Research Article

FORMULATION AND EVALUATION OF KETOPROFEN TRILAYERED MATRIX TABLET

K. Navaneetha ^{*1}, T. Saritha ², B. Venkateswara Reddy ³, N. Jabili ², B. Soujanya ⁴

¹Department of Pharmaceutics, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana, India

²Department of Industrial pharmacy, St.Paul's College of Pharmacy, Hyderabad, Telangana, India

³Department of Pharmaceutics, Santhiram College of Pharmacy, Nandyal, Kurnool, Andhra Pradesh, India

⁴Department of Pharmaceutical Analysis, St.Paul's College of Pharmacy, Hyderabad, Telangana, India

*Corresponding Author Email: navaneetha.kn222@gmail.com

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ABSTRACT

The aim of the present work is to design and evaluate the controlled release Ketoprofentrilayered matrix tablets, to release the drug for prolonged period of time, which follows zero order kinetics by maintaining a constant drug level in the plasma. Formulations were prepared by using different ratios of polymers like Hydroxy propyl methyl cellulose (K100 & 6 cps) and Ethyl cellulose. The FTIR analysis assured compatibility of drug and excipients. Trilayered tablets containing middle drug core layer and either side of core layer, a barrier polymer layers present, prepared by wet granulation method. After formulation development, the trilayered tablets were evaluated for their appearance, hardness, friability, weight variation, disintegration time, assay, *in-vitro* drug release and stability studies. Core granules which have shown the desired drug release were selected to prepare the trilayered matrix tablets. Based on the evaluation studies FF8 formulation was optimized. FF8 showed *in-vitro* drug release of 95.8% for 24h which is shown to have better release than marketed preparation hence considered as most promising preparation. Drug release values of optimized formulation (FF8) were subjected to mathematical kinetic modeling, and the correlation coefficient (R^2) values drug release follows zero-order (0.994) kinetics and mechanism of drug release is by KorresmayerPeppas model (0.993). FF8 formulation subjected for accelerated stability study for 3 months and the formulation was found to be stable during the study period.

Keywords: Ketoprofen, Trilayered matrix tablets, Controlled release, HPMC 6cps, Ethylcellulose.

INTRODUCTION

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms.^{1,2} Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms.³⁻⁶

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant.⁷⁻⁹ Hydrophilic polymers are widely used in the formulation of modified release oral dosage forms. Various synthetic polymers (hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, poly methyl methacrylates, etc) and natural materials (xanthan gum, guar gum, chitosan, etc.) have been tried by various researchers.¹⁰ Hydrophilic polymers are quite popular in formulating oral controlled release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology. It has been shown in case of hydrophilic matrices, swelling as well as erosion of the polymer occurs

simultaneously and both of them contribute to the overall drug release rate¹¹⁻¹⁵.

The advantages of using the matrix system as a barrier to control the drug release, as opposed to the polymer membrane are, the thickness of the barrier layer can be adjusted more easily than the spray coating of polymer, and it is possible to incorporate the desired drug into the barrier layer. Sometimes two or more matrixing agents are used to overcome the disadvantages of a particular matrixing agent or to achieve a desired drug-release pattern¹⁶. The basic mechanisms/processes of drug liberation from such system is governed by swelling/erosion, dissolution/diffusion, osmosis, ion-exchange, polymer coating/membrane barrier, specific geometry and surface modification.^{16,17}

A new multi-layer tablet design has been proposed for constant drug release: Geomatrix[®] Technology. It consists of a hydrophilic matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both faces of the core. The presence of the coatings modifies the hydration/swelling rate of the core and reduces the surface area available for drug release. The receding drug zone in the middle (matrix) layer may be balanced by opening up of newer surface due to erosion of the coat layer. Thus these coatings provide a modulation of drug release profile and shift the typical time-dependent release rate towards constant drug release.¹⁸

MATERIALS AND METHODS

Materials

Ketoprofen was obtained from trinity pharma labs, Hyderabad. HPMC, Sodium carboxy methyl cellulose and talc were procured from S.D. Fine chemicals Ltd, Mumbai, ethyl cellulose and dibasic calcium phosphate from Evoniks pharma pvt. ltd, Hyderabad, starch and magnesium stearate were obtained from Qualigenes fine chemicals Ltd, Hyd.

Formulation of controlled release Ketoprofen Trilayered matrix tablets¹⁹⁻²²

The Trilayered matrix tablets of Ketoprofen were prepared by wet granulation method. The first step in the formulation was to develop the middle hydrophilic layer so as to give at least 90% drug release during 12 hours ($t_{90\%}$). The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This hydrophilic layer would then be sandwiched between hydrophobic layers so as to continue the drug release for 24 hours, the release being of constant rate type.

The matrix tablets containing 100mg/tab drug were prepared by wet granulation method with HPMC and other excipients and for hydrophobic layer, the polymer, Dibasic calcium phosphate is used. The tri-layered tablets were prepared by placing first the portion of hydrophobic layer granules in tablet die, followed by

hydrophilic layer granules, topped by hydrophobic layer powder. This system was compressed to give tri-layered tablets.

The size of hydrophobic barrier layer of 150 mg on both sides (top and bottom layers) and that of hydrophilic core layer was 350 mg. The preparation of tri-layered matrix tablets includes the following steps:

- Preparation of hydrophilic core granules of Ketoprofen for the matrix formulation.
- Preparation of hydrophobic barrier granules for rate controlling of drug release.
- Compression of hydrophobic layers on both sides of the core layer.

Preparation of Ketoprofen matrix core granules

Eight formulations (F1-F8) for matrix core granules were prepared by wet granulation procedure using non-ionic hydrophilic polymers HPMC K100 and HPMC 6cps, DCP as filler, starch paste 10% as binding agent. The cohesive mass obtained was passed through sieve number 18, dried at 50°C for 1hr in a tray dryer. Then the granules were lubricated with magnesium stearate and talc in 1:1 ratio, as shown in Table 1. The core granules were evaluated for drug release studies and the formulation which shows satisfactory drug release was selected to prepare the trilayer tablets.

Table 1: Formulation trials for Ketoprofen core layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ketoprofen	100	100	100	100	100	100	100	100
HPMC K 100	105	122.5	140	157.5	-	-	-	-
HPMC 6 cps	-	-	-	-	105	122.5	140	157.5
Starch paste (10%)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Sodium carboxy methyl cellulose	35	35	35	35	35	35	35	35
Dibasic calcium phosphate	103	85.5	68	50.5	103	85.5	68	50.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight (mg)	350	350	350	350	350	350	350	350

Preparation of barrier layer granules

The barrier layer containing anionic sodium CMC, ethyl cellulose (EC) were prepared by wet granulation technique. The polymers EC, sodium CMC and 10% starch paste were mixed

well and the resulting wet mass was passed through sieve no 18 and dried at 30°C for an hour. To increase the flow property of the granules and to prevent its adhesion to die and punches the granules were lubricated with talc and magnesium stearate as shown in Table 2.

Table 2: Formulation trials of Barrier layer

Ingredients	A	B	C	D	E	F
Sodium CMC	22.5	30	37.5	45	52.5	60
Ethyl cellulose	7.5	7.5	7.5	7.5	7.5	7.5
Starch paste (10%)	Qs	Qs	Qs	Qs	Qs	Qs
Dibasic calcium phosphate	117	109.5	102	94.5	87	79.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Total weight (mg)	150	150	150	150	150	150

Compression into tri-layered tablets

Tri-layered matrix tablets containing Ethyl cellulose as release retardant layer on both sides of middle layer containing Ketoprofen and HPMC were prepared as follows:

- The granules mixture required for a core and barrier layers were weighed accurately.
- Initially, the volume of die cavity; (11mm, round) was adjusted equivalent to the weight of tri-layered matrix tablets (650mg).
- Then the pre weighted amount of granules equivalent to bottom layer (150mg) was taken and placed in the die cavity and slightly compressed for uniform spreading and upper punch was lifted up.
- The 350mg of the drug containing middle layer formulation was placed over the bottom layer in the die cavity and again slightly compressed and upper punch was lifted up.
- The remaining volume of the die cavity was filled with pre weighted (150mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered matrix tablets.

- Tri-layered matrix tablets of each composition were compressed and tested for their friability, hardness, drug content and drug release characteristics.

EVALUATION TESTS

Evaluation of pre compression parameters

The flow properties of the prepared granules were estimated by determining the Angle of repose, Carr's index, and hausner's ratio. The angle of repose was measured by the fixed funnel and free standing cone method. The Bulk density and Tap densities were determined for the calculation of Hausner's ratio and Carr's Index.^{23,24}

Evaluation of Tri-Layered Matrix Tablets²⁴⁻²⁶

Friability: A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

$$\% \text{ Friability} = \text{Final weight} / \text{Initial weight} \times 100$$

Assay: 20 tablets were accurately weighed and powdered. 10mg equivalent powder was dissolved in 50ml distilled water and sonicated for 15 minutes. It was filtered and washed with distilled water. Filtrate and washings were combined. Final volume was made up to 100ml with distilled water. Absorbance of this solution was determined in a UV spectrophotometer at 260nm. Amount of Ketoprofen in tablets was calculated by using regression equation.

In-vitro drug release determination: The core granules (core layer) prepared was evaluated initially for the drug release and the best formulation was selected to prepare the trilayered matrix tablet. These trilayered matrix tablets were then evaluated for the release of drug from the matrix tablets using the dissolution test apparatus, USP 2 (paddle method) and the buffer used is phosphate buffer pH 7.4 which is maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. the RPM is set as 50 and samples were withdrawn at specified time intervals, after each aliquot withdrawal, the volume of dissolution medium was maintained constant by replenishment with the fresh medium at 37°C . The aliquots were suitably diluted, if required, and analysed by using Shimadzu UV-Visible Spectrophotometer.²⁷

Drug release models: Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. To describe the kinetics of the drug release from matrix tablet, mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-of fit test.²⁸⁻³⁰

- The zero-order kinetics (equation 1) describes the systems in which the drug release rate is independent of its concentration.
- The first order kinetics (equation 2) describes the systems in which the drug release rate is concentration dependent.
- Higuchi (equation 3) described the release of drug from an insoluble matrix as square root of time dependent process. The Higuchi square root model also gives the drug release from a planer surface of an insoluble heterogeneous matrix

by diffusion through the intragranular openings created by porosity of the matrix tablet.

- In case of Korsmeyer-Peppas model, the drug release from such devices having constant geometry will be observed till the polymer chains rearrange to equilibrium state. Korsmeyer-Peppas model (equation 4) describes the fraction released Q_t/Q_∞ as power function of time t for short time period.

$$\begin{aligned} Q_t &= K_0 t & \dots\dots\dots 1 \\ Q_t &= Q_0 (1 - e^{-k_1 t}) & \dots\dots 2 \\ Q_t &= K_H \sqrt{t} & \dots\dots\dots 3 \\ Q_t / Q_\infty &= K_k t^n & \dots\dots 4 \end{aligned}$$

Q_t – is the amount of drug release in time t , Q_0 – is the initial amount of the drug, F – is the fraction of drug release in time t , n – exponent value, And K_0 , K_1 , K_H , K_{HC} and K_k are release rate constants for zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model rate equations respectively.

Stability studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and shelf lives to be established.

ICH specifies the length of study and storage conditions as follows

- Long term testing $25^\circ\text{C} \pm 2^\circ\text{C} / 60\% \text{ RH} \pm 5\%$ for 12 months
- Accelerated testing $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \text{ RH} \pm 5\%$ for 6 months
- In the present study, stability studies were carried out at $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$, for a specific time period up to 90 days for developed formulation.
- Samples were removed after 4, 8 and 12 weeks intervals and studied for visual appearance, Ketoprofen content, and in-vitro drug release.

RESULTS AND DISCUSSIONS

Evaluation of matrix tablets

Release profiles of Ketoprofen core layer formulations (F1-F8)

The matrix tablets of Ketoprofen were prepared without the barrier layers. All the formulation trials were subjected to in-vitro dissolution studies to determine the release profiles and represented in the table-3. The formulations F2 & F3 showed complete drug release in just 8 to 10 h. The formulation F4, F5 & F6 showed 85-86% of drug release up to 12h. The formulations F1 & F7 showed 90 - 92% of drug release in 12h but they showed very high amount of drug release in the first hour. After observing the release profiles of all the formulations, the formulation F8 was found to follow a near zero order release. It releases about 98.9% of the drug by the end of 12hours, where the release was found to be dependent on the concentration of the drug in the matrix tablet. In accordance with the above results, the formulation F8 was chosen to form the active layer of the trilayer tablets which were formulated later.

Table 3: Release profile of Ketoprofen core layer formulations F1-F8

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
1	27±0.05	27.5±0.08	38±0.03	19.4±0.12	22.8±0.5	20.3±1.2	27.8±0.05	10.0±0.02
2	42.6±0.03	39.1±0.02	48.2±0.05	30.3±0.08	45±0.12	34.4±0.5	41.1±1.2	19.5±1.2
4	63.8±0.5	56.3±0.12	59.5±0.03	54.1±0.04	54.8±0.03	47.0±0.08	50.7±0.05	35.3±0.02
6	76.1±0.02	73.0±1.2	75.8±0.05	62.6±0.08	59±0.12	59.2±0.03	61.7±0.5	53.5±0.02
8	83.0±0.05	100.7±1.2	96.8±0.05	70.8±0.02	69.5±0.5	65.4±0.12	85.7±0.03	67.1±0.05
10	89±0.12		100±0.03	76±1.2	79±0.02	72.0±0.5	88.3±0.02	85.0±1.2
12	90.9±0.03			85.2±0.05	87.7±0.5	85.5±0.03	92.4±1.2	98.9±0.05

* All values are the mean of six readings ± SD

Flow properties of trilayer tablets granules

All the powder mixtures belonging to different formulations were tested for micromeritic studies in order to determine the flow properties. All the powder mixtures showed good flow with formulations AF8-FF8 and are represented in the Table 4.

Table 4: Flow properties of trilayer tablets

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Carr's index (%)
AF8	0.623± 0.04	0.785± 0.02	23.6	8.5
BF8	0.615± 0.4	0.659± 0.01	33.8	7.4
CF8	0.586± 0.02	0.785± 0.02	24.4	8.0
DF8	0.675±0.14	0.795±0.03	25.1	9.3
EF8	0.715±0.5	0.770±0.03	25.5	7.0
FF8	0.695±0.2	0.695± 0.01	23.0	8.1

Evaluation of trilayer tablets for physical parameters

The physical properties of all the tablets are within the limits and the hardness ranges in between 5-7kg/cm². The assay results showed the percentage of drug from 94-99%. The tablets did not develop any cracks during manufacturing and there occurred no layer separation during the process of evaluation and the results are given the Table 5.

Table 5: Physical evaluation of trilayer tablets of Ketoprofen

S.no	Tests	AF8	BF8	CF8	DF8	EF8	FF8
1	Physical appearance a) Color b) Surface texture c) Shape d) Cracks	Off white Smooth Flat, trilayered Absent	Off white Smooth Flat, tri-layered Absent	Off white Smooth Flat, tri-layered Absent	Off white Smooth Flat, tri-layered Absent	Off white Smooth Flat, tri-layered Absent	Off white Smooth Flat, tri-layered Absent
2	Hardness (kg/cm ²)	6	7	6	5	5	7
3	Friability (%)	0.28	0.15	0.26	0.30	0.34	0.17
4	Weight variation (mg)	648±5	649±5	650±5	649±5	648±5	651±5
5	Assay (%)	95.5	97.7	96.6	98.4	94.1	99.5
6	Layer separation during dissolution	Absent	Absent	Absent	Absent	Absent	Absent

In-vitro dissolution studies of Ketoprofen trilayered tablets formulated in different trials

The formulation AF8 showed 96% of drug release in just 20h whereas the formulations BF8 & CF8 showed drug release 90-93% in 24 h but the release was not orderly. The formulation DF8 & EF8 showed drug release 99% in 20 h. The formulations

FF8 showed drug release of 95.8% after 24 h, and the drug release profile was found to be linear and predetermined. Hence the formulation FF8 was chosen to be the optimized formula based on its physical parameters as well as release profile and the formulation was compared with the marketed (Ketonac) product's release profile. The results are mentioned in the Table 6.

Table 6: In-vitro dissolution studies of Ketoprofen trilayered tablets

TIME (hours)	AF8	BF8	CF8	DF8	EF8	FF8
1	15.3±0.51	19.5±0.30	8.1±0.08	9.0±0.78	5.5±0.57	11.5±0.21
2	17.4±0.30	21.7±0.51	14.5±0.78	18.8±0.57	9.5±0.21	16.9±0.54
4	31.9±0.08	24.6±0.30	37.6±0.51	30.7±0.21	28.0±0.57	24.8±0.78
6	48.7±0.52	38.2±0.08	40.9±0.30	43.2±0.51	36.6±0.78	32.8±0.57
8	60.7±0.21	50.5±0.52	57.9±0.08	47.5±0.30	41.5±0.51	40.7±0.21
12	74.8±0.57	67.4±0.52	65.5±0.52	73.7±0.08	52.2±0.30	57.2±0.51
16	81.7±0.78	75.5±0.21	78.0±0.52	81.6±0.08	80.5±0.30	81.5±0.51
20	95.5±0.54	85.5±0.52	91.5±0.08	98.5±0.30	99.5±0.51	88.3±0.21
24		90.7±0.65	93.4±0.51			95.8±0.30

*All values are the mean of six readings ± SD

Cumulative percentage drug release from formulation FF8 and marketed product

The formulation FF8 showed linear release of drug and the release was independent of the drug concentration in the tablet, whereas innovator showed initially high concentration of drug release which later declined as duration of dissolution increased.

The results showed that the release of drug from innovator product was not linear and the release was dependent of the drug concentration in the tablet and is represented in the Table 7 and Figure 1.

Table 7: Cumulative % drug release from FF8 and marketed product

Time (h)	Cumulative % Drug Release	
	FF8	Marketed product (Ketonac)
1	11.5	16.3
2	16.9	24.4
4	24.8	40.8
6	32.8	57
8	40.7	75.2
12	57.2	98.8
16	75.5	
20	88.3	
24	95.8

Figure 1: In-vitro dissolution profile of FF8 and Marketed product

Kinetics of optimized formulation FF8

- The drug release from formulation FF8 was explained by zero order kinetics as the plot showed highest linearity ($r^2=0.994$), as the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release is independent of its concentration.

- The ' r^2 ' value of Higuchi plot was found to be 0.983 indicating that the drug release included diffusion as one of the release mechanisms.
- Based on the ' n ' value from the Korsmeyer-peppas equation the mechanism for drug release was determined. The ' n ' value of formulation was found to be 0.766, which refers to non fickian diffusion indicates combination of both diffusion and erosion controlled rate release. Interpretation is given in the Table 8 and Figures 2-5.

Table 8: Kinetics of optimized formulation FF8

Kinetic Model	ZERO Q Vs T	FIRST Log % Remain Vs T	HIGUCHI Q Vs $\sqrt{T}$	PEPPAS Log C Vs Log T
Slope	3.8674	-0.0561	23.136	0.7669
Intercept	7.9217	2.1436	20.303	0.9252
R^2	0.9943	0.8782	0.9831	0.9937

Figure 2: Zero order plot of FF8

Figure 3: First order plot of FF8

Figure 4: Higuchi plot of FF8

Figure 5: Korsmeyer- peppas plot of FF8

Stability studies

Stability studies have been carried out for the optimized formulation FF8 for 12 weeks at temperatures ranging from 40 °C and 75% RH and the results are given in the Table 9. The tablets remained physically stable after storage and they did not show any change in the release profiles even after the stability tests.

Table 9: Results of accelerated stability testing – Formulation FF8

Formulation FF8	Storage condition		Storage duration (week)	Visual appearance	<i>In-vitro</i> drug release profile (%)	Hardness (kg/cm ²)
	Temperature (°C)	Humidity (% RH)			In 24 h	
	40	75	0	No change	95.8	5.2
			4	No change	95.1	5.0
			8	No change	95.4	4.8
12			No change	94.5	4.9	

CONCLUSION

The effect of polymer level on drug release was studied by preparing matrix tablets containing different concentrations of HPMC K 100 and HPMC 6 cps by wet granulation method. The different release rates from these formulations were obtained from in-vitro dissolution studies. From the results it was observed that the release rate was greatly influenced by the polymer concentration. In order to obtain a formulation which releases more than 90% of drug within 12h, eight formulation trials of the active layer have been prepared and the drug release follows zero order kinetics similar to marketed product. Hence the formulation trial F8 showed about 98.9% drug release in 12 h, where the drug release was dependent on concentration of drug in the tablet. Trilayered matrix tablets were prepared by using formulation F8 as the active core and different concentrations of ethyl cellulose and Na CMC were used to form barrier layers on either side of the active layer. The assay results showed a drug content of about 95-100% with no layer separation during dissolution. The dissolution studies of the trilayer tablets showed their drug release within 20-24 h but the release is not in a linear manner for all the tablets. The formulation F with F8 as active core forming a trilayer tablet FF8 showed a drug release of about 95.8% in a linear manner and follows zero order kinetics i.e., drug release was independent of its concentration, whereas the marketed product showed a release of 98% in 12 h in a non-linear manner. The zero order plot of the formulation showed a highest linearity ($R^2=0.994$) followed by first order ($R^2=0.878$). The release data was fitted into Higuchi's model ($R^2=0.983$). So, the drug

diffuses at a comparatively slower rate from the matrix which is referred to as square root kinetics (or Higuchi's kinetics). Mechanism of drug release is explained by Korsmeyer-Peppas equation. The release exponent 'n' was 0.766, which refers to non fickian diffusion indicates combination of both diffusion and erosion controlled rate release. Accelerated stability studies were carried out for the optimized formulation FF8 in a ranges of temperature from 40 °C and humidity 75% RH. The results showed that there was no change in the appearance and physical properties of the tablets at the end of 12 weeks. The drug release was observed for nearly 24h even after the end of the stability studies and the release manner was similar to earlier. Hence this study resulted in the development of Ketoprofen controlled release trilayer matrix tablets which was superior to the marketed product, thus fulfilling the objective of the study.

REFERENCES

1. Tapaswi Rani Dash, Pankaj Verma. Matrix Tablets: An Approach towards Oral Extended Release Drug Delivery, International Journal of Pharma Research & Review, 2013; 2(2):12-24.
2. Ali Nokhodchi, Shaista Raja, Pryia Patel, Kofi Asare-Addo. The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems, BioImpacts, 2012; 2(4): 175-187.
3. Robinson Joseph R, "Controlled-Release Drug-Delivery Systems", Chapter-27, "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins, 20th ed, 2002, Vol. 1, Pp. 903-914.

4. Patel Harnish, Panchal Dhrupesh R., Patel Upendra, Tushar, Brahmbhatt Mayur Suthar, "Matrix Type Drug Delivery System: A Review", *Journal of Pharmaceutical Science and Bioscientific Research*, 2011; 1(3): 143-151.
5. Goodhart, F. W., Mc Coy, R. H., Ninger, F. C., Release of water - soluble drug from a wax matrix timed - release tablet, *J. Pharm. Sci.*, 63 (1974) 1748 - 1751.
6. Jain NK. Controlled and novel drug delivery. 1st ed. New Delhi: CBS publishers & Distributors Pvt. Ltd; 1997.
7. Chughlsha, Seth Nirmata, Rana A.C, Gupta Surbhi. Oral sustained release drug delivery system: An overview, *Int. Res. J. Pharm.* 2012; 3(5):57-62.
8. Hildgen, P., McMullen, J. N., A new gradient matrix formulation and characterization, *J. Controlled. Rel.*, 1993; 34: 263 - 271.
9. Danckwerts, M. P., Development of a zero - order release oral compressed tablet with potential for controlled tableting production, *Int. J. Pharm.*, 1994; 112 (1994); 34 - 45.
10. Sansom Lloyd N. Oral extended- release products. In: *Therapeutic Guidelines Ltd*, 1999; 22: 88-90.
11. Fassihi RA, Ritschel WA, Multiple-layer, direct-compression, controlled-release system: in vitro and in vivo evaluation, *Journal of Pharmaceutical Sciences*, 1992; 82: 750-754.
12. Yang, L., Fassihi, R., Zero - order release kinetics from a self - correcting floatable asymmetric configuration drug delivery system, *Journal of Pharmaceutical Sciences.*, 1996; 85: 170 - 173.
13. Qiu Y., Chidambaram N., Flood K, Design and evaluation of layered diffusional matrices for zero-order sustained-release, *Journal of controlled Release*, 1998; 51: 123-130.
14. Conte U., Colombo P, Maggi L, La Manna A, Compressed barrier layers for constant drug release in Swellable matrix tablets, *STP Pharma Sci*, 1994; 4: 107-113.
15. Fassihi, R., Rit - schel, W. A., Multiple - layer, direct compression, controlled release systems invitro invivo evaluation, *Journal of Pharmaceutical Sciences*, 1993; 82: 750 - 754.
16. Conte, U., Maggi, L., Colombo, P., La Manna, A., Multi - layered hydrophilic matrix as constant release device (Geomatrix™ systems). *Journal of Controlled Release*, 1993; 26: 39 - 47.
17. Yang, L., Fassihi, R., Modulation of diclofenac release from a totally soluble controlled release drug delivery system, *Journal of controlled Release*, 1997; 44: 135-140.
18. Benkorah, A. Y., McMullen, J. N., Biconcave coated, centrally perforated tablets for oral controlled drug delivery, *J. Controlled Rel.*, 1994; 32: 155 - 160.
19. ThawatchaiPhaechamud, Kotchamon and Garnpimol, Three-layered matrix tablets of Propranolol, *Asian Journal of Pharmaceutical Sciences*, 2008; 3 (6): 260-268
20. LadaniAniket, Dr.PatelMandev and Patel Vipul, Fabrication of Multi-Layer Matrix Tablets Of Venlafaxine Hydrochloride Using Hypromellose And Xanthan Gum, *Int. J. Drug Dev. & Res.*, 2011; 3 (3): 291-299.
21. Narayana Charyulu, SakhiaDarshan, ManavadariaKeyur, Bera Dinesh, Nisha G. Shetty, Shastry C. S., Design and evaluation of three-layer matrix tablet of Losartan Potassium capped with Eudragit and HPMC Combination, *International Journal of Research in Pharmaceutical Sciences*, 2012; 3 (2): 319- 325.
22. Izhar Ahmed Syed, Lakshmi NarsuMangamoori, Yamsani Madhusudan Rao, Formulation and Characterization of Matrix and Triple -Layer matrix tablets for Controlled Delivery of Metoprolol tartrate, *International Journal of Pharmaceutical Sciences and Drug Research* 2011; 3(1): 23-28
23. K. Navaneetha, Y. Upendar Rao, Dr. B. Venkateswara Reddy, T. Lavanya, Ch. Divya, K. Revanth Chandra. Formulation and Evaluation of Sustained Release Matrix Tablet of a Model Anti-Hypertensive Drug Using Natural Polymers, *International Journal of Current Trends in Pharmaceutical Research*, 2014; 2(4): 494-501.
24. L. Raimar, K. Jae Seung, and L. A. Gordon. Pharmacokinetics of and immediate release, a controlled release and a two-pulse dosage form in dogs. *Eur. J. Pharm. Biopharm.*, 2000; 60: 17-23.
25. M.Ravali, K.Navaneetha, B.Venkateswara Reddy, N.Karthik. Formulation and Evaluation of Controlled Release Matrix Tablets of Simvastatin, *World Journal of Pharmaceutical Research*, 2014; 3(4): 1706-1721.
26. B.Venkateswara Reddy, K.Navaneetha. Formulation and Evaluation of Sustain Release Tablets of Ramipril, *pharmatutor magazine*, 2014; 2(7):110-119.
27. Sandeep chavan, Sanjayantwar, Design and evaluation of once - daily sustained release matrix tablets of Nicorandil, *International journal of pharmacy and pharmaceutical sciences*, 2011; 3(2): 13-18
28. Nair A, Gupta R, Vasanti S. In vitro controlled release of Alfuzosin hydrochloride using HPMC-based matrix tablets and its comparison with marketed product. *Pharm Dev Tech*. 2007;12:621-5.
29. B.Venkateswara Reddy, K.Navaneetha. Formulation Development and In-Vitro Characterization of Bilayer Tablets of Amoxicillin and Famotidine. *International journal of pharma wave*, 2015; 1(3):112-122.
30. B.Venkateswara Reddy, K.Navaneetha. Formulation and Evaluation of Sustained Release Matrix Tablets of Zileuton. *Universal journal of pharmacy*, 2015; 04 (01): 66-71.

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