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# Prediction of *in vitro* Drug Release Mechanisms from Extended Release Matrix Tablets using SSR/$R^2$ Technique

[1]J. Singh, [1]S. Gupta and [2]H. Kaur
[1]Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147 002, India
[2]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Mohali, India

*Corresponding Author: Harmeet Kaur, Department of Pharmacy, PDM College of Pharmacy, Srai Aurangabad, Bahadurgarh, India*

## ABSTRACT

Drug release from polymers may be erosion or diffusion based or combination of these processes. Various equations and models are available for relating drug release. Most of the decisions are made on basis of similarity of original and predicted release profiles (predicted by fitting release data in various models or equations). In this study, decision for release pattern has been made on basis of SSR/$R^2$ for model drug ofloxacin from laboratory developed Extended Release (ER) matrix tablets. Three batches A, B, C having HPMC, sodium alginate and 50:50% mixture of HPMC:sodium alginate were prepared. The USP Dissolution apparatus 2 was used for ofloxacin release and swelling-erosion studies of different batches in SGF, buffer of pH 6.2 and SIF. The batch C, ofloxacin matrix tablet composition was finalised on basis of <30% release within 1 h in SGF, >85% release upto 8 h in SIF and conformity to shape of profile within 1-7 h dissolution in buffer of pH 6.2. Instead of use of SSR and $R^2$ on individual basis, SSR/$R^2$ expressed ofloxacin release mechanisms in good agreement to physically observed swelling-erosion behaviors of matrix tablets in all pH conditions.

**Key words:** Erosion-swelling, regression, HPMC, sodium alginate, equations, ofloxacin

## INTRODUCTION

The swelling, diffusion and erosion have been used to predict the release behaviour from swellable matrix systems based upon hydroxypropylmethyl cellulose (Colombo *et al*., 1995). The molecular weight of polymer, equilibrium water content in the polymer, water-polymer interactions and diffusion coefficient of water, effect of drug: hydroxypropyl methyl cellulose ratio, drug and polymer particle sizes, compaction pressure, absence and presence of lubricants, water transport, polymer chain disentanglement and viscosity grades of polymers determine the mechanism and rate of drug release from Extended Release (ER) matrix tablets (Narasimhan and Peppas, 1997; Ford *et al*., 1985a-c). Various models and equations like zero-order (Eq. 1), first-order (Eq. 2), Higuchi (Eq. 3), Hixson-Crowell (Eq. 4), Weibull (Eq. 6 and 7), Baker-Lonsdale, Korsmeyer-Peppas (Eq. 8), quadratic, logistic, Gompertz and Hopfenberg models have been used after linearization to predict mechanisms of drug release (Piotrovskii, 1987; Polli *et al*., 1997; Costa and Lobo, 2001). The $R^2$ value has been used by various workers as goodness of fit parameter (Gao *et al*., 1995; Mesnukul and Phaechamud, 2009). Even some worker have used sum of squares of residuals (SSR)

and $R^2$ as final criteria (Thakkar *et al.*, 2009). Gohel and coworkers have shown that deviation predicted on basis of SSR, F and $R^2$ as individual entities may result in error upto 16% from ideal release (Gohel *et al.*, 2000). In actual this $R^2$ cannot be considered as true indicator of goodness of fit statistics in either linear or non-linear relationships. The $R^2$ mainly reports variability in the data that is accounted for the model and its calculation involves use of mean value. So with increasing number of data points the value of $R^2$ goes on increasing and that's why it is not a good parameter for goodness of fit calculations solely. The various models applied for release behavior prediction have been explained here as:

The zero-order is expressed as:

$$Q_t = Q_0 - k_0 t \quad (1)$$

where, $Q_t$ is amount of drug released or dissolved at time t, $Q_0$ is amount of drug released or dissolved at time $t = 0$, $k_0$ is zero order release rate constant. This is ideal behavior for a dosage form and leads to minimum fluctuations in drug plasma levels. This is expressed mainly by osmotic pump systems.

The drug release is said to be of first-order if it obeys the following equation:

$$\ln Q_t = \ln Q_0 - k_1 t \quad (2)$$

where, $Q_t$ is amount of drug released or dissolved at time t, $Q_0$ is amount of drug released or dissolved at time $t = 0$, $k_1$ is first-order release rate constant. This behavior is exhibited by most of the pharmaceutical dosage forms and the drug release in such cases decreases with time. The drug release from swellable matrix systems may show different relationships with time. According to Higuchi relationship, the amount of drug released per unit surface area is proportional to the square root of time. This equation explains diffusional release rate as indicated below:

$$Q_t = k_H t^{1/2} \quad (3)$$

where, $k_H$ is Higuchion rate constant, $Q_t$ has same meaning as defined earlier. Hydrophilic matrices and transdermal systems mainly exhibit Higuchi type drug release (Heng *et al.*, 2001).

According to Hixson-Crowell model, the surface area of a regular or uniform sized particle is proportional to the two-third power of its volume. Thus, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the weight of the particles. This may be written as:

$$W_0^{1/3} - W_t^{1/3} = k_s t \quad (4)$$

where, $k_s$ is constant incorporating surface-volume proportionality and has dimensions of the cube root of weight per unit time, $W_0$ is initial amount of drug in dosage form and $W_t$ is amount remaining in dosage form at time t. This equation is applicable when initial geometric shape of the tablet is maintained. The equation upon rearrangement after dividing with $W_0^{1/3}$ yields

$$(1 - f_t)^{1/3} = 1 - k_\beta t \quad (5)$$

where, $k_p$ is constant and $f_t = 1-(W_t/W_0)$ represents the fraction of drug dissolved at time t (Cobby *et al.*, 1974).

Weibull equation (Costa and Lobo, 2001) can be written as follows:

$$M = 1-\exp[-(t-T_t)^b/a] \quad (6)$$

where, M is the accumulated fraction of the drug in solution at time t, a is the time scale of the process, $T_t$ is the lag time before the start of release of the drug, b is the shape parameter which characterizes the curve as exponential when b = 1, sigmoidal when b > 1 and parabolic when b<1. The equation may be converted to straight line equation by log transformation as indicated:

$$\text{Log}\,[-\ln(1-M)] = b \log(t - T_i) - \log a \quad (7)$$

Korsmeyer and Peppas (1984) and Ritger and Peppas (1987) developed an empirical equation to analyze both Fickian and non-Fickian release of drug from swelling as well as non-swelling polymeric delivery systems. The equation is represented as under:

$$M_t / M_\infty = k\, t^n \quad (8)$$

where, $M_t/M_\infty$ is fraction of drug released at time t, n is diffusional exponent and is indicator of the mechanism of transport of drug through the polymer, k is kinetic constant (having units of $t^{-n}$) incorporating structural and geometric characteristics of the delivery system. The release exponent n = 0.5 and 1.0 for Fickian and non-Fickian diffusion from slab and n = 0.45 and 0.89 for Fickian and non-Fickian diffusion from cylinders, respectively. A value of n = 1 actually means that, the drug release is independent of time regardless of the geometry. The model is applicable in those swellable systems where swelling is not > 25% of its original volume. This equation can be used to analyze only first 60% of release, regardless of geometric shapes. According to Ford *et al.* (1987) n = 0.5 for $(\text{time})^{1/2}$ kinetics and n = 1 for zero-order release.

Another equation for drug release by heterogeneous erosion from matrices is known as Hopfenberg equation and is defined as:

$$M_t/M_\infty = 1 - [1 - k_0\, t/C_0\, a_0]^n \quad (9)$$

where, $M_t$ is the amount of drug released at time t, $M_\infty$ is the amount of drug released at infinite time or when dosage form gets exhausted in total and $k_0$ is the erosion rate constant. $C_0$ is the initial concentration of drug in the matrix and $a_0$ is the initial radius of sphere or cylinder or half the thickness of slab and corresponding values of n are 1, 2 and 3 for slab, cylinder and sphere (Costa and Lobo, 2001), respectively.

As the release mechanism prediction is common practice in extended release matrix tablet formulations, the model drug ofloxacin has been chosen as it is soluble in aqueous solutions between pH 2-5, sparingly to slightly soluble in aqueous solutions at pH 7 and freely soluble at pH>9 at room temperature (Lee and Robinson, 1987). Ofloxacin being rapidly and uniformly absorbed after oral administration and having bioavailability of about 100% is a good candidate for the development of oral extended release dosage form in this study. The extended drug release products of freely soluble and highly permeable drugs present themselves as promising candidates

for establishing IVIVC of their performance, since they represent controlled dissolution rate properties. Further, as per AAPS/FDA (Carrico, 1996), dissolution is a sensitive and reliable surrogate for bioequivalence testing. In addition the dissolution specification ought to have minimum three time points: (1) early to exclude dose-dumping, (2) at least one point to ensure compliance with shape and (3) one point to assure that most of the labelled dose has been released. The aim of the study was to rectify the use of conventional regression parameters (SSR, $R^2$) for estimating drug release mechanisms by modifying their application technique as SSR/$R^2$, which is not best but at least can reduce error in predictions rising due to use of these parameters individually in many academic institutes.

## MATERIALS AND METHODS

**Materials:** Ofloxacin (assay 99.8%) was provided by Ranbaxy, New Delhi, India. Hydroxypropylmethyl cellulose (3000 cps) and sodium alginate were purchased from S.D. Fine-chem. Ltd., Mumbai, India. Simulated gastric fluid (SGF) without enzyme of pH 1.2, Simulated Intestinal Fluid (SIF) without enzymes of pH 7.5±0.1 and phosphate buffer of pH 6.2 were prepared as per USPXXIII. All the chemicals used were of AR grade.

Different equipment like hand operated tableting machine, Sieves (ASTM No. 10, 16 and 22) and hardness tester (Pfizer type)- Hicon, New Delhi, India, Tablet friability tester (Roche type)-Tab. machines, Mumbai, India and IR Moisture balance of Indian Equipment Corporation, Mumbai, India were used in manufacturing of granules, tablets and as quality control tools at different stages. For the analysis purpose the Beckman UV-visible spectrophotometer, USA and for dissolution/swelling-erosion studies the dissolution apparatus of USP type 2, make Remi Electronics, India were used. The temperature of lab was maintained at 27±2°C throughout the experimentation (June-July 2009).

**Tablet preparation and quality control:** The ofloxacin extended release matrix tablets were prepared by mixing appropriate amounts of different ingredients in mortar as shown in Table 1, followed by granulation. The drying temperature during granulation was 60±2°C. The granules were compressed into final 9 mm beveled, flat face tablets using hand operated punching machine. Various quality control tests were carried out on granules and tablets in order to assure the quality at various stages and standardization of ofloxacin matrix tablets. Three lots were prepared for each of the batches A, B and C. All the tablets were prepared on the same day to minimize variations. The samples for testing were taken from pooled lots of each batch. The granules and matrix tablets were characterized with respect to various quality control tests like angle of repose, moisture content of granules, weight variation, friability and hardness.

Table 1: The composition of ofloxacin matrix tablets

| | Batch | | |
|---|---|---|---|
| Ingredients (mg) | A | B | C |
| Ofloxacin | 300 | 300 | 300 |
| HPMC | 120 | -- | 60 |
| Sodium alginate | -- | 120 | 60 |
| Magnesium stearate | 3 | 3 | 3 |
| Talc | 2 | 2 | 2 |
| Total weight | 425 | 425 | 425 |

**Release of ofloxacin from matrix tablets:** The USP apparatus 2 (paddle type) was used to test ofloxacin release (12 units per dissolution media) from matrix tablets. The ionic strength of all dissolution medium were adjusted to 0.15 M by using NaCl (Kostemicz *et al*., 2002). The dissolution medium were heated to 45°C by gentle stirring and immediately filtered under vacuum through membrane filter (0.45 μm). Vigorous stirring was continued under vacuum for 5 min to deaerate all medium. Each time dissolution medium were maintained at 37±0.5°C and stirred at 50±5 rpm. A aliquot (2 mL) sample were withdrawn at different intervals upto 8 h and filtered through membrane filter of 0.45 μm aperture. The volume of medium was replenished with an equal volume of fresh medium. The absorbance of drug in each sample was determined spectro-photometrically at absorbance maxima (293 nm for SGF, 286 nm in buffer of pH 6.2 and 288 nm in SIF) directly or after appropriate dilutions with dissolution medium. The concentration of drug was determined by using weighted regression equation generated in laboratory. The selection criteria proposed was (1) <30% release (no dose dumping) of ofloxacin in SGF upto 1 h (2) >85% release (almost complete release) of ofloxacin in SIF upto last time point, i.e., 8 h in our case and (3) compliance with the shape of dissolution profile, i.e., no bulges or abrupt changes for 1-7 h especially in buffer of pH 6.2.

**Swelling-eroding of matrix tablets:** The method reported by Bettini *et al*. (1994) was modified to determine radial swelling (6 units per dissolution media). The cylindrical matrix tablets were locked in between transparent glass plates. The transparency of glass plates facilitated measurement of increase in diameter of matrix tablets and measurement of hike in releasing area during swelling. The locked matrix tablets assembly were put into vessels of USP XXIII dissolution apparatus 2 having 900 mL medium in each vessel and set at 50±5 pm while maintaining at 37±0.5°C. The device containing locked matrix tablets were removed at fixed time intervals to study the swelling phenomenon. The concentrations of drug in simulated gastric fluid without enzymes (SGF), buffer of pH 6.2 and simulated intestinal fluid (SIF) were measured spectrophotometrically at 293, 286 and 288 nm, respectively.

**Mechanism of ofloxacin release from matrix tablets:** The mechanism of drug release used here is predicted by using various release models, e.g., zero-order, first-order, second-order, Higuchi, Hixson-Crowell, Baker-Lonsdale, Korsmeyer-Peppas, Hopfenberg, Weibull, analogues of Korsmeyer-Peppas models, Gompertz and others like quadratic equations, logistic and polynomial equations. The models were transformed into straight-line equations and the best fitness of the model was chosen on the basis of ratio of $R^2$ and SSR instead of using these individually. This is general consideration that models expressing $R^2 \cong 1.0$ always show least value of SSR or vice-versa, but this may not be case in actual as $R^2$ measures the proportion of the variation of the observations around the mean that is explained by the fitted regression model and no variation tells that all of the variation is explained by the mean. In 1991 Casualty Actuarial Society Forum, D. Lee Barclay wrote a statistical note on trend factors: the meaning of r-squared. Through, simple graphical examples. Barclay showed that the coefficient of variation $R^2$ is, by itself, a poor measure of goodness-of-fit (Barclay, 1991).

The SSR do not rely on mean value instead it measures the difference between actual and model predicted values. But in linear equations we have to give weightage to both, so co-use of both as $SSR/R^2$ was proposed in this study. The model showing best SSR and $R^2$ value will exhibit overall lowest $SSR/R^2$ value.

## RESULTS AND DISCUSSION

**Quality characterization of granules and matrix tablets:** The angle of repose of granules indicated good flow properties of granules for all the three batches. The moisture content was also found to be <3.0% in all cases. The weight variation and friability of matrix tablets were found to be <5.0 and <1.0% for all the three batches respectively (Table 2).

**Release of ofloxacin from matrix tablets:** Selection criteria in our study was on the basis of <30% release in SGF during first hour of release studies (for knocking out possibilities of dose dumping), >85% in SIF upto last time point (8 h in this study) and conformity to the shape of profile for in between time i.e., 1-7 h, especially in buffer of pH 6.2.

In reference to Fig. 1, batch A satisfied only single condition of the selection criteria, i.e., <30% release in SGF (no dose dumping) but not >85% release in SIF, hence batch A was rejected.

Batch B also satisfied only single condition of the selection criteria i.e., >85% release of ofloxacin in SIF but not <30% release in SGF, so batch B was also rejected.

Only batch C satisfied both conditions of the Carrico (1996), i.e., <30% release in SGF (no dose dumping) and >85% release of ofloxacin in SIF while maintaining smooth release for in between time points in buffer of pH 6.2. This is the similar criteria as specified by Cartwright and Matthews (1994) for bioequivalence studies of modified oral dosage formulations during approval. Therefore, batch C was finalised as accepted batch on basis of release studies.

**Swelling-eroding of matrix tablets:** The area vs. time plot (Fig. 2) revealed that release of ofloxacin from batch A matrix tablets was erosion based in all the three media, but rapid erosion has been observed in SGF and slow erosion in SIF and buffer of pH 6.2.

Release of ofloxacin from batch B was of swelling type in SGF and erosion type in buffer of pH 6.2 and SIF.

For the selected batch C, it was slow swelling type in SGF and slow erosion type in SIF and buffer of pH 6.2.

All these swelling-erosions of matrix tablets acted as physical observations and used as correlations between actual physical observations and predicted mechanisms of drug release from matrix tablets.

**Mechanism of ofloxacin release from matrix tablets:** The SSR and $R^2$ values have been given in Table 3 for different models or equations after linearization. In SGF, the minimum SSR/$R^2$ is

Table 2: The quality characteristics of ofloxacin granules and matrix tablets

| | Batch (n = 3) | | |
|---|---|---|---|
| Characteristics | A | B | C |
| **Granules** | | | |
| Angle of repose (Funnel method) | 29° | 31° | 27° |
| Moisture (%)-IR moisture balance | 2.2 | 2.9 | 1.9 |
| **Matrix tablets** | | | |
| Weight variation (%) (n = 20) | ±3.0 | ±4.0 | ±2.0 |
| Friability (%)-Roche friabilator (n = 20) | 0.206 | 0.109 | 0.203 |
| Hardness (kg $cm^{-2}$)-Pfizer hardness tester (n = 5) | 11.5 | 15.0 | 12.0 |

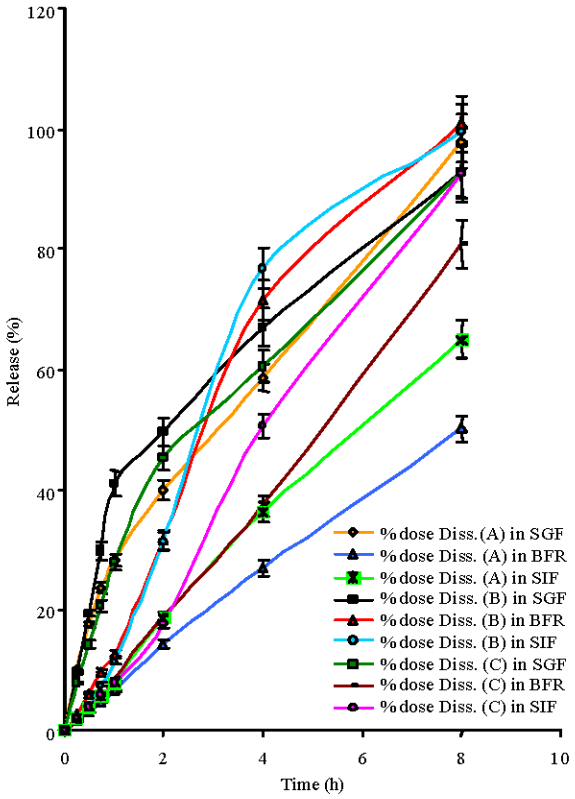


Fig. 1: Dissolution release profiles of batch A, B and C matrix tablets of ofloxacin

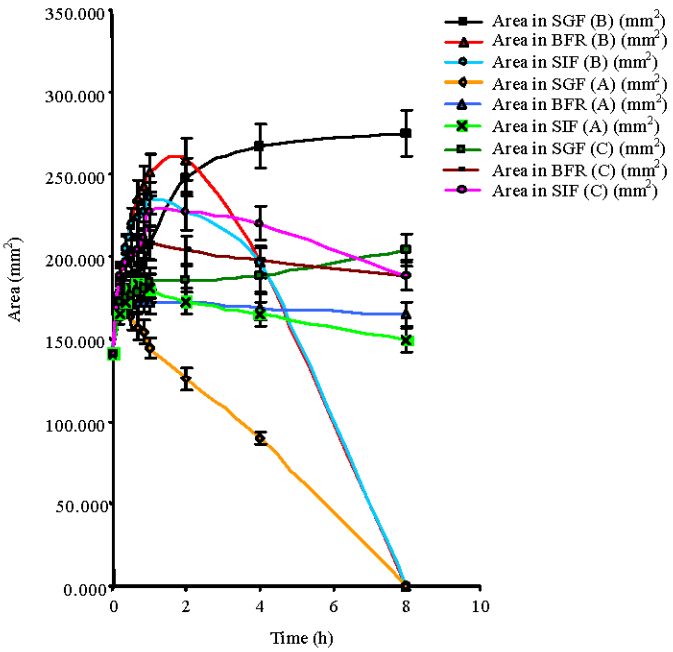


Fig. 2: Radial swelling-erosion profiles of batch A, B and C matrix tablets

Table 3: Values of SSR and $R^2$ obtained after application of various models and equations

| | Batch | | | | | |
|---|---|---|---|---|---|---|
| | A | | B | | C | |
| Results | SSR | $R^2$ | SSR | $R^2$ | SSR | $R^2$ |
| **SGF** | | | | | | |
| Zero | 113.684 | 0.987 | 364.319 | 0.909 | 222.742 | 0.921 |
| First | 9615.120 | 0.625 | 3773.382 | 0.459 | 2699.209 | 0.543 |
| Higuchi | 352.372 | 0.972 | 31.307 | 0.992 | 49.757 | 0.982 |
| Hixson | 1493.641 | 0.957 | 195.000 | 0.958 | **134.311** | **0.951** |
| Weibull | 448.956 | 0.879 | 86.449* | 0.785* | **135.139** | **0.718** |
| Korsmeyer | 983.466 | 0.554 | 422.443 | 0.661 | 508.456 | 0.631 |
| Hopfenberg | 35740.899 | 0.766 | 821.252 | 0.774 | 471.160 | 0.790 |
| **Buffer pH 6.2** | | | | | | |
| Zero | 46.561 | 0.936 | 45.339 | 0.995 | 26.030 | 0.993 |
| First | 903.634 | 0.730 | 15880.378 | 0.793 | 2909.833 | 0.848 |
| Higuchi | 49.001 | 0.934 | 1089.037 | 0.858 | 469.348 | 0.868 |
| Hixson | 37.888 | 0.946 | 943.821 | 0.946 | 97.630 | 0.543 |
| Weibull | 254.613 | 0.599 | 265.715 | 0.821 | 81.147 | 0.698 |
| Korsmeyer | 484.731 | 0.957 | 2039.602 | 0.752 | 194.286 | 0.654 |
| Hopfenberg | 124.517 | 0.797 | 20906.353 | 0.536 | 1591.264 | 0.635 |
| **In SIF** | | | | | | |
| Zero | 11.143 | 0.992 | 69.202 | 0.992 | 7.826 | 0.997 |
| First | 8401.728 | 0.346 | 101648.955 | 0.430 | 14794.217 | 0.359 |
| Higuchi | 152.597 | 0.888 | 1228.789 | 0.946 | 259.098 | 0.883 |
| Hixson | 17.904 | 0.989 | 1536.076 | 0.925 | 29.953 | 0.988 |
| Weibull | 621.263 | 0.188 | 1866.019 | 0.319 | 1054.384 | 0.191 |
| Korsmeyer | 684.954 | 0.175 | 4267.082 | 0.946 | 1199.819 | 0.174 |
| Hopfenberg | 412.959 | 0.685 | 40773.998 | 0.501 | 778.817 | 0.666 |

The bold values for batch C in SGF are having almost similar SSR values but remarkably different $R^2$ values

for zero-order equation indicating erosion based ofloxacin release from batch A matrix tablets and Higuchi (swelling) type from batch B and C matrix tablets in SGF. This prediction was similar to the one obtained from the swelling-erosion graph (Fig. 2).

In buffer of pH 6.2, minimum SSR/$R^2$ was found for Hixson-Crowell model, indicating erosion based release from batch A tablets. This was further proved from the value of next minimum SSR/$R^2$ which was in case of zero-order equation. For batch B and C, again release was zero-order (erosion) as proved from minimum SSR/$R^2$ and swelling-erosion graph.

In SIF, for all the batches, the zero-order (erosion) equation was leading mechanism of ofloxacin release as explained from minimum SSR/$R^2$ values and radial-swelling erosion graph.

Furthermore, the value of SSR for batch B in SGF marked with asterisk sign is second-least value of SSR (86.449) after 31.307 that is first-least in the corresponding column, but the value of $R^2$ is not second-highest, instead it is fourth-highest, proving the fact that models having highest value of $R^2$ may not have least SSR value always or best fit. This proves the statement of (Barclay, 1991). Similarly Kletting *et al.* (2009) also criticized the conventional use of SSR and $R^2$. No doubt, if we relate the mechanisms on basis of either SSR or $R^2$ basis individually, we will get different orders or category lists of mechanisms for a single batch in single pH condition. So, use of either of these parameters individually in model based release predictions (Soni and Chotai,

2010) is not recommended, instead these shall be used in combined form to describe the best fit as these both are applicable for regression methods. The use of simple parameters sometime become non-descriptive as it may show somewhere incompatible mechanisms happening together in the same dosage formulation, i.e., occurance of time dependent (Higuchi release) and time independent (zero-order) releases simultaneously for the same drug (Obitte *et al*., 2010).

## CONCLUSION

The SSR/$R^2$ is better than relying only on $R^2$ as goodness of fit value and this shall also not be considered that equation having best $R^2$ value always have best SSR value. These both if used in some relationship may give more genuine justification about choice of equations, but individually these may be misleading in formulation development. Now the days more efficient goodness of fit parameters are available for concluding the results, but this attempt has been not taken because use of $R^2$ is still prevailing at many formulation development places. Batch C composition (300 mg ofloxacin, 60 mg HPMC, 60 mg sodium alginate) complied the extended release matrix tablet profile criteria in different pH conditions in-vitro, hence finalized as final product.

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