Research Article

FORMULATION AND OPTIMIZATION OF KETOROLAC TROMETHAMINE HCl FAST DISINTEGRATING TABLETS BY EXPERIMENTAL DESIGN

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ABSTRACT

Objective: The aim of the present work was to formulate and evaluate oral disintegrating tablets of Ketorolac tromethamine HCl by statistical experimental design. The Ketorolac is an NSAIDs drug, which has high solubility and high permeability (BCS class I). **Methods:** Tablets were prepared by direct compression technique using dehydrated Banana powder (*Musa acuminata*) and *Plantago ovata* powder (Ispaghula) as independent variables. *In vitro* disintegration time and % drug release were selected as dependent variables. The model was found to be linear and the curvature effect was significant. Therefore, study resorted to composite design for optimization. **Results:** DSC studies indicated that the drug and excipients were compatible. Pre-compression parameters had shown fairly good flow properties. The directly compressed tablets were evaluated for pharmaco technical properties and were found to be within specified limits. Kinetic studies revealed that drug release from all formulations followed first order release. Based on simulation given by the software most economical batch which was in desired range was selected. **Conclusion:** The statistical model is mathematically valid as the experimental values and predicted values suggested by the model were relatively close to each other. The results demonstrated the effectiveness of the proposed design for development of Ketorolac tromethamine HCl fast disintegrating tablets with optimized properties.

Keywords: Super disintegrants, experimental design, Ketorolac Tromethamine.

INTRODUCTION

In the present era, NSAIDs are the most widely preferred drugs which are very effective in the treatment of treating pain, fever and inflammation. Many of these side effects may be prevented by careful considerations of patient risk factors and have subsequent preventive strategies. Ketorolac a non-steroidal anti-inflammatory drug (NSAIDs) used for treating inflammation and pain. Apart from Ibuprofen and naproxen, Ketorolac is more effective NSAID in reducing pain from both inflammatory and non-inflammatory causes. It is widely used for short-term management (up to 5 days) of moderately severe acute pain¹. Ketorolac tromethamine a non-steroidal anti-inflammatory drug (NSAID), commonly used to reduce post-operative pain associated with the surgical treatment of spine deformities and to treat pain associated with surgery. Its shows its effect by inhibition of prostaglandin synthesis². It is a BCS class – I drug with high solubility and high permeability and conventional intake leads to gastric ulceration, bleeding and other gastric complications.

Many of the existing fast disintegrating formulations were prepared or formulated using synthetic disintegrants available at higher cost. But by using natural super disintegrates we developed the formulation of Ketorolac fast disintegrating tablets³. “Fast disintegrating tablet” disperses rapidly in the mouth and avoids usage of water and shows fast dispersion in the oral cavity before swallowing. The faster the drug into solution, quicker the

absorption and onset of clinical effect. The dissolution and bioavailability of drugs with poor solubility can be enhanced by administering the tablet as fast dissolving tablet⁴. In the present study the tablets were formulated using dehydrated banana powder and ispaghula mucilage powder which are naturally obtained at low cost. Experimental designs are mostly commonly used in the formulation development as they reduce the experimental trials and formula can be optimized by fewer trials⁵. Dehydrated banana powder and ispaghula were selected as independent variables, disintegration time and *In vitro* dissolution time were selected as dependent variables.

Hence the present study aimed at formulation and development of Ketorolac tromethamine fast dissolving tablets by use of natural super disintegrants, which offers several benefits and the action starts within few minutes of administration to relieve pain there by providing fast relieve of pain with minimum local gastric side effects by 2² factorial design⁶. It is an experimental design, which uses dimensional factor space at the corner of the design space. Factorial designs are used in experiments where the effects of different factors or conditions on experimental results are to be elucidated⁷.

MATERIALS AND METHODS

Ketorolac tromethamine HCl, Dehydrated banana powder, Ispaghula mucilage powder, Mannitol, Microcrystalline

cellulose, Aspartame, Magnesium stearate, Talc. All the materials and reagents were of analytical grade.

Preparation of dehydrated banana powder

Bananas were purchased from local market of Ananthapuramu. Peels were removed and fruits were sliced. Sliced pulp was washed with distilled water to remove water soluble contents. 0.2% w/w methyl paraben was added as preservative. Sliced pulp was ground in domestic mixer and dried in oven at 45°C for 24 hours to get constant weight and sieved through Sieve No. 80⁸.

Preparation of ispaghula mucilage powder (*Plantago ovata*)

Ispaghula seeds were taken and soaked in sufficient quantity of water for overnight. This mixture was boiled for 1 hr at 80°C and brought to room temperature. The mucilage was extracted by squeezing ispaghula seeds in a muslin cloth. Obtained mucilage was taken in a petri plate and dried in a hot air oven at 60°C for 1

hr. The obtained powder was stored in an air tight container for further use⁹.

Formulation of Ketorolac tromethamine HCl blend by geometric mixing

Ketorolac tromethamine HCl fast disintegrating tablets were prepared by direct compression method according to the formula given in Table-1. A total of five formulations (F1 to F5) of Ketorolac tromethamine HCl fast disintegrating tablets were prepared using natural super disintegrants namely dehydrated banana powder and ispaghula mucilage powder¹⁰. All the ingredients were passed through mesh no. 60 separately and collected. The drug, mannitol and microcrystalline cellulose were mixed uniformly with geometric mixing to get a uniform mixture. Required quantity of super disintegrants and aspartame were taken for each specified formulation and mixed with the above mixture. Finally, magnesium stearate and talc were added and mixed well¹¹. All the ingredients concentrations in the formulation were mentioned in table 1.

Table 1. Formulation of Ketorolac tromethamine HCl fast disintegrating tablets

Ingredients	F1	F2	F3	F4	F5 (mg)			
					A	B	C	D
Ketorolac tromethamine HCl	10	10	10	10	10	10	10	10
Dehydrated Banana Powder	9	15	9	15	12	12	12	12
Ispaghula mucilage Powder	8	8	16	16	12	12	12	12
Mannitol	80	80	80	80	80	80	80	80
Microcrystalline cellulose	137	131	129	127	130	130	130	130
Aspartame	4	4	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Total weight (mg)	250	250	250	250	250	250	250	250

Evaluation of Pre compression parameters

Bulk density (BD)

The bulk density was determined by transferring the accurately weighed blend sample into the 100ml graduated cylinder by keeping it in a slanting position. The initial volume and weight were noted. Ratio of weight of the sample to the volume it occupied was calculated¹².

Tapped density (TD)

Tapped density was determined by transferring the accurately weighed blend sample into 100ml measuring cylinder which was placed in electrolab tapped density apparatus (method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped for 10 times and the volume was measured. Further additional 500 tapings were made, and the volume was noted. Continue the tapings to 1250 if the difference between the volume measured after 10 and 500 tapings was more than 2ml¹³.

Hausner ratio (HR)

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula (Table 2).

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk density}$$

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Compression of Ketorolac tromethamine HCl fast disintegrating tablets

The mixed blend of drug and excipients were compressed using 7 mm punch on 12 stations "B" tooling rotary tablet punching machine to produce convex faced tablets¹³.

Evaluation of physical parameters of tablets

Average weight

Ten tablets were selected randomly from each formulation and weighed individually and together to check for weight variation. The average weight was noted, and standard deviation was calculated. In all the formulations the tablet weight variation is allowed up to $\pm 5\%$.

Thickness

Thickness was measured using a Vernier callipers scale. The tablet thickness was controlled within a $\pm 5\%$ variation of the standard value¹⁴.

Hardness

Hardness of randomly selected tablets was measured using Monsanto tablet hardness tester. For each formulation five tablets were tested¹⁴. It is expressed in kg/cm².

Friability

Twenty-six tablets were weighed and placed in the Roche friabilator apparatus and friabilator was run at 25 rpm for 4 minutes. These tablets were de dusted and weighed again. The percentage friability was measured using the formula¹⁴

$$\%F = \{1 - (W_f / W_i)\} * 100$$

Where,

%F= Friability in percentage

W= Initial weight of tablet

W_f= Final weight of tablets after de dusting

Drug content

Three tablets from each formulation were weighed individually and powdered. The powder equivalent to 10 mg of Ketorolac tromethamine HCl was weighed and dissolved in 10 ml in pH 6.8 buffer. From this solution 1 ml was taken and made up to 10 ml using pH 6.8 buffer and the solution was analysed at 314nm by UV-visible spectrophotometer using pH 6.8 buffer as the blank.

In vitro disintegration time

The test was carried out in a disintegration apparatus using distilled water as disintegration medium (at 37°C ± 0.2°C). A tablet was placed in each of six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds ¹⁵.

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. 10 ml of water containing Eosin, a water-soluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time ¹⁵.

In vitro dispersion time

Tablet was added to 10 ml of phosphate buffer solution (pH 6.8) at 37±0.5°C. Time required for complete dispersion of a tablet was measured.

In vitro dissolution study

In vitro dissolution of Ketorolac tromethamine HCl from fast disintegrating tablets was determined using USP dissolution test apparatus II (Paddle type). The dissolution test was performed using 900 ml of PBS (pH 6.8) at 37 ± 0.5°C. The speed of rotation of paddle was set at 50 RPM. At a pre-determined time interval (5min); 5 ml samples were withdrawn, filtered through Whatman filter paper. Absorption of solution was checked by UV spectrophotometer at 314 nm and drug release was determined from standard curve.

Statistical analysis and optimization

Data obtained from all fast disintegrating tablet formulations were analysed using Sigma Tech software and used to generate the study design. The best fitting model was selected based on comparisons of several statistical parameters, provided by Sigma Tech software. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F test and P values were also calculated using the software. The relationship between the dependent and independent variables was further elucidated by simulation.

Table 2. Evaluation of pre compression parameters

Formulation code	Bulk density (g/cm ³)*	Tapped density (g/cm ³)*	Compressibility Index (%)	Hausner 's ratio	Angle of repose*
F1	0.318±0.040	0.401±0.032	20.69825	1.261006	28°.30±0.041
F2	0.330±0.022	0.385±0.034	14.28571	1.166667	27°.54±0.020
F3	0.310±0.020	0.402±0.022	22.88557	1.296774	35°.66±0.021
F4	0.338±0.040	0.420±0.055	19.52381	1.242604	34°.08±0.043
F5	0.330±0.022	0.400±0.020	17.5	1.212121	30°.91±0.026

All values are expressed as mean ± standard deviation (*n=3)

Table 3. Evaluation of Ketorolac tromethamine HCl fast disintegrating tablets-1

Batch code	Average weight (mg)*	Thickness (mm)*	Hardness (kg/cm ²)*	Friability (%)*
F1	251±2.6	4.10±0.09	2.5±0.112	0.53±0.054
F2	250±1.6	4.18±0.023	2.3±0.110	0.24±0.112
F3	250±1.8	4.19±0.518	2.6±0.649	0.45±0.198
F4	250±1.3	4.21±0.603	2.5±0.755	0.22±1.163
F5	250±1.1	4.16±0.263	2.7±0.250	0.45±0.682

All values are expressed as mean ± standard deviation (n=10*, n=6**)

Table 4. Evaluation of Ketorolac tromethamine HCl fast disintegrating tablets-2

Batch code	Drug content (%)*	Disintegration time (sec)*	In vitro dispersion time (sec)*	Wetting time (sec)*
F1	88.97±0.24	66±0.31	45±0.78	40±0.318
F2	90.7±0.77	49±0.65	36±0.12	33±1.56
F3	77.9±0.31	60±0.28	50±0.33	45±0.88
F4	84.42±0.22	55±0.37	39±0.25	34±0.206
F5	91.07±0.63	68±0.60	57±0.55	42±0.318

All values are expressed as mean ± standard deviation (n=3*)

Table 5. Statistical analysis of DoE experimental observations with 2 variables

S. No.	Coefficient	Name of Variable	Coefficient values	SS% (% of sum of squares)
1	b0	-	57.5	-
2	b1	DBP	-5.5	77.0701
3	b2	IMP	0.0	0.0
4	b12	DBP, IMP	3.0	22.9299

Table 6. Results of ANOVA for response Y1 (*In vitro* disintegration time)

S.No.	Source of Variance	SS	DF	MS	F-value	Fstd at 0.1p	Fstd at 0.05p	Fstd at 0.01p
1	Model	157.0	3	52.3333	9.22337203	4.19	6.59	16.7
2	Error	0.0	4	0.0				
3	Total	157.0	7					
Curvature Effect		-7.2795 to 28.7795						
95% Confident Level of Curvature effect					Linear			

Table 7. Statistical analysis of DoE experimental observations with 2 variables

S. No.	Coefficient	Name of Variable	Coefficient values	SS% (% of Sum of squares)
1	b0	-	86.7475	-
2	b1	DBP	2.8125	31.0013
3	b2	IMP	-4.0875	65.4602
4	b12	DBP, IMP	0.9475	3.5185

Table 8. Results of ANOVA for response Y2 (*In vitro* drug release)

S No.	Source of Variance	SS	DF	MS	F-value	Fstd at 0.1p	Fstd at 0.05p	Fstd at 0.01p
1	Model	102.0622	3	34.0207	9.2233720	4.19	6.59	16.7
2	Error	0.0	4	0.0				
3	Total	102.0622	7					
Curvature effect		-15.316 to 25.961						

Table 9. Comparison of experimental results with predicted responses Ketorolac tromethamine HCl fast disintegrating tablets formulation

Ingredient	Composition (mg/tab)	Response	Predicted value	Experimental value	Standard error
DBP	15	Y1 (DT) (sec)	49	52	1.5
IP	8	Y2(DR) (%)	92.7	95.4	1.35

Figure 1. DSC of Pure Drug

Figure 2. DSC of Optimized Formulation

Figure 3. Pie diagram showing contribution to factors to disintegration time (Y1)

Figure 4. Bar chart showing contribution of factors to disintegration time (Y1)

Figure 5. *In vitro* drug release of ketorolac tromethamine HCl from formulations (F1-F5)

Figure 6. Bar chart showing contribution of factors to % drug release (Y2)

Figure 7. Pie diagram showing contribution of factors to % drug release (Y2)

RESULTS

In order to define the “design space” the critical formulation variables (independent variables) and the responses able to measure the product quality were defined based on prior knowledge and preliminary studies. The independent variables considered for fast disintegrating tablet formulations were concentrations of dehydrated banana powder and ispaghula mucilage powder quantity, since they were considered critical in determining responses *in vitro* disintegration time and % drug release. Based on the number of parameters or variables and their levels, 2^2 factorial design with 4 replicates was selected for Ketorolac tromethamine HCl fast disintegrating tablets optimization. Fast disintegrating tablets were prepared by direct compression method.

Compatibility studies

Differential Scanning Calorimeter (DSC)

Differential Scanning Calorimeter (DSC) DSC thermographs revealed that the melting point of the pure drug is 173 °C and that of the drug in the formulation is 167.1 °C. Presence of dehydrated banana powder and ispaghula mucilage powder (Super disintegrants) reduced the melting point of Ketorolac tromethamine HCl (pure drug) in optimized formulation and hence solubility is enhanced, as illustrated in figure 1&2.

ANOVA was used to identify significant effect, coefficient of determination $R^2 = 0.881$. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p < 0.05$). The critical value of F is 6.59, obtained F value (i.e. 9.2233) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p < 0.05$ i.e. indicates significance at that level of probability. R^2 model found to be significant hence this model has been used for predictions.

Final equation in terms of coded factors

$$Y1 = 57.5 - 5.5 X_1 + 0.0 X_2 + 3.0 X_1 X_2$$

Final equation in terms of actual factors

$$Y1 = 57.5 - 5.5 \text{ DBP} + 0.0 \text{ IP} + 3.0 \text{ DBP IP}$$

Where $Y1 = \text{Invitro disintegration time}$ $X1 = \text{DBP}$, $X2 = \text{IMP}$

The polynomial equations were used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative). The results of the multiple linear regression analysis revealed that disintegration time decreased with increase in banana powder, disintegration time increased with increase in ispaghula mucilage powder (Figure 3 & 4). R^2 value was found to be 0.881, found to be greater than 0.70 suggesting that this model is reliable for all CQAs Hence used to establish predictions based on simulation for developing Robust method.

In vitro drug release (Y2)

Drug release for all formulations was found to be in the range of 78.9 % to 102.56% (Figure 5).

In vitro drug release data was analyzed and found that interaction of X was highest with (65.46%) and a positive sign of the coefficient (3.518%). It indicated that the increase in the amount of X_1 , increased the drug release. (Table 7)

ANOVA was used to identify significant effect, Coefficient of determination $R^2 = 0.947$. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p < 0.05$). The critical value of F is 6.59, obtained F value (i.e. 9.223) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p < 0.05$ i.e. indicates significance at that level of probability. R^2 model found to be significant hence this model has been used for predictions. R^2 model found to be significant hence this model has been used for predictions. The relationship between $Y2$ Vs X was found to be linear as shown by Sigma tech software, shown in table 8. By entering the values in Sigma tech at two variable optimization modules, the following statistical quadratic model has been obtained.

Final equation in terms of coded factors

$$\text{Drug release (Y2)} = 86.7475 + 2.8125 X_1 - 4.0875 X_2 + 0.9475 X_1 X_2$$

Final equation in terms of actual factors

$$Y2 = 86.7475 + 2.8125 \text{ DBP} - 4.0875 \text{ IP} + 0.9475 \text{ DBP IP}$$

Where $Y2 = \text{In vitro drug release}$ $X1 = \text{DBP}$, $X2 = \text{IMP}$

The polynomial equations were used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative). The results of the multiple linear regression analysis revealed that drug release increased with increase in Banana powder, drug release decreased with increase in Ispaghula mucilage powder (Figure 6 & 7). Dehydrated banana powder due to its rapid capillary activity with faster wetting, highest dispersion time and pronounced hydration with little tendency to gel formation showed faster drug release. R^2 value was found to be 0.947, found to be greater than 0.70 suggesting that this model is reliable for all CQAs. Hence used to establish predictions based on simulation for developing robust method.

DISCUSSION

Banana powder and ispaghula mucilage powder are soluble in water. Angle of repose for banana powder and ispaghula mucilage powder were found to be 34.12 and 34.48 respectively, which indicates a better flow property. Angle of repose has been used to characterize the flow properties of powders, it also related to inter particulate friction or resistance to movement between particles. Density differences between the formulations were negligible and the density values of formulations were well within limits, indicating that the prepared dry blend were non-aggregated and indicated good free flowing property. The value of compressibility index was in the range of 14.28 % to 22.88 % and HR was in the range of 1.16 to 1.29. The values are shown in Table 2. The obtained data of post-compression parameters such as Average weight, thickness, hardness, friability, drug content, disintegration time, wetting time are shown in (Table 3 & 4). Tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications. The thickness of tablets was found to be 4.10 to 4.21 mm which shows uniform thickness due to uniform die fill. Hardness of the tablets was found to be 2.3-2.7 kg/cm². In all the formulations, the friability values were less than 1% and meet the Indian pharmacopoeia (I.P) limits. The percentage drug content of all the tablets were found in the range of 77.9-91.07% of Ketorolac tromethamine HCl, which was within the acceptable limits. The result of disintegration time of all the formulations was found to be 49-68 Seconds. It was observed that increase in concentration of dehydrated banana powder decreased disintegration time due to due to its rapid capillary activity and pronounced hydration with little tendency to gel formation and the results are in consistent with wetting and water absorption time. Increase in disintegration time of ispaghula mucilage powder due to reduction in solubility and increase in wetting time. The wetting time for all formulations was found to be in the range of 33±1.56 to 45±0.88 sec. (Table 4).

In vitro dispersion time for all the formulations was found to be 36±0.12 to 57±0.55 sec. *In vitro* disintegration data was analyzed and found that X_1 was highest with SS ratio (77.07%) and a negative sign of the coefficient (-5.5). It indicated that the increase in the amount of X_1 decreased the disintegration time. R^2 model found to be significant hence this model has been used for predictions. The relationship between Y_1 Vs X is linear as shown by Sigma Tech software. The results of the coefficients revealed that disintegration time decreased with increase in banana powder, disintegration time increased with increase in ispaghula mucilage powder. R^2 value was found to be 0.881 found to be greater than 0.70 suggesting that this model is reliable for all CQAs Hence used to establish predictions and contours/design space for developing Robust method (Table 5 & 6).

The best fit model with the highest correlation coefficient values or determination coefficients (R^2) for all the formulations was the

first order model. *In vitro* drug release data was analyzed and found that interaction of X_1 with SS ratio (31.0%) and a positive sign of the coefficient (2.81). It indicated that the increase in the amount of X_1 , increased the drug release. The relationship between Y_2 Vs X is linear as shown by Sigma Tech software. The results of the coefficients revealed that drug release increased with increase in banana powder, drug release decreased with increase in ispaghula mucilage powder. Dehydrated banana powder due to its rapid capillary activity with faster wetting, dispersion and pronounced hydration with little tendency to gel formation showed faster drug release. R^2 value was found to be 0.947, found to be greater than 0.70 suggesting that this model is reliable for all CQAs Hence used to establish predictions and contours/design space for developing Robust method (Table 7 & 8). The permitted composition dehydrated banana powder as 15 mg and ispaghula mucilage powder 8 mg all other ingredients remained same. Then Ketorolac tromethamine HCl fast dissolving tablets were formulated successfully and the statistically optimized formulation fulfilled all the physicochemical criteria (F5). *In vitro* disintegration time and *in vitro* drug release were carried out on the prepared optimized formulation to verify the theoretical prediction and were found to be 52 seconds and 95.4% respectively. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within 1.5 %. The experimental values were in agreed with the predicted values confirming the predictability and validity of the model (Table 9).

CONCLUSION

It can be concluded that the drawbacks of the conventional dosage forms of Ketorolac tromethamine HCl minimized by formulating Ketorolac tromethamine HCl fast disintegrating tablets using natural super disintegrants. In this study, the concentration of various super disintegrants were observed to have a profound and interactive effect on the disintegrating time and drug release as shown by the model obtained using central composite design. The data observed showed this experimental design was successfully applied to optimize the concentration of various super disintegrants to formulate fast disintegrating tablets with desirable properties of low disintegrating time and high drug release. It can be concluded that central composite design could be successfully applied for the development of Ketorolac tromethamine HCl fast disintegrating tablets with fewer numbers of trials and better quality attributes.

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