IJBPAS, July, 2021, 10(7): 2307-2320

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

# DEXIBUPROFEN MODIFIED RELEASE GEL EVALUATION OF *IN VITRO* PROFILE AND ITS PHARMACOKINETIC PARAMETERS USING VARIOUS MATHEMATIC MODELS

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**Received 6th Aug. 2020; Revised 25th Sept. 2020; Accepted 26th Oct. 2020; Available online 1st July 2021**

https://doi.org/10.31032/IJBPAS/2021/10.7.5549

## ABSTRACT

The aim of the present work is to study the *in vitro* diffusion profile, predict pharmacokinetic parameters and drug release mechanism from the Dexibuprofen loaded modified gel by using different mathematical models. Dexibuprofen loaded novel modified gel was formulated by prototype using Chitosan and Sepineo P 600 as polymers. The *in vitro* diffusion release study was performed by using Franz diffusion cell apparatus and samples withdrawn upto 300 minutes at a periodic interval. The *in vitro* diffusion release data were collected, correlated and predicted to determine zero order, first order, Higuchi, Korsmeyer Peppas and Hixson-Crowell with different mathematical models. The selected formulated topical gels (FR3, FR10 and FR18) were compared with the marketed product for drug release, release kinetics and mechanism. The criterion for the best fit model was based on the highest degree of correlation coefficient of drug release profile of Dexibuprofen loaded novel modified gel. All the three formulated gels shown an excellent release, but the FR18 has released 98.78% of

drug at the end 300 minutes when compared with other formulations and marketed product. All the topical gels followed zero order release kinetics. All the three formulated, FR3, FR10 and FR18, topical gels showed better pharmacokinetic parameters when compared with the marketed product. From the findings, it is concluded that the drug release pattern of Dexibuprofen FR 18 loaded modified gel obeyed Korsmeyer Peppas power law which is Super case II transport type of drug release mechanism.

**Keywords: Dexibuprofen, Pharmacokinetic parameters, Franz Diffusion Cell, Release Order of Kinetics, Drug Release Mechanisms, Sepineo P 600**

## INTRODUCTION

Topical gels system can deliver more amounts of drug at localized area when compared with other drug delivery system. It offers greater advantages like overcoming of first pass metabolism and maximum amount of drug reaches systemic circulation leads to improved local pharmacological action. Generally topical gels provide better pharmacological actions against local analgesic, anti-inflammatory and anaesthesia when compared with oral drug delivery system **[1]**. Topical gel avoids gastric irritation and degradations due to metabolism, which are caused when administered orally. Main disadvantage of topical dosage forms is permeation of drugs through skin. The drug release is based on factors like physicochemical properties of the base and drug used in the topical dosage form. It can be overcome by using permeation enhancers. The topical dosage form properties like homogeneity, pH, skin irritation, viscosity and coefficient of spreading are evaluated **[2]**.

Diffusion and drug release mechanisms play a vital role in oral, modified release, ointments, creams and other semisolid dosage forms for controlled delivery of drugs. Both are applicable in designing and optimizing of targeted drug delivery systems, controlled release delayed and sustained release dosage forms **[3].** Diffusion is process in which quantity of drug enters in to medium with respect to time under experimental conditions of surface tension, temperature and composition of solvent **[4]**. Whenever the drug particles reach gastro-intestine fluid, immediately it will form a diffusion layer. In gastrointestinal system, the drug particles penetrate across the fluid to the GI membrane and reaches for circulation **[5]**. Higher the diffusion rate increased the bioavailability, which leads to maximum efficacy and confirms quality of the product **[6].** It also confirms the minimal variation in bioavailability between the batchesand maximum *in vitro – in vivo* correlation. The diffusion has to be

performed in a similar condition to the *in vivo* environment **[7]**. The following three are considered as key diffusion theories:

- Diffusion layer theory
- Penetration theory (Danckwert model)
- Interfacial barrier theory

Diffusion process is basically regulated by the affinity between the solid substance and the solvent. This process involves two steps. The first step involves the release of drug particles

from the solid matter in to the liquid layer surrounding particles surface. It is followed by the movement of drug particles to the solution from interface of solid/ liquid.

**(i) Dissolution Layer Theory**

Nernst and Brunner initially suggested dissolution layer theory, which is accepted and employed generally to depict the dissolution behaviour of drugs molecules. In this theory, it is considered that dissolution layer, thickness h cm, is immediate to the drug surface of a dissolving molecule. The formation of interface between solid and liquid is considered to be immediate for a saturated solution (Cs) of the drug particles in the diffusive layer. When the solute diffuses across the layer and reaches the solvent interface lead to an even concentration (C). The diffusion rate is regulated by dissolution of Brownian movement of the drug molecules in the dissolution layer. The rate of dissolution is performed by the dissolution of the drug particles from the diffusive layer to the bulk concentration as per the Fick's first law: **[5]**

$$\mathbf{Q = - D_f \, dc/dx}$$

where Q = quantity of drug crossing via unit surface area per time,

Df= coefficient of diffusion and

dc/dx= gradient of concentrations

When a time t, the quantity between the limit of the diffusive layer and bulk concentration, Ct.

**(ii) Danckwert's Theory**

This theory did not recognise the presence of diffusive layer but it assumes the presence of macroscopic eddies mass or packets. These eddies masses get always substituted by fresh and expose to fresh drug surface every time, hence it is also called as surface renewal theory.

**(iii) Interfacial barrier theory:**

In this theory, it can be assumed that the interface of the solid/liquid is not instantaneous because of high activation free energy barrier that is to be enclosed by the solid may dissolve. Hence, the diffusion mechanism is as similar to diffusion layer theory, with the quantity at the maximum of the diffusive layer of liquid when $Q_t$ after time t. The diffusion rate in the diffusive layer is comparatively quick in when compared with the presence of the

energy barrier, thus it is considered as the rate limiting step in the diffusion process.

**Fundamentals of drug release kinetics**

**Laws of drug release kinetics**

**Noyes-Whitney law:** Noyes-Whitney was proposed on the basic concepts of determination of drug release as:

$dQ/dt = K (Qs-Qt)$

where dQ/dt is diffusion rate of drug; K = diffusion rate constant,

Qs = quantity of drug in the diffusive layer;

Qt = quantity of the drug in the bulk solution at time t.

**Fick's law of diffusion:**

In this law, drug particles move from higher to lower concentration till it attains equilibrium and as diffusion rate increases as concentration will also increase through the membrane, thus expressed mathematically as:

$$\mathbf{dQ/dt = D.A.K_{m/w}(Q_s-Q)/h}$$

**where,**

**dQ/dt = diffusion rate, expressed in mg/ h**

**D = coefficient of diffusion, expressed in $m^2/s$,**

**A = absorbing membrane surface area, expressed in $m^2$**

**$K_{m/w}$= Partition coefficient,**

**$Q_s$– Q= difference between the drug quantity present GI fluid and plasma (mg/ ml),**

**h = thickness of the membrane, $cm^2$.**

The aim of the present work is to predict the pharmacokinetic parameters and mechanism of drug release kinetics was studied for the Dexibuprofen loaded topical gel using various mathematic models.

## METHODOLOGY

**Formulation of Dexibuprofen Loaded Novel Modified Gel**

The Dexibuprofen loaded novel modified gel was formulated using chitosan and Sepineo P 600 as polymers and other ingredients at different concentrations.. Using Dexibuprofen loaded novel modified gel *in vitro* diffusion release, prediction of various pharmacokinetic parameters and drug release mechanism were studied in the article **[8]**.

***In Vitro* Diffusion Profile Study**

*In vitro* diffusion profile was studied for the optimized formulations (FR3, FR10 and FR18) and marketed product. It was performed by using vertical Franz diffusion cell apparatus containing 0.22µm dialysis membranes. Around 200mg of formulated topical gel was weighed and placed in a synthetic dialysis membrane. Apparatus consists of donor and receptor chamber with magnetic stirrer, which is a tailor made. The donor (volume) and receptor (diffusion area) chamber can hold a maximum volume of 250 ml and 5 $cm^3$ respectively. *In vitro* diffusion profile studies **[9]**. Donor compartment was filled with sample whereas recipient compartment contained phosphate buffer (pH 7.2). Magnetic bar with teflon coating was put in recipient chamber and rotated at 50 rpm. Temperature of Franz diffusion

cell was kept at 37°C±1°C by circulating heated water in the outer jacket. Samples were removed at 0 to 5th hr while absorbance was determined at 280nm using UV spectrophotometer after suitable dilution with phosphate buffer. The amount of Dexibuprofen dissolved was determined by comparing the UV absorbance of the Sample solution with that of the Standard solution. The data analysis was performed by comparing the releasing efficiency (PE) values **[10-11]**.

**Prediction of drug permeation by mathematical models**

Many mathematical models are derived to predict the *in vitro* drug release profile of a drug. Once the Drug release profile was constructed the drug permeation can be predicted by the use of following models. The following drug release mechanisms were tried to predict.

**Zero Order Model [5]**

As per the pharmacokinetics concepts, drug release from the dosage form can be represented by the equation:

$A_0-A_t = K_0t$

$A_t= A_0 + K_0t$

$A_t$= Amount of drug released at time t,

$A_0$ = Initial Amount of drug at time t=0,

$K_0$=Rate constant for zero order kinetics, and unit is $hr^{-1}$.

Zero order kinetics is defined as the process by which drug will be released constantly from a dosage form and the drug level will be maintained at steady state in the blood till all the drug is released from the dosage form. Therefore, data of drug release kinetics derived from *invitro* drug release profile. A graph can be plotted between cumulative drug permeation *vs*. time. Therefore, zero-order rate constant (k) can be calculated from slope of the graph plotted as well as correlation coefficient ($r^2$). This will provide whether the dosage form follows zero order kinetics or not. This model was predicted in the release profile of all the six selected formulation and estimations were performed and presented in the graphical presentations **(Figure 2)**.

The graph plotted between cumulative percentages of drug permeation versus time explains that all the selected formulations has drug permeation from dosage form which follows the principle of zero order release kinetics, values ($r^2$=> 0.97).

**First order model [5]**

The drug permeation that follows first order kinetics can be represented by the following equation:

$$\mathbf{DA/dt=-K_1A}$$

$K_1$ = Rate constant first order rate constant, unit is $hr^{-1}$.

The first order of kinetics is defined as the rate of reaction is directly proportional to the concentration of drug. The first order of

kinetics follows a perfect linear model. After integrating and rearranging the above equation it can be represented as follows:

$\log A = \log A_0 - K_1 t/2.303$

$K_1$= Rate constant for first order kinetics and unit is $hr^{-1}$

$A_0$= Initial amount of the drug

A= Percentage of drug remaining at time t.

Using *in vitro* diffusion data and various mathematical equations, drug release kinetics were computed and predicted. The data were plotted between log cumulative percentages of drug remaining *vs.* time. The first order rate constant was calculated from the slope and confirmed by using correlation coefficient ($r^2$) for all the three selected formulations and marketed product. The data are provided in the graph **(Figure 3)**. The estimated correlation coefficient values are less when compared with zero order kinetics for their respective formulations.

**Higuchi model [12]**

Drug release mechanism based on diffusion and/ or diffusion from a drug delivery system. Many mathematical equations are postulated to predict the mechanism of drug release from drug delivery system. In the recent days this model is believed to be one of the generally used and highly accepted models for controlled release concepts. The Higuchi model is expressed as below in mathematical equation:

$$Q=A\sqrt{D(2A_0 - A_s) A_s t}$$

**where Q = cumulative amount of drug released over time against unit area,**

**$A_0$= initial drug concentration,**

**$A_s$= drug solubility in the medium and**

**D = diffusion coefficient of the drug in the medium.**

This relationship is valid until total depletion of the drug in the dosage form is achieved. This model is explains the release of fairly soluble and poorly soluble in water from solid and semisolid drug delivery system. The diffusion from a planar spherical heterogeneous drug delivery system, where the concentration of drug in the dosage is less than its solubility and the release happens via pores in the matrix and expressed in the following equation: **[13, 14]**

$$Q = \sqrt{(D\delta/\tau) (2A - \delta A_s) A_s t}$$

**where D = diffusion coefficient of the drug in the medium;**

**$\delta$ = porosity of the medium and**

**$\tau$ = tortuisity of the medium**

Tortuisity is defined as the product of radius, pores and canals in the medium. After simplifying the above equation, Higuchi model can be expressed as below:

$$Q=K_H \times t_{1/2}$$

**where, $K_H$= Higuchi diffusion constant.**

The obtained data were plotted in a graph between cumulative percentage drug release and square root of time. Hence, the Higuchi model results in a linear Q against $t_{1/2}$ plot showing slope which is equal to $K_H$

and the medium follows $t_{1/2}$ kinetics. Therefore, if the coefficient of correlation is high in the plot then it can be interpreted as that mechanism follows diffusion controlled release. While predicting Higuchi model few following assumptions are to be considered:

(i) the initial concentration of drug in the solvent is higher than the medium solubility

(ii) maintained 100% sink conditions

(iii) constant drug diffusivity and

(iv) minimal or no polymer swelling

The sink condition is maintained by ensuring the amount of the drug released in the diffusion medium <15% of its saturation solubility. Hence, this model was applied for all the selected formulations in (Cumulative % drug release against Square root time) and evaluation was done in the graphical presentation **(Figure 4)**.

The graphical representation of cumulative % of drug release versus time explains that drug release from F10 and F18 formulation follows Higuchi release mechanism model as the drug release profile is nearest to the regression line and having highest value of correlation coefficient ($r^2$= 0.9967) when compared with other formulations.

**Korsmeyer Peppas Model: [15]**

After establishing the key drug release mechanism as type of diffusion controlled, derived from Higuchi equations. To know the mechanisms of diffusion from the matrix, the release data were fitted into the Korsmeyer and Peppas equation (KP). The KP equation illustrated the drug release from a polymer and type of diffusion, which is provided in the following equation:

$$\mathbf{At/A\infty = K_{kp}t^n}$$

**Where At/A∞ =fraction of drug released at time t,**

**$\log(At/A\infty) = \log K_{kp} + n \log t$,**

**At = amount of drug released in time t,**

**A∞ = amount of drug released after time ∞,**

**n = drug release exponent,**

**$K_{kp}$= rate constant for Korsmeyer Peppas.**

In order to find release kinetics a graph was plotted between log cumulative % drug release log(At/A∞) and log time (log t). Thus, n value is considered to describe various mechanism of release as given in the **Table 4**. Hence, KP model was used in the release profile for three formulations (F3, F10 and F18).

It is evident from the slope **(Table 4)** of FR3, FR10, FR18 and marketed product that FR3 follows Super Case II transport, which is implied by the diffusion exponent of release **[16]** i.e.FR3 is having maximum slope (0.9999).

**Hixson- Crowell Model: [15]**

The Hixson-Crowell model explains the drug release only when there is a variation in surface area and particle size. Thus, particles with uniform area are relative to the cube root of its volume. Based on this principle Hixson - Crowell determined an

association among the drug release and time, which is represented in the following equation:

$$A_0^{1/3} - A_t^{1/3} = K_{HC}t$$

where

**$A_0$= initial amount of drug in the pharmaceutical dosage form**

**$A_t$= remaining amount of drug in the pharmaceutical dosage form at time t**

**$K_{HC}$= Hixson-Crowell constant describing surface volume relation**

To find the release a graph is plotted between cube root of drug % of remaining and time. The above equation is employed to predict diffusion profile from the proposed dosage form. Thus, coefficient of correlation from above the equation is found to be high, may infer that variation in area of surface through the diffusion process and have significant influence in drug release. Hence, HC model was used in the drug release profile for F6 formulation and data are provided in the **Table 4**. It was interpreted that variation in surface area and size of the drug with gradual diffusion over the time.

## RESULTS AND DISCUSSION

### Diffusion Studies

The *invitro* drug permeation profile was plotted and using various mathematical equations pharmacokinetic parameters like maximum concentration [$C_{max,}$ (mg)], maximum concentration at time [$T_{max}$ (hr)],concentration at initial [$C_0$ (µg/ mL)], rate constant [k (hr-1)], volume of distribution [Vd (L)], half life [$t_{1/2}$ (hr)], clearance [Cl (L/ hr)], area under curve [AUC (µghr/ mL)], area under curve at last part [AUC of last part (µghr/ mL)] were also studied. The same was interpreted in the form of graphical representation and calculated by correlation coefficient ($r^2$) represented in **Table 3, 4**. The correlation coefficient having maximum (nearest to one) value establishes the appropriate mathematical model which follows drug release mechanism **[17]**.

***In-vitro* percentage of cumulative drug permeation from formulated topical gels:**

Cumulative percentage of drug permeation from various formulated topical gels is summarized in the **Table 1** and graphically represented in **Figure 1**. At the end of 300 minutes permeation was found to be 98.12%, 98.31%, 98.78% and 89.09% for the FR3, FR10, FR18 and marketed product respectively. Among the nineteen optimized formulations FR3, FR10 and FR18 has selected for further studies and shown good drug release (about > 98%) and statistically significant (P > 0.01).

The FR3 ($r^2$ = 0.9947), FR10 ($r^2$ = 0.9895), FR18 ($r^2$ = 0.9788) and marketed product ($r^2$ = 0.9884) follows zero order kinetics perfectly when compared with first order kinetics based on coefficient correlation values. The data are graphically represented

in the **Figure 2** for the zero order kinetics, whereas first order kinetics data are provided in the **Figure 3**.

The maximum concentration ($C_{max}$) for FR3, FR10, FR18 and marketed product were observed as 11.89, 12.56, 13.77 and 9.24 mg respectively. Among the three optimized formulations and one marketed product, FR18 has the $C_{max}$ as 13.77 mg and found to be higher than the marketed product also. The maximum time at which maximum concentration ($T_{max}$) for FR3, FR10, FR18 and marketed product were observed as 2.00, 2.15, 2.10 and 2.45 hrs respectively.

The concentration at time zero ($C_0$) for FR3, FR10, FR18 and marketed product were calculated as 20.60, 21.76, 20.63 and 21.02µg/ mL respectively. Among the three optimized formulations and one marketed product, FR10 has the maximum $C_0$ as 21.76 µg/ mL and found to be higher than the marketed product also. The elimination rate constant (k) were estimated as 0.0100, 0.0139, 0.0097 and 0.0134 $hr^{-1}$ for FR3, FR10, FR18 and marketed product. Among the three optimized formulations and marketed product, FR10 has the maximum k as 0.0139 $hr^{-1}$and found to be lesser than the marketed product also. The volume distribution ($V_d$) for FR3, FR10, FR18 and marketed product were calculated 4.83, 4.60, 4.85and 4.58 L respectively. Among the three optimized formulations and marketed product, FR18 has the maximum $V_d$ as 4.85 Land found to be higher than the marketed product also. The half-life ($t_{1/2}$) of the drug was calculated as 6.92, 4.98, 7.14 and 5.16 hours for FR3, FR10, FR18 and marketed product. FR18 has the maximum $t_{1/2}$ as 7.14 hr and found to be higher than the marketed product also.

The clearance (Cl) was estimated as 0.48, 0.64, 0.47 and 0.62 L/ hrfor the selected optimized formulations FR3, FR10, FR18 and marketed product respectively. Among the three optimized formulations and marketed product, FR10 has the maximum Cl of0.64 L/hr and found to be similar to the marketed product also. Area under the curve (AUC) for FR3, FR10, FR18 and marketed product was calculated as 2331.56, 962.79, 2496.53 and 479.26µg.hr/mL respectively. Among the three optimized formulations and marketed product, FR18 has the maximum AUC as 2496.53 µg.hr/mL and found to be higher than the marketed product also. Area under the curve of last part for FR3, FR10, FR18 and marketed product was calculated as 1879.70, 504.41, 2042.56 and 656.25 µg.hr/mL respectively. Among the three optimized formulations and marketed product, FR18 has the maximum AUC as 2042.56 µg.hr/mL and found to be higher than the marketed product also. The data are provided in the **Table 2**.

*In vitro* pharmacokinetic parameters ($C_{max}$, $T_{max}$, $C_0$, k, $t_{1/2}$, $V_d$, Cl, AUC and AUC of last part) and release mechanism were studied for FR3, FR10, FR18 and marketed product. When compared with various kinetic models, it was observed that the formulated topical gel follows Korsmeyer Peppas power law equation and found to be maximum correlation coefficient ($r^2$ = 0.9999). Among the formulated topical gel and marketed product, drug release profile of FR3perfectly follows Super case II transport when compared with FR18. Higuchi square root model states the type of diffusion, which was calculated by value for F10, $r^2$ which is higher than 0.98 which indicates that the drug release from the topical gel system follows diffusion mechanism **[18]**. The data are provided in the **Figure 4** for the Higuchi model (FR3, FR10, FR18 and marketed product), whereas for the Koresmyer Peppas and Hixson Crowell models data are provided in the **Table 3** and **Table 4** respectively.

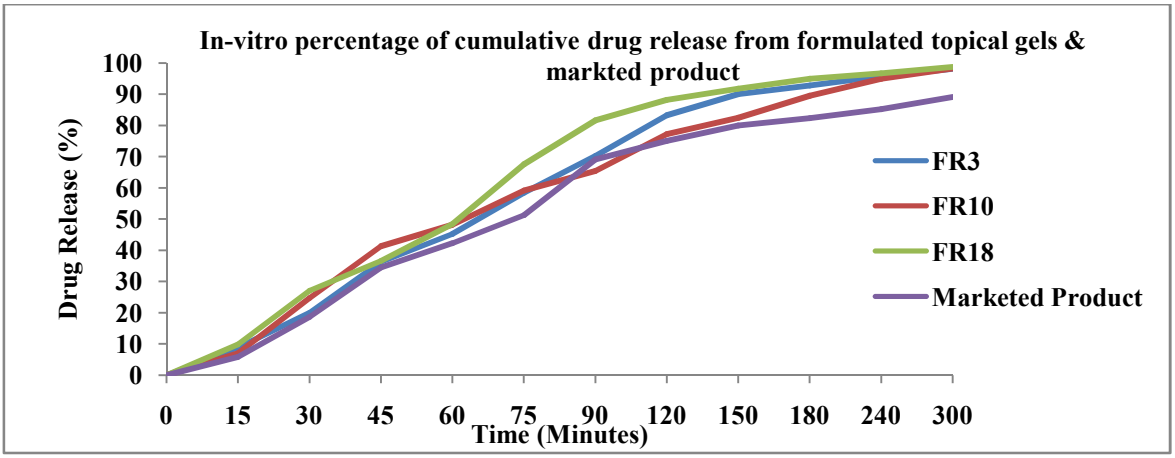


**Figure 1: In-vitro percentage of cumulative drug release from formulated topical gels & marketed product**

**Table 1: *In-vitro* percentage of cumulative drug permeation the selected formulations**

| Time (Minutes) | Drug Release (%) | | | |
|---|---|---|---|---|
| | FR3* | FR10* | FR18* | Marketed Product |
| 15 | 8.83±0.02 | 7.02±0.12 | 9.82±0.14 | 5.83±0.02 |
| 30 | 20.02±0.14 | 24.71±0.13 | 27.12±0.06 | 18.66±0.06 |
| 45 | 36.32±0.02 | 41.30±0.12 | 36.64±0.14 | 34.43±0.17 |
| 60 | 45.21±0.03 | 48.25±0.14 | 48.42±0.12 | 42.23±0.23 |
| 75 | 58.42±0.12 | 59.22±0.16 | 67.62±0.06 | 51.33±0.37 |
| 90 | 70.22±0.03 | 65.46±0.18 | 81.61±0.13 | 69.09±0.48 |
| 120 | 83.32±0.06 | 77.20±0.11 | 88.24±0.15 | 75.05±0.28 |
| 150 | 90.09±0.72 | 82.44±0.67 | 91.79±0.81 | 79.97±0.57 |
| 180 | 92.87±0.81 | 89.58±0.74 | 95.02±0.73 | 82.32±0.71 |
| 240 | 95.85±0.93 | 95.03±0.83 | 96.78±0.91 | 85.2±0.96 |
| 300 | 98.12±1.03 | 98.31±1.15 | 98.78±1.12 | 89.09±1.01 |

**The experiment was repeated for 6 times in each formulation and values are expressed in mean±SD; * P Value is < 0.01**

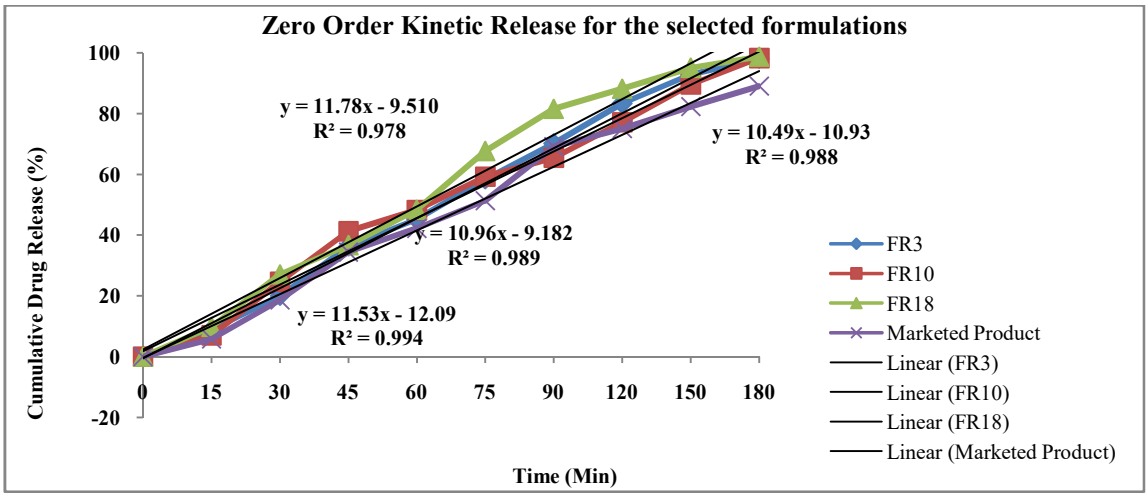


**Figure 2: Zero Order Kinetic Release for the selected formulations**

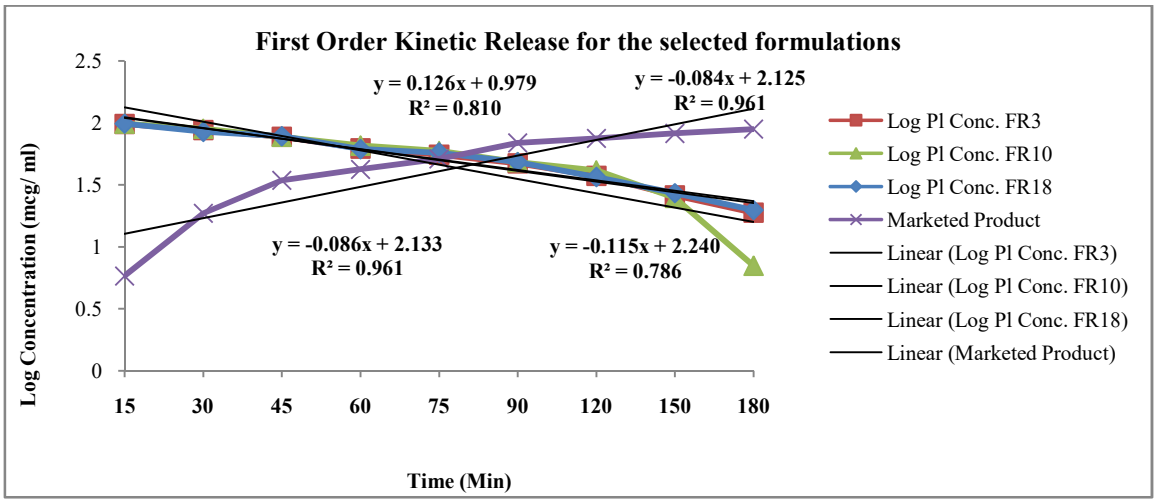


**Figure 3: First Order Kinetic Release for the selected formulations**

**Table 2: Pharmacokinetic Parameters for the Selected Formulations**

| Pharmacokinetic Parameters | FR3 | FR10 | FR18 | Marketed Product |
|---|---|---|---|---|
| $C_{max}$(mg) | 11.89 | 12.56 | 13.77 | 9.24 |
| $T_{max}$ (hr) | 2.00 | 2.15 | 2.10 | 2.45 |
| $C_0$ (µg/ mL) | 20.69 | 21.76 | 20.63 | 21.02 |
| k (hr-1) | 0.0100 | 0.0139 | 0.0097 | 0.0134 |
| Vd (L) | 4.83 | 4.60 | 4.85 | 4.58 |
| $t_{1/2}$ (hr) | 6.92 | 4.98 | 7.14 | 5.16 |
| Cl (L/ hr) | 0.48 | 0.64 | 0.47 | 0.62 |
| AUC (µg.hr/ mL) | 2331.56 | 962.79 | 2496.53 | 479.26 |
| AUC of last part (µg.hr/ mL) | 1879.70 | 504.41 | 2042.56 | 656.25 |

**Table 3: Koresmyer Peppas Model for the Selected Formulations**

| | FR3 | FR10 | FR 18 | Marketed Product |
|---|---|---|---|---|
| k | 2.7547 | 2.4993 | 3.0265 | 2.2091 |
| n | 0.6911 | 0.7147 | 0.6715 | 0.6317 |
| Sum of Sq. Difference | 17.9385 | 179.8806 | 36.8641 | 26.9078 |
| $r^2$ | 0.9999 | 0.9883 | 0.9968 | 0.9712 |

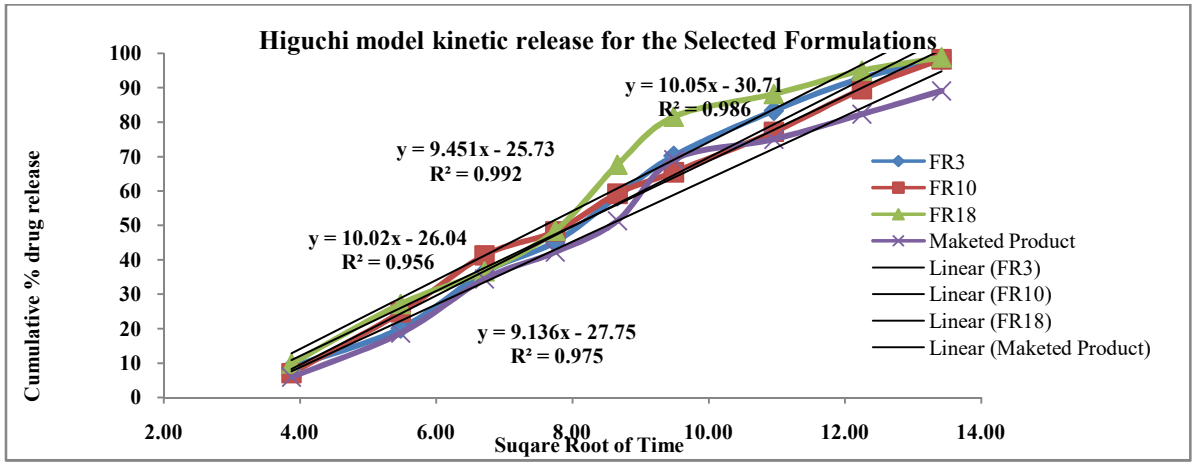


**Figure 4: Higuchi model kinetic release for the Selected Formulations**

**Table 4: Hixson Crowell Model for the Selected Formulations**

| | FR3 | FR10 | FR18 | Marketed Product |
|---|---|---|---|---|
| k | 21.542 | 21.542 | 21.541 | 21.480 |
| n | 0.00009 | 0.0001 | 0.00009 | 0.00008 |
| $r^2$ | 0.9849 | 0.9463 | 0.9808 | 0.9371 |
| Cube Root | 193.80 | 172.26 | 193.80 | 168.33 |

## CONCLUSION

Mathematical equations act an important part in the prediction of drug release mechanism from any dosage form. It plays a vital role in identifying the kinetics of drug release from a dosage form. The formulations were prepared in this research work exhibit a controlled manner of release profile from the polymers Chitosan and Sepineo P 600. The drug release from FR3 formulation was observed to be best fit in the Korsmeyer Peppas model ($r^2$=0.9999) which shows that drug release from F6 formulation as a square root of time dependent process and diffusion controlled. The diffusion profile was also plotted for Hixson –Crowell model ($r^2$=0.9849 for FR3) which explains that variation in surface area and drug size with the gradual diffusion over time. Korsmeyer Peppas model is a power tool show diffusion type of diffusion that was calculated by n that is nearer to 0.99 that shows the release of drug follows Super case II transport. The present study concludes that the drug release depends on concentration of polymer. A decrease or increase in polymer concentration has effect on it. Effect of penetration enhancers can be obtained to increase the solubility in the vehicle. The findings of this study also suggest that the overall kinetic parameters are better when compared with the marketed product.

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