Study the Using of Nanoparticles as Drug Delivery System Based on Mathematical Models for Controlled Release

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***Abstract*:-This study based on the pharmacokinetic modeling which was designed to realize a mathematical models with the objective to quantify and characterize drug behavior, here six mathematical models such as zero-order, first-order, higuchi's equation, korsmeyer-peppas, hixson-crowell's cube root equation and Tanh function were applied to different nano-structures that were designed as drug delivery system, in order to compared and test the drug release kinetics, then choose the optimal model that released the entire drug for extended periods of time in the bloodstream. The data of drug release from various nanoparticles structure were drawn out from literature and then were applied to the mathematical models that mentioned above. The results showed that the Tanh function model had the highest correlation coefficient (R2 = 0.9848) and it was applicable to the drug that needs the whole amount of release and prolonged period of time. From this result, it can be summarized that the Tanh function can be used to describe the drug release effectively and successfully.**

Keywords: **Nanoparticles, Drug Delivery System, Mathematical Models, Controlled Release**

I. INTRODUCTION

Over the years there has been a great challenge for scientists as many studies have been conducted to study the organism's response to drugs. Since the environment is constantly changing and is followed by an increase in the number of diseases and thus an increase in the number of vaccines, it was difficult to make judgments about what quantity and/or type of immune responses the vaccine may need [1, 2]. For decades, the interest of a pharmaceutical research has been a prominent trend in modifying drug delivery systems due to the need of delivering the drugs through the nano-carriers to the targeted tissue [3]. In order to ensure that the drugs have reached the targeted site with the required concentration, which did not have any absorption through the unwanted tissues or has been considerable part of the dose is actually wasted or removed from that tissue too quickly, additionally it may have destroyed these medicines in the way before reach the target location. So delivered the drug to the relevant receptors will contribute to raising the therapeutic efficiency and reduce the potential side effects and thus maintain the impact of therapeutic levels in plasma in a predefined time period [4, 5] and in order to overcome these limitations, by taking advantage of nanoparticulate drug delivery systems as a small size and its ability to deliver drugs to small places inside the body, their ability to modified, such as the chemical and physical properties and the surface properties moreover, their ability to enter tissues and cells easily without being identified and attacked by the immune system [6] a new drug dosage forms have been developed [7] based on the mathematical models for controlled the drug release which are helps to know and expect the results of the product formulations in advance without the need to perform the experiment several times which will contributes to reducing the cost and time and thus achieve the patient's safety and the efficiency of the drugs. Furthermore, understanding of all influential phenomena affecting drug release kinetics. As well as, use of the polymer nanoparticles drug delivery systems for controlled drug and drug targeting is a suitable option. The appropriate mathematical model choosing depends directly on the drug type and concentration of both drug and encapsulation material and the nano size which these parameters will apply to the parameters of the mathematical equation [8]. Moreover, the best model choosing depends on the desired accuracy and predictive ability of the model.

II. METHODS

In order to conduct this study, the MATLAB program was used, where the drug release behavior of the six models was simulated and determined and the data that was extracted from [9, 10] study was applied as listed in Table 1 , where they conducted the study in the laboratory using hydrohydrodynamic technique to produce nanoparticles. After that each model equation were converted to MATLAB language and then fitted the equations in the MATLAB curve fitting toolbox for the purpose of determine the goodness of fit (R^2-R^2adj) values which calculate the correlation between the data where the model that shows the high linearity (R^2=1 or near to 1) is the one that performed best. Finally, each model equation was fitted using curve fitting tool and the results were compared.

Table 1: Nanoparticles formulation parameters using Tanh function

Formulation Parameters			Tanh function model Correlation Coefficient		
Case	Drug (mg)	Polymer (mg)	Diameter (nm)	R^2	Adjusted-R^2
C1	1	1	52	0.9848	0.9834
C2	1	2	56	0.9664	0.9643
C3	1	3	59	0.9742	0.6742
C4	1	4	65	0.9654	0.9622
C5	2	4	63	0.9346	0.9284
C6	3	4	61	0.9508	0.9461
C7	4	4	58	0.9779	0.9749

III. MATHEMATICAL MODELS

The calculation of the quantitative data of the release becomes easier when using mathematical models. In addition, this models contributes to many fields, especially when used in the field of delivery systems, it helps to understand and predict the total pharmaceutical drug release kinetics from the various structures of nanoparticles [11]. The use of the mathematical models for the simulations will give a convergence results that approximately to the reality, also its contribution to the modification and improvement of the design of delivery systems and to the simplification of biological complexity [12]. The methods based on mathematical models include many mathematical equations, some of which are used to describe the release at the way of desolation; it is a process in which the solid matter is dissolved in a solvent where this process can be described by transferring the mass from the solid phase to the liquid phase. Examples of models that release the drug by decomposition are the zero-order, hixson-crowell and korsmeyer-peppas models. The Higuchi model is one of the example that used to describe the drug release by diffusion, which depends on the concentration gradients of the nanoparticles components [13, 14]. The mathematical models have two approaches such as model dependent and Independent which can be used to compare in vitro release profiles and here we will focus in the model-dependent approaches to evaluate the release patterns and this model are:

A) Zero-order kinetic model

This model is used to describe drugs that are released slowly with a constant concentration which can be characterized as ideal kinetics model, where it's maintaining the drug levels constant during the delivery process in blood plasma, because of the drug release rate is not dependent of its concentration [15]. This model can be applied to describe the release of the drug from the coated forms of dosing, products with low-solubility in water and the osmotic systems. [16, 17].

Model Expression:

$$Q_t = K_0 t$$

Where Q_t = the rate of drug released in time t, K_0 = zero-order model constant unit of inverse time.

B) First-order kinetic model

This model cannot explain the mechanisms that based on the theories because of its difficulty. Thus, this kinetics model is used to describe the absorption of drugs release and its elimination from the body [18] and also, to describe the drug that contained water soluble in the porous material.

Model Expression:

$$Q_t = Q_\infty(1 - e^{-K_1 t})$$

Where Q_∞ = the total fraction of drug released, Q_t = the rate of drug released in time t, and K_1 = the first-order constant.

C) Higuchi kinetic model

Higuchi proposed his models of water solubility and low solubility in the solid and semi-solid matrix [19]. This model is often characterized by the use of water. In this systems there are two mechanisms which responsible for controlling the rate of release of drug: swelling and erosion/degradation, resulting in a layer on the surface of the drug and thus, prevent the entry of more water and prevent the release of more drug, resulting in decline the drug over time [20, 21].

Model Expression:

$$Q_t = K_H t^{1/2}$$

Where Q_t = the rate of drug released in time t, K_H = Higuchi dissolution constant.

D) Hixson-Crowell kinetic model

This model takes into account that the particle surface area is uniform in size and corresponds to its cuboid root [13, 22, 23]. When nanoparticles are released, a change occurs in the diameter and surface area of these particles. This form is applied in the form of doses such as tablets, where the decomposition is parallel to the surface of the drug [24].

Model Expression:

$$Q_t = Q_\infty(1 - (1 - \alpha t)^3)$$

E) Korsmeyer-Peppas kinetic model

This model describes the mechanism of drug release from the polymer nanoparticles system, which was derived as a simple

relationship to detect these mechanisms [25], where the first 60% of the drug release data were fitted in this model [26].

Model Expression:

$$Q_t = At^n$$

Where Q_t = the rate of the drug in time t, A = the nanoparticles constant incorporating geometric structure feature, and n = the release exponent that indicates the release rate mechanism.

F) Tanh function

This function, which is derived from theoretical analysis during the process, is used because of the need for a model that applicable for the entire release process of a homogeneous particle, unlike the other models that apply to a part of the process. This model approximates the release of close to 100% where was derived by [27] based on the same diffusive release model as used by Korsmeyer-Peppas.

Model Expression:

$$Q_t = Q_\infty \tanh\left(\alpha t^{1/2}\right)$$

Where Q_∞ = the total rate of drug released, α = a constant which may be related to the diffusion constant and nanoparticle size and Q_t = the rate of drug released in time t.

we compared the solubility profiles between all these models of Nanoparticle with different structure, (curve fitting tools) was used as a statistical analyzes tool to determine the correlation coefficient (R^2-R^2 adj) and then decide which model that gives the best fits of the parameters data and shows high linearity and describing the whole drug release from the nanoparticles.

IV. RESULT AND DISCUSSION

Drug release kinetics studies were done to the mathematical models that were described in the context of this paper and the drug release for each model was simulated using the MATLAB software environment in order to evaluate which model that is performed best. The Nanoparticle tablets formulation parameters were summarized in Table 1, where the drug weight was ranged between 1 to 4 (mg) and the polymer weight also was ranged between 1 to 4 (mg) and the nanoparticle diameter was ranged from 52 to 65 (nm).

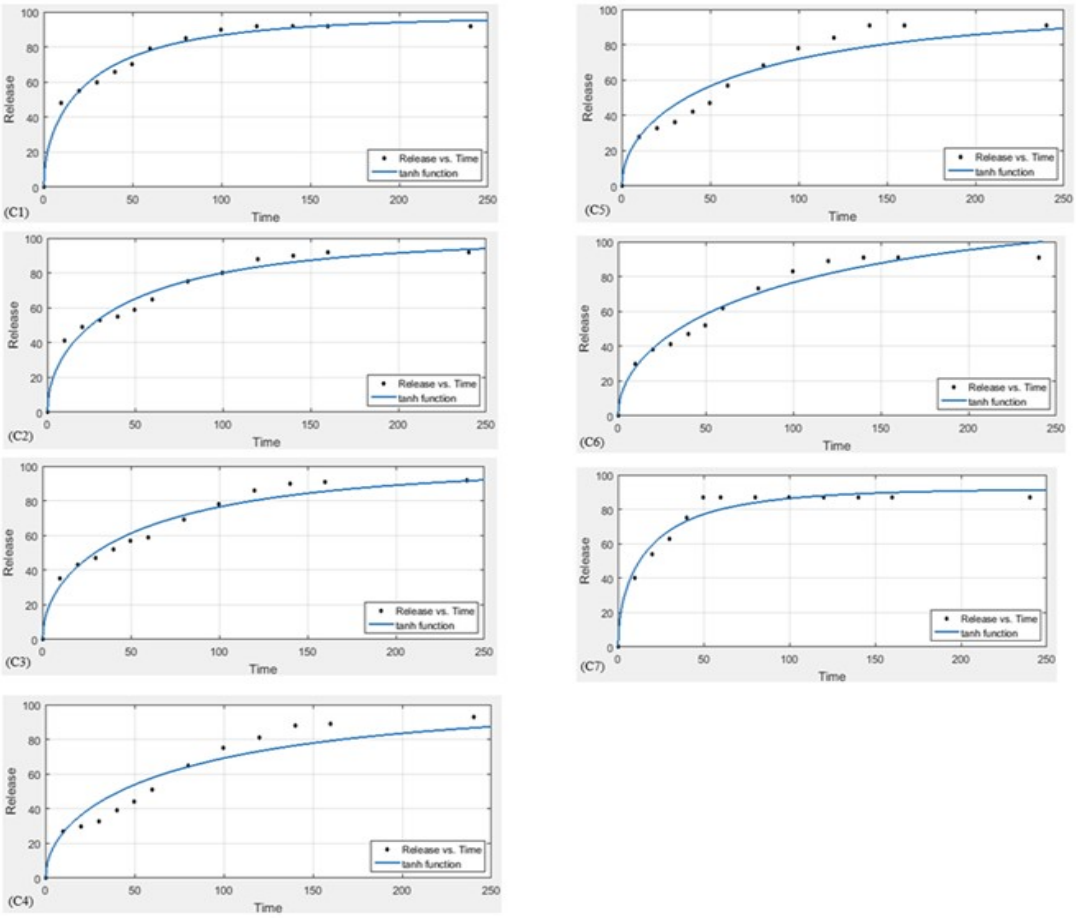

Figure 1: Represent the release behaviour for all cases C1:C7 for Tanh function. Note that: the x-axis illustrates the time in minutes and the y-axis illustrate the drug cumulative release, the dots illustrate the actual release and solid line illustrate the predicted release

As the concentration of the drug equivalent with concentration of the polymer the predict drug diffusional behaviour approximates the actual drug diffusional behaviour which mean there is a strong relation between both drug and polymer concentration and that subsumed under small diameter (Figure 1) show the influence of the drug release by the formulation parameters (drug, polymer weight and the Nano-structure diameter) and the release behavior of the Tanh model. Furthermore, among all the formulations with different models as the goodness of fit for each model was determined, it was found that the release from the prepared nanoparticles with Tanh model was showed the high linearity with good correlation coefficient and was the model that has the longest release duration over more than 240 minutes in (Figure 1) case C1 and C7 presented the best behavior of the Tanh model, where these curves almost imitate all the release points which represent the actual release, the ratio of the drug to polymer in the C1 and C7 formulations were 1:1 and 4:4 and the diameter was 52 and 58 respectively, this shows that Tanh model is performed pest in the case of homogeneous matrix which means this model was performed best as the correlation values of (R^2 =0.9848 and 0.9779) respectively and we can say this model is the best one. The Zero-order kinetics model is used to describe the processes in which the release levels of the drugs from nanoparticle devices are constant, i.e., release a constant quantity at a constant time. Additionally, maintaining constant levels of the drug in the bloodstream [13]. The First-order kinetics are used to describe linear drug release where the concentration of the drug within the nanoparticle device is proportional directly to the rate of elimination of the drug from the plasma, meaning that the higher the concentration of the drug, the faster its elimination rate. The Higuchi model is used to describe the release of the drug from the nanoparticles with matrix structures where the drug is loaded homogeneously in the entire matrix, which transcends the fact that the dissolving drug is carried in the center of the matrix only, and this model has undergone several stages of design, slab systems, then to various geometrics systems and porous systems and also, used in describing drug release for pharmaceutical products based on diffusion and dissolution. [28, 29]. When choosing a model to accurately describe the dissolution process, the Hixson-Crowell model is best suited for this task, where the drug release rate is characterized by a nanoscale that is perfectly homogeneous batch to batch. Also, this model is readily available in bioavailable and clinically. This model fits a set of particles with a regular area of cuboid root size and thus, has a precise process description of the process of release via dissolution to contain information on the changing surface area and diameter of the matrix drugs nanoparticles over time as the largest area is the fastest in dissolution [13, 30]. The Power law or Korsmeyer-Peppas model is used to describe and analyze the release of a drug from a polymeric nanoparticles dosage form such as a hydrogel, or when the release follows several kinetics mechanisms [20] also, used when the controllable process mechanism is incomprehensible, such as a combination more than one type of release mechanism or is a combination of the diffusion of the active principle (Fickian transport) and Case II transport (non-Fickian) (Table 2).

Table 2: Korsmeyer-Peppas Mode Drug release mechanism.

Exponent (n)	Drug Release Mechanism
$n \leq 0.45$	Fickian diffusion (Case I diffusional)
$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
$n = 0.89$	Zero order release (Case II transport)
$n > 0.89$	Super case II transport

This model also shows the release behavior only for the first 60% of the release of the drug [31]. Therefore, there is an urgent need to derive a model that can be applied to the entire drug release process as it was also derived Tanh model.

V. CONCLUSION

It can be said that mathematical models play a key role in studying the kinetics of drug release from the different nanoparticles structures dosage form and as well as it is characterized by low levels of complexity. In this research, a new mathematical model was used, which was derived theoretically during the experiment because of the need for a model that can be applied to the entire drug release. After conducting this study and comparing the six models, we concluded that the Tanh model gave the highest linear value of correlation coefficients (R^2 and adj-R2), where it is clear that the expected release simulates the actual release behaviour of the drug which means that this model can be used to describe the kinetics of drug release from nanoparticles effectively and successfully. The choice of the best model to describe the kinetics of drug release depends largely on the degree of convergence of predicted predictive form of the real form of the drug and this ratio can be easily measured by the linear winding parameters under the name goodness of fit. In fact, In order to achieve accurate and important information in the delivery of the drug to the target place and in the specified time, which in turn will increase the effectiveness of treatment and reduce the possible side effects of the drug was studied the kinetics of the release of drugs from different nanoparticles and that denoted as smart devices that programmed using mathematical models, which contributes significantly to the understanding and description of the process of drug release and simulation its behavior within the body. In addition, due to the increasing number of vaccines and medicines, it is necessary to ensure that the forms of the new dose of these drugs appear dissolution in the right way and appropriate, which will contribute to the safe, effective and reliable application of these drugs. The mathematical models also contribute significantly to anticipating the results of the experience in advance without

the need for further testing which will contribute to reducing cost and time.

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