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MODEL DEPENDANT AND STATISTICAL APPROACHES TO STUDY RELEASE KINETICS OF MELOXICAM RELEASE MATRIX TABLETS

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ABSTRACT

In this paper various mathematical and model dependant approaches were applied to understand the kinetics of drug release of Meloxicam release matrix tablets. In-vitro drug release studies of nine formulations were carried out. ANOVA technique was used to compare the dissolution profile of the drug. Various model dependant methods like Zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer model were used to estimate the kinetics of drug release. For selecting the most appropriate model the goodness-of-fit test, lowest sum of squares residual and square of correlation constant was used. A mathematical approach was used to estimate the deviation in Area Under the Curve (AUC) between predicated and observed dissolution data of the drug. The optimal batch had the lowest difference in percent deviation of AUC at each point. Finally, unpaired t test was used to compare the dissolution profile of the optimal batch with that of the other batches.

KEYWORDS: model dependant, model independent, statistical methods, Meloxicam, AUC, unpaired t test.

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INTRODUCTION

Meloxicam is a member of enolic acid group of non-steroidal anti-inflammatory drugs [1,2.] It is generally used in the treatment of rheumatoid arthritis, osteoarthritis and other joint pains [3]. It is a cyclo-oxygenase inhibitor and is responsible for converting arachidonic acid into prostaglandin H2 which is the first step in the synthesis of prostaglandins which mediates of inflammation. Meloxicam starts to relieve pain about 30–60 minutes after administration [4]. Meloxicam inhibits cyclooxygenase (COX) (the enzyme responsible for converting arachidonic acid into prostaglandin H2) as the first step in the synthesis of prostaglandins, which are mediators of inflammation. Meloxicam at its low therapeutic doses inhibits COX-2 over COX-1 [5]. Its known that drug release from hydrophilic matrices shows a time-dependent profile (i.e., decreased drug release with time because of increased diffusion path length) [6].

In-vitro Dissolution studies of tablets

In-vitro drug release studies of all the formulations were carried out using tablet dissolution test apparatus at 50 rpm. Phosphate buffer pH7.4 was used with temperature 37 ± 1^0C. Samples were withdrawn at different filtered, suitable dilutions were done with distilled water and analyzed spectrophotometrically.

Comparison of dissolution profile

In this statistical method the percent drug dissolved is dependent variable and time is the repeated factor. The different batches (BATCH A- BATCH I) of the MELOXICAM were taken and ANOVA based method was applied on the batches. Our null hypothesis was not rejected. To show that there are no significant differences in the batches of drugs under consideration Tukey Kramer procedure was done.

MODEL DEPENDANT APPROACH

In vitro drug release data were fitted to kinetic models such as zero-order [7], first-order [8], Higuchi equation [9], Hixson-Crowell [10] and Korsmeyer–Peppas model [11] and regression analysis was performed. For each model a graph showing the line of best fit was plotted for all batches. Then sum square of residuals (the square of the difference between observed and predicted values) were calculated for all batches and for all models applied. From the regression analysis the R^2 value that is square of the coefficient of correlation was calculated for all batches. Table 1 shows the different model dependant approaches that have been used in this study.

Table 1
Plots for different models

zero order	Ct versus t
first-order	log Ct versus t
Higuchi equation	Ct versus square root of t
Hixson-Crowell	log %Ct versus log %t
Korsmeyer–Peppas model	log %Ct versus log %t

Statistical approach

AUC (Area Under the Curve) represents the total drug exposure over time . This is useful in determining whether two formulations of the same dose release the same dose of drug to the body. A mathematical approach was used in which the difference in AUC (Area Under the Curve) was calculated for predicted and observed values for all batches for all the mathematical models applied. The best batch showed the least difference.

RESULTS AND DISCUSSIONS

The ANOVA analysis shows that the null hypothesis should not be rejected and there is not much difference of means among all the

batches. The F-value(0.57674)< F-critical(2.033295) so the null hypothesis has to be accepted. To confirm this Tukey Kramer procedure was done on the ANOVA analysis data. It was found that the batches are not significantly different. Amongst all the batches the best batch was identified by taking into consideration coefficient of correlation and sum square of residuals. Table 2 shows the square coefficient of correlation of various batches according to different models. The batch showing the highest square of coefficient of correlation is the best batch. The best model was identified by comparing the sum square of residuals (SSR). Table 3 shows the SSR values of different batches according to different models. The model showing the least SSR is the best fitting model. The best fitting model describes the reaction kinetics of the drug dissolution profile. The AUC the curve analysis shows the batch with the best bioavailability according to each model [12]. Square of coefficient of correlation was found highest for Higuchi model. Table 4 shows the difference in AUC for observed and predicted values for all the models applied on different batches. This value is lowest for the best batch in all the models applied. Unpaired t-test was performed to get a comparative view point of the different batches with respect to the best batch and was organized according to their similarities with respect to the best batch. Table 5 shows the results obtained for the unpaired t-test for the various batches. The batches are organized in descending order according to the values with the most similar batch on the top.

Table 2
Square of coefficient of correlation values for all batches according to different models

BATCHES	0 OREDER	1st ORDER	HIGUCHI	HIXSON CROWELL	PEPPAS'
BATCH A	0.954883	0.809907	0.983897	0.875895	0.980581
BATCH B	0.962473	0.788767	0.987724	0.868602	0.973482
BATCH C	0.968786	0.79925	0.988298	0.878014	0.976597
BATCH D	0.961049	0.764393	0.989314	0.859165	0.968677
BATCH E	0.954381	0.772032	0.980649	0.862147	0.971109
BATCH F	0.963453	0.798882	0.978719	0.904331	0.975854
BATCH G	0.97586	0.792655	0.992292	0.881952	0.979281
BATCH H	0.966062	0.814715	0.977749	0.889429	0.979115
BATCH I	0.965242	0.813972	0.97417	0.892292	0.981566

Table 3
Sum Square of Residuals (SSR) values for all batches according to different models

BATCHES	0 ORDER	1st ORDER	HIGUCHI	HIXSON CROWEL'S	PEPPAS'
BATCH A	516.0184	0.24116	184.1722	7.035932	7.80568
BATCH B	402.3715	0.34533	131.6251	6.16733	6.832198
BATCH C	268.8851	0.336815	100.8015	5.289316	5.855601
BATCH D	390.3744	0.387432	107.101	4.430151	4.886924
BATCH E	432.5021	0.439494	183.4598	3.568004	3.915816
BATCH F	306.3133	0.407583	187.4207	2.663673	2.939962
BATCH G	199.1214	0.34354	63.58027	1.781721	1.960681
BATCH H	272.234	0.37545	179.7954	0.892292	0.981566
BATCH I	256.3111	0.409562	190.4786	31.82842	35.17843

Table 4
Difference in AUC values for observed and predicted dissolution profile for all batches according to different models

BATCHES	0 OREDER	1st ORDER	HIGUCHI	HIXSON CROWELL	PEPPAS'
BATCH A	6.4274	0.0922	1.157	0.2159	0.0033
BATCH B	5.34455	0.1019	1.6243	0.218	0.0029
BATCH C	4.1572	0.1003	1.7187	0.2011	0.0039
BATCH D	5.5934	0.1035	1.1085	0.2208	0.0099
BATCH E	5.6887	0.1153	1.6595	0.2368	0.0068
BATCH F	3.7535	0.1151	2.3526	0.3112	0.0042
BATCH G	3.3362	0.9522	1.476	0.1843	0.0061
BATCH H	4.3148	0.1141	2.5037	0.2189	0.007
BATCH I	4.4284	0.122	2.6183	0.2279	0.0035

Table 5
Arrangement of different batches in descending order according to their similarity with respect to BATCH G

BATCHES	t-TEST VALUES
BATCH G-BATCH C	0.0612
BATCH G-BATCH F	0.1049
BATCH G-BATCH E	0.1991
BATCH G-BATCH H	0.3765
BATCH G-BATCH D	0.5591
BATCH G-BATCH B	0.6148
BATCH G-BATCH I	0.6587
BATCH G-BATCH A	1.2844

Figure 1
Plot for Zero order release plotted as kinetics % of drug release vs. time plot for BATCH A-BATCH I.

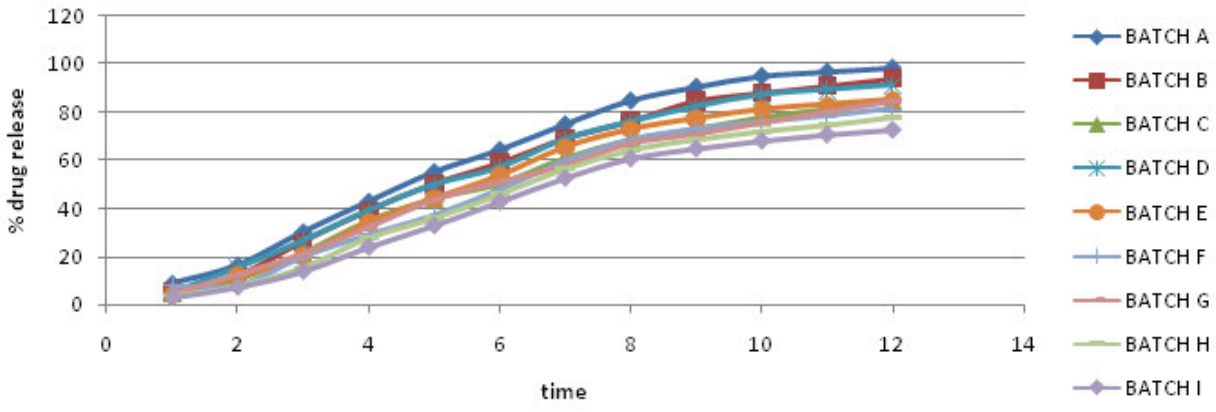


Figure2
Plot for First order release kinetics plotted as log % of drug remaining vs. time for BATCH A-BATCH I

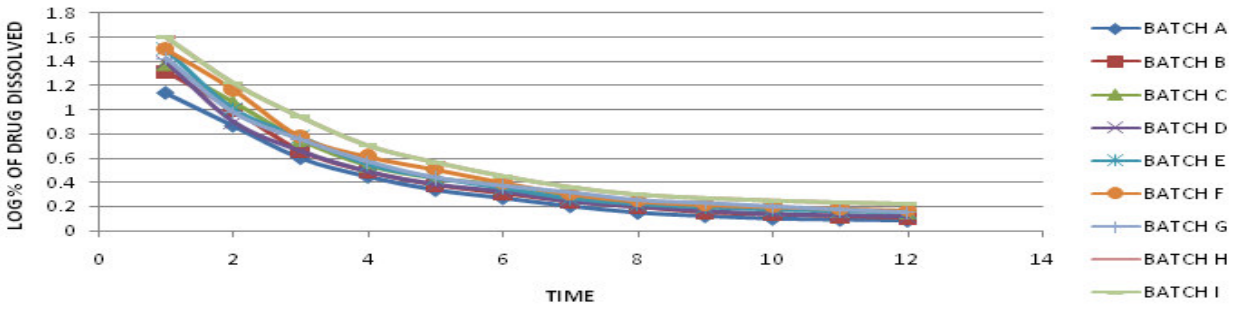


Figure 3
Plot for Higuchi model plotted as % of drug dissolved vs. time for BATCH A-BATCH I

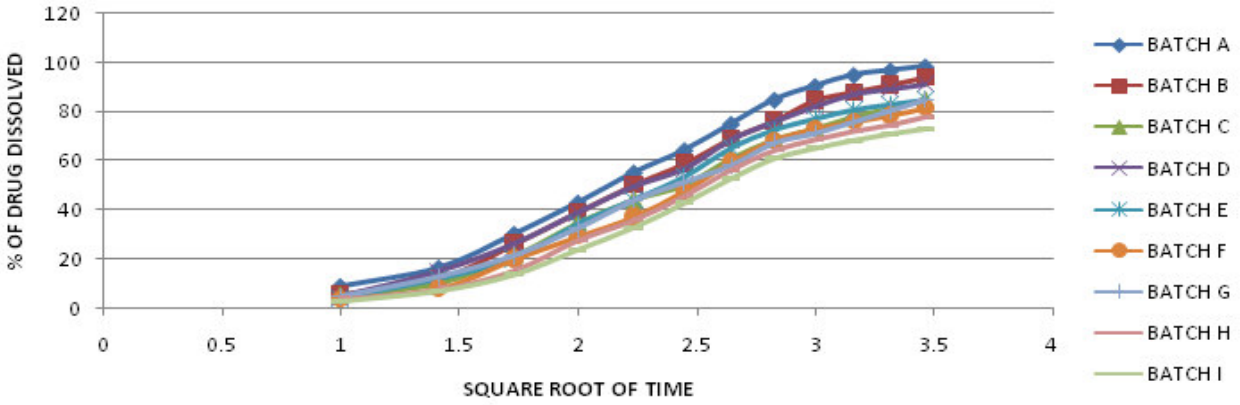


Figure 4
Plot for Hixson-Crowell model plotted as cube root of % drug remaining in the matrix for BATCH A-BATCH I

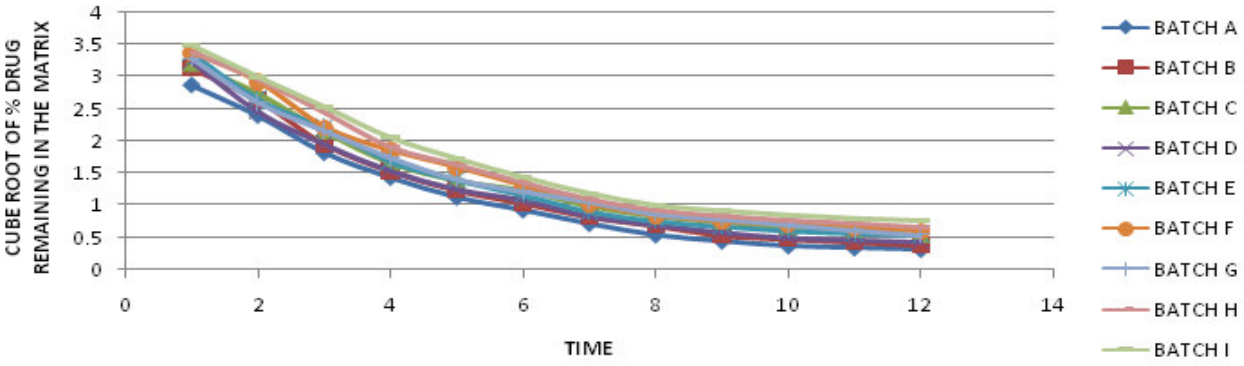
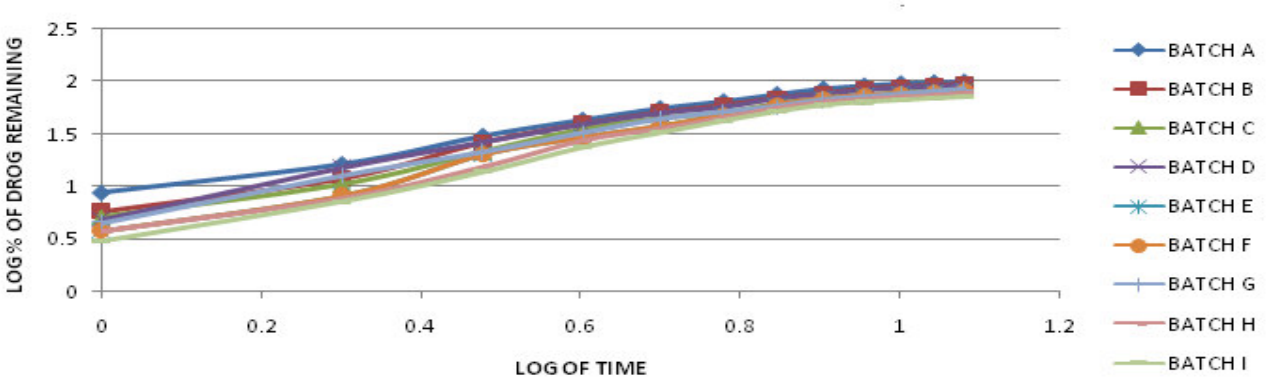


Figure 5
Plot for Korsmeyer–Peppas model plotted as log % of drug remaining vs. time for BATCH A-BATCH I



CONCLUSION

It was found by ANOVA analysis and Tukey Cramer procedure that there is no significant difference in the dissolution profile of all batches Meloxicam drug. Comparing the square of coefficient of correlation values the best batch was identified to be batch G. comparing the sum square of residuals (SSR) values showed the best fitting model to be Higuchi model. In this mathematical approach the difference in AUC values for predicted and observed values were calculated for all batches for all models been applied. The best batch according to each model shows the least difference in AUC for observed and predicted values. Applying the unpaired t-test it was found that the batch c was much similar to the best batch G. As future work nonlinear regression and curve fitting procedure can be applied to get the accurate values for all the models been applied.

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