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COMPUTATIONAL APPROACHES TO STUDY DISSOLUTION KINETICS AND THEIR PROFILES SIMILITUDE OF QUETIAPINE FUMARATE

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ABSTRACT

In this paper the purpose was to describe the kinetics of drug dissolution of six different formulations and using different approaches to compare their dissolution profile. Model independent approaches, including the pair wise procedure, ratio test procedures were used to characterize the drug dissolution profiles. Different mathematical models (zero order, first order, Higuchi model, Weibull model, Hixson Crowell, Korsmeyer-Peppas model) were applied to dissolution data of different formulations. The most appropriate model was chosen from the criteria goodness of fit based on R^2, AIC.

KEYWORDS: Quetiapine Fumarate, Model dependent Approach, Model independent Approach, goodness of fit.

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INTRODUCTION

Quetiapine Fumarate is moderately soluble in water. It is also called Seroquel. It is used for the treatment of schizophrenia, bipolar disorder and also an antidepressant to treat major depressive disorder [4]. It changes the levels of neurotransmitters, including dopamine. It belongs to a class of medications called atypical antipsychotics. Dissolution process is very important for the bioavailability and also for therapeutic potency of various pharmacological treatments. In our present study dissolution profiles of Quetiapine Fumarate are compared using different approaches: Model dependent approach, Model independent approach. In model independent approaches, ratio test and fit factors (f_1, f_2) are commonly used[1]. The model dependent approaches includes zero order, first order, Higuchi model, Hixson Crowell model are used for representation of dissolution data and to evaluate the best fit model. The suitable model for drug dissolution can be selected based on different criteria and the selection of most appropriate model is based on goodness of fit that is R^2, R^2_{adjust}, AIC, SC. The model that has the highest coefficient of determination and smallest AIC is the most appropriate model [1, 10].

MATERIALS AND METHODS

Quetiapine Fumarate from Concord Biotech, Maltodextin, Trisodium dehydrate, Lactose monohydrate, Xantharal, Magnesium stearate, distill water were used. Dissolution was carried out on six different formulations and each formulation had six units. Dissolution was performed using USP XXIV rotating paddle method (Apparatus II) at 37± 0.50C in 900ml of 0.1 N HCl medium at 50 RPM. The sample was withdrawn at a prescribed time interval in dissolution medium and replaced with fresh medium. The samples were filtered through Whatman filter paper no. 41. After suitable dilution solutions percentage of drug release was analyzed using double beam UV spectrophotometer [7].

MODEL INDEPENDENT METHODS

Ratio Test Procedure

Ratio of percentage dissolved, the ratio of mean dissolution time and also standard error were estimated. By using these ratio tests, at a particular time, we compare the two formulation dissolution profile [1]. Standard error of mean ratio was estimated by using

$$SE_{T/R} = \sqrt{\lambda\left(\bar{x}_T/\bar{x}_R\right)^2} \qquad (1)$$

X_T = percentage of mean dissolved of the test

X_R = percentage of mean dissolved of reference

$SE_{T/R}$ = standard error of ratio of Mean of test to reference

Pair wise procedure

It includes dissimilarity factor (f_1) and similarity factor (f_2) [7, 9]. The dissimilarity factor calculates the difference percentage between two curves at each time point. Its value should be close to 100.

$$f_1 = \frac{[\sum_{t=1}^{n} |R_t - T_t|]}{\sum_{t=1}^{n} R_t} \times 100 \qquad (2)$$

The similarity factor [3] measures the similarity between two curves in dissolution percentage. Its value should be close to 15.

$$f_2 = 50 \times \log\{[1 + (\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \quad (3)$$

MODEL DEPENDENT METHODS

Different models that used to describe dissolution curves [1].

Dissolution Model		
Zero Order	$Q_t = Q_0 + K_0 t$	(4)
Higuchi	$Q = K_H t^{1/2}$	(5)
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = Kt$	(6)
First Order	$\log Q_t = \log Q_0 - \frac{K_1 t}{2.303}$	(7)
Weibull	$\log[-\ln(1-m)] = \beta \log t - \log\alpha$	(8)
Korsmeyer-Peppas	$Q = Kt^n$	(9)
Baker Lonsdale Model	$\frac{3}{2}[1-(1-F)^{2/3}] - F = kt$	(10)

AKAIKE INFORMATION CRITERION (AIC)

It is a measurement of goodness of fit and test the applicability drug kinetics model. The suitable model which has the smallest value of AIC is providing the best fit [9].

$$AIC = n \times \ln(SSR) + 2 \times P \quad (11)$$

$$SC = n \times \ln(SSR) + p \times \ln(n) \quad (12)$$

Where SSR = Sum of squares of residues
P = number of parameters in the model
n = number of dissolution data points

RESULTS & DISCUSSIONS

Dissolution models are prerequisites to describe the drug release pattern mathematically and drug release mechanism from dosage form.

Table 1
Pair wise Procedures (f1: Dissimilarity factor; f_2: Similarity factor)

Factor	F4/F2	F5/F2	F6/F2
f_1	7.883	5.964	8.576
f_2	54.661	66.235	52.208

Table 2
Ratio Procedures

Ratio	F4/F2	F5/F2	F6/F2
Mean	0.9234	1.0537	0.9157
Std. Error	0.1723	0.1907	0.1706

Table 1represent that all the formulations were best fitted to the criteria of dissimilarity and similarity. All formulations dissimilarity factor between 0-15 and similarity factors between 50-100 i.e. both dissolution profiles were identical. Table 2 shows the ratio of percentage of mean dissolved.

Table 3
Kinetic parameters for formulation F1 of Quetiapine Fumarate

Model	R^2	$R^2_{adjusted}$	Slope	AIC	SC
Zero Order	0.756	0.6514	3.451	89.020	89.82
Higuchi	0.932	0.9244	19.85	74.985	75.78
Hixson Crowell	0.393	0.3256	-0.108	30.064	30.86
First Order	0.954	0.9489	-0.051	-24.22	-23.42
Baker-Lonsdale	0.938	0.9225	-221.9	167.954	169.15
Weibull	0.811	0.7795	0.599	-14.500	-14.342

Table 4
Kinetic parameters for formulation F4 of Quetiapine Fumarate

Model	R^2	$R^2_{adjusted}$	Slope	AIC	SC
Zero Order	0.784	0.69143	3.423	92.902	93.698
Higuchi	0.937	0.93	19.39	75.506	74.302
Hixson Crowell	0.397	0.33	-0.107	29.749	30.545
First Order	0.972	0.968	-0.051	-30.271	-29.475
Baker Lonsdale	0.953	0.94125	-219.2	161.496	162.689
Weibull	0.771	0.732833	0.519	-14.831	-14.672

When comparing various models for given set of data, the model that has highest value of R^2, R^2_{adjust} and the smallest value of AIC and SC is considered as a best fit model. Table 3 &Table 4 shows the kinetic parameters of different models for formulation F1 & F4. The results showed that F1 & F4 followed the first order model with the highest value of R^2, R^2_{adjust} and the smallest value of AIC and SC. The best fit model for formulation F1&F2 was first order model. According to these criteria all other formulations also followed the first order model. The first order plot is log percentage of drug remaining versus time. Figures are given below show the drug dissolution profile of six formulations. Various kinetic models (zero order, first order, Hixson Crowell, Baker Lonsdale, Weibull) were fitted on different formulations. In Fig.1, Fig.2, Fig.3, Fig.4 and Fig.5, the dissolution profiles generated from zero order,first order, Weibull, Korsmeyer Peppas, Higuchi fits.

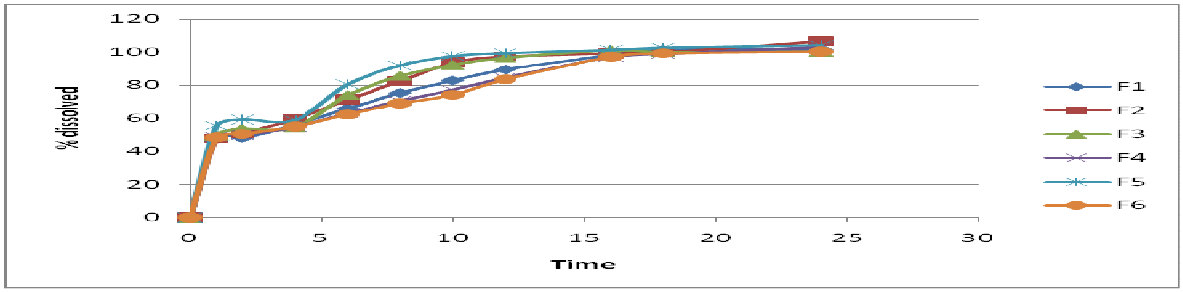

Figure1
Zero Order model

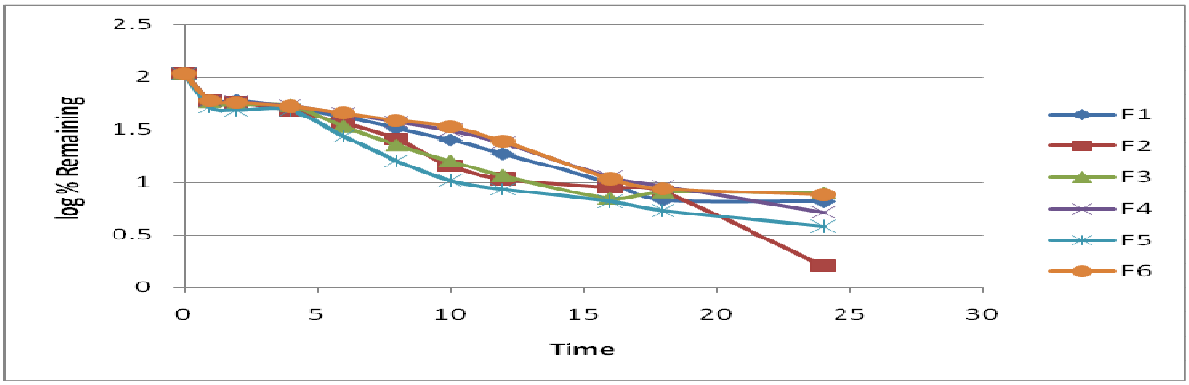

Figure 2
First Order Model

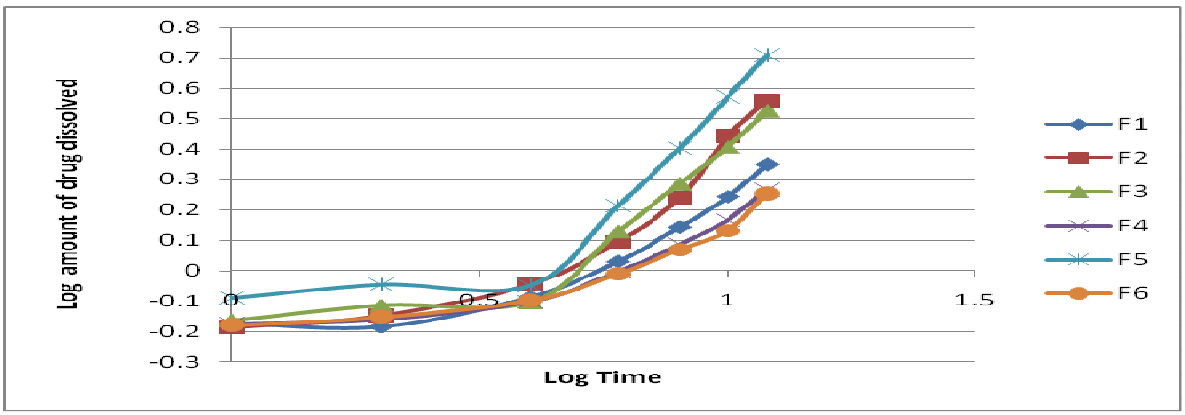

Figure 3
Weibull Model

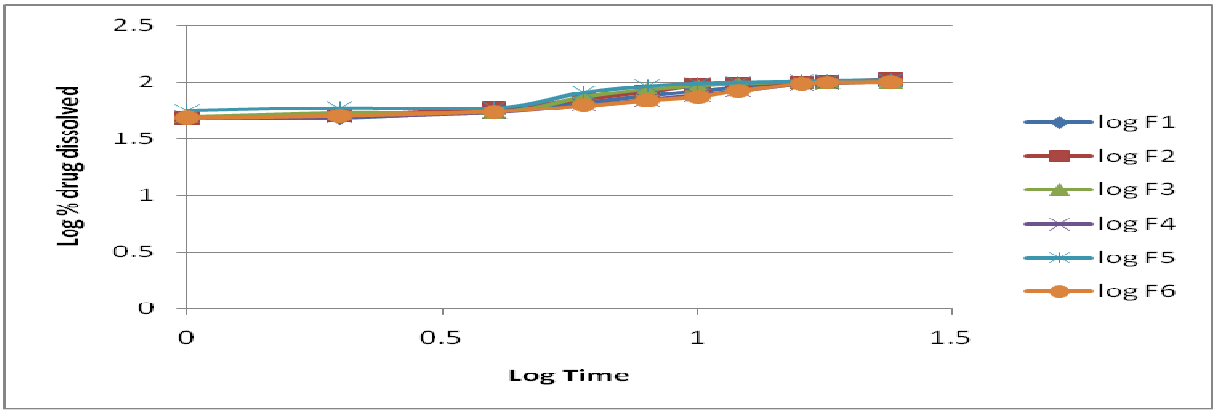

Figure 4
Korsmeyer–Peppas Model

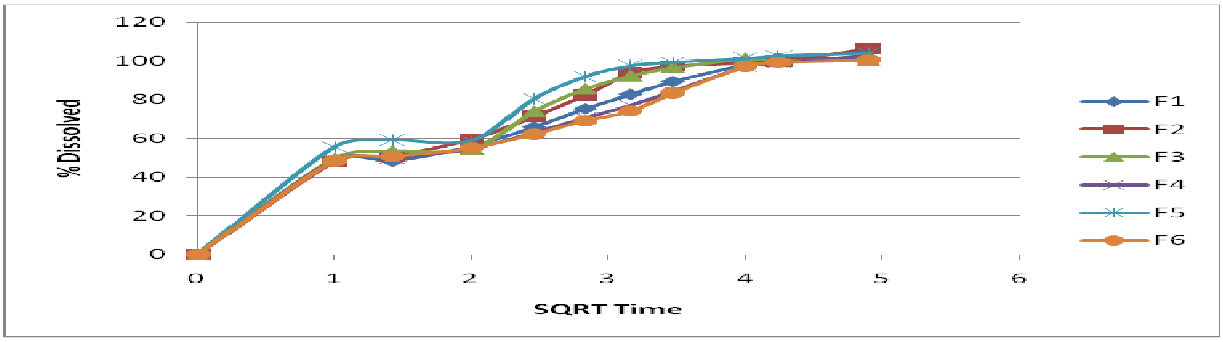

Figure 5
Higuchi Model

CONCLUSION

The dissolution models such as a zero order model, Higuchi model, first order model, Hixson Crowell model, Korsmeyer-Peppas model, Weibull model, Baker Model were used to compare dissolution profiles. The suitable model for all formulations was first order model. The similarity factor of reference formulation with one of test formulation was approximately close to each other and the dissimilarity factor was different to other one. In future we can perform MDT, ANOVA based methods for comparison of the profiles of different drugs.

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