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Mathematical Modeling of Delayed Release Dosage Form Dissolution Test and Bioavailability

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Abstract: ***In this study in-vitro dissolution of modified release diclofenac sodium(DS) dosage form were studied, a100 mg DS tablets were tested under simulated gastric and intestinal medium according to united states pharmacopoeia (USP), the data were modeled mathematically to identify to which model the drug release is fitted using linear regression analysis. In-vivo the pharmacokinetic parameters were evaluated by administrating the drug to seven healthy volunteers, DS concentrations in plasma was measured using revers phase high performance liquid chromatography (HPLC). Primary kinetic parameters*** $AUC_{0\to\infty}$, C_{max}, t_{max} ***and other kinetic parameters where obtained using non compartmental analysis. In-vivo study accomplished using compartmental analysis, the data analyzed as single compartment model with single time variant input and single time variant output. This analysis allows the data to represented in three differential equations, in-vitro the data fitted to Higuchi release model, in-vivo the data fitted to single compartment model, non-compartmental data were in accepted range.***

Keywords: Dissolution, Mathematical modeling, Bioavailability, HPLC

1. Introduction

The drug release and dissolution from solid oral dosage forms was a subject of interest, it has an important role in releasing the drug and subsequent gastro intestinal absorption. The analysis of the values obtained in dissolution test is easier to be represented using mathematical equations, which represent the dissolution results as function of time, sometimes these mathematical models build on theoretical basis. Dissolution of drug from solid oral dosage forms has been represented freuently by four kinetic models, where the dissolved amount C is function of time t or C=f(t), some definitions of C(t) equations were used, like zero order, first order, Hixon-crowell, and higuchi models [1,2].

Bioavailability or biological availability is defined by the rate and extent to which the drug active ingredients is absorbed in-vivo, and become available in the systemic circulation, the definition of bioavailability has developed with time by different meanings, its considered to be a key pharmacokinetic parameter that represent the part of drug administrated by any non-vascular route that gain reaching to the systemic circulation [3].Practically it determined by the drug level in blood by special extraction techniques, the plasma concentration is measured using the reversed phase (high performance liquid chromatography) HPLC [4].The absolute bioavailability represents the actual percentage of the administrated dose and it ranges from (0 to 100) that reaches the systemic circulation [3,5]. It can be calculated by comparing the results obtained by administration of the drug orally and intravenously [6].

The study of modified release dosage forms has special importance because of their release profile which gives approximately steady level of drug for long period of time. So these dosage forms have time coursecharacteristics of drug and location are selected to accomplish therapeutic to perform convenient therapeutic objectives which not offered by conventional dosage forms, and it include extended and delayed release dosage forms [7].

Modified release dosage forms or prolonged release dosage forms are dosage forms having lower release than that of traditional dosage forms, they are frequently used for drugs that has short elimination half-life to reduce the repetition of daily administration and for drugs that has adverse effect related to high fluctuations of plasma concentration[8]. Although the absorption of diclofenac sodium following oral dose is extremely rapid, only 60% of the drug reaches the systemic circulation due to extensive first-pass effect,'' Rapid systemic clearance of diclofenac necessitates repeated dosing. Therefore, extended release formulations of diclofenac offer the advantage of once daily dosage regimen'' [9]. The importance of bioavailability study that it used to study the pharmacokinetic parameters using non compartmental analysis also the compartmental analysis have their special importance in drug development ,compartmental models are hypothetical structures that used frequently to describe drug fate in biological system following its administration, with one time variant input and output, in one compartment model the body is depicted as homogenous unit assuming that the drug attain instantaneous distribution of the drug throughout the body and that the drug equilibrates instantly between tissue thus the drug concentration versus time profile shows monophasic response [10].

2. Literature Survey

Nasir M. Idkaidek et.al, in 1998 [8], fitted data from sustained-release and enteric-coated oral formulations, and the suppository formulation of diclofenac sodium simultaneously fitted to two compartmental model with two absorption sites using special program.

Rani M. et.al, in 2003 [9], designed and evaluated osmotic pump (OP) tablets with the aim to deliver diclofenac sodium (DS) in a controlled manner, In vitro evaluation was done in various release kinetics models using the regression coefficient analysis. In vivo evaluation was performed on six healthy human volunteers and various pharmacokinetic parameters (Cmax, tmax, AUC0–24, MRT) and relative bioavailability were calculated, the results were compared with the performance of two commercial tablets of DS.

Buchwald et.al, in 2003 [10] investigated and proposed a new, differential equation-based IVIVC method that directly relates the time-profiles of in vitro dissolution rates with in vivo plasma concentrations by using one or multi compartment pharmacokinetic models and a corresponding system of differential equations.

3. Materials and Method for Dissolution Test

3.1 Chemicals

USP(United States pharmacopeia) references standard of Diclofenac Sodium (Samara, Iraq). Reagents: Hydrochloric acid (Merk, Germany), Ortho-phosphoric acid (Merk, Germany). Sodium Hydroxide (Merk, Germany), Equipments: Simadzu UV spectrophometer Electrolab. Tablet Dissolution Test machine, These studies were conducted at 37±0.5°C on an USP specification dissolution rate test apparatus type II (Paddle apparatus) with seven section assembly according to the (USP 30) procedure with some modification For in vitro dissolution studies for simulated gastric medium (pH 1.2) and simulated intestinal medium (pH 6.8) as it required.

3.1.1Simulated gastric medium Preparation

(0.1 N HCl, pH 1.2) For 0.1N HCl, 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient amount of water to produce 1000 ml.

3.1.2 Simulated intestinal medium Preparation (Buffer pH6.8)

20 ml of Sodium Hydroxide (25%) was diluted with 0.1 N Hcl to 1000 ml adjusting pH to 6.8 by adding 1.2 ml O-phosphoric acid. The dissolution test was performed using 900 ml of medium at 37±0.5°C and 50 rpm. The medium was preheated to 37°C and in the vessels, paddle rotation was started and the system was allowed to equilibrate for 15 min. Each vessel, vessel position, and corresponding tablet result were given same number.

At the same time, every tablet result was identified with a particular vessel and position. The total time of dissolution was 12 hours in which the first 2 hours the tabletswere subjected to simulated gastric media (0.1N HCl pH 1.3) and the later 10 hours the tablets were subjected to simulated intestinal media (Buffer pH 6.8).

3.2. Acid stage

900 ml of 0.1N HCl was placed in each vessel and the apparatus was placed. Seven tablets from the selected formulation were thrown in the vessel. The time of the acid stage was carried out for 2 hours. After each hour 5ml of sample solution was withdrawn, filtered and diluted. Replaced with fresh testing medium and the released drug were assayed by using UV spectrophotometer at 276 nm.

3.3. Buffer stage

After 2 hours operation in the acid stage, The acid replaced with phosphate buffer pH (6.8 ±0.05), the medium was pre heated to 37^0C ±0.5. The operation was continued for 10hours. At specific time points (5 ml) of the solution was taken from the dissolution medium and immediately replaced with equal volume of fresh testing medium. The samples was then filtered by filter paper and diluted 10 times, analyzed at 276nm for diclofenac sodium by UV spectrophotometer (Shimadzu, Model UV-160A, Kyoto, Japan). The amounts of drug present in the samples were calculated with respect to standard solution of (prepared according to United states pharmacopoeia) USP reference standard test drugs.

3.4. Analysis of release data:

The description of dissolution profiles has been completed using different releaseprfile models. The data were evaluated according to the following four equations, where equation (1) represents the zero orderrelease kinetic, equation (2) represents the first order release kinetics, equation (3) represent Higuchi release model and equation (4) represent Hixon- Crowell model:

$$\text{Zero order: } M_t = M_0 + K_0 t \quad \dots (1)$$

$$\text{First order: } \ln M_t = \ln M_0 + K_1 t \quad \dots (2)$$

$$\text{Higuchi model: } M_t = K_H \sqrt{t} \quad \dots (3)$$

Hixon-Crowell model:

$$\sqrt[3]{M_0} - \sqrt[3]{M_t} = K_s * t \quad \dots (4)$$

Where M_t is the amount of dissolved drug at time t, M_0 the initial amount of drug, K_1 is the first order release constant, $K_0$the zero order release constant, K_H the Higuchi rate constant, K_s the Hixon-Crowell release constan, The correlation coefficient (R^2) was used as an indicator of the best fitting, for each of the models considered'' [11, 12].

4. Materials and Method for Bioavailability Test

4.1 Instrumentation

High performance liquid chromatography (HPLC, KNAUER) HPLC column ODS (C18) (KNAUER); Membrane filters (0.45µm pore size) (Sartorius, Germany).

4.2 Sampling

The blood samples were drawn from the vein of arm. The blood samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after the oral drug administration. The blank blood samples were taken from all volunteers. The blood samples were withdrawn in EDTA tubes then transformed to special glass centrifuge tubes. At each sampling time, 5mL of blood was drawn by disposable syringe plasma was separated using centrifuge and stored in

freezer below -20°C until used for analysis of Diclofenac sodium.

4.3. Method of HPLC assay

A system (KNAUER) equipped with a UV detector (series 200 UV- visible set at 283nm) and C18 (5µm) reversed phase column (250 × 4.6 mm I.D.) was used; The mobile phase consisted of a mixture of acetonitrile and 0.01M ammonium acetate buffer in ratio of 60:40. The pH of mobile phase was 3.4, it was kept in this level by glacial acetic acid. Flow rate was 1.5 mL/min. Further, the method was validated with standard solution (10 g/ml) diclofenac sodium.

4.3.1. Assay procedure

Standard solution (10µg/ml) of diclofenac sodium were prepared daily by dissolving the drug in the mobile phase. 2mL of acetonitrile was added to 1mL of plasma samples to precipitate the proteins and then vortexed for 1 minute. It was then centrifuged for 5 minutes at 3500 rpm. After centrifugation, the layer of supernatant fluid was transfered to another test tube and evaporated to dryness under nitrogen flux. The residue was then dissolved in 400µl of mobile phase and 20µl injected into the injection port. Serum diclofenac concentrations were measured by reversed-phase HPLC with ultraviolet detection.

4.4. Pharmacokinetic analysis

Maximum plasma concentration (C_{max}) and the time needed to reach maximum concentration (T_{max}) were directly determined from the profile of plasma concentration versus time. The area under the plasma concentration versus time curve from 0 to t ($AUC_{0\to t}$) was calculated by the linear trapezoidal rule. The area under the curve from (0 hour to infinity) ($AUC_{0\to\infty}$) was estimated by adding the area under the curve from 0 to t ($AUC_{0\to t}$) to area from t to infinity ($AUC_{t\to\infty}$), where $AUC_{t\to\infty} = C_t/K_e$, with C_t defined as the last measured plasma concentration at time t, and k_e the slope of the terminal portion of the ln (plasma concentration) versus time curve. The elimination half-life ($t_{1/2}$) was calculated using the following relationship $t_{1/2}$= ln (2)/K_e. ''The half-life of diclofenac sodium in plasma varies from 1-3 hours (Adeyeye& Li, 1990; \Reynold, 1993; Willis et al., 1979; Degen et al., 1988; Said & Sharaf, 1981 and Landsdorp et al., 1990)''. [13, 14, 15]

4.5. Compartmental analysis

One of important oral route is the sustained release formulations. The vehicle in which they are supplied has been modified so that not all the entire drug is available for absorption. This means that some fraction of the drug fi, is available immediately, and some fraction fr, [fr = (1-fi)] is released with first order kinetics, described by a constant k_r . Release kinetic represented by three differential equations, equation (5) represents the rate of change of the initial dose enter to the body:

$$D = D_0 * f_r * e^{-k_r t} \quad \dots (5)$$

Equation (6) represents the concentration of drug in the GI tract:

$$G = \frac{D_0 * f_r * k_r}{k_a - k_r}\left(e^{-krt} - e^{-kat}\right) + D_0 * f_i * e^{-kat} \dots (6)$$

Equations (7) represent the concentration of the drug in the body:

$$B = \frac{Do*fr*ka*kr}{(ka-kr)(k_e-kr)}\left(e^{-krt} - e^{-k_e t}\right) + \frac{Do*fi*ka - \left[Do*fr*ka*\frac{kr}{ka-kr}\right]}{(k_e-ka)}\left(e^{-krt} - e^{-k_e t}\right) \dots (7)$$

Where D is the initial amount in the body.
G concentration of drug in the Gut.
B concentration of drug in the body.
D_0 Is the administrated dose in (mg/kg).
k_a Absorption rate constant.
k_r The first order release constant.
k_e The elimination rate constant.
t time.
f_i Fraction released immediately.
f_r Fraction released with first order manner.[10]

5. Results and Discussion

5.1 Results

The invitro dissolution behaiver of diclofenac sodium tablets were studied to describe its in-vitro dissolution behavior in simulated gastric medium (pH 1.2) for 2 hours, and in simulated intestinal medium (pH 6.8) for 8 hours using USP dissolution apparatus, the fraction released versus time is shown in (Table 1). 25% drug release within 2 hours in simulated gastric medium. And it were fulfill the USP in vitro dissolution specification 80% drug release within the next 8 hours in simulated intestinal medium, The drug release mechanism was determined by regression coefficient (R^2) for each release kinetics as shown in Table(2). After plotting the drug release data that obtained experimentally according to the four release models mentioned previously. A Higuchi release kinetics Fig.(3) was predominant than the first order Fig.(2), zero order Fig(1), and Hixon-crowell Fig.(4) release kinetics.

Table 1: Accumulative % released in invitro dissolution test

Accumulative % released	Time in (hr)
0	0
1.81	1
2.257	2
12.205	2.17
21.75	2.5
33.8	3
49.08	4
63.1	5
68.25	6
74.67	7
83.92	8
96.04	10

Table 2: Release constants, y-intercept, and correlation coefficients of applied kinetic models

Release kinetic	Release constant	y-intercept	R^2
Zero order	11.129	4.75	0.9439
First order	0.156	2.178	0.8837
Higuchi model	48.994	54.225	0.9668
Hixoncrowell	0.434	3.497	0.7939

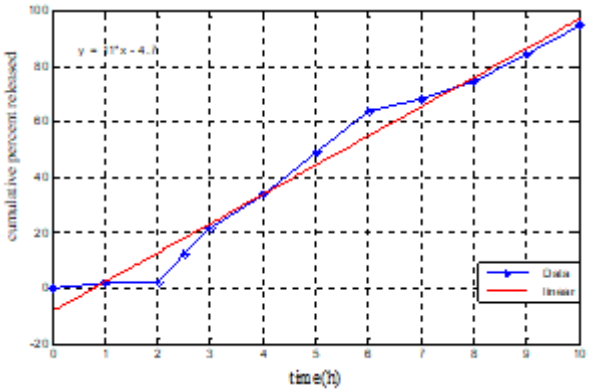

Figure 1: Zero order release kinetic of Diclofenac sodium.

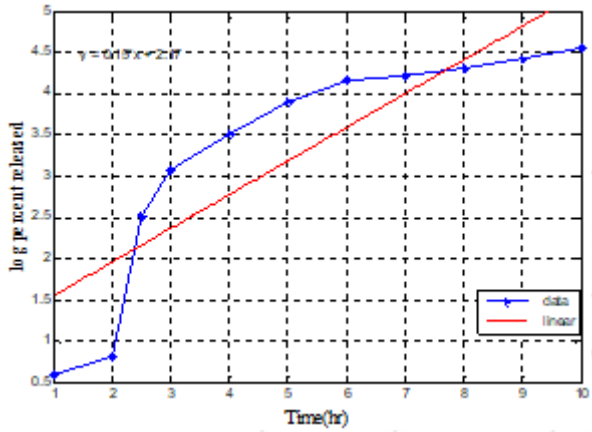

Figure 2: First order release profile of Diclofenac sodium

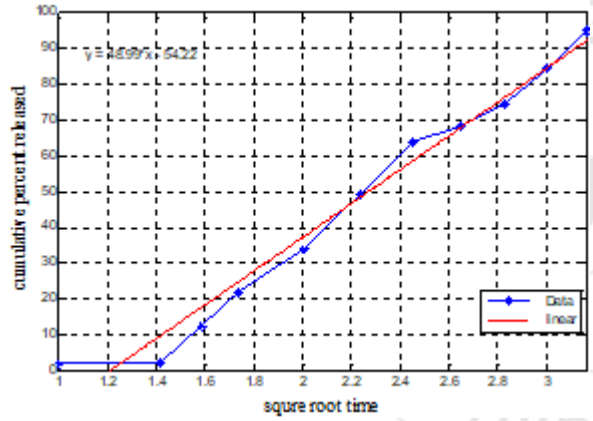

Figure 3: Higuchi release profile of Diclofenac sodium

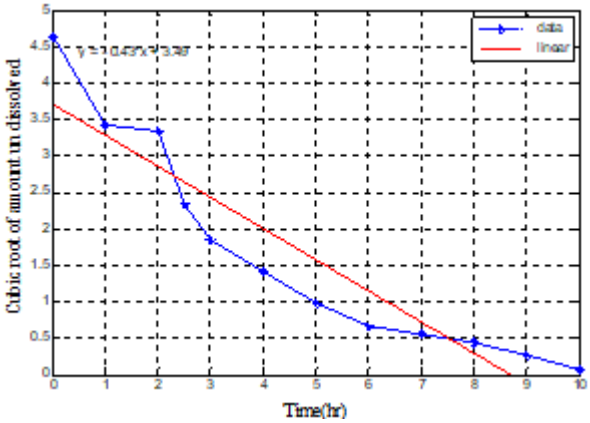

Figure 4: Hixon-crowell release profile of Diclofenac sodium

Plasma concentration versus time profile of diclofenac sodium after an oral dose of 100 mg delayed release tablet was measured plotted as shown in Fig(5) and its pharmacokinetic parameters are statistically evaluated as shown in table (3).

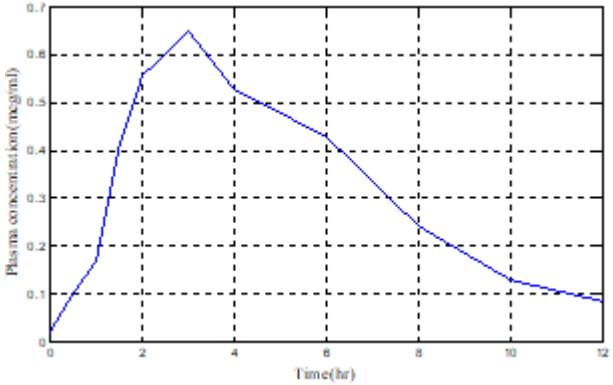

Figure 5: Mean plasma concentration in (/ml) of seven healthy volunteers.

Table 3: Pharmacokinetic parameters obtained from bioavailability test

Parameter name	Parameter value Mean± SD
AUC0→t (µg.h/ml)	3.892±0.228
AUC0→∞ (µg.h/ml)	4.224±0.162
AUMC0→∞ (µg.h^2/ml)	24.871±0.134
Tmax(h)	3±0.5
Cmax(µg/ml)	0.649±0.331
Ka(h^{-1})	0.699±0.162
Kel(h^{-1})	0.259 ±0.162
$t_{1/2}$(h)	2.675 ± 0.514
MRT(h)	5.736±1.07
Vd/F (L)	91.405±1.48
Cl/F(L/h)	23.674±0.790

were, AUC0→t is the area under the curve from time zero to t, AUC0→∞ area under the curve from zero to infinity, AUMC0→∞ area under the curve from zero to infinity, Tmax is the time needed to reach the maximum concentration, Cmax the maximum plasma concentration, Ka absorption rate constant, Kel elimination rate constant, t1/2 half-life time, MRT mean residence time, Vd/F volume of distribution, Cl/F clearance. Then the drug is analyzed as single compartmental model for sustained release drug in three differential equations as shown above, data obtained from in vitro and in vivo tests are applied to the above three equations (5,6,7) and three plots shown in Fig (6,7,8)obtained:

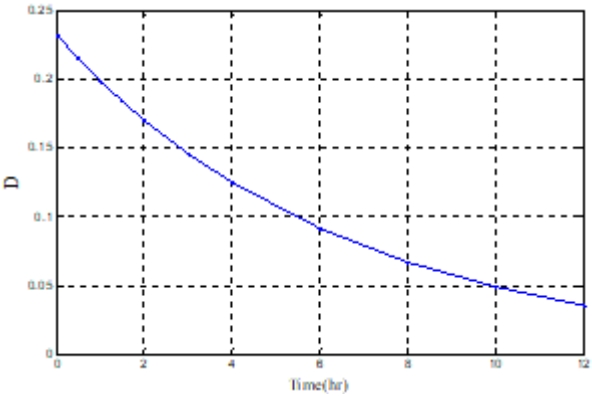

Figure 6: The rate of change of the initial amount inter the body (D) versus time.

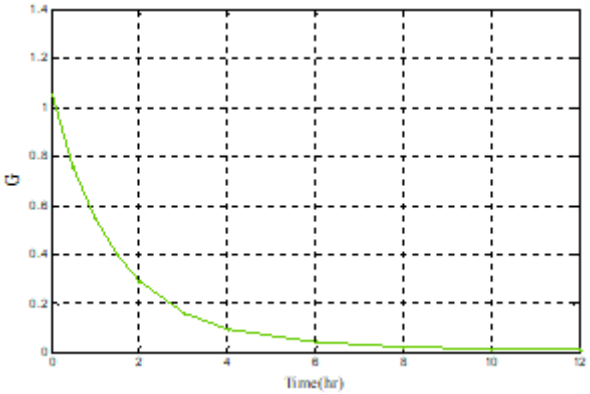

Figure 7: The rate of drug concentration in the GI tract(G) versus time.

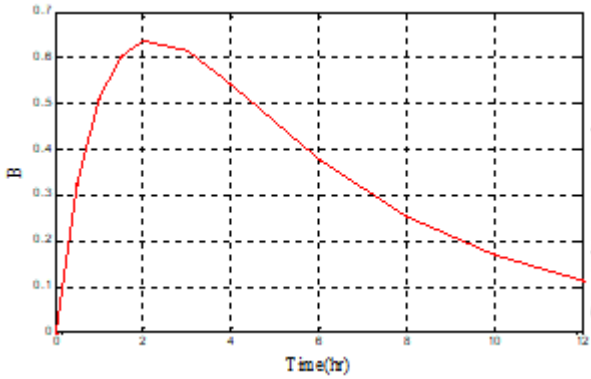

Figure 8: The rate of concentration change in body (B)

5.2. Discussion

The diclofenac sodium is NSAID (non-steroidal anti-inflammatory drug) that is used widely. diclofenac sodium delayed release tablets were studied, in-vitro dissolution study shows that the tablets fulfill the USP in vitro dissolution specification, The drug release mechanism was determined by multiple correlation coefficients (R^2) for each individual tablet. A Higuchi release kinetics has higher correlation coefficient than the first order, zero order, and hixon-crowel release kinetics. Higuchi model describes drug release based on Fikcs law diffusion process, square root time dependent. This relation can be used to describe the drug release from several types of modified release pharmaceutical dosage forms the low release rate of active ingredients from tablet helps in keeping the concentration of blood with in the systemic circulation with in the therapeutic window and prevent the cure fluctuation.

In vivo behavior of delayed release diclofenac sodium were studied using HPLC technique, today, HPLC is a powerful technique for highly specific and quantitative measurements of low levels of analytes in biological samples, The mean plasma concentration-time curve was shown in Figure (5), The mean values of pharmacokinetic parameters estimated by non compartmental and compartmental method were shown in Table (3), these parameters are in accepted range, the absorption rate constant (k_a) were higher than elimination rate constant (k_e) which indicate that the absorption rate is faster than elimination rate which again helping to keep the drug concentration in systemic circulation constant for long period of time.

Compartmental analysis for extended release drug where performed using data obtained from in-vitro and in-vivo tests. The plots obtained from in Fig (6,7,8) show the movement of drug inside absorption site, GI-tract and body and their rate of change with respect to time, the rate of change of drug inside body show delayed release, The correlation between the plasma concentration versus time and the rate of change of drug in body is 0.702.

6. Conclusion

1) The tested delayed release drug follow Higuchi release kinetic, which used to describe diffusion controlled mechanism.
2) The drug is one of modified release formulations, type delayed release it show prolonged release patterns neither, it characterized by delay its release until reach the high PH of the intestine.
3) The plasma concentration versus time profile have higher absorption rate than its elimination.
4) Invitro release kinetic invivo bioavailability and compartmental analysis are important parameters to describe the movement of the drug inside body, and they are very important tools in drug delivery systems development to improve the drug action.

7. Future Scope

Using Artificial Neural Network (ANN) in prediction of Drug Delivery systems and Pharmaceutical Research.

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Khawla Rasheed received B.Sc. and M.Sc. in Biomedical Engineering in 2001 and 2015, respectively from Al-Nahrain University/ College of Engineering/ Biomedical Engineering Department. She studied the drug delivery systems of modified release dosage forms and finite element analysis of medical implants. She teaches in Ibn-Sina University for medical and pharmaceutical science.