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Modeling Kinetics and Transport Mechanism Study of Poorly Soluble Drug Formulation in High Acidic Medium

Maha Al-Ali [a*], **Laith I. Al-Ali** [b]

a Petroleum and Gas Refining Department, College of Petroleum Processes Engineering, Tikrit University, Tikrit, Iraq.
b Mathematics Department, College of Education for Pure Science, Tikrit University, Tikrit, Iraq.

Keywords:
Release kinetics; Microwave radiation; Fickian diffusion; Non-Fickian diffusion; Case II transport; Modeling.

Highlights:

- *Microwave radiation and hot air heating were used to prepare drug pills.*
- *Various kinetics models were used to study the drug release mechanism of all pills.*
- *The Peppas-Sahlin and zero-order models matched the drug release profile of all pills.*
- *Non-Fickian diffusion and case II transport were the controlled mechanisms of pills.*
- *New models were modified to describe the kinetics of the drug release of pills.*

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*Corresponding author:

Maha Al-Ali
Petroleum and Gas Refining Department, College of Petroleum Processes Engineering, Tikrit University, Tikrit, Iraq.

Abstract: Some medicinal particles are poorly soluble in highly acidic solutions, particularly those subjected to various production processes. Therefore, the present research investigated the kinetics and mechanisms of the drug release rate of newly formulated solid pills in a low pH medium. Three pills were prepared: one from a non-moisturized powder mixture (PILD) and the other two, PILC and PILM, from the dried powder mixtures, which were dried using hot-air heating and microwave radiation, respectively. These pills were subjected to drug release tests, and the outcomes were considered in the kinetics investigation using various models. Zero-order, Hixson–Crowell, First-order, Higuchi, Hopfenberg, Korsmeyer-Peppas, Logistic, and Peppas-Sahlin were the kinetic models used to inspect the release rate mechanism of these tablets. It was found that the Peppas-Sahlin and zero-order were the most reliable models to represent the drug release profile of all prepared pills with very high accuracy, estimated by $R^2 > 0.99$. The Hixon and first-order models were the weakest to characterize this work outcome. This work also applied these models to describe the controlling mechanism of the drug release for each prepared pill. It is detected that the non-Fickian diffusion and polymer chain relaxation control the PILC's release behavior. However, case II transport and super case II transport with erosions is the dominant mechanism for PILD and PILM pills, respectively. Additionally, new semi-empirical models were modified to describe the kinetics of the solid release of those tablets with greater accuracy.

دراسة النمذجة والحركية وآلية انتقال التركيبات دوائية ضعيفة الذوبان في وسط عالي الحموضة

مها العلي [1]، ليث ابراهيم العلي [2]

[1] قسم تكرير النفط والغاز/ كلية هندسة العمليات النفطية/ جامعة تكريت/ تكريت - العراق.

[2] قسم الرياضيات/ كلية التربية للعلوم الصرفة/ جامعة تكريت/ تكريت - العراق.

الخلاصة

بعض الجزيئات الدوائية تكون ضعيفة الذوبان في المحاليل شديدة الحموضة، خاصة تلك التي تخضع لعمليات إنتاج مختلفة. في هذا البحث، تم دراسة حركية وآليات معدل انحلال المادة الدوائية للحبوب الصلبة المصنعة حديثًا في وسط ذا رقم هيدروجيني منخفض. تم تحضير ثلاثة أنواع من الحبوب، احدها من خليط مسحوق غير رطب (PILD) والنوعين الآخرين، PILC وPILM من خليط مسحوق مجفف الذي تم تجفيفه باستخدام طريقتي التجفيف باستخدام الهواء الساخن وطريقة استخدام الإشعاعات الميكروويفية، على التوالي. تم إخضاع هذه الحبوب لاختبارات تحلل الدواء وتم أخذ النتائج بعين الاعتبار في التحقيق الحركي باستخدام نماذج رياضية مختلفة وهي الأكثر شيوعا في هذا المجال. وهذه النماذج هي Zero order, Hixson–Crowell, first order, Higuchi, Hopfenberg, Korsmeyer-Peppas, Logistic, and Peppas-Sahlin. وقد وجد أن Peppas-Sahlin وZero-order هما النموذجان الأكثر تطابقا لتمثيل ملف تحلل الدواء لجميع الحبوب المحضرة بدقة عالية جدًا تقدر بـ R^2>0.99. كان نموذج Hixon ونموذج first order من أضعف النماذج في وصف نتيجة العمل هذه. قام هذا العمل أيضًا بدراسة وصف آلية التحكم في إطلاق الدواء لكل حبة من الحبوب المحضرة. تم الكشف عن أن سلوك إنحلال حبوب PILC يتم التحكم فيه عن طريق الانتشار الذي لا يتبع قانون Fick وتفكك سلاسل البوليمر. ومع ذلك، فإن انتقال المادة المسمى case II transport و super case II transport مع التآكلات هي الآلية السائدة لحبوب PILD وPILM، على التوالي. فضلاً عن ذلك، تم بناء نماذج شبه تجريبية جديدة لوصف حركية الإطلاق والانحلال الصلب لتلك الأقراص بدقة أكبر.

الكلمات الدالة: هضم لاهوائي، غاز حيوي، روث البقر، سطح ممتد، هاضم منزلي.

1.INTRODUCTION

The medication or drug release is the mass transport of the drug over time at a specific rate to provide the proper pharmacology depending on the nature of the drug and dissolution medium [1, 2]. Drug release is a significant factor of a therapeutic system, which creates a condition of absorbing the therapeutic or the active ingredient to support and extend the drug activity in the human body [3, 4]. As the medications differ in ingredients and properties, the dissolution or release patterns also differ. The solid drug quantity dissolution as a function of time is described by applying some mathematical kinetic models. The mathematical models are derived either from the theoretical analysis or the empirical equations [5-7]. Kinetic models are therefore used to interpret the drug release over time depending on the concentration. Historically, the drug release theory was developed over time and the researchers created and modified many mathematical models to describe it. For example, Noys and Whitney (1897), Brunner and Tollozko (1900), Nernst and Brunner (1904), Hixon and Crowell (1931), Edwards (1951), Nelson (1957), Higuchi (1961), Levich (1962), Permarowski (1986), John G. and Wanger (1970-1981), FDA (1987-200), and others [8]. The process of drug dissolution is stated using many kinetic models to optimize and modify the design of the therapeutic device [9-11] and yield an active and safe drug [12]. The most common models used are the zero-order, the Hixson–Crowell, the first-order, the Korsmeyer-Peppas, the Higuchi [13-15], and others. The Zero-order model is designed for the systems with a drug dissolution/release rate independent of its concentration and is used for low soluble matrix tablets [16, 17]. The First-order model is used to describe the systems of release rate dependent on drug concentration, in which reduction of the amount of drug released with time is the responsible behavior of this model [18, 19]. Hixson-Crowell depends on diminishing the diameter and surface area of the dissolved tablets with time [20]. Higuchi's model relies on Fickian diffusion of the insoluble matrix release rate with the square root of time, in which the logarithm plot approaches 0.5 if the release rate is a diffusion-controlled process [7]. The Hopfenberg model describes the drug release that depends on the surface eroding of the drug matrix [21]. It applies to different tablet shapes, such as infinite cylindrical, spherical, and slab tablets [21-23]. Korsmeyer-Peppas depends on exponent value α, which refers to the dissolution rate mechanism of the drug as diffusion, erosion, or swelling [24, 25]. Additional mathematical models are used in other studies to describe the drug release for different matrix tablets. For example, Ritger-Peppas and Peppas-Sahlin were used to describe the release of sodium salicylate from HPMC tablets and showed high fitting [23]. Hence, the Peppas-Sahlin model is considered in the present work as it matches many drug releases well. Mathematical models of drug dissolutions are interestingly investigated to explore the optimum physical and chemical properties of the formulated drug, minimize the experiments required to optimize the drug formulation, discover the mechanism of drug releases such as diffusion, erosion, and swelling or a combination of more than one behavior, optimize the drug release kinetic with active and safe treatment, predict the drug release profile to enhance drug bioavailability and stability, and to design a new drug delivery system [1, 22, 26, 27]. In general, drug release

mechanisms can be categorized into a diffusion mechanism, an erosion mechanism, or a combination of diffusion and erosion [16]. Diffusion release is the main responsible mechanism in the matrix planar drugs with a 0.5 value of release exponent [18]. Erosion dominates the low viscous hydrophilic polymer and the low water-soluble and low diffusive drugs [28]. Moreover, for polymers of low viscosity and resistant gel structures, a combination of diffusion and erosion release systems are mostly the governor kinetics of release [16]. These kinds of drugs are called non-Fickian drugs because they have anomalous release depending on the release exponent lying between $0.45 < \alpha < 0.89$ [16, 29]. Whereas, for the drugs of α, the release indicative equals 0.89 refers to case II transport mechanisms, and for α more than 0.89 illustrates super case II transport [30-32]. However, Holowka and Bhatia [33] classified the release systems of pharmaceutical drugs into two: the release controlled by the active agents and bioinert polymer molecules and the release sustained by a mixture of agents. On the other hand, the drug release from surface-eroding pills of different shapes was evaluated by Hopfenberg. He established a general mathematical equation to describe the release rate of a drug from pills with slab shape, sphere shape, and infinite cylinder shape to display the heterogeneous erosion [22]. This model considers pill erosion as the limiting step of the drug release rate with no influence from the resistance of diffusion property within time to the internal or external eroding of the pill [22]. In the present work, the kinetics and mechanisms of drug release of different types of new naproxen sodium (SNX) pills, including the non-moisturized base powder and the moisturized base powder, which is dried using microwave radiation and hot air, were considered. Thus, this study aims to inspect the kinetics and mechanisms of the drug release or dissolution of novel pills that dried using microwave radiation and compare it to the mechanism of those dried by the hot-air technique and the pills with a non-moisturized powder mixture base in a 1.3pH medium. This study is accomplished by applying eight kinetics models comprising the Zero-order, Hixson–Crowell, First-order, Hopfenberg, Korsmeyer-Peppas, Higuchi, Logistic, and Peppas-Sahlin models.

2.METHODOLOGY

2.1.Materials

Table 1 illustrates the materials used in this work and their specifications. The first three materials were purchased from Sigma-Aldrich. More chemicals were provided by the Laboratory of Chemical Engineering at RMIT University, such as sodium chloride and hydrochloric acid.

2.2.Preparations Stage

Three types of pills were prepared by compacting their powder mixtures. The non-moisturized base powder pill was prepared using the non-moisturized powder mixture that consisted of 100 g of SNX, 80 g of CMS, and 20 g of PVI [34]. The PILM and PILC were prepared from the moisturized base powder mixture comprised of the same components of PILD in addition to 20wt% of DIW [35, 36]. The moisture was removed from the wet mixture using a hot-air furnace to be compacted using compacting pressure with 29-30 N to form PILC [37]. Similarly, another part of the moisturized powder was dried by microwave radiation using an accelerated microwave reactor system (MARS5, USA). The dried powder was compacted using the same compressing power to form PILM. These prepared pills were subjected to a highly acid medium prepared by dissolving NaCl (2 g) in DIW (0.8 L) and adjusted to 1.3 acidity using HCl. The dissolved drugs of PILD, PILC, and PILM concentrations were measured using a Cary 60 UV-vis spectrophotometer at 261 nm wavelength. Samples were withdrawn every five minutes during the first hour followed by nine samples at each hour. All these samples were filtered using a PTFE membrane (45 mm) to measure their concentrations.

2.3.Powders Characteristics

The textural properties of the mixture particles affect the materials' dissolution. Therefore, different characterization tests were considered. The morphology using SEM, crystallinity, amorphous and crystal sizes using XRD, specific surface area, and particle size using a Master-Sizer Analyzer were considered.

Table 1 Materials Used in the Experimental Work with their Specifications.

Material name	Appearance	Molar mass (g/mol)	Density(g/mL)	Purity (%)
Sodium-Naproxen (SNX)	Odorless crystalline powder	252.2	0.5-0.9	0.98-100
Polyvinylpyrrolidone (PVI)	White to light yellow powder	111.1	1.2	≤ 100
Cellulose-Microcrystalline (CMS)	White to off-white powder	370.4	0.6	0.98
Sodium chloride (NaCl)	crystalline solid powder	58.4	2.2	95
Hydrochloric acid (HCL)	Colorless, transparent liquid	36.5	0.8	37
Deionized water (DIW)	Colorless	18	1.0	100

2.4.Kinetic Models

Several kinetic models were selected to discover the drug release patterns and examine the variation in the drug release mechanism of SNX-prepared tablets because different drug formulations have different dissolution rates [38]. Those kinetic models include the Zero-order, Higuchi, Peppas-Sahlin, First-order, Korsmeyer-Peppas, Hopfenberg, Logistic, and Hixson–Crowell. Regression factor R^2 was used to indicate the best model fit for each prepared tablet's dissolution. The most common mathematical models and their descriptions, which were used in this study to fit the experimental dissolution profiles of the prepared tablets, are as follows:

Zero-Order Model: This model assumes that the release rate of a drug is independent of its concentration, and it is ideal to have prolonged pharmacological action. It applies to a matrix tablet with low-soluble drugs [1, 6, 14, 33]. Active ingredients dissolution or release rate is limited in non-dis-integrating forms, assuming a very slow-drug release, i.e., no variations in the equilibrium conditions [3], as denoted by Eqs. (1)-(3):

$$C_{tz} - C_i = K_z . c \quad (1)$$

$$f_i = K_z . t \quad (2)$$

$$C_{tz} = C_{zo} + k_z t \quad (3)$$

Where f_i is a fraction of dissolved active ingredient during time t; C_{tz} is the drug concentration released into the medium with t; k_{zo} is the Zero-order constant, which is equal to the amount of active ingredient released into the medium during Δt of time; and C_{zo} is the initial concentration of active ingredient released, generally equals zero.

First-Order Model: Although it is not easy to express the First-order kinetics of drug release using a basic theory, in this model, the drug release is based on the diffusive flux to concentration and implemented to describe the elimination or absorption of various medications [3]; see Eqs. (4) and (5). This model depends only on concentration change with time. It is used to describe the medicinal dosage forms comprising water-soluble medications in a porous material [1, 14].

$$\frac{dC_t}{dt} = -k_{1f} C_{tf} \quad (4)$$

$$\ln C_{tf} = \ln C_{of} - k_{1f} t \quad (5)$$

Where C_{tf} is the concentration of the drug released into the medium with time, C_{of} is the initial concentration of a drug, and k_{1f} is the First-order model constant.

Higuchi Model: Highuchi has developed many theoretical models to define the solid and semi-solid drug release in a medium with low solubility and very high solubility [3]. In this model, Eq. (6) illustrates that the drug release (Fickian or non-Fickian diffusion) is proportional to the square root of time in linear correlation. It applies to different modified-release matrix pills, geometries, and porous systems [1, 30, 39, 40]. However, Higuchi assumed many statements to apply this model to the drug release profile of the medications [3]. Higuchi assumed that the drug's initial concentration was much higher than its solubility, the drug dosage was much greater than the drug molecule size, in-directional diffusion with constant diffusivity, pill swelling was negligible, and reached the perfect sink condition [3].

$$C_{tH} = k_{hg}\sqrt{t} \quad (6)$$

where C_{tH} is the concentration of the drug released into the medium with time, and k_{hg} is the Highuchi constant of the drug released.

Korsmeyer-Peppas: A semi-empirical model applied to define the release rate of a drug from polymeric systems. This model adopts that the drug release is based on the exponent α value as an indicator of drug release mechanism as diffusion, erosion, or swelling. It describes the release of drugs from a polymeric system, as shown in Eqs. (7) - (9). Table 2 classifies the mechanisms of the drug release of different tablet geometries. As the prepared pills were cylindrical, then when $\alpha \leq 0.45$, the release of a drug is Fickian diffusion. $0.45 < \alpha < 0.89$ is non-Fickian solute diffusion (Anomalous) diffusion, $\alpha = 0.89$ is a case I transport, and $\alpha > 0.89$ is super case II transport: erosion pertains to Zero-order kinetics [1, 6].

$$f_i = \frac{C_{tk}}{C_f} = k_{kp} t^{\alpha} \quad (7)$$

$$C_{tk} = k_{kp} + t^{\alpha} \quad (8)$$

$$ln C_{tk} = ln k_{kp} + ln t^{\alpha} \quad (9)$$

Where f_i is the amount of the active ingredient released, C_f is the concentration of the drug at the equilibrium, C_{tk} is the amount of drug released over time t, k_{kp} is the drug release velocity constant or the constant of the correlation between geometrical characteristics and structural modifications of the pills, and α is the exponent of drug release as a function of time t.

Table 2 Drug Release Mechanism for Pills with Different Geometries [3].

Matrix Shape	Release Exponent	Release Mechanism
Sphere	$\alpha = 0.43$	Fickian diffusion
Cylinder	$\alpha = 0.45$	
Flat	$\alpha = 0.50$	
Sphere	$0.43 < \alpha < 0.85$	Anomalous transport
Cylinder	$0.45 < \alpha < 0.89$	
Flat	$0.50 < \alpha < 1.0$	
Sphere	$\alpha = 0.85$	Case I Transport
Cylinder	$\alpha = 0.89$	
Flat	$\alpha = 1.0$	
Sphere	$\alpha > 0.85$	Case II Super Transport
Cylinder	$\alpha > 0.89$	
Flat	$\alpha > 1$	

Hixon-Crowell Model: Hixson and Crowell express the drug release as a function of tablet diameter and surface area. They suggested that the area of a particle is proportional to the cube root of its volume. It was assumed that the diffusion did not control the release rate; however, it controlled the drug particles dissolution does. Therefore, it applies to therapeutic dosage forms such as tablets [1, 14]. In this kinetics, the dissolution rate of the drug appears in planes parallel to the drug form surface. Also, they considered that the pill's geometry was constant with decreasing pill surface with time, as Eqs. (10)-(12) describe [3].

$$f_i = 1 - \frac{C_{tx}}{C_{ox}} \quad (10)$$

$$\sqrt[3]{1 - f_i} = 1 - K_{HX}t \quad (11)$$

$$\left(C_{ox}^{1/3} - C_{tx}^{1/3}\right) = k_{hx}t \quad (12)$$

Where f_i is the fraction of the drug dissolved on time t, C_{tx} is the concentration of the drug released into the medium with time, C_{ox} is the initial concentration of a drug, and k_{hx} is the Hixon-Crowel constant of release.

Logistic model: The drug release is based on an S-shape distribution [41]. This model almost represents the S-shaped polymer swelling of the drug matrix. The Logistic model assumes the rapid swelling of polymer followed by slow distribution [41, 42], Eq. (13).

$$C_{tg} = \frac{K_{lg}}{1+exp\left[-t-\frac{k_{lg1}}{k_{lg2}}\right]} \quad (13)$$

where C_{tg} is the concentration of drug released into the medium with time t; and $K_{lg} = 1$, k_{lg1}, and k_{lg2} are the Logistic model constants of release.

HOPFENBERG Model: Drug release normally occurs with drug films of different geometrical forms, such as planar, spherical, or cylindrical films. The Hopfenberg model describes drug release from spherical, cylindrical, or planar films, with heterogeneous erosion from erodible polymers, as illustrated in Eqs. (14) and (15) [3]. This kind of release depends on external and internal diffusion resistance, which is controlled by time and matrix erosion [3].

$$\frac{C_{tb}}{C_{fb}} = 1 - \left[1 - \frac{k_{ob}.t}{C_{ob}.a_{ob}}\right]^{\delta} = 1 - [1 - k_{hb}.t]^{\delta} \quad (14)$$

$$k_{hb} = \frac{k_o}{C_o.a_o} \quad (15)$$

where C_{tb} is the drug released the amount at the time t, C_{ob} is the initial concentration of the drug in the pills, C_{fb} is the amount released at infinite time, k_{ob} is the erosion grade constant, and a_{ob} is the initial radius of the cylinder or sphere considered as the half part of the film thickness. According to the geometrical shape, the exponent δ equals 1 for film, 2 for cylinder, and 3 for sphere pills.

Peppas-Sahlin Model: The drug release is conceivably based on Fickian diffusion and relaxational mechanisms in an anomalous release of the drug from a semi-rigid to a flexible state and hence generates a relaxation of polymer chains for any shape (films, cylinders, or spheres) [3, 43]. Therefore, Eq. (16) characterizes Fickian diffusion in the first term on the right side and case II relaxation in the second term on the right side. The power coefficient (γ) represents the pure Fickian diffusion for all geometrical shapes (films, cylinders, or spheres) with controlled release [3]. The values of exponent γ are changeable depending on the tablet or pill diameter and thickness.

$$\frac{C_{ts}}{C_{fs}} = k_{ps1}t^{\gamma} + k_{ps2}t^{2\gamma} \quad (16)$$

Where C_{ts} is the drug released amount at time t, C_{fs} is the drug released amount at a time of ∞, k_{ps1} *and* k_{ps2} are Peppas-Sahlin constants of the drug release rate [22], and γ is an exponent indicator of the drug release in relation to tablet diameter and thickness [3]. Regression statistical factor R^2 was used to indicate the best model that fits the empirical drug released in the simulated dissolution medium for all prepared tablets, Eq. (17). The more R^2 approaches 1, the more appropriate model to represent the experimental data.

$$R^2 = 1 - \left[\frac{\sum_{i=1}^{N}(\emptyset_{i,pred} - \emptyset_{i,exp})^2}{\sum_{i=1}^{N}(\overline{\emptyset}_{i,pred} - \emptyset_{i,exp})^2}\right] \quad (17)$$

Where $\emptyset_{i,exp}$ is the i^{th} experimental amount of drug released, $\emptyset_{i,pred}$ is the i^{th} predicted amount of drug released, and $\overline{\emptyset}_{i,pred}$ is the mean value of predicted drug release.

3.RESULTS AND DISCUSSION

3.1.Drug Dissolution Test

Figures 1 (a and b) illustrate the drug dissolution rate of the three prepared pills, i.e., PILC, PILM, and PILD, in the highly acidic medium during one hour and ten hours of test, respectively. Figure 1(a) shows the concentration of the dissolved pills in the medium with 1.3 pH within the first 60 minutes of the test, indicating the slight release of the pill concentration in the medium. After one hour, the highest cumulative concentrations in the medium were 8.2, 5.5, and 3.6 mg/L for PILD, PILM, and PILC, respectively. Figure 1(b) proposes the low dissolution of all tablets in the 1.3 pH medium even after ten hours of testing. The maximum release with PILD was less than 20% after ten hours due to the solubility characteristic of naproxen material [44]. Naturally, naproxen is sparingly dissolving in a highly acidic solution (low pH) due to the presence of the carboxylic group in the naproxen chemical structure [45]. As shown

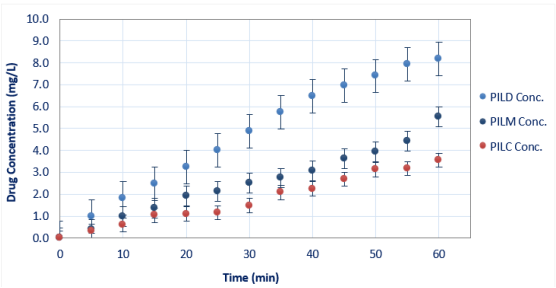
in Fig. 1, the release of PILD was higher than PILC and PILM, ranging from 8.15 to 33.1 mg/L. While it ranged from 5.5 to 25.9 mg/L and 3.6 to 27.5 mg/L for the PILM and PILC, respectively. The highest dissolution rate of PILM is attributed to the non-moisturized base powder of the pill; thereby no drying process was required. However, microwave radiation reduced the particle size and increased the surface area of the dried powder with a more amorphous structure than when hot-air drying was used [37, 45]. Hence, the PILM dissolution rate was higher than the PILC. It is clear from Fig. 1 that the drug released for all types of pills was prolonged dissolution, and the drug concentration in the medium slightly increased with time. This phenomenon is desired in some medications when the slow release of the active drug ingredient is required to achieve the favorite therapeutic goal [46].

3.2.Structural Test Results

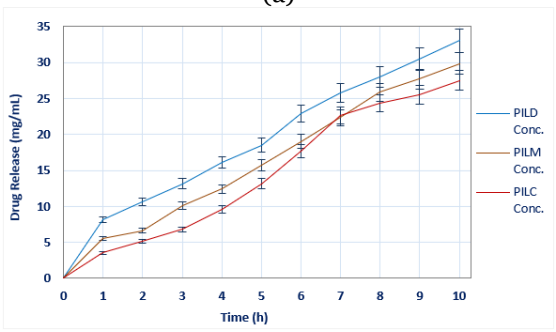
The results of the textural characteristics of the base powder mixture of PID, PILM, and PILC obtained from SEM, XRD, and Master-Sizer Analyzer tests are summarized in Table 3 [47].

3.3.Kinetic Analysis of Dissolution Data

Eight semi-empirical models were applied to this work's experimental data of the drug releases of SNX pills. The drug release kinetic models, i.e., Zero-order, Higuchi, Hixon, First-order, Hopfenberg, Korsmeyer, Peppas-Sahlin, and Logistic models, fit the drug dissolution profile of the PILD, PILM, and PILC pills at different degrees of harmonizing. As shown in Fig. 2, the Higuchi model is in favorsof fitting the dissolution rate of PILD tablets with R^2 equal to 0.9506. Followed by PILM and PILC with 0.903 and 0.8895 of R^2, respectively. According to Higuchi's implications, Fickina or non-Fickian diffusion was responsible for dissolving insoluble tablets [23]. This kinetic applies to different matrix tablets and is relevant for different geometries and porous systems [26]. Therefore, the acceptable matching of this model considers the drug diffusion of pills constant in one dimension without noticeable swelling of tablet polymers [30, 33]. Also, the Higuchi kinetics of diffusion interprets the slow dissolution rate of tablets, which depends on the square root of the dissolution time [19]. Comparably, Higuchi and other kinetics models were studied to examine the drug release kinetics from maleic anhydride-grafted chitosan film. Statistical accuracy regression was 0.7491 and 0.9861 for the sample with 100 and 200 wt/wt of MA/Chitosan, respectively [48]. This result is close to that obtained with the Higuchi model in the present study. Likewise, the Hopfenberg model was in good matching to the drug release for all pills, particularly for PILM pills with R^2 of 0.9685. It also well describes the drug release from the other tablets with a range from 0.9253 to 0.9006 of R^2 for PILM and PILC, respectively, Fig. 3. As mentioned earlier, this model defines the correlation between the drug release and tablet surface-eroding polymer and is applicable when the surface area stays constant during the degradation stage [7, 11, 49]. In the same way, Jafari and Kaffashi found that although three kinetics models were fitting the drug release of Dex-HEMA-PNIPAAm nano-gels, the Hopfenberg model was well matching its release [10]. It is clear from Fig. 4 that the zero-order model greatly matched the drug release of PILD, PILM, and PILC with very high R^2 values: 0.9985, 0.9947, and 0.9853, respectively. According to the Zero-order model, the drug release was independent of its concentration [6, 33]. The release in flat/slab tablets essentially depends on the erosion of the polymer layer of the tablet and, at the same time, the release of the active material in that layer [3]. In the case of spheres or cylinders pills, as in the present case, the erosion rate decreased with time due to lessening in exposed surface area. Thus, the drug release is mainly correlated to erosion [3]. Singhvi and Singh (2011) presented the sustained release formulation of Ibuprofen drug with high matching to the Zero-order model with R^2 of 0.9672 [2]. Similar outcomes were obtained from the drug release kinetics study by Abdelkader et al. (2021) for niosomal formulations of lomefloxacin HCl after twelve hours of the test. Their study showed that the erosion of their medication sample was the release dominant mechanism [50].



(a)



(b)

Fig. 1 Drug Release Rate of PILD, PILC, and PILM in an Acidic Medium (a) During the First Hour and (b) 10 Hours.

Table 3 Pills Textural Properties.

Pill type	Size (μm)	Specific surface area (m^2/kg)	Crystalline/Amorphous (%)
PILD	25.4	363.8	63.7/36.3
PILM	30.3	333.0	47.2/52.8
PILC	44.1	242.6	47.5/52.5

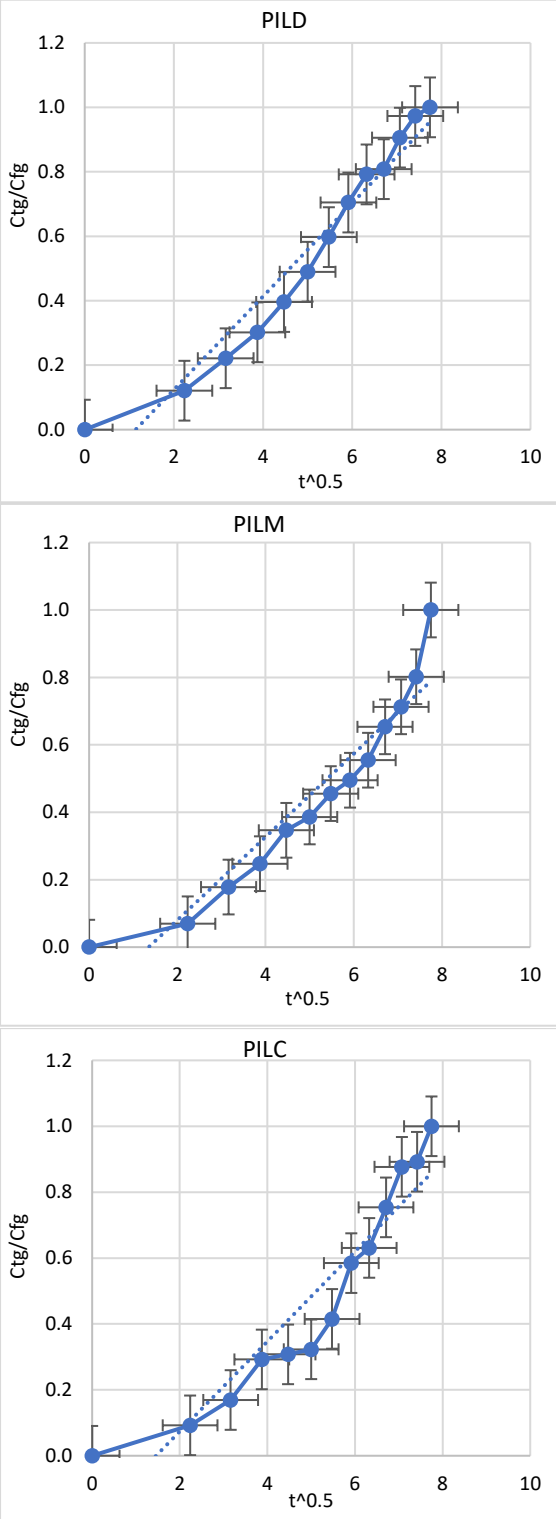


Fig. 2 Higuchi Model of Pills PILD, PILM, and PILC.

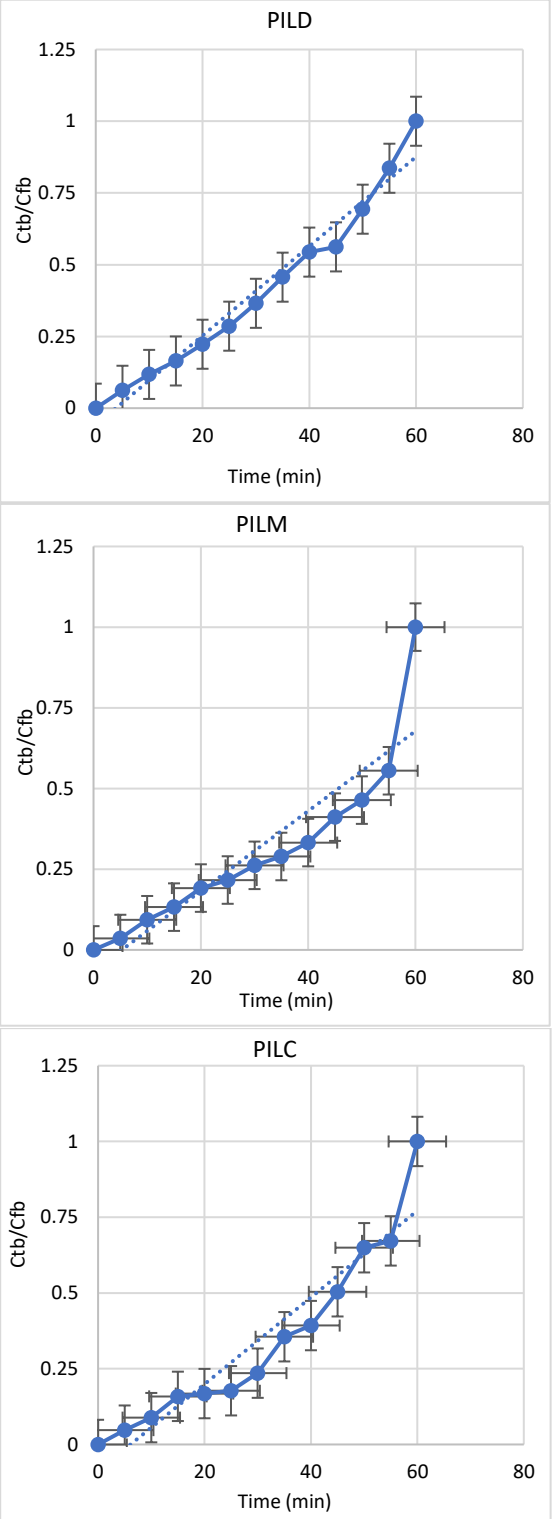


Fig. 3 The Hopfenberg Model of Pills PILD, PILM, and PILC.

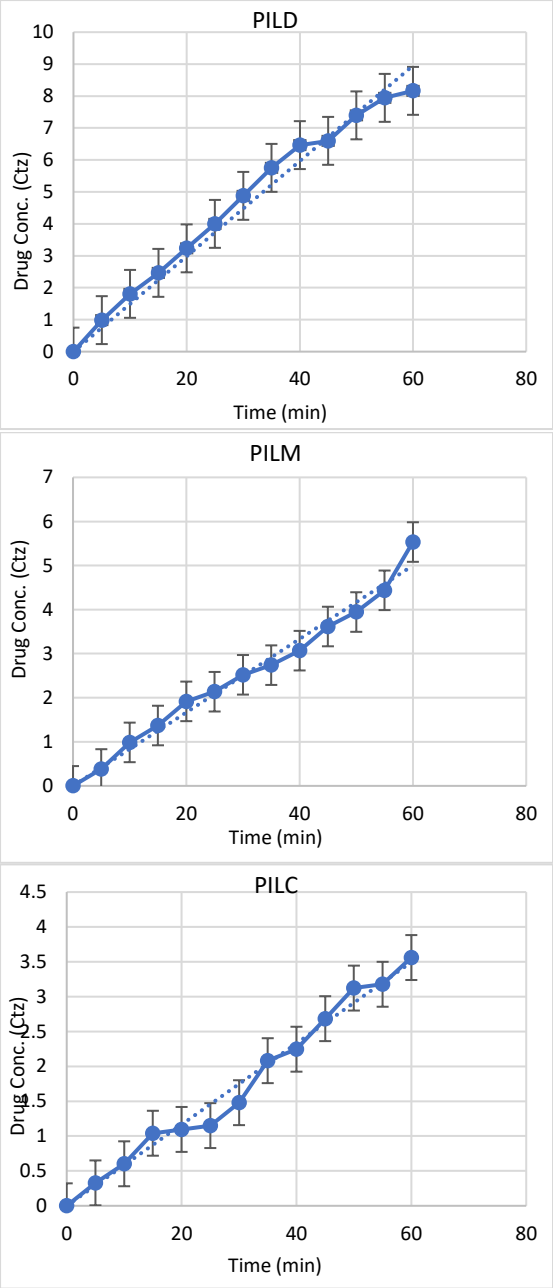


Fig. 4 Zero-Order Model of Pills PILD, PILM, and PILC.

Figure 5 displays the high linearity of fitting the Peppas-Sahlin model to the drug release profile of all tablets, with R^2 approaching 0.9998 for PILD and 0.9998 for each PILM and PILC pills. This model indicated that the release of drugs from the above tablets was controlled by diffusion (Fickian diffusion) and the relaxation of polymer chains available in the drug excipients [43]. The values of exponent γ were changeable depending on the tablet or pill diameter and thickness. According to the prepared pills PILD, PILM, and PILC with 13 mm diameter and 2.42.7 mm thickness, it was found that γ value was 0.5 [3]. The first term of Eq. (16), $k_{ps1}t^{\gamma}$, with a constant value of k_{ps1} (0.12 – 0.15), refers to the diffusion mechanism, and the second term, $k_{ps2}t^{2\gamma}$, of the above equation refers to the polymer relaxation and degradation with constant k_{ps2} ranged from 0.4 to 0.15. According to the Peppas-Sahlin model, the relaxation mechanism appears larger than the diffusion mechanism in all pills, with k_{ps2}/k_{ps1} ranging from 1.1 to 1.3, Table 2. Thus, anomalous transport is confirmed again with this model to be the dominant mechanism of the drug release of PILD, PILM, and PILC pills. Similar results were obtained by Verano-Naranjo et al. (2021) when they studied the drug release kinetics of their samples using the Peppas-Sahlin model [51]. Their results revealed that the degradation part (relaxation) with k_{ps2} was larger than the diffusion part, which agrees with the present results [51].

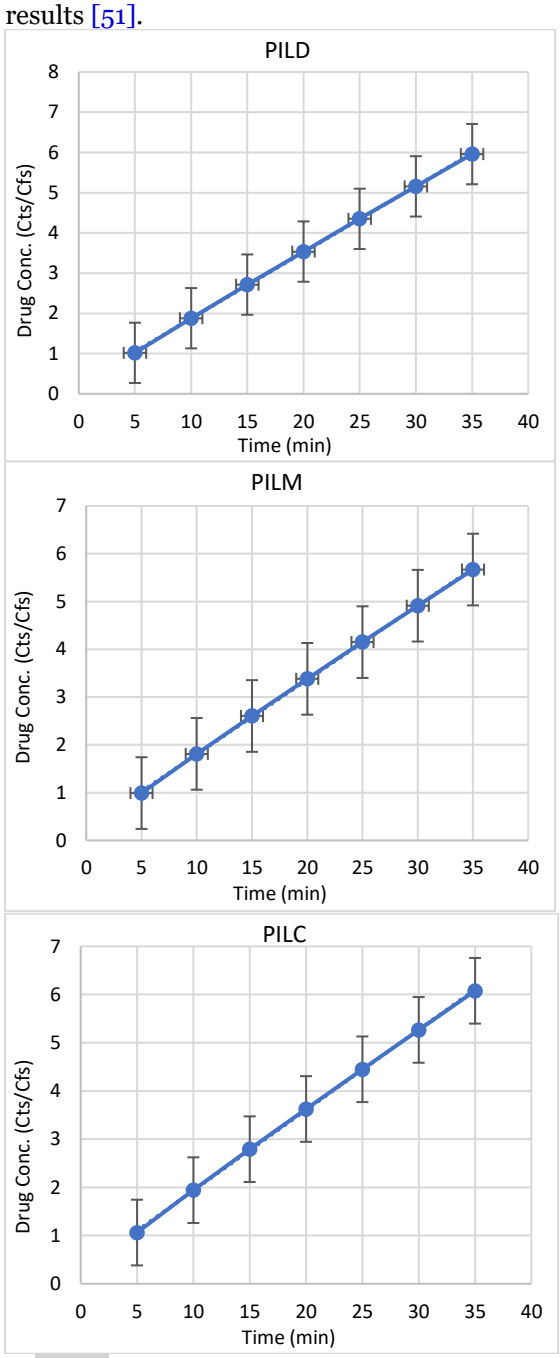


Fig. 5 Peppas-Sahlin Model of Pills PILD, PILM, and PILC.

On the other hand, the Korsmeyer-Peppas model fits the experimental data of the drug release of the prepared tablets with high R^2 ranging from 0.9695 for the PILM to 0.9997 for the PILC, as shown in Fig. 6. Applying the Korsmeyer model and determining the release indicator α value described the mechanism controlling the drug release of the prepared tablets. The value of α is an indicator of the dissolution mechanism. For cylindrical pills, as shown in Table 2, the dissolution was Fickian diffusion if α less than 0.45 and anomalous transport when α lies between 0.45 and 0.89. However, the dissolution exponent equal to or more than 0.89 refers to case II transport or super case II transport, respectively [19]. As illustrated in Table 4, the exponent α was 0.89 for the PILD. This value indicates that the diffusion of this type of pill was case II transport. While α =1 for the PILM pills, i.e., the release was of case II super transport. However, the PILC pills had α of 0.87 (Table 4), which refers to the anomalous diffusion, a combination of Fickian and non-Fickian diffusion, meaning that the dissolution of these tablets was controlled by diffusion and erosion mechanisms [1, 6, 33, 52]. This mechanism is similar to the dissolution of nicorandil and theophylline matrix tablets with release indicative α of 0.71 and 0.7, respectively [19]. However, the super case II transport was the responsible mechanism for the drug release for PILM by erosion with $\alpha \cong 1$ (see Table 4), indicating that this erosion was connected to the Zero-order kinetics [1, 6], confirmed by the high matching of the Zero-order model to the drug release of PILM with R^2 of 0.9949. Moreover, case II transport was the mechanism of release of the PILD due to the high α value of 0.89, which is also related to the Zero-order kinetics [1, 6, 22, 32], which is consistent with the high fit linearity with the Zero-order model of these tablets, indicating their slow release was experimentally observed. The release of the drug in case II transport stabilized with time, and the water or the biological fluid penetrated the tablets, boosting the polymer swelling and erosion, transporting it to another state and hence destructor and disintegrating the polymer chain [2, 31, 52]. This result of the high value of the release indicative α is similar to that stated by Karasulu et al. (2000). In their study, the release system had a high value of α (=2) for their cylindrical shape tablet, and the mechanism was of super case II transport [49]. Also, the ketoprofen release profile and the mathematical modeling (Korsmeyer-Peppas and Peppas-Sahlin models) were studied by Naranjo et al. (2021), who showed that the initial release governed by diffusion and with different kinetics [51].

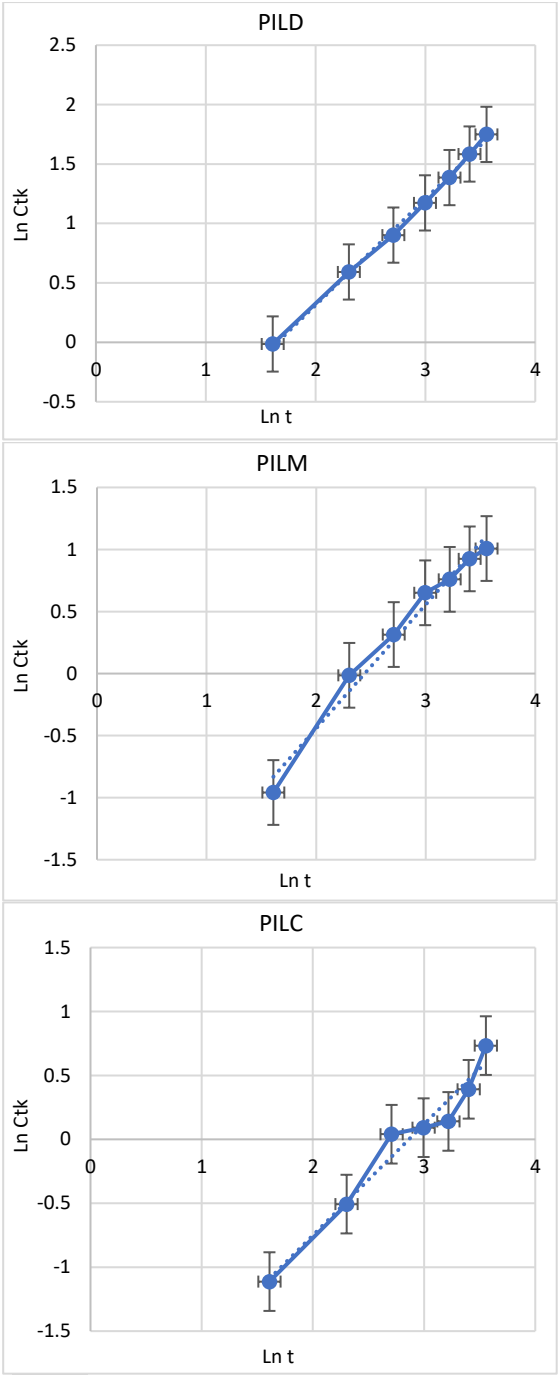


Fig. 6 The Korsemeyer-Peppas Model of Pills PILD, PILM, and PILC.

In contrast, the low values of R^2 with 0.8821, 0.8551, and 0.8388 for PILD, PILM, and PILC, respectively, indicated the weak matching of the First-order model to the experimental data of the drug release compared to the other models, as shown in Fig. 7. The First-order model indicated that the drug concentration was not the responsible mechanism of the drug release in those tablets [1, 14]. The results of Saidi, Dabbaghi, and Rahmani (2020) study agree with the present results, where the First-order model weakly fitted the release profile data of diclofenac sodium with 0.7509 (the highest R^2 obtained) [53].

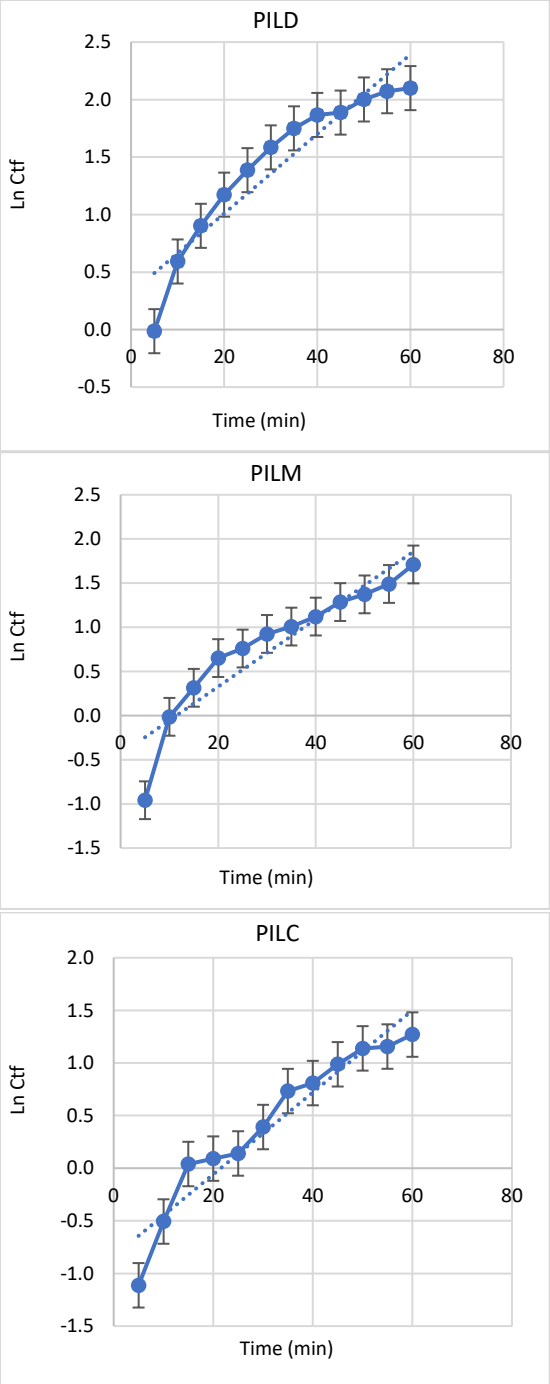


Fig. 7 First-Order Model of Pills PILD, PILM, and PILC.

Similarly, Figs. 8 and 9 illustrate that the Hixon and Logistic models were less fitting to the drug release profile data of all prepared pills than the above models. The R^2 values of the Hixon model ranged from 0.7513 for PILC to 0.7766 for PILD, and the logistic model ranged from 0.8819 for PILC to 0.8872 for PILD. Hixon's model assumed that the drug release rate was controlled by the drug formulation particles, not the drug diffusion [1, 14]. This result conflicts with the other models that highly matched the present experimental data. Hence, the drug formulation insignificantly affected the release rate of the drug.

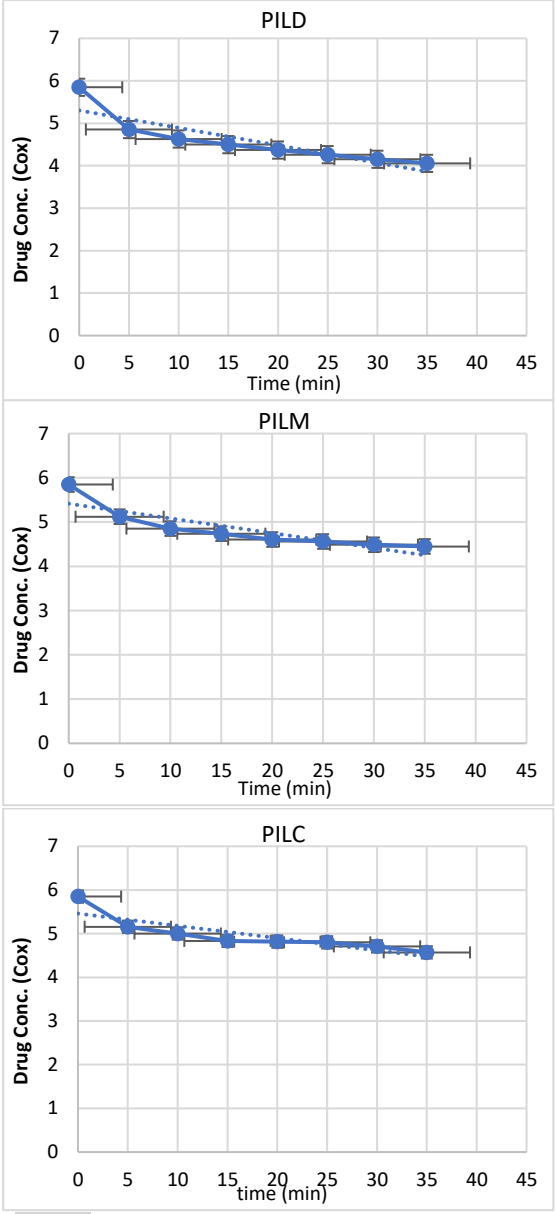


Fig. 8 Hixon Model of Pills PILD, PILM, and PILC.

The logistic model was applicable to pills or tablets that had a drug release of an S shape. This type of drug release was not noticed for all the prepared tablets [41], interpreting the low fitting of these models to the pills mentioned above. The drug release of bupivacaine was investigated using the Hixon model in addition to other models, such as Zero-order, First-order, Second-order, Higuchi, and others [54]. However, the Hixon model was not the best one to fit their experimental data, which is similar to the present work results in terms of ineffectual matching of the Hixon model to the empirical data [54]. Also, Ghosal (2012) compared the logistic and log-logistic models with the Zero-order, First-order, Higuchi, Ritger-Peppas, Peppas-Sahlin, and other models to match the drug release mechanisms for modified hydrophobic HPMC-based gels. They stated that all models fit well, but the first was the best [41].

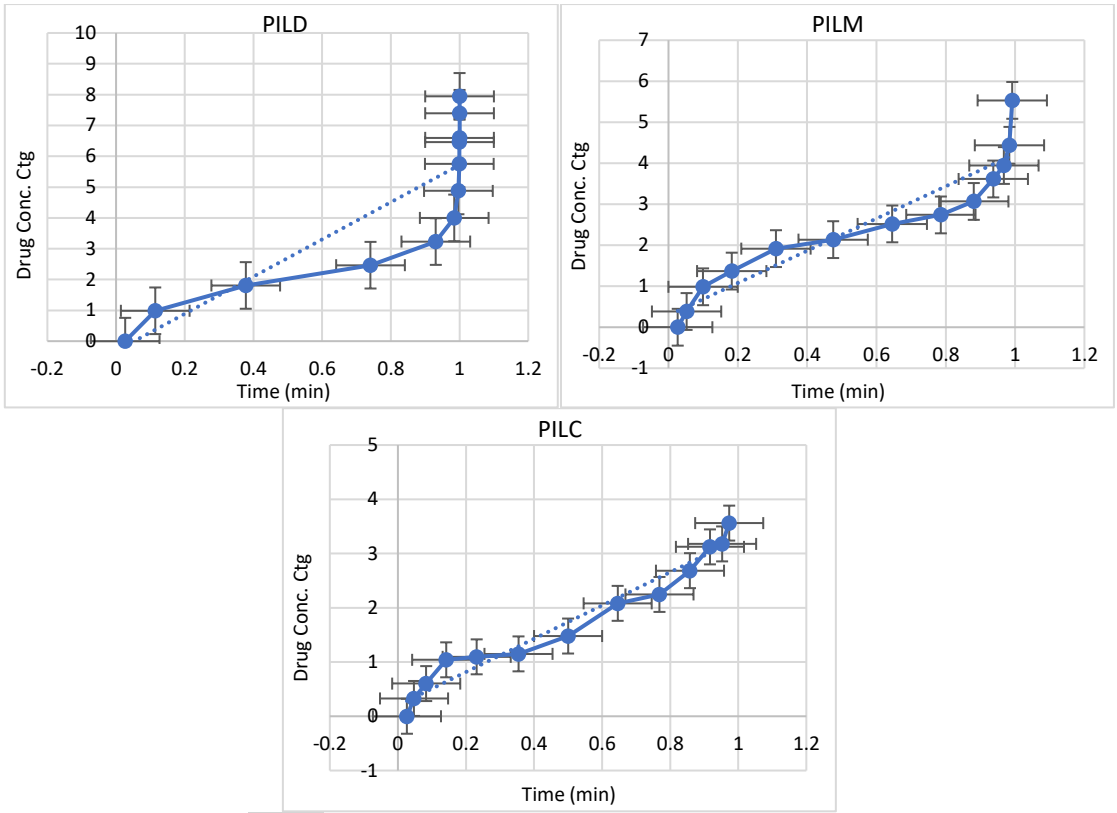


Fig. 9 Logistic Model of Pills PILD, PILM, and PILC.

Table 4 Drug Release Models Characteristics and their Linear Regression R^2.

No.	Model Name	Model Parameter	PILD	PILM	PILC
1	ZERO - ORDER $C_{tz} = C_{zo} + k_z t$	k_{oz}	0.149	0.083	0.058
		R^2	0.9952	0.9949	0.9953
2	FIRST - ORDER $\ln C_{tf} = \ln C_{of} - k_{1f} t$	k_{1f}	0.037	0.035	0.033
		R^2	0.8821	0.8551	0.8388
3	HIXSON - CROWELL $\sqrt[3]{C_{ox}} - \sqrt[3]{C_{tx}} = k_{hx}\tau$	k_{hx}	-0.041	-0.033	-0.028
		R^2	0.7744	0.7667	0.7513
4	HIGUCHI $C_{tH} = k_{hg}\sqrt{t}$	k_{hg}	0.145	0.123	0.136
		R^2	0.9509	0.9030	0.8895
5	KORSMEYER - PEPPAS $lnC_{tk} = lnk_{kp} + lnt^{\alpha}$	k_{kp}	0.090	0.087	0.083
		α	0.89	≈ 1.0	0.87
		R^2	0.9695	0.9804	0.9997
6	PEPPAS-SAHLIN $\frac{C_{ts}}{C_f S} = k_{ps1} t^{\gamma} + k_{ps2} t^{2\gamma}$	k_{ps1}	0.12	0.13	0.15
		k_{ps2}	0.15	0.14	0.14
		k_{ps2}/k_{ps1}	1.3	1.1	1.1
		γ	0.5	0.50	0.50
		R^2	0.9999	0.9998	0.9998
7	Logistic $C_{tg} = \frac{K_{lg}}{1 + exp\left[-t - \frac{k_{lg1}}{k_{lg2}}\right]}$	K_{lg}	1.0	1.0	1.0
		k_{lg1}	3.6	3.6	3.6
		k_{lg2}	0.31	0.14	0.12
		R^2	0.8872	0.8851	0.8819
8	HOPFENBERG $\frac{C_{tb}}{C_{fb}} = 1 - \left[1 - \frac{k_{ob}.t}{C_{ob}.a_{ob}}\right]^{\delta} = 1 - [1 - k_{hb}.t]^{\delta}$	k_{hb}	0.016	0.012	0.014
		δ	2	2	2
		R^2	0.9685	0.9253	0.9006

Table 4 summarizes the analysis characters, including the model's constants, the drug release exponent, and the statistical regression factor of the drug release models, which describe the manner of the drug release of each pill. In summary, the Zero-order and Peppas-Sahlin models were the most proper, consisting of the experimental profiles of the non-moisturized powder pills, PILD, and the tablets prepared by removing the moisture using microwave radiation, PILM, and hot-air drying, PILC. The Higuchi, Hopfenberg, and Korsmeyer Peppas' models resulted in the second matching to the empirical data. The Hixon and First-order models were the weakest models to represent this work outcome. The Zero-order model was of good matching and the dominant model to describe the drug dissolution for most kinds of tablets, indicating the slow dissolution or disintegration of the

drug in the solution [6]. Also, it indicates that the dissolution was independent of the drug concentration. This kind of release is beneficial for long-term pharmacological action [1]. Applying these models showed differences in the release kinetics of SNX drug tablets in a highly acidic medium with 1.3 pH. Based on the Korsmeyer model, as shown in Table 4, the kinetics of release of the PILC tablets were non-Fickian diffusion controlled by the combination of diffusion and erosion mechanism. However, swelling and erosion of super case II release were responsible for the release behavior of PILM, where their dissolutions were independent of concentration. These potential variations in the release mechanism can be attributed to the differences in the particle size distribution, the particle surface area, and the crystallite or amorphous structure of the dried particles. The small size, large surface area, and high amorphous and less crystallite structure increased solubility and had more intendancy to dissolve than particles of a large size and small surface area [55]. Fewer crystalline and more amorphous structures after drying improve the dissolution rate of the drug [56, 57]. Moreover, the physical and chemical properties of the active pharmaceutical ingredients and the polymers forming drug tablets affected the drug release rate [2]. The mechanism of super case II transport occurs when water or a biological solvent penetrates through the amorphous areas of the drug-polymer and begins to degrade these areas, hence promoting drug release [23]. This mechanism may explain why those pills, particularly the PILD and PILM, had different styles of release because they had different percentages of amorphous and physiochemical.

3.4.New Models

Some studies create empirical or semi-empirical kinetic models, such as the semi-theoretical model by Siepmann and Peppas, to describe water transport in glassy polymers [30]. Similarly, in the present work, semi-empirical models were modified for each kind of tablet to represent the release kinetics of those entire tablets with high linearity compared to the experimental data, as shown in Table 5. Figure 10 also indicates the partition plot between the experimental data profile and predicted data. Figure 10 suggests an extremely high matching between the empirical and predicted data. MRSE, Chi-Square, SSE, and R^2 were the statistical criteria used to examine the new model's accuracy. The more approaching R^2 to 1 and the lesser values of RMSE, SSE, and Chi-Square, the more accurate the fitting. The present work model provided extremely high accuracy with R^2 ranging from 0.9961 to 0.9996, SSE ranging from 0.0008 to 0.311, Chi-Square ranging from 0.0549 to 0.5113, and MRSE ranging from 0.195 to 0.595.

Table 5 The New Modified Models of the Kinetic Release of the Prepared Tablets.

Model	Model Characteristics		
	PILD	PILM	PILC
Created Models $C_t = k_1 \times t^{n-1} + k_2 \times t$	k_1= 2.45 k_2 = 1.50 n = 0.90	k_1= 1.10 k_2 = 1.53 n = 0.05	k_1= 0.06 k_2 = 1.25 n = 2.54
MRSE	0.1951	0.251	0.5950
CHI SQUARE	0.0549	0.0907	0.5113
SSE	0.00008	0.0004	0.0311
R^2	0.9996	0.9994	0.9961

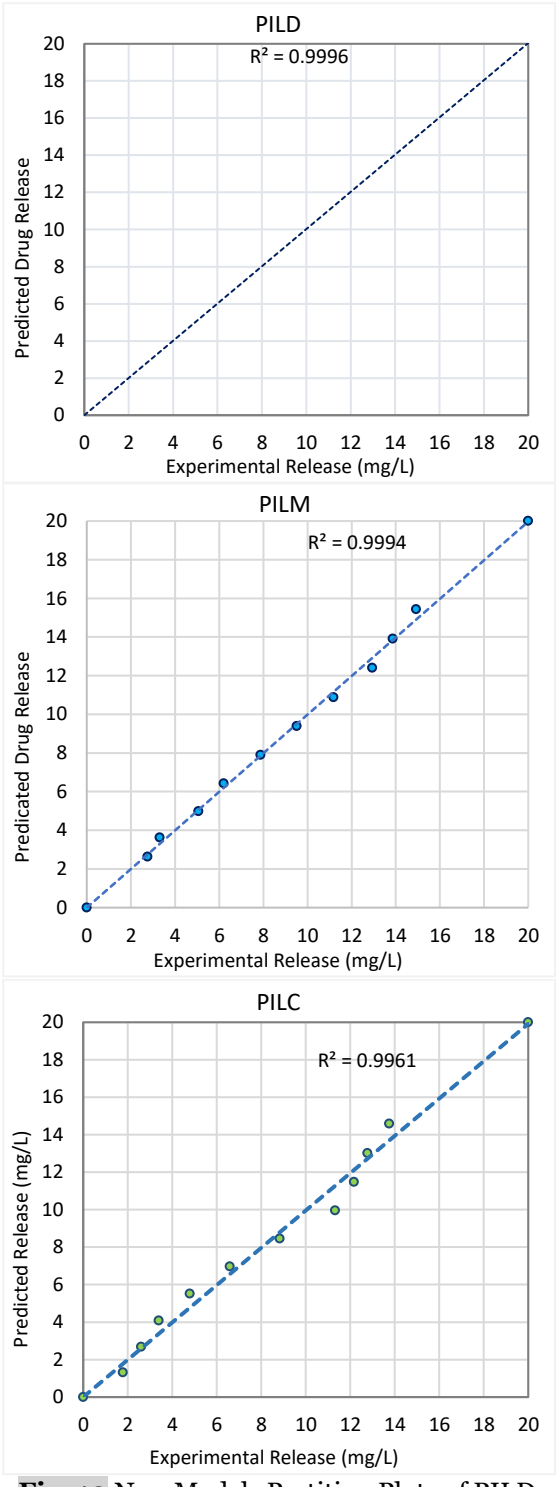


Fig. 10 New Models Partition Plots of PILD, PILM, and PILC.

4.CONCLUSIONS

The dissolution profile of SNX drug pills in a highly acidic solution with 1.3 pH was used to study the drug release kinetics. Pills were prepared using microwave radiations as a dryer and compared to other tablets prepared by hot air drying and the non-moisturized powder. The Zero order, Higuchi, First-order, Hopfenberg, Hixson–Crowell, Korsmeyer-Peppas, Logistic, and Peppas-Sahlin models were used to examine the dominant kinetics and mechanism of the drug release. It was found that Peppas-Sahlin and the Zero-order models harmonized to the drug release of all pills with very high values of R^2 ranging from 0.9949 to 0.9999. The analyses of the Zero-order and Hixon-Crowell models disclosed that the drug concentration, surface area, and diameter changed as a function of time were not the driving forces of the drug release of all pills. The slow dissolution of pills in the medium was also confirmed by the high matching of the Zero-order model to the drug release data. Korsmeyer's model revealed that the non-Fickian diffusion was the most applicable mechanism represented by diffusion and the relaxation or erosion of polymer chains specifically for the PILC. On the other hand, the pills PILM and PILD were governed by the case II transport and super case II transport of release, respectively. It can be concluded that those eight models mentioned above are valuable to understanding and analyzing the release mechanism of the prepared tablets, in particular, the microwave radiation pills. Peppas-Sahlin > Zero-order > Korsmeyer-Peppas > Hopfenberg > Higuchi > Logistic > First-order > Hixson–Crowell was the order of models that fitted the work profile data. Finally, new modified semi-empirical models were built and included in the present work to translate the behavior of those formulated tablets by different drying techniques, showing very high linearity, reaching 0.9996 R^2.

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NOMENCLATURE

$C_{tz}, C_{tf}, C_{tH}, C_{tk}, C_{tx}, C_{tg}, C_{tb}, C_{ts}$	Concentration of drug released to the medium.
C_{zo}, C_{of}, C_{ox},	Initial concentration of species A (mol/l)
C_f, C_{fb}, C_fs	Concentration of the drug at the equilibrium
f_i	Amount of the active ingredient released
$K_z, k_{1f}, k_{hg}, k_{kp}, k_{hx}, K_{lg}, k_{lg1}, k_{lg2}, k_{hb}, k_{ps1}, k_{ps2}$	Constants of drug release kinetics models
$\emptyset_{i,exp}$	i^{th} experimental amount of drug released
$\emptyset_{i,pred}$	i^{th} predicted amount of drug released
$\overline{\emptyset}_{i,pred}$	Mean value of predicted drug release.
Greek symbols	
α	Exponent power of the Korsmeyer-Peppas model
Υ	Exponent power of the Peppas-Sahlin model
δ	Exponent power of the Hopfenberg model
Subscripts	
SNX	Sodium naproxen
CMS	Cellulose-microcrystalline
PVI	Polyvinylpyrrolidone
PILD	Pills prepared from the non-moisturized powder
PILM	Pills prepared by drying the moisturized powder using microwave radiation
PILC	Pills prepared by drying the moisturized powder using hot-air
DIW	Deionized water

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