EVALUATION OF DRUG RELEASE KINETICS FOR DICLOFENAC SODIUM 100MG ORIGIN BRAND MATRIX TABLET.

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ABSTRACT

The development of controlled release drug delivery systems has increased, the release of drug from the dose is the most important step in controlled release dosage form design and to confirm the release is done properly, the kinetic study must be take placed which described the overall release of drug from the dosage forms, because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of in vitro drug dissolution data to predict in vivo bio-performance can be considered as the rational development of controlled release formulations. The aim of this study is to evaluate drug release parameters as per various release kinetic models. The tablets were characterized by physical and chemical parameters and results of assay% for the three batches were found as 102.07(S.D = 1.11), 99.87(S.D = 1.45) and 100.52 (S.D = 1.72).within acceptable limits (90-110%). Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model was based on linearity (coefficient of correlation). The drug release data for drug fit well to the by zero order kinetics which give the highest r^2 value (0.993), with anomalous release mechanism.

Keywords: Diclofenac sodium; sustained release; dissolution; kinetics.

INTRODUCTION

Numerous studies have been carried out in order to achieve a desirable release rate of several non-steroidal anti-inflammatory drugs to treat rheumatoid arthritis, and osteoarthritis. (1). Recently, Davies published an interesting review based on the important clinical concern when NSAIDs are prescribed (2). Diclofenac Sodium, one of the most useful NSAIDs agent, it is a practically insoluble compound in acidic solution (pKa=4.0), but dissolves in intestinal fluid and water. In chronic inflammatory diseases like rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other nonrheumatoid arthropathies treatment is usually prolong and large doses are required (3). Diclofenac sodium a phenylpropionic acid derivative is established as first-line NSAID for rheumatoid arthritis and chronic arthropathies. The mechanism of action of Diclofenac sodium involves not only inhibition of prostaglandin synthesis but also decreased production of pro-inflammatory cytokines such as interleukin 1β and tumour necrosis factor α; inhibition of leucocyte leucotriene B4 and nitric oxide; and possibly a positive effect on the production of oxyradicals and signaling transduction via the NFκB pathway. In therapeutic use, diclofenac sodium proved to have a favourable risk: benefit ratio and predictable adverse effects (4). Thus for patient compliance, improve bioavailability, minimize total drug quantity, minimize accumulation on chronic use and reduce fluctuation in drug level sustained release of

diclofenac sodium is desirable. The delivery from these systems often follows a certain time course determined by the selection of the polymer and the geometry of the matrix. There are many types of matrix systems where the release can be expressed using different mathematical models. The first system is a solid matrix that does not disintegrate nor swell during dissolution but dissolves from the surface that is exposed to a dissolution medium and only the drug at the surface is released. the second matrix system, the matrix does not change during dissolution (insoluble, no disintegration, and no swelling). Polymers that are hydrophobic or cross-linked polymers often are used for the matrix. The drug solid is dissolved inside the matrix and is released by diffusing out of the matrix. The third matrix system is based on hydrophilic polymers that are soluble in water. For these types of matrix systems, water-soluble hydrophilic polymers are mixed with drugs and other excipients and compressed into tablets.

Hydrophillic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance (5). Drug release from hydrophillic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. Hydroxypropyl methylcellulose (HPMC) is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods (6).

Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses (7). Various studies of drug release mechanism, effect of formulation variables on HPMC matrices are based on direct compression (8). Several mathematical models have been published, to elucidate the water and drug transport processes and to predict the resulting drug release kinetics (9,10,11,and 12). The mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into consideration. Each model makes certain assumptions and due to these assumptions, the applicability of the respective models is restricted to certain drug–polymer systems (13).

The aim of this work was to evaluate drug release parameters as per various release kinetic models and to determine the mechanism of drug release of diclofenac sodium used as 100mg per tablet for 12 hrs.

MATERIALS AND METHODS

The following materials were used: Diclofenac sodium working standard (Aarti Drugs Limitid. India). Chemical reagent as analytical grade (Methanol and Hydrochloric acid from Across-Germany, but Acetonitrile, Sodium tri-hydrogen phosphate and Sodium hydroxid from Scharlau , Spanish)

Sample collection

Samples were purchased from pharmacies, all samples collected in sufficient quantity for analysis. Three different batches from the origin brand were selected in correct expiry date.

Calibration curve

An accurately weighed quantity of USP diclofenac Sodium working standard was dissolved in a mixture of acetonitrile and water (43 : 57), then quantitatively diluted with a mixture of acetonitrile and water (43 : 57) to obtain a solution having a known concentration of about 200 mg per ml. Different conc. Table (3) were prepared by dilution with buffer solution and measured at wave length 276 nm using UV spectrophotomer (Varian; company - USA). This process was repeated at different time and the main results of absorbance were taken and plotting against conc. to get the linearity figure (1).

Evaluation of tablets

Tablets were subjected to various physical tests which include weight variation, thickness, hardness (OSK Fujiwara Hardness Tester, Tokyo, Japan), friability (Friabilator, H.Jurgens GmbH & Co., Bremen, Germany) as per BP official methods. *In vitro* release study was performed using USP apparatus type II at 50 rpm (Pharma test, Germany). The dissolution medium used was 900 ml phosphate buffer pH 7.8 for 12 hrs; maintained at $37 \pm 0.5°C$. The drug release was evaluated by taking sample of 5 ml (which were replaced with fresh medium) at predetermined time intervals (of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h) and conc. was measured at ($\lambda = 276nm$) after filtration and suitable dilution (UV Spectrophotometer, Varian company, USA). Drug content was analyzed using HPLC (Water company, USA) as per official method of diclfenac sodium (14).

Process validation

Hardness, thickness and weight variation was evaluated and data was compared for all three batches. *In vitro* release profile and assay results were also evaluated and compared with predefined criteria. If the results of the product fulfill with this test, the labeling indicates that it meets USP dissolution test.

Table (1) Indicates amount of dissolved tablets at times.

Time (hours)	Amount dissolved
1	not more than 28%
2	between 20% and 40%
4	between 35% and 60%
6	between 50% and 80%
10	not less than 65%

Data analysis

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate equation (Eq.) (1) describes the systems where the drug release rate is independent of its concentration (15). The first order Eq. (2) describes the release from system where release rate is concentration dependent (16). Higuchi (17) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian

diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (18).

$$C_o = k_o t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time .

$$\log C = \log C_0 - Kt / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$f\,t = Q = KH \times t_{1/2} \quad (3)$$

Where, KH is the Higuchi dissolution constant.

$$Q0_{1/3} - Qt_{1/3} = KHC\,t \quad (4)$$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation. The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixson-crowell cube root law).

Mechanism of drug release

Korsmeyer (19) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model: *n*

$$Mt / M\infty = Kt^{n} \quad (5)$$

Where Mt / M∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices.

Table 2: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS AND DISCUSSION

The result of the calibration curve show in figure (1) give high linearity and regression coefficient equal (0.995) this indicate the validity of UV spectrophotometer in this study.

Table (3) Show the main absorbance value against its concentration.

Number of sample	Concentration (mg/ml)	Absorbance
1	0. 01	0.0207
2	0.03	0.0489
3	0.08	0.1391
4	0.16	0.2966
5	0.18	0.3381
6	0.22	0.4434
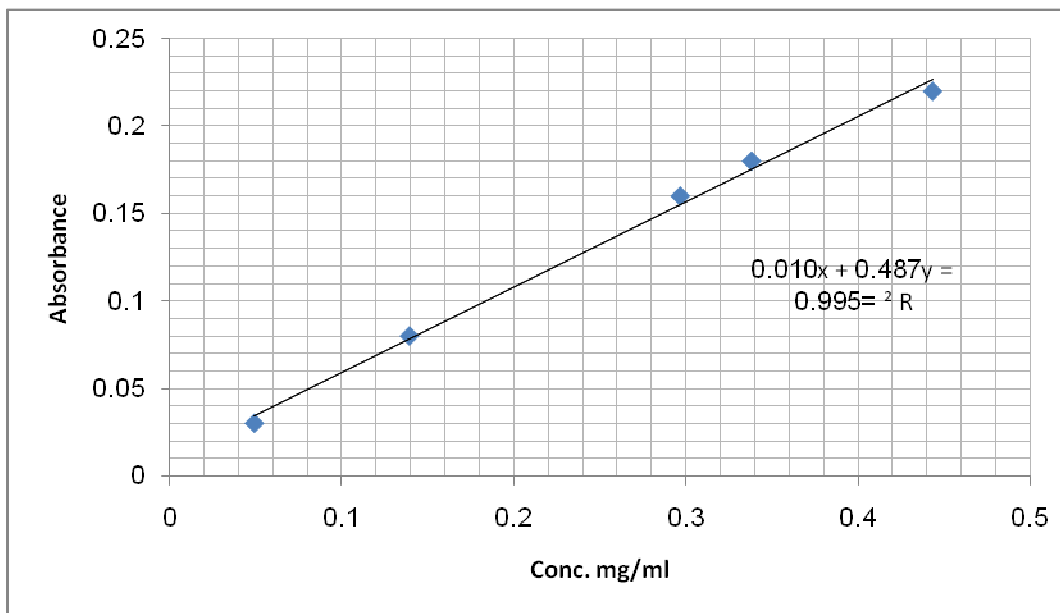
Figure (1) Calibration curve of diclofenac sodium

Weight variation was within limit of ±7.5% and mean drug content value obtained was 102.07 (S.D = 0.011) which was found satisfactorily within limits 90 – 110%.

In-vitro dissolution studies and duration of release

For the controlled release under investigation, the release should follow three steps. First step is the penetration of the dissolution medium in the tablet matrix (hydration). Second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet, to the surrounding dissolution medium (20).

Table (5)*: Illustrate the dissolution profile for diclofenac sodium for three different batches

B.N	% dissolution profile test		
Time	S0257	S0005	S0016
1	3.49	3.21	3.2
2	6.14	6.71	5.58
3	19.69	13.53	15.37
4	24.88	18.71	20.61
5	36.35	26.97	26.63
6	40.98	34.68	35.20
7	47.14	49.58	47.27
8	52.80	58.93	57.32
9	69.99	71.15	70.09
10	81.35	80.86	80.58
11	86.01	88.48	89.09
12	96.71	96.02	97.39

From the dissolution profile data, after 12hr.the% cumulative amount of drug release was 96.71%±0.14%, 96.02%±0.14% and 97.39%± 0.14% for the three batches respectively from 100 mg preloaded matrix.

The data described good dissolution behaviour and that seen in the figure (2) below.

The data obtained from dissolution profile was fitted for zero order , first order , higuchi model , Hixson-crowll model and korsmeyer- peppas equation . the regression coefficient (r^2) have the highest value with zero order , higuchi model and korsmeyer-peppas as shown in table (6).
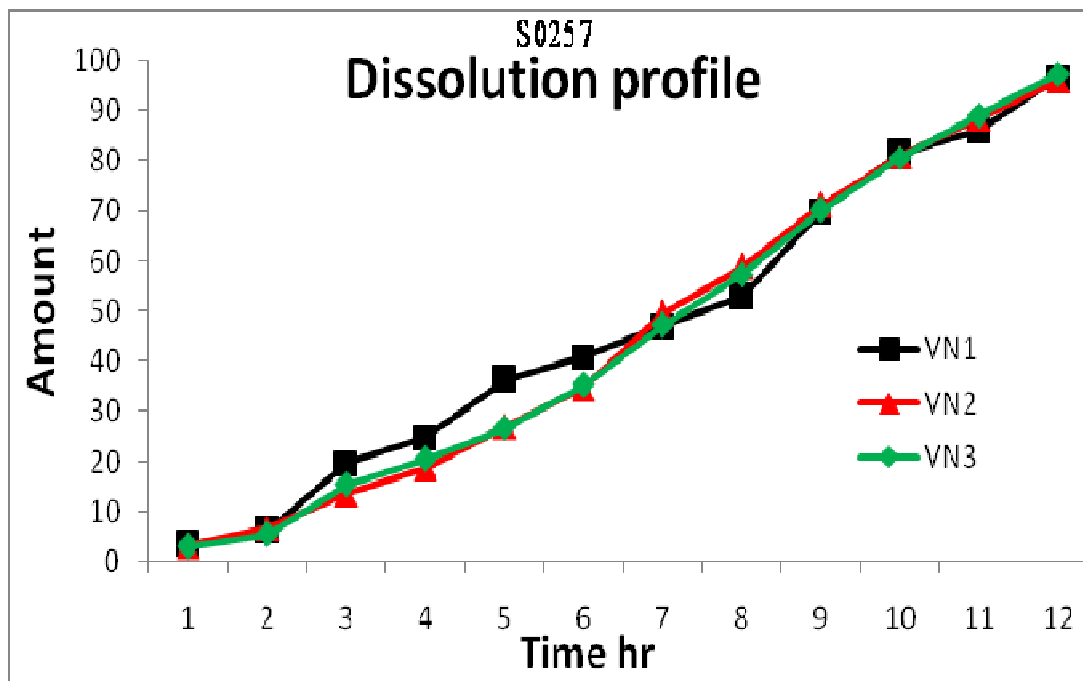

Figure (2): Illustrate the dissolution profile for three different batches of diclofenac sodium.
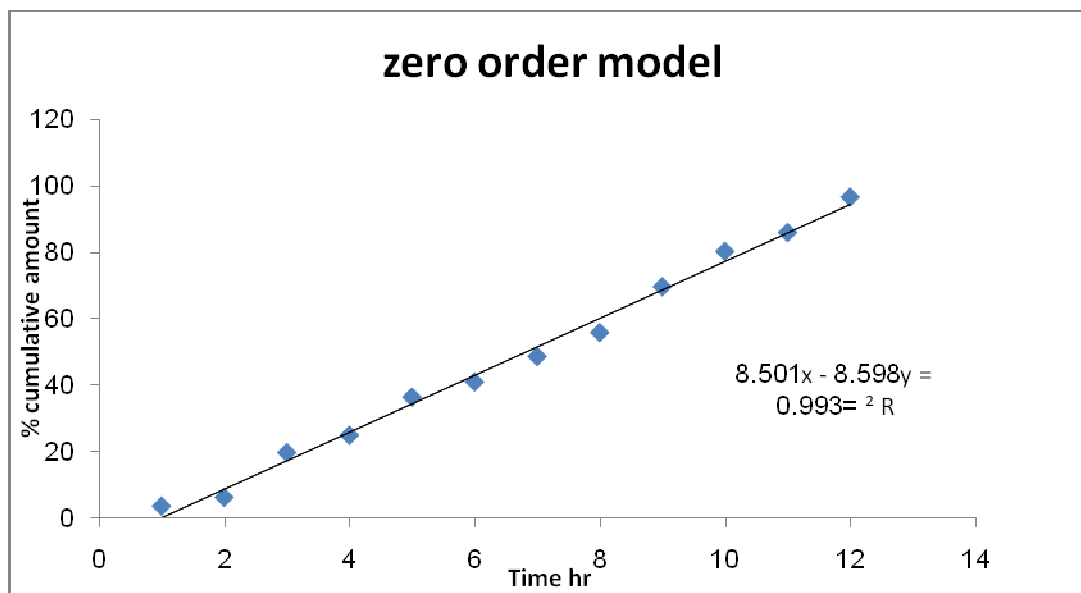

Figure (3): Zero order release model of diclofenac sodium SR.

Drug Release Kinetic.

Table (6)*: Illustrate the kinetic parameters for diclofenac sodium SR. (100mg).

Model	Parameters	B.N/ S0257	B.N/ S0005	B.N/ S0016
Zero order	r^2	0.993	0.99	0.990
	K_0	8.59	9.04	9.06
First order	r^2	0.793	0.839	0.783
	K_1	0.244	0.248	0.26
Higuchi	r^2	0.957	0.944	0.942
	K_H	39.04	40.79	40.78
Hixson-Crowell	r^2	0.899	0.918	0.90
	K_{HC}	0.25	0.26	0.266
Korsmeyer-peppas	r^2	0.968	0.992	0.984
	K_{KP}	3.36	3.36	3.40
	n	0.88	0.91	0.90

In zero order model figure (3) show the highest value of (r^2) equal 0.993 indicate that zero order is the actual model through which the drug is released and that the erosion(case II transport) has greater role in drug release [21] .

In higuchi model figure (4), the (r^2) value equal 0.957 which also indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion. [22, 23].
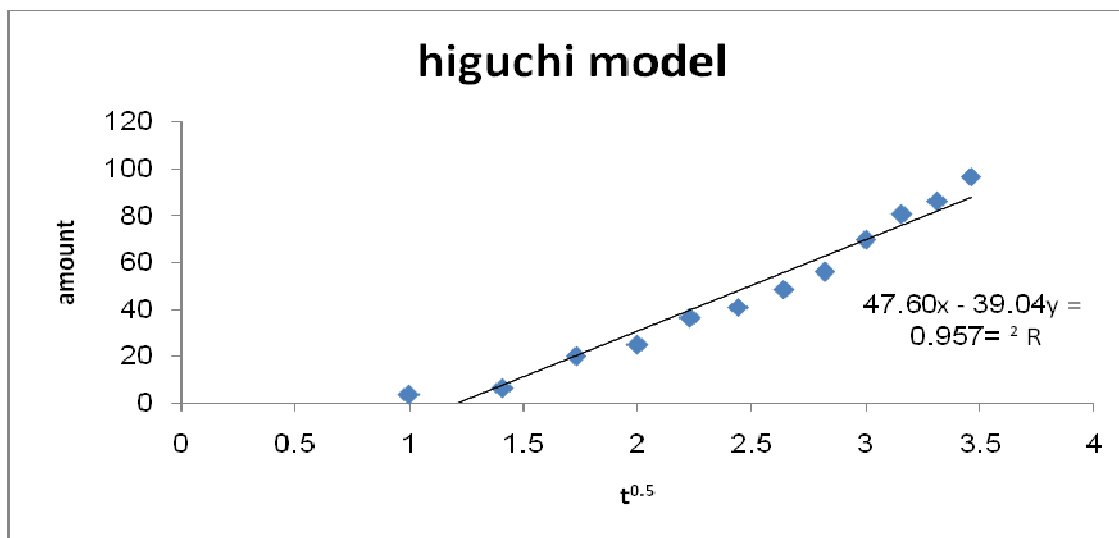
Figure (4): Higuchi release model of diclofenac sodium SR.

In Hixson-Crowell model Figure (5) the applicability of data (r^2) is equal 0.899 which indicate a little change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time (23). Where the surface area effect in the drug dissolution and release from the matrix.
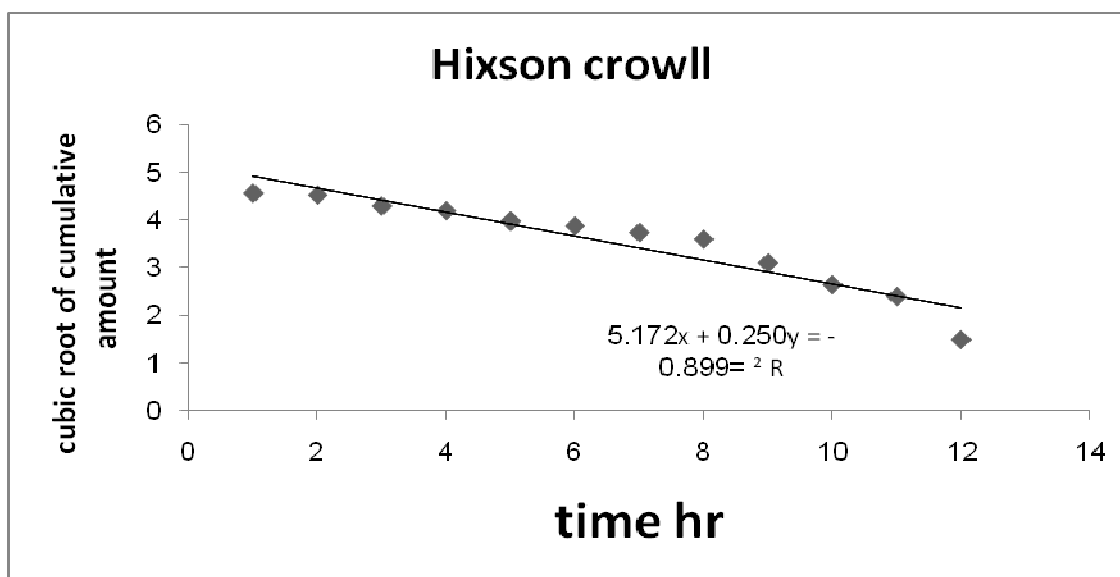

Figure (5) show Hixson-Crowll release model of diclofenac sodium SR.

The release data also fitted with korsmeyer-peppas equation figure (6) by incorporating the first 60% of release data mechanism of release can be indicated according to Korsmeyer where (n) is the release exponent, indicative of mechanism of drug release.

Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in

hydrophilic glassy polymers which swell in water or biological fluids.This term also includes polymer disentanglement and erosion (24).

The value of (r^2) equal 0.965 and indicated combined effect of diffusion and erosion mechanisms for controlled drug release (25). The diffusional exponent (n) values of three batches are (0.88 , 0.91 and 0.90) for slab geometric tablets indicate anomalous transport mechanism which mean combination of two processes diffusion and erosion.
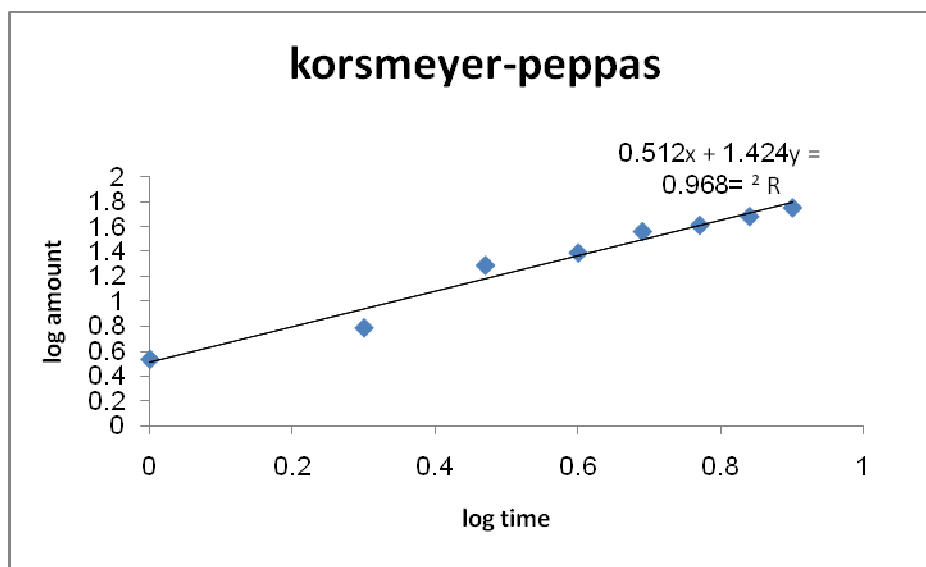

Figure (6): korsmeyer-peppas model of diclofenac sodium SR

According to above discussion it is clear that the predominant kinetic model that describe the drug release from matrix system is zero order model because it has the highest (r^2) values .so the zero kinetic constant (k_0) is applied as release rate constant for all three batches which calculated as mean of three batches are equal 8.87 mg/hr $\pm$ 0.26.

Also, the higuchi model has high (r^2) value and describe drug release from matrix system . the korsmeyer-peppas equation explain why the zero order and higuchi models got high (r^2) values. In korsmeyer-peppas equation when the exponent 'n' takes the value of n =1, the case corresponds to the zero-order kinetics. For slabs, the mechanism that creates the zero-order release is known among polymer scientist as case-II transport (erosion) .(26), When n= 0.5 the equation of korsmeyer-peppas described special state of higuchi model and the diffusion mechanism of release .

In the experimental data on korsmeyer-peppas equation (n) values of the three brand batches describe anomalous release , that is mean two mechanisms diffusion and erosion have been occurred, so the two model have high (r^2) values, but the zero order has higher value than higuchi ,so the erosion is the predominant mechanism of release.

The first order has the lowest (r^2) value, so this model don't describe the drug release and the dissolution data not applicable in this model as shown in figure no 7.
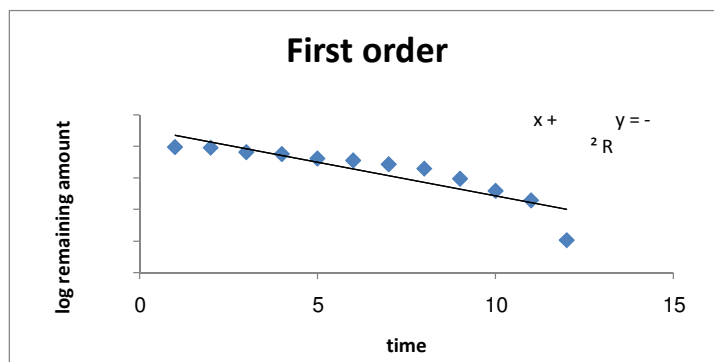
Figure (7): First order model of diclofenac sodium SR.

CONCLUSION

Diclofenac sodium sustained release matrix tablet was release kinetics of this drug correspond best to zero order model and drug release mechanism as per n value of Korsmeyer & Peppas (Power law) cannot be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion.

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