IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
July 2018 Vol.:12, Issue:4

Formulation and Evaluation of Sustained Release Matrix Tablet of Ketoprofen

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 23 June 2018
Accepted: 29 June 2018
Published: 30 July 2018

Keywords: Sustained release tablet, matrix system, Ketoprofen, HPMCK15M, HPMCK100M

ABSTRACT

The objective of this work is to develop sustained release matrix tablets of ketoprofen using a combination of HPMC polymers like (HPMC K4M, HPMC K15M, HPMC K100M). The quantity of polymer mix was optimized by using simplex centroid design. The matrix tablet was prepared by using a direct compression method and evaluated for *in-vitro* drug release studies. The statistical model generated displayed good predictive ability. The optimized formulation released16.62 % drug release at 2nd hand 85.05 drug release at 8th h. The release had a similarity factor of 88.62 % with that of commercial sustained release formulation.

INTRODUCTION:

Oral sustained-release formulations need to guarantee therapeutic plasma levels for an extended period of time thereby, improving the patients' compliance by allowing once-daily oral administration.[1] Ketoprofen is a non-steroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. Ketoprofen has pharmacologic actions similar to those of other prototypical NSAIDs, which inhibit prostaglandin synthesis. Ketoprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and alleviate moderate pain. [2] It is one of the most interesting compounds and is widely used in the treatment of rheumatoid arthritis, ankylosing spondylitis, and abdominal osteoarthritis cramps associated with menstruation.[3] Recently, additional interest in ketoprofen lies in their possible therapeutic benefits in the prevention of various cancers including colorectal and lung cancers and even in the treatment of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. [4]Short half-life (1.5 to 2 hours) necessitates administration of the drug three times a day.[5]This leads to noncompliance with treatment and as a result, various attempts to sustain ketoprofen delivery have been reported as led to the design of sustained release matrix tablet of ketoprofen.[6]Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. in tablets, using hydrophilic polymers with high gelling capacities as base excipients are of three different grades of HPMC K4 M, K15 M and K100 M, which can lead to rheological synergism between these three grades of HPMC and optimized using simplex centroid optimization model.[7]The adjustment of the polymer concentration, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates.[8]

MATERIALS AND METHODS:

Ketoprofen gift sample was obtained from (BEC Chemical PVT.LMD.Raigad, India) and hydroxypropylmethylcellulose HPMC (K4M, HPMC K15M, HPMC K100M) (Colorcon, asiapvt. Lmt. Goa, India) and all ingredient obtained from the local supplier.

Drug-excipient compatibility study

The drug-excipient interaction was studied by FTIR spectroscopic technique. The spectrum of ketoprofen and ketoprofen mixtures with K4M, K15M, K100M were stored at elevated

temperature (40^0C) for two weeks and IR Spectra were recorded using Jasco V-730 spectrophotometer.

Formulation of matrix tablet

Sustained release matrix tablets of ketoprofen were prepared by direct compression. The formulation contained a varying proportion of different grades of Hydroxypropyl methylcellulose (HPMC) namely HPMC K4M, HPMC K15M, HPMC K100M) shown in table 1.

The 3 factorial simplex centroid design was applied to optimize the concentration of HPMC Grades.

The active ingredient, Ketoprofen, different grade polymer HPMC K4M, HPMC K15M, HPMC K100M, then powder blend was mixed for 10 min. all compositions table2.subjected to precompression analysis such as bulk density, tapped density, compressibility index, the angle of repose were determined by standard procedures reported in the literature.[10]The blends were then compressed *at the* constant pressure on *Rimek Mini press II MT* tablet press make Karnavati using B tooling. The composition of seven optimized was meant in table 2.

Mixture design - Simplex Centroid Design

A simplex centroid design was adopted to optimize the formulation variables [22]. Mixture design was used to optimize the formulation with HPMC K4M, HPMC K15M, HPMC K100M as independent elements. Percent drug release matrix 2nd and 8thhour were selected as dependent variables.[9]

Table 1. Code factor and levels of simplex centroid design.

Code factor	Level	Factor 1 The quantity of HPMC K15M	Factor 1 The quantity of HPMC K4M	Factor 1 The quantity of HPMC K100M
0	Low	33.33	33.33	33.33
1	High	100	100	100

The composition of 7 optimization runs as per experimental design is given in table 2.

Table 2. Composition of 7 optimization runs as per simplex centroid

Formulation	Ketoprofen	HPMC K15M	HPMC K4M	HPMC K100M	Talc	Magnesium stearate
F1	200	0	100	0	3	3
F2	200	100	0	0	3	3
F3	200	0	0	100	3	3
F4	200	50	0	50	3	3
F5	200	50	50	0	3	3
F6	200	0	50	50	3	3
F7	200	33.33	33.33	33.33	3	3

(All quantity taken in mg)

Pre-compression analysis

The Tablet evaluated was an angle of repose, bulk density, tapped density, Carr's index was determined as per the procedure is given in the literature.[10]

Post-compression analysis

The hardness, friability uniformity drug content of tablet was conducted as per procedure reported in the literature.[10,11]

***In-vitro* drug release studies**

Dissolution study of all tablet formulations was done in rotating basket (USP method I) in pH 7.4 phosphate buffers at 37 ± 0.5 °C at 100 rpm, the pH of 7. Samples of 5 ml were taken at time intervals of 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 10.0,11,0 and 12h filtered through 0.45 µm. Then all samples were analyzed spectrophotometrically (UV–Visible spectrophotometer, LABINDIA UV-3000) at a wavelength of 260 nm.[12,13]

Estimation of drug content

Twenty tablets were triturated and the quantity of powder equivalent to 200mg of ketoprofen is accurately weighed and transferred to 100ml of volumetric flask and extracted with phosphate buffer pH 7.4, keeping in a sonicator for 2 h. Then Solution was filtered, suitably

diluted and absorbance was measured at 260 nm using a double beam UV spectrophotometer (LABINDIA UV-3000) against phosphate buffer as blank.[14]

Similarity factor

The similarity factor (f) is used for release profile comparison between the test formulation and marketed preparation.

$$f_2 = 50 \times \log\left\{ \left[1 + (1/n)\sum_{j=1}^{n} |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\}$$

It is a logarithmic transformation of the sum squared error of differences between the test Tj and reference products Rj over all time points

Where 'n' is a number of pull points, 'Rj' is reference profile at time point t, 'Tj' tests profile at same time point t. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profile are identical and tends to 0 when dissimilarity increases.[15]

Kinetic modeling of drug release:

The dissolution profile of all the batches was fitted to various models such as zero-order, first order, Higuchi and Korsmeyer and Peppas, to ascertain the kinetic modeling of drug release.[16,17]

RESULT AND DISCUSSION

Calibration curve of Ketoprofen:

The ketoprofen show linearity in phosphate buffer pH 7.4 (R^2=0.9978) in the concentration range of 5-30 µg/ml. the equation of line ware Y= 0.0578×- 0.011.fig 1

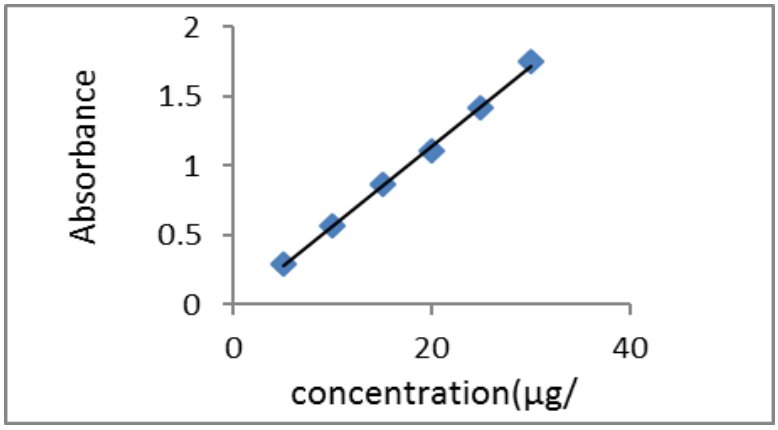

Figure 1: Calibration curve of ketoprofen.

Drug-excipient compatibility:

Table 3: Characteristic peaks of pure Ketoprofen

Sr.no	Type of bond	Type of vibrations	Actual frequency(Cm-1)	Observed frequency(Cm-1)
1	C-H	Stretching	3200-2500	2985.91
2	C=O	Stretching	1443.31	1417.73
3	C=C	Stretching	1395-1600	1591.33
4	C-O	Stretching	1059-1268	1232.55

The FTIR spectrum of pure ketoprofen shows a weak peak at 2985.91 cm^{-1} due to the presence of Aromatic C-H stretch. It shows a characteristic peak at 1417.33 cm-1 for C=O stretch of keto group and 1591.33 cm^{-1} for C=O stretch of carboxylic acid, a weak peak at 1443.31 cm-l, 1232.55cm^{-1} for CH deformation of CH symmetrical. All these peaks of pure Ketoprofen were present in the FTIR graphs and show excellent compatibility with pure ketoprofen and various grade HPMC polymers like HPMC K4M, HPMC K15M, HPMC K100M.

Formulation of Tablets

Formulation of Matrix tablets was done by direct compression method.

Table 4: Composition of formulations of sustained release tablets of Ketoprofen.

Formulation	Ketoprofen	HPMC K15M	HPMC K4M	HPMC K100M	Talc	Magnesium stearate
F1	200	100	0	0	3	3
F2	200	0	100	0	3	3
F3	200	0	0	100	3	3
F4	200	50	50	0	3	3
F5	200	50	0	50	3	3
F6	200	0	50	50	3	3
F7	200	33.33	33.33	33.33	3	3

All the weights of ingredients are taken in mg.

Pre-compression analysis properties of tablets blends.

Table 5: Pre-compression parameters of excipient blend for 7 optimization runs. *(n=3)*

Formulation	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose
F1	0.476	0.556	14.29	1.12	26.6
F2	0.455	0.526	13.64	1.14	27.4
F3	0.417	0.469	11.13	1.13	24.5
F4	0.435	0.500	13.04	1.15	28.3
F5	0.430	0.494	12.94	1.12	23.2
F6	0.468	0.526	11.05	1.17	29.9
F7	0.465	0.526	14.84	1.15	26.5

The bulk density ranged between 0.430-0.476 is good for matrix tablets compression, tapped density ranged between 0.469 - 0.556, Carr's index ranged between 11.05-14.84, Hausner ratio was between the 1.12-1.17and angle of repose was between 24.5-29.9 show excellent flow properties

Post-compression analysis

The post-compression analysis of matrix tablets blend is summarized in Table 6

Table 6: Post-compression analysis

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Diameter (mm)	Thickness (mm)	Friability (%)	Drug content (%)
F1	302±1	5.6±0.10	10.01±0.01	4.35±0.02	0.17±0.02	97.32±0.6183
F2	306±1	6.6±0.25	10.02±0.01	4.18±0.01	0.25±0.04	97.82±0.5458
F3	305±3	5.8±0.35	10.04±0.01	4.31±0.03	0.35±0.01	98.02±0.3827
F4	303±2	6.7±0.21	10.03±0.01	4.35±0.04	0.27±0.03	97.83±0.7930
F5	304±4	5.4±0.15	10.01±0.01	4.25±0.03	0.35±0.04	92.20±0.4589
F6	302±1	6.5±0.31	10.05±0.01	4.28±0.02	0.17±0.06	96.06±0.6808
F7	305±2	6.6±0.32	10.03±0.01	4.33±0.02	0.30±0.09	98.21±0.2857

Prepared matrix tablets were hardness 5.4-6.7 kg/cm2 and Friability was shown 0.17-35 ≤ 1.0 % w/w acceptable ranged; drug content was 92.20-98.21 %.

Drug profile of ketoprofen sustained release matrix

The dissolution drug release profile of ketoprofen sustained release matrix of simplex centroid batches are shown in fig 1. From release profiles of the matrix we can see that formulation F1 to F7 show drug releasebetweenthan10- 20% at 2nd hand release between 45.24 to 89.58 % at 8th h.

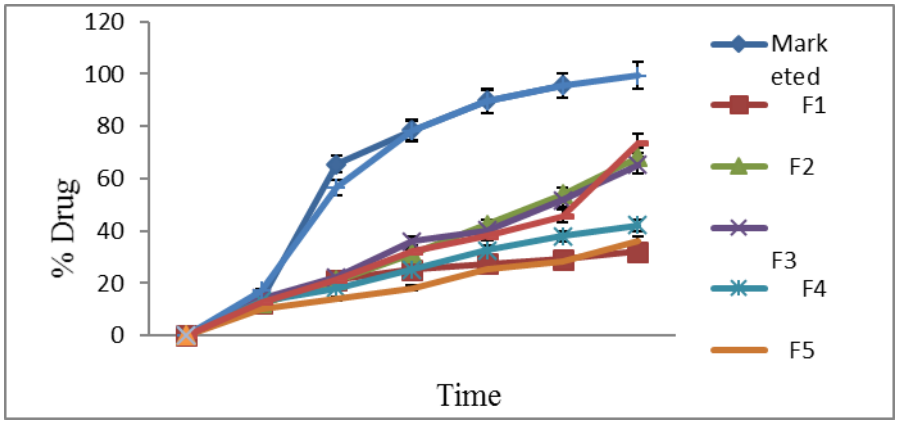

Figure 2: Drug release profile of formulation of F1-F7 of Simplex centroid.

Kinetic modeling of drug release

Table 7: Kinetic modeling of drug release.

Formulation	Zero-order	First order	Pappas	Matrix	Hixson-Crowell	Best fit model
	R2	R2	R2	R2	R2	
F1	0.9751	0.9752	**0.9977**	0.9773	0.9752	Peppas
F2	**0.9978**	0.9977	0.9289	0.9931	0.9971	Zero order
F3	0.9926	**0.9927**	0.9827	0.9429	0.9921	First order
F4	0.9776	**0.9858**	0.9424	0.9775	0.9775	First order
F5	0.9798	0.9800	**0.9882**	0.9691	0.9799	Peppas
F6	0.9967	0.9957	0.9175	**0.9981**	0.9965	Matrix
F7	0.9649	0.9650	0.0.9842	**0.9979**	0.9650	Matrix

The graphical representation of % drug release against time represents that drug release of ketoprofenmatrix tablet follows Higuchi drug release model. As the drug release profile is very close to the regression line and has the highest value of the coefficient of correlation, that the indicated matrix is the best-fitted model ($R^2$0.9981,9979).

Table 8: Similarity factor for optimized and marketed formulation.

Optimized formulations	f2 value	Consideration
Optimized batch	88.62	Similar

Optimization of ketoprofen sustained release matrix

The equation for drug release at 2nd and 8th h equation 1 and 2 respectively indicate the profound effect of HPMC 15 and K100 on drug release at 2nd h. whereas it was HPMC K4 M which influenced release at 8th h. Together the polymers retarded the release which may be attributed to rheological synergism between the polymer grades

1) For 2nd h release:

$$+10.37 * A + 12.50 * B + 16.38 * C - 12.22 * AB - 11.07 * AC + 5.58 * BC \ldots\ldots (1)$$

2) For 8th h release:

$$+75.80 * A + 49.47 * B + 38.10 * C - 35.22 * AB + 25.15 * AC - 30.25 * BC \ldots \ldots (2)$$

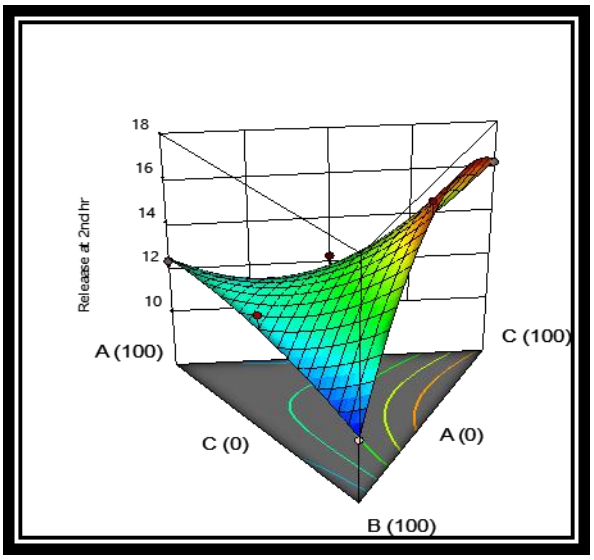

Figure 3: 3D response Surface plot for drug release at 2h

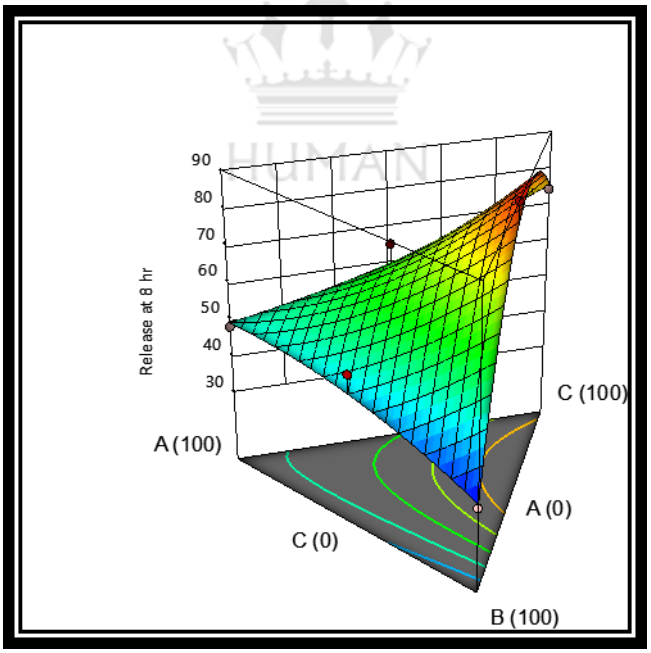

Figure 4: 3D response Surface plot for drug release at 8 h.

Table 9: Regression analysis, associated p-value and F value for all two responses.

Response	R2	Adjusted R2	Predicted R2	Model F-value	Model P-value	Adequate precision
2^{nd}hr % drug Release	0.9993	0.9956	0.6901	271.32	0.0500	46.73
8^{th} h % drug Release	0.9998	0.9987	0.9110	293.27	0.0500	98.02

Table 10: Validation of mode

Optimized formulation	Response variable	Experimental value	Predicted value	Percentage prediction error	Desirability
	Y1	17.135 %	16.62%	0.32	0.99
	Y2	85.26%	85.05%	- 0.21	0.94

Here, Y1: Response at 2^{nd} hr, Y2: Response at 8^{th} hr.

Table 11: Composition of optimized batch

Ingredients	Quantity in mg
Ketoprofen	200
HPMC K4M	14.83
HPMC K15M	33.33
HPMC K100M	51.83
Talc	3.00
Microcrystalline cellulose	3.00
Total	305.99

Criteria given for optimization was drug release of 10-20% at 2^{nd} h and 75–90%h at 8^{th} h. The composition of the optimized batch is described in table 8 which is similar to toF6. The evaluation of the prepared optimized batch showed good agreement with predicted results Table 9, low %error shows the prognostic abilities of the model are robust and hence the model is validated.

The release profile of the optimized batch, when compared with selected marketed formulation on basis of similarity factor f2, showed that formulations were similar (f2= 88.62).

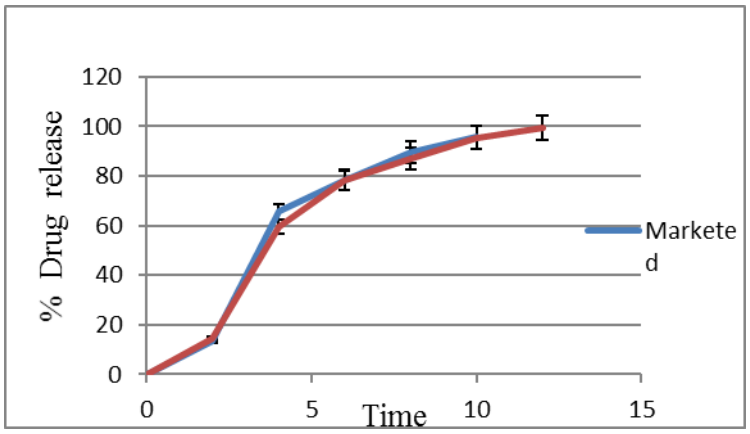

Figure 5: Drug release of marketed formulation and optimized batch (F6).

CONCLUSION

In the present study, A simplex centroid design was applied to observe the combined effect of the three variables in the formulations. at a higher level of HPMC K100M on the amount of drug released at drug release at 2ndhr 16. % and at 8thhr drug release at 85.05%, respectively. It was concluded the combination polymer shows better release in combination and so HPMC K100Mwas increased it showed the retardant release. Optimized formulation F6 was shown better drug release then marketed formulation.HPMC was release retardant polymer hence, it better for preparation of sustained release formulation, the release had similar with marketed formulation 88.62 %. Optimized formulation was fitted in matrix release kinetics 0.9981.

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