \pm 0.01$ (pH = 7) were found. This probably expresses a more complicated dissolution mechanism as the Higuchi model is fulfilled for high values of R^2.

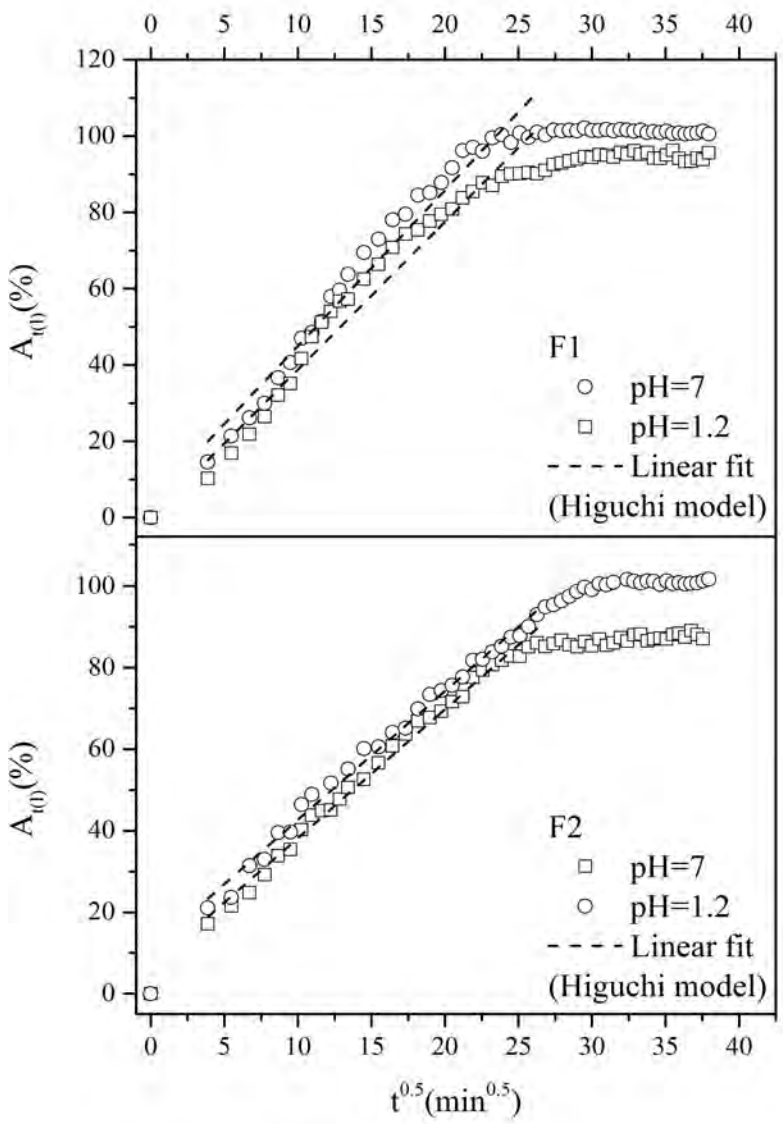

Fig. 3 Linear fit (Higguchi model) of F1 and F2 dissolution profile. F1 – hydrophilic matrix tablet, F2 – lipophilic matrix tablet, dissolution medium pH 1.2 (circle) and pH 7 (square), temperature 37 °C, dissolution time 24 hours, paddle apparatus at a stirring rate of 125 rpm, Higuchi model fit (dash)

Conclusion

The use of reaction kinetics in order to describe the release of active substance from the solid drug formulations has been presented. The dissolution kinetics usually monitors an increase of active substance amount in the dissolution medium as a function of time, but the reaction kinetics is concerned with the time-dependent conversion of the reactants into the products. Therefore, the generally known kinetic equations had to be transformed, when it was necessary to distinguish between the amount of active substance in the solid drug form and the amount of active substance in the dissolution medium. A non-linear time

dependence obtained for the released amount of drug (behaving according to the first-order kinetics), was used for evaluating the dissolution profiles by means of the regression analysis. By applying the non-linear regression, the experimental data have not been affected by linearization. The non-linear fit to the experimental data by the first-order kinetic model could then be compared with a fit by the empiric Weibull model. Then, it has been found that, for hydrophilic F1 formulation, the shape parameter *b* in the Weibull model is near to one, which means that this empiric model corresponds to the first-order kinetic model. Based on the respective release exponent from Korsmeyer-Peppas equation it has also been confirmed that the release kinetics of F2 formulation fulfils the Higuchi diffusion model.

Because the evaluation of the dissolution data by regression analysis is quite common practice, it should be noticed that the linearization of the experimental data might give rise to an experimental error and, therefore, the use of nonlinear regression for untransformed dissolution data seems to be more suitable.

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