ejpmr, 2024, 11(7), 423-431

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF KETOROLAC TROMETHAMINE SUSTAINED RELEASE MATRIX TABLET USING *HIBISCUS ROSA–SINENSIS* LEAVES MUCILAGE AND HPMC E50

Elakkiyamani* and S. Merina Josephine

Department of Pharmaceutics, PPG College of Pharmacy, Coimbatore.

***Corresponding Author: Elakkiyamani**

Department of Pharmaceutics, PPG College of Pharmacy, Coimbatore.

Article Received on 13/05/2024 **Article Revised on 03/06/2024** **Article Accepted on 24/06/2024**

ABSTRACT

The present study was aimed to evaluate the Sustained release matrix tablet Keterolac Tromethamine was. formulated by natural and synthetic polymers to check the percentage drug release of drug in particular time limit . Ketorolac Tromethamine is a Non Steroidal Anti- inflammatory drug. KT is used for the short-term treatment of moderate to severe pain in adults. It is usually used before or after medical procedures or after surgery. Reducing pain helps you recover more comfortably so that you can return to your normal daily activities. In this synthetic polymer is an HPMC E50 and Natural polymer is *Hibiscus rosa-sinensis* in this research. In this study observed that by increasing the concentration of polymers had retarding effect on the drug release from the polymer matrices. The matrix tablet consist of F1, F2, F3, F4, F5, F6 six types of formulation was prepared by direct compression method. The prepared tablets were characterized for pre compression, post compression, in- vitro percentage release studies by using a different ratio's of polymers on release characterestics. The results of pre and post compression parameters were found within the standard pharmacopeial limits Formulation containing 60% of Hibicus mucilage is able to sustain 50% of drug over a period of 8 hrs part.

KEYWORDS: Keterolac Tromethamine, Hibiscus rosa-sinensis, HPMC E50.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in the part the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.[1] The conventional dosage forms are rapidly replaced by this novel controlled release techniques. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[2] The introduction of matrix tablet as a sustained release had made a new phase for the novel drug delivery system. Hydroxypropyl methylcellulose was the mostly used hydrophilic polymer to prolong the drug release pattern due to its gelling property, rapid hydration, and robust mechanism, choice in viscosity grades, non-ionic nature, reproducible release profile, cost effectiveness and good compressibility property.[5]

Sustained release system implies to the pharmaceutical dosage form formulated for retardation of release of therapeutic agent such that its appearance in the systemic circulation was delayed or prolonged and its plasma profile was sustained in duration. The onset of pharmacologic action was delayed and duration of therapeutic effect also delayed.[6] The aim of this work is to formulate a sustained release matrix tablets using natural gums as a matrix forming materials.

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on infield of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. The advantages of natural plant based excipients include low cost, natural origin, free from side effects, biocompatible, bioacceptable, renewable source; environmental friendly processing, local availability, better patient tolerance as well as public acceptance.

They improve the national economy by providing inexpensive formulations to people, using locally available materials. Cashew nut tree gum is a polysaccharide comprising galactose, arabinose, rhamnose, glucose, glucurine acid and other sugar residues. It has been used as matrix former for controlled

release tablet. Primarily cashew gum is used in industrial application for binding books, as adhesives for envelopes, label, stamps and posters. HPMC is used as matrix former represents non digestible material which forms gel in situ. The release of drug from these systems is controlled by penetration of water through a gel layer produced by hydration of polymer and diffusion of drug through the swollen, hydrated matrix, in addition to the erosion of gelled layer. The extent to which the erosion or diffusion controls the release depends on polymer selection as well as on the drug-polymer ratio used in the formulation. High drug polymer ratios result in formulations from which drug release is controlled by attrition.

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms. In actual practice direct compression of drug, retardant material, additives is done to form a tablet in which drug particles are embedded in the matrix core of the retardant. Dry or wet granulation technique may also be employed for the preparation of this type of tablets. Among the different strategies to prolong the drug action, formulation of matrix tablet has gained immense popularity now a day because it has the advantage of simple processing and a low cost of fabrication.

The loading dose is most convenient to include in a separate layer or in a coating applied to the tablet. An equation was developed by higuchi to explain the drug release from the matrix base, which was later on extrapolated to the diffusion of solid drug dispersed in homogenous polymer matrices. Sustained release matrix tablet can be prepared in two ways, one is direct compression of the powder blend containing the drug, polymer and other additives, and another one involves granulation prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients.

Sustained Release

SRF's describes the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period of time. Time depends on the dosage form. In oral form it is in hours, and in parenteral it is in days and months. Ex: Aspirin SR, Dextrin SR.

Advantages

- Decreased local and systemic side effects.
- Better drug utilization.
- Improved efficiency in treatment.

Disadvantages

- Decrease systemic availability in comparison to immediate release convention as dosage forms.
- Retrieval of drug is difficult in case of toxicity in case of toxicity, poisoning or hypersensitive reaction.
- Reduced potential for dosage adjustment of drug normally administered in varying strengths.

Potential Advantage of Sustained Release Dosage Form

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.
- Employ a less total drug.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing.

Recent Trends in Sustained Drug Delivery System: Sustained release dosage forms are categorized as:

1. Single unit dosage form.
2. Multiple unit dosage form.
3. Mucoadhesive system.

Polymers used in matrix tablet

Hydrogels: Polyhydroxyethylemethylacrylate (PHEMA), Crosslinked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene-oxide (PEO), Polyacrylamide (PA) (5).

Soluble polymers: Polyethyleneglycol (PEG), Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC).

Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides.[6]

Non-biodegradable polymers: Polyvinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyetherurethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

Mucoadhesive polymers: Polycarbophil, Sodium carboxy methyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Xanthan gum, Guar gum, Karaya gum, Locust bean gum

MATERIALS AND METHODS

Materials

Keterolac Tromethamine from Gift sample from Yarrow chemicals, Mumbai. HPMC E50 from Loba chemie, Mumbai. Lactose from Loba chemie, Mumbai. Avicel pH from Kemphasol laboratories, Mumbai. Talc from Loba chemie, Mumbai. Magnesium sterate from Himedia laboratories,Nashik.

Preformulation studies

Pre-formulation involves the application of biopharmaceutical principle to the physic- chemical properties of drug substance and are characterized with the goal of designing optimum drug delivery system. It pays a significant role in anticipating the formulation problems.

Preparation of Standard Calibration curve of Ketorolac Tromethamine

The standard calibration curve of Ketorolac Tromethamine was constructed using phosphate buffer pH 7.4 as solvent. Accurately weighed 10mg of Ketorolac Tromethamine was dissolved in 100 ml phosphate buffer pH 7.4 to get a stock solution of 100µg/ml. From these stock solution aliquots of 0.5, 1, 1.5, 2, 2.5,ml were withdrawn and further diluted with buffer to obtain a concentrations ranging from 5, 10, 15, 20, 25µg/ml. The absorbance of the resulting solutions was measured at 323nm on a UV spectrophotometer using phosphate buffer pH 7.4 as blank. The standard curve was obtained by plotting a graph of absorbance v/s concentration (µg/ml). (83)

Preparation of phosphate buffer p H 7.4

Accurately 50ml of 0.2M potassium dihydrogen phosphate was measured and transferred to 200ml volumetric flask and 0.2M sodium hydroxide was added to it. Volume was made to 200ml with distilled water and mixed well. The pH of the buffer was adjusted to 7.4 with 0.2 sodium hydroxide.

Preparation of 0.2M potassium dihydrogen phosphate solution

Accurately weighed 27.12g of potassium dihydrogen phosphate was dissolved in 1000ml of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution

Accurately weighed 8g of sodium hydroxide pellets were dissolved in 1000ml of distilled water and mixed.

Mucilage extraction

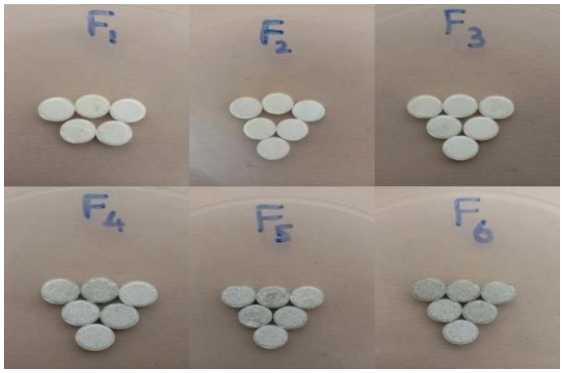
The fresh leaves of *Hibiscus rosa-sinensis* were collected and cleaned repeatedly with adequate water to remove dirt and debris. The washed leaves then dried until crispy nature. The leaves were then crushed and then kept soaking for 5–6 h. The leaves then were boiled for 30 min and let stand for 1 h for complete release of the mucilage. The mucilage was extracted using an eightfold muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of the filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, grounded, passed through sieve mesh #80 and stored in a desiccator at 35°C and 45% relative humidity till use.[84]

Preparation of Ketorolac Tromethamine matrix tablets

The sustained release matrix tablet of Ketorolac Tromethamine was prepared by using direct compression method. Various concentrations 20%, 40%, and 60%, of natural and synthetic polymers were used. Total six formulations were developed using constant 400 mg of ketorolac tromethamine with varying amount of excipients. The polymers used are Hibiscus rosa-sinensis leaves mucilage as natural polymer and Hydroxy Propyl Methyl Cellulose as synthetic polymer.[85]

Formulation of Ketorolac Tromethamine sustained release matrix tablets

Component	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Ketorolac tromethamine	200	200	200	200	200	200
Hibiscus rosa-sinensis leaves mucilage	80	120	160	-	-	-
HPMC E50	-	-	-	80	120	160
Lactose	54	34	14	54	34	14
Avicel PH	54	34	14	54	34	14
Talc	8	8	8	8	8	8
Magnesium stearate	4	4	4	4	4	4
Total weight of each tablet	400	400	400	400	400	400



RESULT

Mucilage characterization Taxonomical classification

Based on Taxonomical classification *Hibiscus rosa-sinensis* is classified under the Kingdom of Plantae, Class of Magnoliopsida, Order of Malvales, and family as Malvaceae.

Table 13: Taxonomical classification.

Kingdom	Plantae
Class	Magnoliopsida
Order	Malvales
Family	Malvaceae
Genus	Hibiscus
Species	Rosa- sinensis

Physical characterization

The extracted leaves mucilage powder appeared in greenish colour with characteristic odour. The granules are slowly soluble in hot water producing viscous solution. Fresh *Hibiscus rosa-sinensis* leaves produced

10 gm of dried mucilage per kg. The percentage weight loss on drying is 8.82± 0.58 and percentage moisture content is 9.70± 0.77.

Table 14: Physical characterization of *Hibiscus rosa-sinensis* leaves.

Physical properties	Observation
Appearance	Greenish Powder
Odour	Characteristics
Solubility	Soluble in hot water forming viscous solution
% yield	10 g / kg

Flow properties

Dried *Hibiscus rosa-sinensis* leaves mucilage powder has an excellent flow properties based on Angle of repose 19.36 ± 0.404, Bulk density 0.63 ±0.012 g/cm3, and Tapped density 0.72± 0.018 g/cm3. Based on USP, Carr's index with value of 9.40 ± 0.168% and Hausner's ratio of 1.15± 0.002 noted values in excellent range of flowability. The mucilage now regarded very suitable to be used in tablet manufacturing.

Table 15: Mucilage flow properties.

Flow properties	Observation
Angle of repose	19.36 ± 0.404
Bulk density	0.63 ±0.012
Tapped density	0.72± 0.018
Carr's index	9.40 ± 0.168
Hausner's ratio	1.15± 0.002

9.1.1 Analytical method development by UV Spectroscopy

Determination of λ max (wavelength of maximum absorption)

Maximum absorption of KT in UV spectrophotometer was found to 323nm

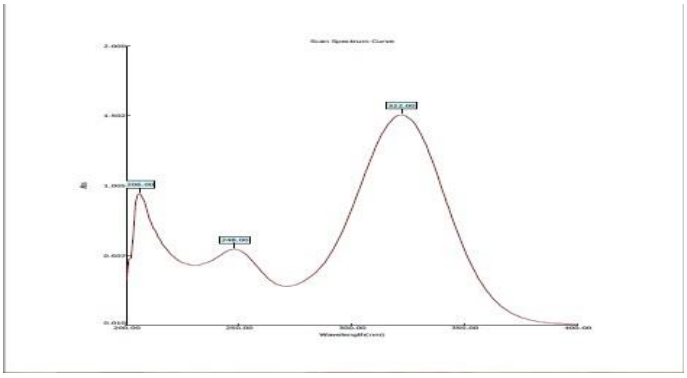


Figure 3: Scanned spectrum of Keterolac Tromethamine.

Absorbance of different concentrations of KT in phosphate buffer 7.4:

Table 16: Standard graph of KT in phosphate buffer 7.4.

Concentration	Absorbance
1	0.058
2	0.065
3	0.085
4	0.103
5	0.125
6	0.146

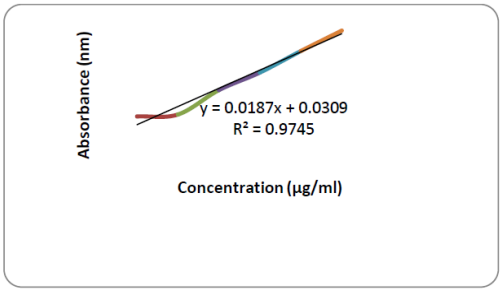


Figure 4: Calibration curve of KT in phosphate buffer 7.4.

9.1.2 Characterization of pre-compression blend

The pre-compression blend for matrix tablets was characterized with respect to Angle of repose, Bulk density, Tapped density, Carr's index. Angle of repose was found to be 25.37 to 29.70and carr's index values were less than 18 for all batches which indicates good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all batches indicates good flow properties.

Pre-compression parameters of different formulations

Batch Code	Parameter				
	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose(⁰)
F1	0.384	0.456	15.74	1.182	29.70
F2	0.351	0.447	15.18	1.179	28.38
F3	0.367	0.465	13.65	1.161	25.37
F4	0.385	0.452	14.38	1.174	29.54
F5	0.382	0.457	14.14	1.165	28.09
F6	0.389	0.446	15.87	1.179	27.95

Table 18: Physical evaluation of matrix tablets.

Batch code	Parameters				
	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	0.39± 3.65	5.29 ± 0.19	4.19 ± 0.15	0.59	97.8
F2	0.40± 2.44	5.65 ± 0.18	4.18 ± 0.19	0.54	96.4
F3	0.41± 3.63	5.87 ± 0.23	4.16 ± 0.12	0.59	99.13
F4	0.40± 3.87	5.57 ± 0.17	4.17 ± 0.08	0.67	97.42
F5	0.39± 3.54	5.67 ± 0.18	4.07 ± 0.17	0. 65	98.57
F6	0.42± 3.36	5.37 ± 0.24	4.15 ± 0.11	0.71	99.74

The physical parameters like weight variation, hardness, thickness, friability of the tablets were within the pharmacopoeia limits.

Table 19: Dissolution Profile of F1- F3formulations.

Time (hrs)	Formulation Code		
	F1	F2	F3
0	0.0	0.0	0.0
0.125	1.35±0.20	1.37 ±0.10	1.12 ±0.15
0.25	6.75 ±0.65	6.75 ±0.45	4.95 ±0.198
0.5	11.7 ±0.09	6.97 ±0.31	6.75 ±0.54
1	14.85 ±0.12	13.5 ±0.24	10.1 ±0.86
2	25.2 ±0.251	21.15 ±0.49	12.8 ±0.87
3	37.8 ±0.35	27.45 ±0.24	18.3 ±0.36
4	44.1 ±0.39	36 ±.54	23.17 ±0.44
5	48.37 ±0.45	44.55 ±0.17	36.9 ±0.43
6	51.3 ±0.68	49.5 ±0.71	40.5 ±0.78
8	58.94 ±0.16	53.55 ±0.39	64.77 ±0.57
20	67.95 ±0.62	57.6 ±0.41	72.54 ±0.35
22	83.25 ±0.53	70.42 ±0.35	81.3 ±0.63

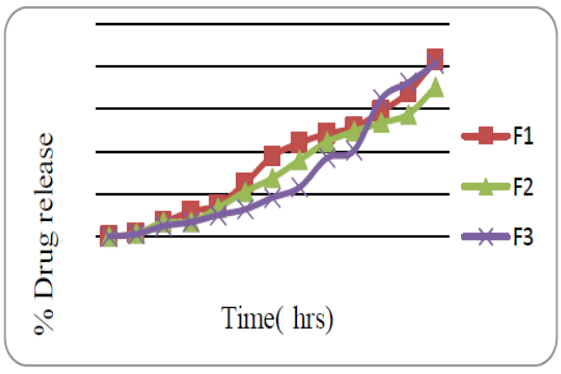


Figure 5: In vitro dissolution plot of KT matrix containing HPMC E50 (F1-F3).

First order kinetics

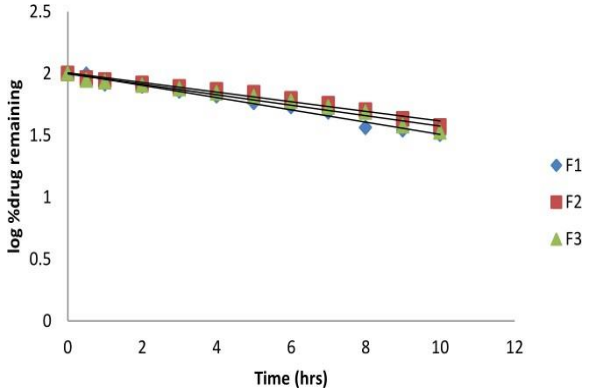


Figure 6: First order plot of KT matrix containing HPMC (F1-F3).

Zero order kinetics

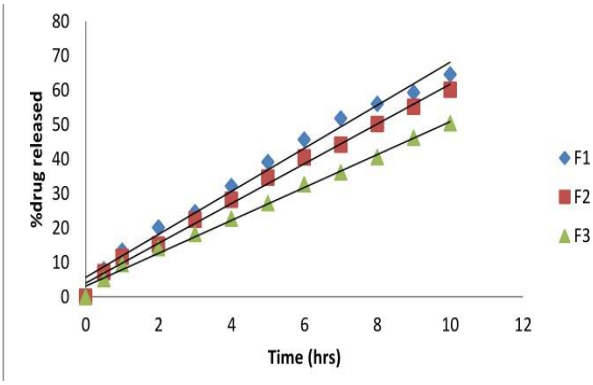


Figure 7: Zero order plot of KT matrix containing HPMC(F1-F3).

Higuchi plot

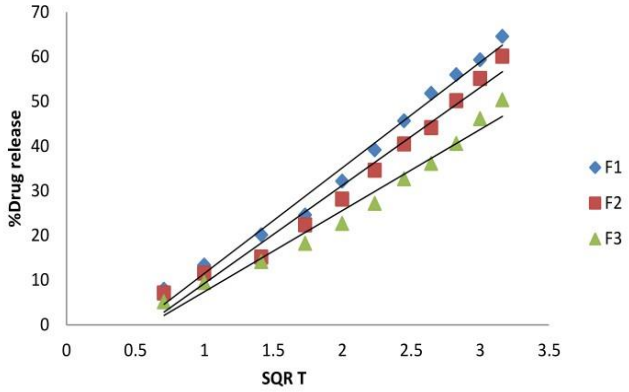


Figure 8: Higuchi plot of KT matrix containing HPMC (F1-F3).

Peppas plot

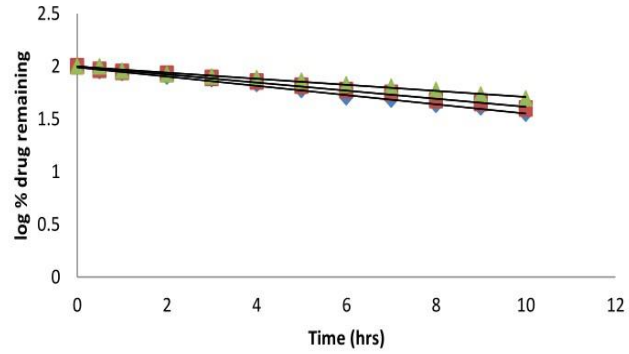


Figure 9: Peppas plot of KT matrix containing HPMC (F1-F3).

Table 20: In vitro release kinetics of ketorolac tromethamine sustained tablets using HPMC E50(F1-F3).

Formulation	Zero order	First order	Higuchi	Peppas	
	R2	R2	R2	R2	N
F1	0.974	0.963	0.984	0.991	0.753
F2	0.983	0.969	0.995	0.982	0.501
F3	0.973	0.970	0.964	0.998	0.587

In-vitro drug release of ketorolac tromethamine SR tablet formulations

Table 21: Dissolution profile of F4- F6formulations.

Time (hrs)	Formulation Code		
	F4	F5	F6
0	0.0	0.0	0.0
0.125	2.47±0.17	2.25 ±0.34	2.47 ±0.34
0.25	5.62 ±0.28	6.74 ±0.16	4.72 ±0.29
0.5	9.67±0.51	8.1±0.51	6.52 ±0.17
1	14.85 ±0.485	10.8 ±0.42	9.45 ±0.61
2	22.72 ±0.67	18 ±0.71	13.5 ±0.69
3	30.37 ±0.34	22.74±0.49	22.27 ±0.39
4	49.5 ±0.15	39.82 ±0.64	31.5 ±0.12
5	51.75 ±0.74	41.85 ±0.91	37.8 ±0.37
6	57.15±0.46	47.25 ±0.34	47.08 ±0.53
8	62.55 ±0.24	63 ±0.18	53.8 ±0.14
20	75.54 ±0.59	85.5 ±0.37	83.75 ±0.28
22	87.75 ±0.54	96.75 ±0.587	99 ±0.67

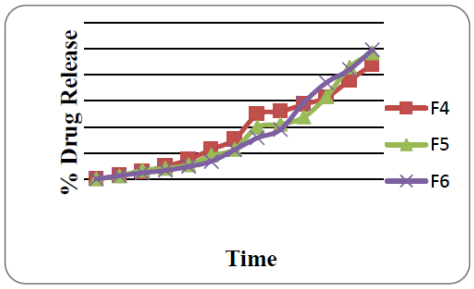


Figure 10: Release profile of ketorolac tromethamine from matrix tablets containing *Hibiscus rosa- sinensis leaves* mucilage (F4-F6).

First order kinetics

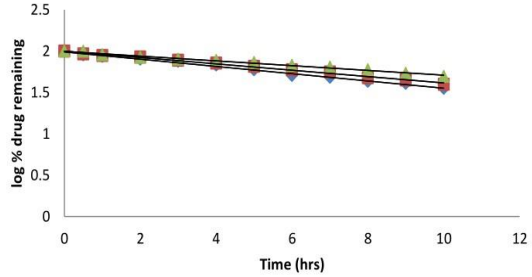


Figure 11: First order plot of KT matrix containing *Hibiscus mucilage* (F4-F6)

Zero order kinetics

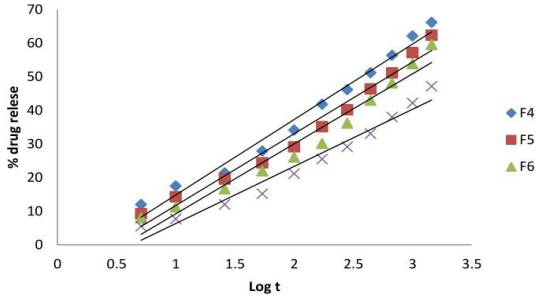


Figure 12: Zero order plot of KT matrix containing Hibiscus mucilage (F4-F6)

Higuchi plot

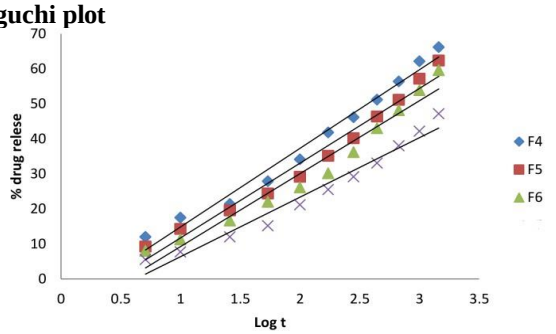


Figure 13: Higuchi plot of KT matrix containing Hibiscus mucilage (F4-F6)

Peppas plot

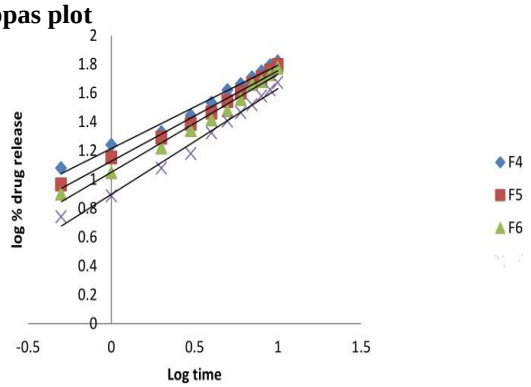


Figure 14: Peppas plot of KT matrix containing HPMC (F4-F6).

Table 22: In vitro release kinetics of ketorolac tromethamine sustained tablets using Hibiscus mucilage (F4-F6).

Formulation	Zero order	First order	Higuchi	peppas	
	R2	R2	R2	R2	n
F4	0.913	0.973	0.963	0.982	0.542
F5	0.955	0.960	0.947	0.984	0.760
F6	0.958	0.997	0.91	0.992	0.633

DRUG EXCIPIENT COMPATIBILITY STUDIES

No change in physical appearance was observed during compatibility studies with excipient. The results are given below,

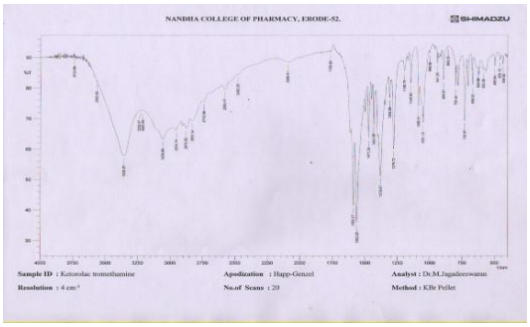


Figure 18: FT-IR graph of Ketorolac Tromethamine.

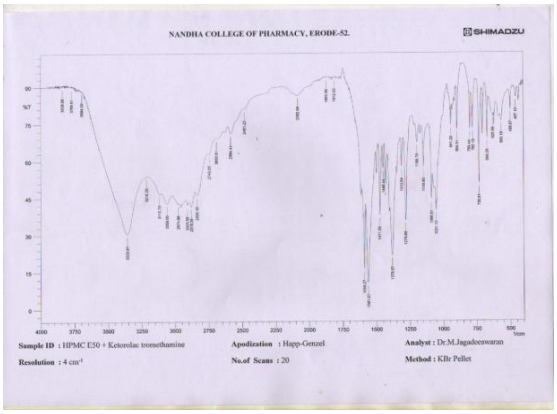


Figure 19: FT-IR graph of Drug with HPMC.

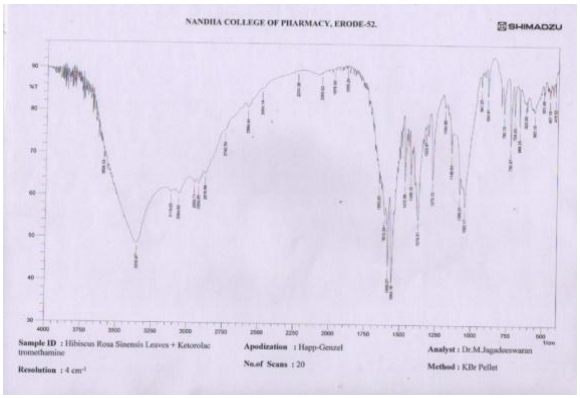


Figure 20: FT-IR graph of Drug with Hibiscus extract.

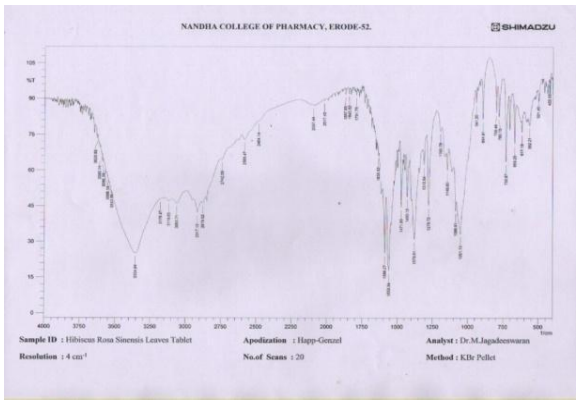


Figure 21: FT-IR graph for Hibiscus Tablet formulation.

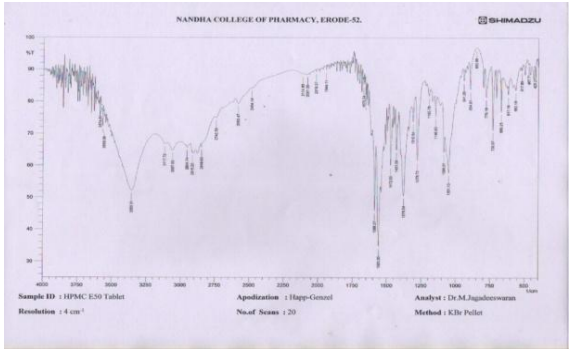


Figure 22: FT-IR graph for HPMC Tablet formulation.

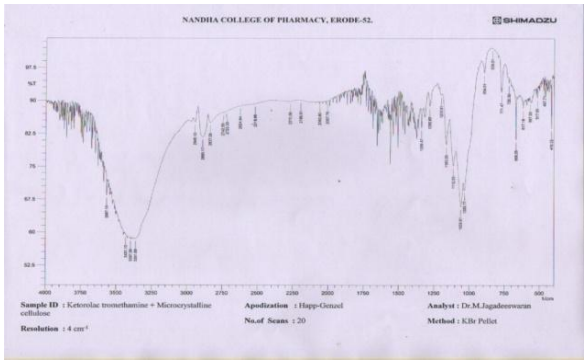


Figure 23: FT-IR graph for Drug with Microcrystalline cellulose.

DISCUSSION

Sustained drug delivery system was aimed to release the medication in a prolonged rate to maintain plasma drug levels. The drugs having shorter half life are suitable for the sustained drug delivery system. The main objective in designing sustained delivery system is to reduce dosing frequency and thereby increasing the action. 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. 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.

The drug content of the matrix tablets was determined according to in-vitro standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount.

For an natural polymer preparation mucilage was extracted the yield was weight. Final weight of the mucilage was 10 gm. Dried Hibiscus rosa-sinensis leaves mucilage powder has an excellent flow properties based on Angle of repose 19.36 ± 0.404, noted values in excellent range of flowability. The mucilage now regarded very suitable to be used in tablet manufacturing.

In analytical method developed by UV Spectroscopy in this Maximum absorption of Ketorolac Tromethamine in UV spectrophotometer was found to 323nm. The pre-compression blend for matrix tablets was characterized with respect to Angle of repose, Bulk density, Tapped density, Carr's index. Angle of repose was found to be 25.37 to 29.70 and carr's index values were less than 18 for all batches which indicates good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all batches indicates good flow properties.

Fourier Transform Infrared Spectroscopy (FT-IR) The sample of Keterolac Tromethamine and physical mixtures were prepared in the form of KBr pellets and subjected for scanning from 4000 to 400 cm -1 using FT-IR spectrometer.

In pre compression parameters the dry powders are tested by FT-IR technique. Based on this we determine the moisture content present in the samples. Disintegration also done by this technique.

It passes all the pre and post compression evaluation technique. Dissolution test to analyse the percentage drug release of the different formulation. In this we formulate three natural and three synthetic formulations to evaluate the release of the tablet.

By this evaluation finally conclude the all formulations having particular amount of drug release particularly natural polymers release the 50% of medicament in 8th hour.

CONCLUSION

Sustained release matrix tablets of Ketorolac Tromethamine were successfully prepared by direct compression method. All the matrix formulations were subject to quality control tests such as hardness, weight variation, friability, thickness, drug content, and in vitro release studies.

All the physical parameters complied with pharmacopoeia specifications and the in vitro release data was fitted into various kinetic models. Formulation containing 60% of Hibicus mucilage is able to sustain 50% of drug over a period of 8 hrs.

FT-IR studies proved that no physical incompatibility exited between the drug and excipients.