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Research Paper

Comparative analyses of Weibull model and conventional kinetics models of drug release of formulated multi-component tablets

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ABSTRACT

The kinetic study of drug release is an essential requirement to examine the ability of the drug formulation to modulate the typical drug release profile. In the present work, the Weibull model and other traditional drug release models are selected to investigate the release of tablets prepared using different drying techniques in a simulated abdominal solution. These tablets are prepared using electromagnetic microwave irradiation tablet (MVT), convective drying tablet (CVT), freeze drying tablet (FRT), vacuum drying tablet (VAT), and without any drying process tablet (NDT). This study aims to compare Weibull models with other conventional drug release models in inspecting the kinetics of drug release in all tablets. These models are Zero-Order, Higuchi, First-Order, Hixson-Crowell, and Korsmeyer-Peppas. This work delves into the best kinetic model that defines the tablets' release mechanisms, including the new multicomponent tablets (MVT), to ensure their release is in appropriate behavior. The results show that the Weibull model is the best model to present the release profile of all tablets except for MVT and VAT, while Higuchi is the optimal model for. Among the conventional models, Higuchi, Korsmeyer-Peppas, and Hixon-Crowell are the best conventional models to fit all types of tablets. Based on the Weibull model factor, non-Fickian diffusion is the dominant release mechanism for NDT and VAT. Although Fick diffusion controls the drug release mechanism of FTR, CVT, and MVT tablets. Additionally, three modified models were created and found to be more convenient to denote the release of the formulated tablets with very high accuracy.

1. Introduction

Drug release is well known as the rate of mass transfer of the solute to the dissolution medium [1], or it can be defined as the conversion of the drug into a suitable product of pharmacological activity by absorption, distribution, metabolism, and excretion [2]. The drug release or dissolution study is an indication of the physiological variation, and it is important for the new formulated solid dosage [3, 4]. It is considered a criterion of the physiological instability of the dissolved drug in the dissolution medium, which provides critical information about the physical and chemical stability of the drugs [5]. Understanding the drug release mechanism is necessary to ensure possessing the most efficient design of the drug formulation and drug delivery systems. Investigating the release kinetics of the oral drug is one of the vital steps to understanding the responsible mechanism in the drug absorption and drug delivery systems [6]. Also, assessing the drug release kinetics by applying different mathematical models is essential to recognize the nature of the drug release mechanism and to minimize the experiments required to optimize the design of the therapeutic drug system [7, 8]. The drug concentration is normally released within time [9], therefore, the dissolution of solid drug quantity as a function of time is described by applying some mathematical kinetic models that designate the drug release. These models are derived either from theoretical analysis or generally from empirical equations and are used for many objectives [10, 11]. These goals are to optimize the drug release kinetic with an active and safe treatment [12]; design a new drug delivery system [13]; explore the optimum physical and chemical properties of the formulated drugs [14]; discover the kind of drug release mechanism (diffusion, erosion, swelling, or combination of more than one behavior) [15]; and predict the drug release profile to enhance drug bioavailability and stability [16]. Thus, drug properties that affect drug delivery are important and should be optimized to yield active and safe drugs [17]. Drug release has different mechanisms, and they are generally classified into three behaviors: diffusion control, erosion control, and the combination of both diffusion and erosion [6]. Diffusion is the primarily responsible release mechanism in matrix planar drugs [18]. Erosion is most dominant in low viscous hydrophilic polymer, low water solubility, and low diffusivity. However, a combination of diffusion and erosion release systems is mostly linked to polymers of low viscosity and low resistant gel structures [19]. For this purpose, various complex mechanisms models are used to describe and interpret the drug release. The most common or conventional models used are the Zero-order model, First-order model, Hixson-Crowell model, Higuchi model, and Korsmeyer-Peppas model, Table 1. The Zero-order model is designed for systems to have a constant drug release rate independent of its concentration, mostly used for low soluble matrix tablets [10, 20]. In contrast, the decline in the amount of drug released with time is the responsible mechanism in the First-order model [21]. This model is ideal for drug release to achieve a prolonged pharmacological action that depends on drug concentration and is used to describe the release of water-soluble drugs in porous matrices [22]. Higuchi's model depends on the Fickian diffusion of the insoluble matrix release rate with the square root of time [20]. If the logarithm plot approaches 0.5, then the release rate is a diffusion-controlled process [23].

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Nomenclature

AIC	Akaike Information Criterion
CVT	Convective drying tablet
D	Number of observations
FRT	Freeze drying tablet
MRSE	Root Mean Square Error
MSC	Cellulose-microcrystalline powder
MVT	Electromagnetic microwave irradiation tablet
N	Number of observations
n	Number of constants
NDT	Without drying process tablet
NxNa	Naproxen-sodium powder
OE	Overall-Error
PPI	povidone powder
R^2	R-squared
VAT	vacuum drying tablet
X^2	Chi-Square test

Greek Symbols

ϕ_o	Initial amount of drug at time $\tau = 0$
ϕ_r	Amount of drug at time τ
ϕ_∞	Final amount of drug at time τ_∞
τ	Time
$\phi_{i,exp}$	i^{th} Experimental amount of drug released
$\phi_{i,pred}$	i^{th}Predicted amount of drug released
$\overline{\phi}_{i,pred}$	i^{th} Mean value of predicted drug released
γ	An indicator of drug release
β	An indicator of drug release mechanism
k_o	Zero-order model constant
k_t	First-order model constant
k_H	Higuchi model constant
k_{hx}	Hixon-Crowell model constant
k_p	Korsmeyer-Peppas model constant
t_d	Delay time

On the other hand, Korsmeyer-Peppas depends entirely on the exponent Y value, which refers to the dissolution mechanism of the drug as diffusion, erosion, or swelling governed or case II transport [19]. These styles of drugs are non-Fickian and have an anomalous release with exponent power $0.45 < \gamma < 1$ [6]. On the other hand, Holowka and Bhatia (2014) have classified the release systems of pharmaceutical drugs into two systems: the release controlled by the active agents and bio-inert polymer molecules, and the release sustained by a mixture of agents. Abubakr (2009) stated that the drug release normally lies between the diffusion and chemically controlled to the solvent-activated systems [24]. The latest conventional model is Hixson-Crowell which is influenced by the change in the diameter and surface area of the dissolved tablets with time [25]. Many reported studies in the literature used the abovementioned models to explore the drug release of different formulations. For example, Pflieger et al. (2024) applied Korsmeyer-Peppas to identify the release kinetics of 3D-printed theophylline tablets [26]. Nevertheless, the Weibull model is also included to be the comparative model with the other selected conventional models due to its high matching and accuracy. This model is broadly used to assess the slow or rapid release of active pharmaceutical ingredients in drug delivery systems [15,27]. This model has an indicator called β which its value can recognize the type of drug release. It relates the logarithm of time with the logarithm of the drug release. Drug release is based on the exponent Y value as an indicator of drug release mechanism as diffusion or anomalous [28]. Jahromi et al. (2020) compared the Weibull model with several drug release models such as zero order, first order, Higuchi, Hixson-Crowell, the square root of mass, the three-second root of mass, and Korsmeyer-Peppas on Poly lactic-co-glycolic acid–based nanoparticles [20]. In this work, our newly formulated naproxen sodium (NxNa) drug was used to explore its kinetics and mechanisms. NxNa is one of the widely used drugs due to its significant usage in treating different diseases such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis or pain removal [29,30]. It is a non-steroidal anti-inflammatory drug which broadly administrated in a tablet dosage form [31,32]. It is a hydrophilic compound that inclines to absorb moisture during production processes such as wet granulation [33]. Accordingly, drying is an indispensable process to remove the extra moisture from the drug formulation to produce naproxen sodium tablets with the desired activity. In general, common drying, like freeze, vacuum, and convective drying, are frequently used in drying pharmaceuticals. In addition, electromagnetic microwave radiation drying (EMD) is a technique which added to the conventional techniques to be used for drying the wet granules of the formulated NxNa drug. Thus, it is necessary to investigate the drug release kinetics of the tablets prepared from new dosage forms due to the EMD method to discover if they follow the drug release regime. Therefore, this study aims to examine the kinetics of the release of tablets dried using microwave radiation and compare it to the mechanism of those dried by freeze, convective, and vacuum drying in the simulated abdominal or intestinal solution. This study is accomplished by applying the Weibull model, in comparison to five conventional kinetic models, including the Zero-order model, First-order model, Hixson-Crowell model, Higuchi model, and Korsmeyer-Peppas model.

2. Methodology

2.1 Materials

The chemicals purchased from Sigma–Aldrich and used in the current work were naproxen-sodium powder (NxNa), povidone powder (PPI), and cellulose-microcrystalline powder (MSC). The other laboratory-grade chemicals such as sodium hydroxide and sodium dihydrogen phosphate were provided by the Laboratory of Applied Chemistry School at RMIT University, Australia, to prepare a simulated abdominal solution with 6.8 acidity.

2.2 Tablets preparations

Five types of tablets were prepared as the following steps:

1. Prepare a dry powder consisting of NxNa: MSC: PPI in (5:4:1) ratio.
2. Moisturize one part from the dry powder in step 1 by mixing a specific amount of deionized water to form wet powder with 25 *wt%*(dry basis).
3. Divide the wet powder in step 2 into four parts.
4. Dry each part of the four parts using one different technique namely: microwave radiation, convective drying, vacuum drying, and freeze drying.
5. Now we have five samples including the non-moisturized powder and four samples in step 4.
6. Compress 0.4 *g* from each of the five samples using Perkin-Elmer Hydraulic with about 3000 *N* power to form tablets with 13 *mm* diameter and an average thickness of 2.5 *mm*.
7. Tablets and their powders were collected for characterization tests such as XRD, and Master-Sizer tests to be subjected to dissolution (drug release) tests.
8. About 0.8 *L* of deionized water was used to dissolve approximately 1 and 7 *g* of caustic soda and disodium phosphate, respectively. Later, drops of sodium hydroxide were used to adjust the acidity of the solution to 6.8 *pH* and consequently diluted to form 1 *L* of simulated intestinal solution.

2.3 Drug release tests

The drug dissolution was executed to determine the amount of the active ingredient NxNa released from the prepared tablets MVT, FRT, VAT, CVT, and NDT. Each prepared tablet was placed in a known volume of the prepared abdominal solution of 6.8 *pH* at $37 \pm 0.5C$ ° under controlled conditions within a predetermined length of time. The drug release test was executed in triplicate at the same conditions for all tablets using the UV- spectrophotometric technique. The drug release content (R_C) was calculated using Eq. 1, [34,35]. More details about the drug released procedure are available in our previous published work [32].

$$\%R_c = \frac{\phi_{dr}}{\phi_{di}} \times 100 \tag{1}$$

where ϕ_{di} is the initial drug content in the tablet (mg), and ϕ_{dr} is the drug content released to the medium during the dissolution test (mg).

2.4 Kinetics study

The quantitative and qualitative variations and the modifications in the drug formulations or the developments in their production processes and systems can affect the drug release significantly. Various formulations of drugs have different dissolution rates [36]. Therefore, the researchers harnessed different models to describe the drug release kinetics specifically for the new dosage forms which were mostly used in the pharmaceutical industries [37]. Thus, as the microwave radiation technique was used for the first time in our studies to dry the new formulations of the NxNa drug mixture [32], it is necessary to

inspect microwave radiation's impacts on the kinetics and mechanism of the drug release of these tablets. Thus, the most popular models were inspected in this study to describe the drug release kinetics and explain the controlled mechanism with a comparison to the drug releases obtained from the same formulation that dried by convective, vacuum, and freeze drying techniques. Several kinetic models are selected to assess the variation in the drug release mechanism of the prepared NxNa tablets. These kinetic models were Higuchi, Zero-order, First-order, Hixson-Crowell, and Korsmeyer-Peppas. The Zero-order model is applied for tablets with drug ingredients of low-soluble active, Eq. 2. Its kinetic release suits the prolonged action, and it is not dependent on the drug concentration [10, 20, 38].

$$\phi_t = \phi_o \times \tau \tag{2}$$

The First-order model designates the exponential decrease of drug concentration with time, Eq. 3. It is applicable for tablets with formulations consisting of water-soluble pharmaceuticals in porous material [21, 39].

$$\ln(\phi_o - \phi_t) = -k_t \times \tau \tag{3}$$

Hixon-Crowell is the model that is used to describe the particle dissolution or degradation, Eq. 4. It is recognized by the changes that occurred in the tablet's surface area and diameter [25, 40].

$$(\phi_o^{1/3} - \phi_t^{1/3}) = -k_{hx} \times \tau \tag{4}$$

Higuchi, the most common model, is used to define the Fickian or non-Fickian diffusion of the drug with the square root of release time, Eq. 5. This model is applicable to the modified-release tablets with different geometries and porous tablets. It is applicable for water-soluble drug tablets [15, 20].

$$\phi_t = \phi_\infty\ k_H \times \sqrt{\tau} \tag{5}$$

The last model shown in Eq. 6 is Korsemeyer-Peppas, which is used to analyze the drug release based on its drug release exponent γ as shown in Eq. 6, [19, 40].

$$\ln \phi_t = \ln k_p + \gamma \ln \tau \tag{6}$$

The release exponent γ is usually determined by considering the first 60% of a data profile of the drug release [41, 42]. The drug release exponent value is an indicator of the drug release mechanism as diffusion, erosion, or swelling. It is applicable to define the release of polymeric drug forms. For cylinder-shaped tablets, if the value of $\gamma \leq 0.45$, then the drug release is Fickian diffusion [43]. If it lies between $0.45 < \gamma < 0.89$: then the drug release is non-Fickian diffusion or anomalous. It is described as case II transport if $\gamma = 0.89$ or super case II transport if $\gamma > 0.89$. While it is considered as erosion at zero order release if $\gamma = 1$. Table 1 exhibits those mathematical models and their descriptions which are used in this study to fit with the experimental dissolution profiles of the prepared tablets [28]. In comparison to the Korsmeyer-Peppas model, and other models the Weibull model is used in this study to investigate the profile of the drug release of the prepared tablets. This model is broadly used to assess the slow or rapid release of active pharmaceutical ingredients in drug delivery systems [27]. It correlates the logarithm of time and the drug release In a mathematical correlation called the Weibull model [15]. As demonstrated in Eq. 7, there are two linear parameters are obtained from the plot of this model denoted by, β (slope) and α (intercept). The factor β refers to the type of drug release mechanism and α is considered as the scale factor [15].

$$\ln[-\ln(1-\phi_\tau)] = \ln\left(\frac{t_d}{\tau}\right)^{\beta} \tag{7}$$

where: ϕ_r is the amount of drug released at time τ, which is linked to the delay time (t_d) when a 63 percent approximately of the drug is released. Various statistical factors, namely, R-squared, (R^2), Root Mean Square Error (MRSE), Overall-Error (OE), Chi-Square test (X^2) and Akaike Information Criterion (AIC) were used to indicate the best model that fits the empirical drug released in the simulated dissolution medium for all prepared tablets, Eq. 8 to Eq. 12. The high R^2, the lowest MRSE, OE, X^2, and AIC, the high fitting of the model to the data profile.

$$R^2 = 1 - \left[\frac{\sum_i^N (\phi_{i,pred} - \phi_{i,exp})^2}{\sum_i^N (\overline{\phi}_{i,pred} - \phi_{i,exp})^2}\right] \tag{8}$$

$$RMSE = \sqrt{\left[\frac{\sum_i^N (\phi_{i,pred} - \phi_{i,exp})^2}{N}\right]} \tag{9}$$

$$OE = \left[\frac{\frac{100}{N}\sum_i^N \frac{(\phi_{i,pred} - \phi_{i,exp})}{\phi_{i,exp}}}{N}\right] \tag{10}$$

$$X^2 = \frac{\sum_i^N (\phi_{i,pred} - \phi_{i,exp})^2}{N - P} \tag{11}$$

$$AIC = D \times \ln\left(\frac{SSE}{D}\right) + 2P \tag{12}$$

where: ϕ_o is the initial amount of drug at time $\tau = 0$; ϕ_τ is the amount of drug released at time τ, $\phi_\infty$is the final amount of drug at$\phi_\infty, k_o, k_t, k_H, k_p$, *and* k_{hx} are the constants of Zero-order, First-order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas models of the drug release respectively. γ exponent indicator for cylindrical shaped drugs release, $\phi_{i,exp}$ is the $i^t h$ experimental amount of drug released, $\phi_{i,pred}$ is the $i^t h$ predicted amount of drug released, $\overline{\phi}_{i,pred}$ is the mean value of predicted moisture content, N is the number of observations, n is the number of constants, D is the number of observations, and SSE is the summing square of errors i.e $SSE = \sum_i^N (\phi_{i,exp} - \overline{\phi}_{i,exp})^2$.

Table 1. Drug release mathematical models.

Model Name	Mechanism description and applications	References
ZERO-ORDER	Drug release is not reliant on its concentration. It is an ideal drug release to have prolonged action of pharmacological. It applies to matrix tablets with a low-soluble drug.	[10, 20, 38]
FIRST-ORDER	Drug release is exponentially decreasing with time (dependent on concentration). It is used to define the drug tablets with a formulation consisting of water-soluble pharmaceuticals in a porous material.	[21, 39]
HIXSON-CROWELL	Drug release is a function of tablet diameter and surface area changes. It is independent of diffusion, but it is dependent on particles' dissolution or degradation and erosion. It is applicable for pharmaceutical dosage forms such as tablets.	[25, 40]
HIGUCHI	Drug release is based on Fickian or non-Fickian diffusion with the square root of release time. It applies to different tablets of modified release tablets or of different geometries and porous. It is used for the water-soluble drug matrix tablet.	[15, 20]
KORSMEYER-PEPPAS	Drug release is based on the exponent γ value as an indicator of drug release mechanism as diffusion, erosion, or swelling. It applies to define the release of polymeric drug forms. $\gamma \leq$ 0.45: Fickian diffusion; $0.45 < \gamma < 0.89$: non-Fickian solute diffusion (Anomalous); $\gamma = 0.89$: Case II transport; $0.89 < \gamma$: Super case II transport; $\gamma = 1$: erosion @ zero-order release kinetics.	[28, 43]
WEIBULL	Drug release is based on the exponent β value as an indicator of drug release mechanism as diffusion, erosion, or swelling. It applies to define the release of polymeric drug forms. $\beta \leq 0.75$: Fickian diffusion; $0.75 < \beta < 1$: Fickian diffusion and swelling; $\beta = 1$: Case II; transport $1 < \beta$: complex transport.	[28, 44]

3. Results and discussion

3.1 Textural properties results

Table 2 displays the characteristics data obtained from the analyses of XRD and Master-Sizer test results of the prepared tablets, NDT, MVT, FRT, CVT, and VAT. These characteristics include the size of the drug particles Ps, the specific surface area (Sa), and the crystalline and amorphous structure fractions, (Cr) and (Am), respectively [32].

Table 2. Textural properties of the prepared drug formulations.

Powder type	characteristics			
	Cr	Am	Sa (m^2/kg)	Ps (μm)
MVT	0.472	0.528	333.0	30.3
FRT	0.409	0.591	260.0	40.9
CVT	0.475	0.525	242.6	44.1
VAT	0.524	0.476	194.2	59.2
NDT	0.637	0.363	363.8	25.4

3.2 Drug release

The drug contents of the NDT, MVT, FRT, VAT, and CVT versus release test time are determined from the release of active material in the simulated abdominal solution with 6.8 pH and demonstrated in Fig. 1. It is evident that those tablets are dissolved at different rates in the colonic fluids. The % release during the first 60 minutes of those tablets ranges from 91.1 with VAT to 98.4% with FRT, Table 3. Drug release of tablets from the lowest to the highest can be arranged as $VAT > CVT > MVT > NDT > FRT$. The variety in the drug releases of those tablets is influenced by the particle size, surface area, and the extent of amorphous and crystalline structure of the dried particles [32]. Hence, different drying methods produced various tablets in their release due to the varieties in their individual particles. This outcome is consistent with the study of Abubakr et al., who employed different drying methods to dry the B12–loaded Ca-alginate gel beads. That study revealed that each drying method yielded drug particles with different morphology, swelling response, and dissolution rate [24].

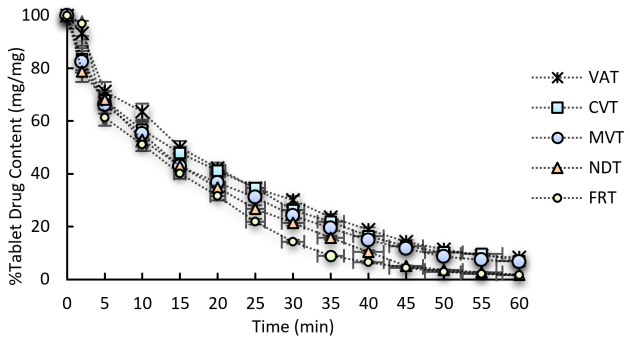

Figure 1. Release percentage of NDT, FRT, MVT, CVT, and VAT in simulated intestinal solution.

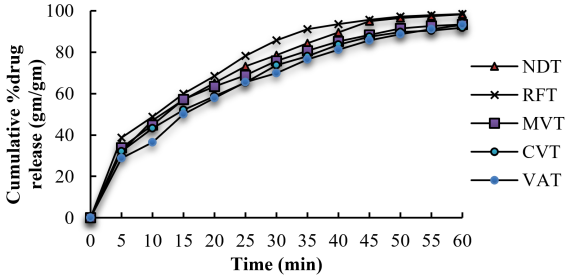

Figure 2. Zero-order model of the drug formulation tablets released in simulated intestinal solution.

Table 3. Cumulative drug released of all prepared tablets in the abdominal solutions after 60 minutes.

Tablet type	% Cumulative drug released
NDT	98.2
MVT	93.4
FRT	98.4
CVT	91.7
VAT	91.1

3.3 Kinetic analysis of drug release

Modeling the drug releases of the NDT, FRT, CVT, VAT, and MVT according to the selected drug release kinetics models are shown in Fig. 2 up to Fig. 6. Table 4 also shows the analysis characters, including the model's constants, the drug release exponent, and the statistical regression factor R^2 of the drug release models, which describe the manner of the drug release of each tablet.

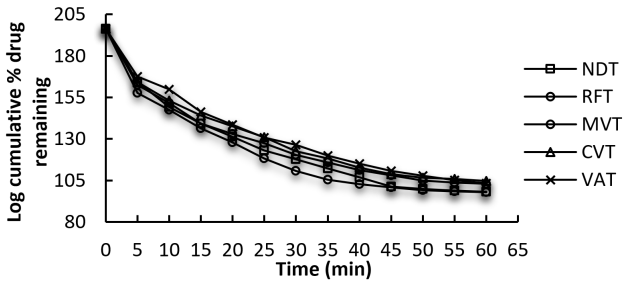

Figure 3. First-order model of the prepared tablets released in simulated intestinal solution.

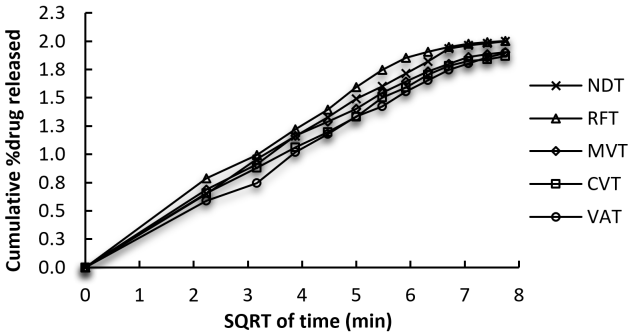

Figure 4. Higuchi model of the drug formulation tablets release in simulated intestinal solution.

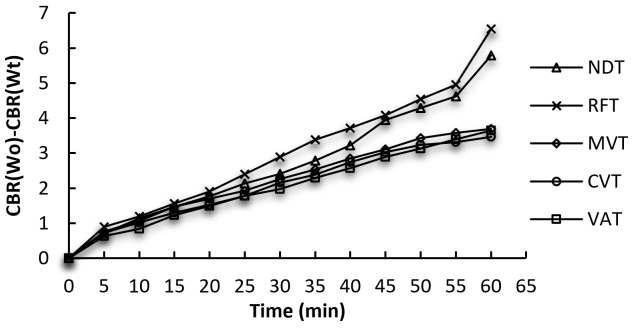

Figure 5. Hixon-Crowell model of the drug formulation tablets releases in simulated intestinal solution.

Figure 2 and Fig. 3 show the drug released with time of the NDT, FRT, CVT, VAT, and MVT tablets when tracking the zero-order and the first-order models. Figure 2 displays that the Zero-order weakly presents the drug release profile of all tablets mentioned above. Although the low values of OE and MRSE, the X^2 values are not very low. Also, the values of the statistical regression of fitting R^2 of the drug release of these tablets with this model are low ranging from 0.4564 for FRT to 0.7036 for VAT. This model is normally applied to matrix tablets with low soluble drugs [45], which is not the case with our tablets due to their high dissolution rate which confirms our results. Figure 3 exhibits the plot of data obtained by applying the first-order model to the drug release of each of the prepared tablets. This model is not in favor of the drug released from the aforementioned tables. This indication is obtained from the good (not very high) values of R^2 (0.8116 to 0.8973), MRSE (-0.144-0.7518), OE (0.532-0.667) and X^2 (0.186-0.208) in comparison to other models. It implies that the concentration of the drug is not the dominant factor affecting the drug

released in the medium [9,46]. Saidi, Dabbaghi, and Rahmani (2020) got a weak match to the first-order model with a medium value of R^2 (= 0.7059) to represent the release profile data of diclofenac sodium and that study agreed with our current results with the first-order model [47]. However, when the Higuchi model is used in the release profile data of all tablets, we get the plots presented in Fig. 4. It can be seen that the model is highly fitting the drug release of NDT, MVT, FRT, CVT, and VAT tablets in the 6.8 pH buffer solution with R^2 ranges from 0.9938 (with NDT) to 0.9994 (with VAT). For example, the experimental data of the drug release of the tablet (VAT) is exceptionally fitted to the Higuchi model with 0.9994 R^2. In addition, the very low values of MRSE, OE and X^2 which range from 0.0009 to 0.021 confirmed the high matching of the Higuch model to the profile data for all tablets. The Higuchi model is applicable to porous systems and relevant to different tablets with different geometries [48]. Also, this model suggests that the drug is released with the square root of time of dissolution in linear correlation which explains the great matching with the rapid dissolution of the drug component in our tablets [49]. Comparably, Higuchi was studied to examine the drug release kinetics from maleic anhydride-grafted chitosan film. Statistical regression of accuracy was found to be 0.9861 for 200 wt/wt of MA/Chitosan [50]. This result is close to that obtained with the Higuchi model in our study. Figure 5 illustrates the drug release of all prepared tablets in relation to the Hixon-Crowell model. This model highly matches the drug dissolution of tablets within the release rate test. Where R^2 appears with its lowest value (0.9744) for FRT to its maximum value (0.9993) for VAT and the lowest of MRSE OE, and X^2 (0.169, 0.054, and 0.546) with CVT, FRT, and NDT, respectively. This model is a very suitable model for drug dissolution in tablet forms. It considers that the drug release is associated with the tablet's surface area and diameter and the drug particle dissolution is controlling the drug release but not the diffusion [9,46]. Therefore, this model shows high fitting to our results. Similarly, Moshayedi, Sarpoolaky, and Khavandi found that Hixon-Crowell was the best model to describe the kinetics of drug release of the crosslinked gelatin/chitosan hydrogels containing zinc oxide nanoparticles loaded with curcumin with 0.9971 R^2 [51]. Also, the drug release of wheat germ agglutinin grafted L-Dopa nanoparticles was in favor of Hixson Crowell with 0.9828 R^2 [52]. According to Higuchi's assumptions, the drug release of tablets is constant diffusion and occurs in one dimension, and there is no significant swelling of tablets [53]. Whereas according to the Hixon-Crowell model, the release is influenced by the tablet surface area and diameter changes due to particle erosion, degradation, and dissolution or drug diffusion [7, 22, 35]. Thus, Higuchi and Hixon-Crowell models closely fit the drug release profile of all the prepared tablets; still, it is necessary to determine the drug release exponent γ of these tablets to confirm their controlled mechanism of release. Additionally, assessing the Korsmeyer model is necessary to estimate the indicator of release α to be able to provide a description of the dominant mechanism of tablet drug release. Figure 6 displays the Korsmeyer-Peppas model when fits the experimental data of the drug release of the prepared tablets. The figure shows the high harmonization between the obtained data and the model data with high R^2 varies from 0.9786 for the VAT to 0.9997 for the CVT and the values of RMSE, OE and X^2 do not exceed 0.097, 0.034, and 0.145, respectively. As a result, Korsmeyer-Peppas is highly fitting the release kinetics of all tablets, and the CVT is remarkably shaped by this model. From the slopes of the plots for all tablets, α value is obtained for each tablet to discover the drug release mechanisms. From the Korsmeyer-Peppas model, the release exponent γ for the NDT is found equal to 0.52. From the interpretation of γ value based on the information provided in Table 1, the diffusion of this tablet is non-Fickian [45,46]. This value of γ which is more than 0.45 and less than 0.85, suggests an anomalous diffusion of NDT. That means, it is controlled by the diffusion and erosion or relaxation release mechanisms [54]. VAT achieves the highest drug release exponent with γ equal to 0.53. According to this exponent value, the mechanism of VAT release is a non-Fickian diffusion as well. It suggests that the dissolution is controlled by polymer relaxation, swelling, and diffusion [45,46,53,54]. Hence, the drug releases its active ingredient by combining erosion and diffusion mechanisms [41] and is probably controlled by the tablet diameter and surface area. These results of NDT and VAT tablets agree with the non-Fickina diffusion release of the formulations of poly-lactide-co-glycolide which was reported by Raval et al, (2012). Their model exponent values γ ranged from 0.543 to 0.895 which proposed the diffusion and erosion drug transport [55]. Also, Pflieger et al. (2024) revealed that anomalous transport was the dominant mechanism for the 3D-printed theophylline tablets when they used the Korsmeyer-Peppas model [56]. For FRT with 0.40 γ, however, the release is considerably pure/Fickian diffusion because it is controlled by Fick's first law of diffusion [54]. According to Fick's first law of diffusion, the dissolution is independent of drug concentration [7], and it may occur because of the small size of drug particles compared to the tablet matrix thickness [8]. This case is compatible with the characteristics of the FRT particles, as shown in Table 2 with a mean diameter equal to 40.9 µm. Similar results were reported by Jahromi et al (2020) with the Fickian diffusion of the drug release rate of the polylactic-co-glycolic acid (PLGA-based nanoparticles) proved by the obtained exponent of release value with 0.43 [21]. The release exponent (= 0.46) of MVT, also describes the anomalous and non-Fickian diffusion [56], as that of NDT and VAT. This kind of dissolution combines two mechanisms: drug diffusion and polymer chain erosion [53, 54]. Obviously, the release kinetics of MVT do not obey one mechanism of release, and it is controlled by both the degradation and erosion of polymer chains and the diffusion of the active material (NxNa). The release exponent value γ of CVT is also less than that of the NDT and close to that of MVT. This value of γ reveals the responsibility of non-Fickian diffusion behavior with a very high linearity [45, 46]. Thus, the dissolution regime of CVT is also not pure diffusion; it is a combination of erosion with degradation and diffusion mechanisms. This anomalous mechanism is similar to the dissolution of nicorandil and theophylline matrix tablets with release indicative α of 0.71 and 0.7, respectively [49]. The degradation was also the controlled mechanism of the crosslinked gelatin/chitosan hydrogels containing zinc oxide nanoparticles loaded with curcumin [51]. Among the above models, the overall three models of the goodness equivalence description for the drug release of the prepared multi-component tablets are the Higuchi, Korsmeyer-Peppas, and Hixon-Crowell. It was reported, from the literature, that Higuchi and Korsmeyer-Peppas were also the best models fitted to the release of theophylline floating beads [41], and the Higuchi diffusion model was in favor of the release of cefpodoxime proxetil drug [49], chitosan-tripolyphosphate, chitosan-formaldehyde, and chitosan-glutaraldehyde matrices [57], and metronidazole drug [58]. Although the Zero-order was enclosed of the goodness of cefpodoxime proxetil release with R^2 = 0.9708 [49], the Zero-order and the First-order models in this work are not well-intentioned to represent the release of the tablets with their lower values of R^2. That means the erosion is the controlled mechanism of their tablets. In terms of the Weibull model, as shown in Fig. 7, it appears that this model is highly fitting the release rate of all the prepared tablets at close values of the statistical factors. That is approved from the high values of R^2 (0.9842 - 0.9967), approaching 1, the lowest MRSE (0.023 - 0.038), lowest OE (0.801 - 1.107), and lowest X^2 (0.008 - 0.22). In particular, the Weibull model highly matches the profile data of drug release of FRT with 0.9967, CVT, and MVT with 0.9951 and 0.9949, respectively. Similarly to the Korsmeyer-Peppas model, we evaluated the drug release of all tablets using the release behavior index β. It is found that β for the NDT and VAT is 0.794 and 0.913, respectively. As the value of β lies between 0.75 and 1, then, the transport of the aforementioned tablets is a combination of diffusion, erosion, and swelling [44]. These mechanisms of NDT and VAT are analogous to that obtained from the Korsmeyer-Peppas model which indicates the anomalous diffusion which means diffusion plus erosion. However, β value dropped to 0.37 with the FRT, and that refers to the Fickian diffusion of drug release. This is because β is less than 0.75, as shown in Table 1. This matches the results obtained from the Korsmeyer-Peppas model for FRT which indicates pure diffusion transport. The other tablets MVT and CVT are controlled with Fickian diffusion as well due to the low value of β which is estimated by 0.44 and 0.43. However, the Korsmeyer-Peppas model for these tablets reveals anomalous diffusion. This is probably due to the value of Y with 0.46 and 0.45 which is very close to the limit of pure diffusion ($Y < 0.45$) [28]. As a result, Fick diffusion is the dominant mechanism of FRT, MVT, and CVT while the anomalous diffusion is the controlled mechanism for NDT and VAT. These results are in agreement with the study of Kobryń et al. (2017) who employed the Weibull model to investigate the drug release of horse chestnut seed using different hydrogel formulations. According to β, they found that the drug release was Fickian diffusion for their samples [59].

As an overall result, two primary kinetics are controlling the release mechanism of those entire tablets. The pure diffusion mechanism of the FRT is probably due to the ratio of the small particle size to tablet thickness and the highest amorphous structure, which affects their release mechanisms. Nevertheless, the non-Fickian diffusion is the most dominant mechanism of release for the NDT, MVT, CVT, and VAT. Where the water degrades the crystalline polymer in two stages. Firstly, water starts to penetrate through the amorphous areas of the polymer, and secondly, it degrades these areas and hence promotes drug release. [58] this mechanism can explain what happened with those entire tablets having different release styles because they have different percentages of amorphous and crystalline structures and different physical properties. Therefore, the tendency of MVT to the non-Fickian diffusion and erosion release can be ascribed to its particle properties affected by drying using microwave radiation. Comparable results were obtained with the study of Arisoy and Comoglu (2020). The kinetics of drug transport of their sample, wheat germ agglutinin grafted L-Dopa nanoparticles, was based on polymer degradation

and drug diffusion [52].

Table 4. Kinetics models characters and regression factors values.

Model Name	Model parameter	NDT	FRT	MVT	CVT	VAT
ZERO-ORDER $\phi_\tau = k_o\tau$	k_o	2.083	2.145	1.982	1.930	1.905
	OE	0.258	0.126	0.190	0.171	0.294
	X^2	13.58	3.424	6.645	5.011	14.46
	$MRSE$	0.940	0.472	0.658	0.571	0.970
	AIC	17.78	10.00	13.75	12.15	18.14
	R^2	0.5932	0.4564	0.5334	0.6020	0.7036
FIRST-ORDER $\ln(\phi_o - \phi_\tau) = -k_1\tau$	k_1	0.067	0.067	0.067	0.067	0.070
	OE	0.620	0.665	0.567	0.532	0.571
	X^2	0.201	0.208	0.192	0.186	0.193
	$MRSE$	0.359	0.7518	-0.144	-0.509	-0.111
	AIC	0.067	0.067	0.067	0.067	0.070
	R^2	0.8591	0.8116	0.8462	0.8678	0.8973
HIXSON-CROWELL $\sqrt[3]{\phi_o} - \sqrt[3]{\phi} = k_{hx}\tau$	k_{hx}	0.086	0.094	0.059	0.056	0.058
	OE	0.057	0.054	0.070	0.070	0.070
	X^2	0.546	0.665	0.629	0.593	0.571
	$MRSE$	0.188	0.208	0.202	0.169	0.192
	AIC	-6.04	-3.47	-4.185	-4.97	-5.45
	R^2	0.9798	0.9744	0.9805	0.9789	0.9930
HIGUCHI $\phi_\tau = \phi_\infty k_H\sqrt{\tau}$	k_H	0.299	0.309	0.291	0.265	0.264
	OE	0.004	0.006	0.004	0.004	0.003
	X^2	0.007	0.007	0.002	0.002	0.0009
	$MRSE$	0.021	0.021	0.011	0.011	0.008
	AIC	-25.30	-24.89	-31.92	-32.02	-36.27
	R^2	0.9994	0.9950	0.9976	0.9974	0.9938
KORSMEYER-PEPPAS $\ln\phi_\tau = \ln k_p + \ln\tau^\gamma$	k_p	1.677	1.480	1.589	1.553	1.692
	OE	0.031	0.034	0.033	0.031	0.029
	X^2	0.1091	0.1449	0.110	0.0917	0.0711
	$MRSE$	0.084	0.097	0.085	0.077	0.068
	AIC	-16.97	-13.27	-26.81	-19.22	-22.53
	R^2	0.9975	0.9903	0.9924	0.9998	0.9786
	γ	0.52	0.40	0.46	0.44	0.53
WEIBULL $\ln[-LN(1-\phi_\tau)] = \beta\ln\tau_d + \ln\tau^\alpha$	α	0.06	0.006	0.014	0.010	0.048
	OE	0.010	0.010	0.008	0.009	0.011
	X^2	0.017	0.022	0.009	0.008	0.010
	$MRSE$	0.033	0.038	0.024	0.023	0.026
	AIC	-19.98	-18.42	-23.54	-24.15	-22.84
	R^2	0.9858	0.9967	0.9949	0.9842	0.9951
	τ_d	18.8	16.9	20	23.4	23.5
	β	0.79	0.37	0.45	0.43	0.91

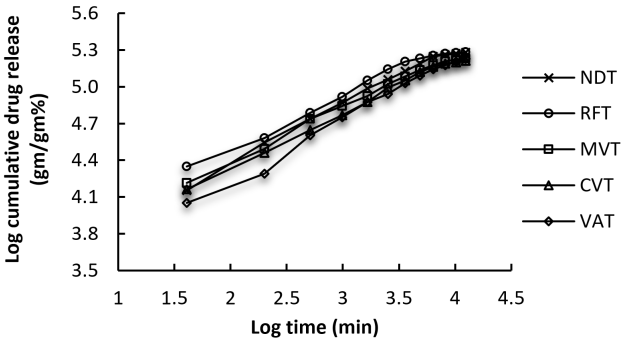

Figure 6. Korsmeyer-Peppas models plots of drug formulation tablets release in simulated abdominal solution.

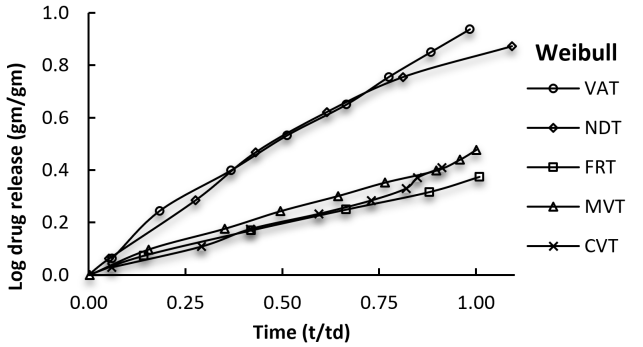

Figure 7. Weibull models plots of drug formulation tablets release in simulated abdominal solution.

3.4 Comparative analysis

AIC factor is used to compare between the Weibull model and other conventional models. The lowest of AIC, the best fitting to data, the most appropriate model of presenting the drug release. Therefore, AIC is determined for all models including all tablets. The obtained values of AIC, R^2, MRSE, OE and X^2 are considered and plotted in Fig. 8 as a maximum level equal to 100 to avoid the unfairness towards the negative values of some of these criteria. It is evident, from Fig. 8, that there is a big difference in AIC values of Zero-Order and First-order models to that of the Weibull model for all tablets, which means the latter is the best model to fit the release of drug of all tablets. Although the AIC values of Hixon-Crowel are not high, they are still greater than those of the Weibull model, which generates the latter as the best. However, Higuchi shows different results from the previously mentioned models, where its AIC values are less than the Weibull model. Thus, Higuchi has proved to be better than the Weibull model for all tablets. On the other hand, there are slight fluctuations in the values of the AIC of Korse-Peppas in comparison to the Weibull model. It appears that the Weibull model is better than the Korsemeyer-Peppas for NDT, FRT, and CVT while the latter is better for MVT and VAT by a very slight difference. Thus, both models are satisfying to present the drug release of these tablets with very high accuracy. Comparably, Jahromi et al. (2020) suggested that the Weibull model in comparison to zero order, first order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas was the rightest model that suits the drug release for several formulations of lactic-co-glycolic acid–based nanoparticles [20]. Also, García-Curiel et al. stated that the Weibull model was of the goodness of fitting to the drug release of drugs (class III) with the addition of brewers-spent grain intense in arabinoxylans with 0.993 R2 [60]. In summary, Higuchi, Weibull, and Korsmeyer-Peppas are the first three models in favor of the drug release of these tablets.

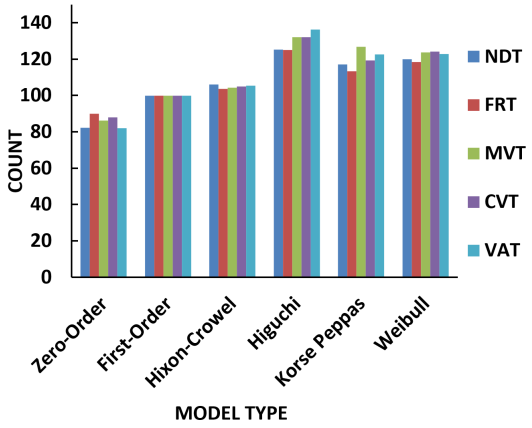

Figure 8. Comparative analyses between the Weibull model and other conventional models.

3.5 Drying techniques and drug release kinetics

In general, erosion, swelling, breaking up, dissolution, and diffusion are the usual steps of drug release [15]. However, the preparation and processing of drug tablets can significantly affect the tablets particles thereby their release behaviors. For instance, Askarizadeh et al. (2023) stated that particle size is one of the factors governing drug releases [15]. These experienced

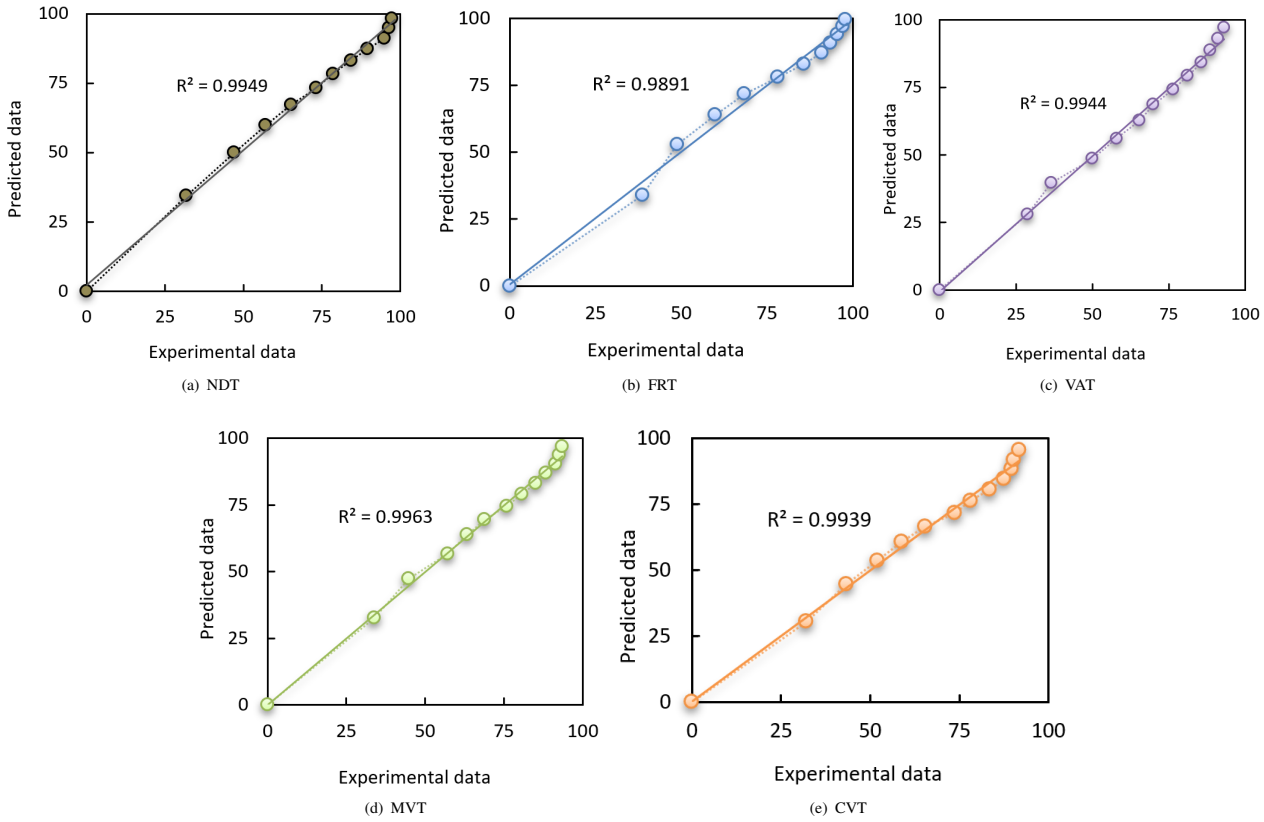

Figure 9. Parity graphs of the newly created models for NDT, FRT, VAT, MVT and CVT.

NxNa formulations tablets have diversity in their release kinetics in the 6.8 pH buffer solution. FRT tablets have a small particle size, high amorphous structure, and highest drug release (Higuchi constant k_H = 0.309) are controlled by pure diffusion [8, 61, 62]. However, tablets VAT are of the lowest release (k_H = 0.264) in anomalous diffusion nature due to the degradation of their large particles and high crystallinity, and that is noticed from the changes in the tablet surface and diameter. CVT is of the second low dissolution (k_H = 0.265), where non-Fickian diffusion is the responsible mechanism of the drug release. The drug release profile of the aforementioned tablets is to some extent similar to those of vitamin B12 loaded calcium alginate gel. FRT is of the faster diffusion release, whereas the VAT and CVT are of the slowest non-Fickian diffusion (anomalous) [24]. Microwave radiation drying, the new technique that produces MVT tablets, contains the smallest particle size with a second-high amorphous structure and the second-highest release (k_H = 0.291), the non-Fickian diffusion is also the most dominant mechanism of the release of its tablet. The drug release can be affected by the physical and chemical properties of the drug-active ingredients and their formulation polymers [63]. Thus, the kinetics and mechanism of the drug release of tablets prepared using microwave irradiation as a drying technique is proven to be an acceptable behavior. The characteristics of the dissolved drug materials can be influenced by the preparation or production processes such as drug formulation, wet granulation, drying, etc. [64, 65].

3.6 New developed semi-empirical models

In the literature, semi-empirical models have been improved and published to find the more appropriate description of the drug release to be used for different drugs, particularly the new formulations. For instance, a new model has been created by Siepmann and Peppas (2011) to describe the water transport in glassy polymers. Similarly, in the present study for each kind of tablet, as shown in Table 5, new modified empirical models are built to represent the release kinetics of those entire tablets with more accuracy, as shown in Eq. 13 to Eq. 15.

$$Model-1: \quad \phi_\tau = \alpha \ln \tau + \beta \tag{13}$$

$$Model-2: \quad \phi_\tau = \sigma \tau^{\theta} + \rho \tau^{\partial} \tag{14}$$

$$Model-3: \quad \phi_\tau = \delta \ln \tau^{\omega} + \mu \tag{15}$$

where: ϕ_τ is the amount of drug released at time τ; and α, β, θ, σ, ∂, ρ, δ, ω, *and* μ are the character constants of the newly created models of the *NxNa* drug release. Table 5 shows that Model-1 is the most appropriate to describe the release mechanism of the FRT, and Model-2 is in favor of the VAT. Model-3 is found to be the dominant designation model of the drug release of the NDT, CVT, and MVT. The experimental drug release rate values are compared to those estimated using the new created models, Model-1 for FRT, Model-2 for VAT, and Model-3 for NDT, CVT, and MVT (Eq. 13 to Eq. 15), in parity plots as shown in Fig. 9. From these figures, it is clear that those new created models offer equivalent linearity to the previous kinetic models and can be used to optimize and improve the delivery systems design, particularly for MVT. The highest value of R2 (0.9962), and low value of AIC (-19.18) of Model-3 reveal that this new model is comparable to that of the Higuchi model, Weibull and Korsmeyer-Peppas.

Table 5. New models present the release kinetics of the prepared tablets.

Tablet type	Model name	Model Equation	*AIC*	R^2
NDT	Model-3	$\phi_\tau = 10.2 \ln \tau^2 + 0.30$	-13.75	0.9949
FRT	Model-1	$\phi_\tau = 27.4 \ln \tau + 10.20$	-02.98	0.9891
VAT	Model-2	$\phi_\tau = 12.5\tau^{0.5} + 0.01\tau^{0.25}$	-33.52	0.9944
MVT	Model-3	$\phi_\tau = 9.4 \ln \tau^2 + 0.30$	-19.18	0.9963
CVT	Model-3	$\phi_\tau = 8.9 \ln \tau^2 + 0.38$	-21.56	0.9939

4. Conclusions

This work was executed by including the empirical release data of the new multi-component tablets consisting of NxNa components and polymers to study their release kinetics in the simulated intestinal solution. The focus was on applying the Weibull model and comparing it with the most common kinetic models, namely the Zero-order model, First-order model, Hixson-Crowell model, Higuchi model, and Korsmeyer-Peppas model. The analyses of this study disclosed that the active pharmaceutical ingredient was found to be delivered by non-Fickian diffusion for the NDT, and VAT. This mechanism

included the diffusion and the relaxation or erosion of polymer chains. However, Fickian diffusion was the most controlled mechanism of the FRT, MVT, and CVT. The kinetics of the MVT release was Fickina diffusion more than non-Fickian diffusion. The Weibull model, Higuchi model, Korsmeyer-Peppas model, and Hixon-Crowell model were of the goodness to fit the drug release of all tablets. It can be concluded that those models were convenient for understanding and analyzing the release mechanism of the prepared tablets by microwave radiation and the other drying methods. Additionally, three new modified semi-empirical models were created to describe the release kinetics with high accuracy, particularly MVT. Therefore, this study can contribute to optimizing and improving the drug delivery systems design.

Declaration of competing interest

The authors declare no conflicts of interest.

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This study didn't receive any specific funds.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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