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FORMULATION AND EVALUATION OF MEFENAMIC ACID SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The objective of the present study was to develop once daily sustained release matrix tablets of Mefenamic Acid 200mg by using direct compression method using different polymers like HPMC K4M, HPMC K15M, HPMC K100M. The drug excipient mixtures were subjected pre formulation studies. The Tablet were subjected to physicochemical studies, *In- Vitro* drug release, kinetics studies. FTIR studies shown there was no interaction between drug and polymer. The drug release from optimized formulations was sustained for a period of 12hrs. The kinetic treatment of selected formulation F7 showed that the release of drug follows zero order models. Results of the present study indicated the suitability of hydrophilic polymers in the preparation of matrix based sustained release formulation of Mefenamic Acid.

INTRODUCTION

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal.

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administered dosage forms, the period is measured in hours and critically depends on

the residence time of the dosage from in the gastrointestinal tract. The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities.

Controlled release also denoted systems which can provide some control whether this is of a temporal or spatial nature or both for drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolonged therapeutic blood or tissue levels of the drug for an extended period of time.[1]

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled –release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.

The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Advantages of Sustained Release Dosage Forms[2]

1. The frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient as well.
4. The blood level oscillation characteristics of multiple dosing of conventional dosage forms is reduced.
5. Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
6. The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
7. The total amount of drug administered can be reduced, thus:

- Maximizing availability with minimum dose.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Minimize drug accumulation with chronic dosing.

8. Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
9. Improve efficiency in treatment.

- Cure or control condition more promptly.
- Improve control of condition i.e., reduce fluctuation in drug level.
- Improve bioavailability of some drugs.
- Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bed –time.

10. Economy.

Disadvantages of Sustained Release Formulations

1. Administration of sustained release medication does not permit the prompt termination of therapy.
2. Flexibility in adjustment of dosage regimen is limited.
3. Controlled release forms are designed for normal population i.e., on the basis of average drug biologic half –lives.
4. Economic factors must also be assessed, since more costly process and equipment are involved in manufacturing of many controlled release dosage forms.

MATERIALS AND METHODS

Materials

- Mefenamic Acid is a gift sample from Arrow chemicals Ltd, Mumbai.
- HPMC K4M, HPMC K15M, HPMC K100M w s gift sample from SD Fine Chemicals Ltd, Mumbai.
- Microcrystalline cellulose, Aerosil, Magnesium Stearate was gift sample from SD Fine Chemicals Ltd, Mumbai.

Instruments

- Electronic weighing balance from Citizen Scales
- Hot air oven from New tronic HTA instrument

- pH meter from Electronic india
- Vernier caliper from Pharma Test
- Bulk density apparatus from DBK instruments
- Hardness tester from Monsanto hardness tester
- Friability test apparatus from DBK instruments
- Dissolution Apparatus USP-Type II from Lab India
- UV Spectrometer from Lab India, Mumbai

Preformulation Study

Preformulation studies are an important component of drug development. it provides the scientific basis of formulation development. A comprehensive preformulation study helps in investigation of physic-chemical properties of a drug molecule it also gives the foundation for designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. Efforts spent on preformulation provide cost saving in the long run, by reducing challenges during formulation development.

Preformulation studies can be broadly classified into two classes – (I) fundamental properties and (II) derived properties. Fundamental preformulation properties are specific to the drug molecule and are dependent on the chemical structure of the drug molecule. Derived preformulation properties for solid oral dosage form like tablet, include –characterization of particle properties like morphology and particle size, bulk density, flow properties and compaction behaviour. The last activity performed in pre-formulation studies is the compatibility studies, wherein the physical and chemical stability of the drug molecule is studied in presence of excipients. Obviously, the choice of excipients is dictated by the type of dosage form to be developed.

Preparation of Tablets by direct compression method

The matrix sustained release tablets of Mefenamic acid were prepared by direct compression method using polymers and using microcrystalline cellulose as directly compressible vehicle. Different grades HPMC (HPMC K4M, HPMC K15M, HPMC K100M) were used as redant materials for preparation of tablets. Colloidal silicon dioxide is used as glidant. For preparaetion of matrix sustained release tablets of Mefenamic acid, drug and polymer were weighed accurately, all the ingredients sieved through mesh 40 screen and mixed with other

ingredients and compressed using 12 station rotary tablet compression machine using 9 mm punches.

Table No. 6: Composition of Mefenamic acid sustained release matrix tablets.

S.No	Ingredients mg/tab	Batch Number								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Mefenamic Acid	250	250	250	250	250	250	250	250	250
2	HPMC K4M	50	100	150	--	--	--	--	--	--
3	HPMC K15M	--	--	--	50	100	150	--	--	--
4	HPMC K100M	--	--	--	--	--	--	50	100	150
5	Microcrystalline cellulose	185	135	85	185	135	85	185	135	85
6	Aerosil	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
7	Magnesium Stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total		500	500	500	500	500	500	500	500	500

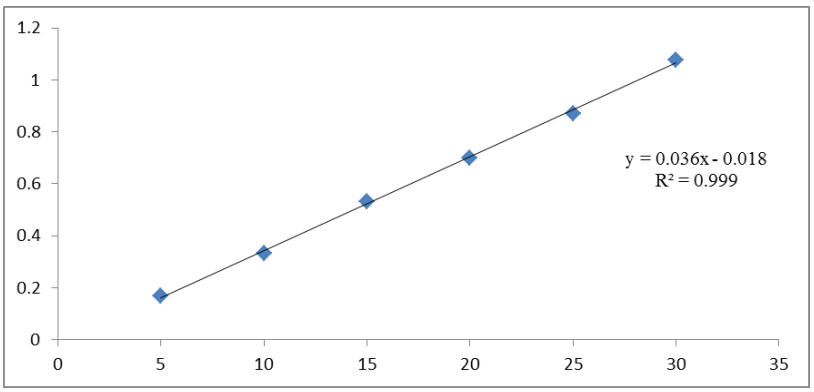
RESULTS

Standard calibration curve of Mefenamic acid using 7.2 phosphate buffer

Standard graph was plotted between concentration and absorbance. Regression equation was obtained. Beer-Lambert's law obeyed in the range from 5 to 25µg/ml. The regression coefficient was found to be 0.999, 7.2 phosphate buffers respectively. The regression equation was used for the estimation of mefenamic acid sustained release tablet and in-vitro release studies. The results were given in the below table.

Table No. 9: Standard graph data for Mefenamic acid using 7.2 phosphate buffer.

S.No	Conc.(µg/ml)	Absorbance
1	5	0.17
2	10	0.334
3	15	0.53
4	20	0.701
5	25	0.872



Conc. (µg/ml)

Figure: 2 Standard graphs for Mefenamic acid using 7.2 phosphate buffer.

Table: 10 Evaluation of pre compressed granules of Mefenamic acid.

Batch Code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibiliy index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.326±0.04	0.446±0.04	26.9±0.3	1.32±0.03	24.56 ±0.4
F2	0.412±0.03	0.506±0.06	18.5±0.1	1.25±0.04	25.12±0.2
F3	0.421±0.04	0.47±0.02	17.1±0.4	1.20±0.05	25.90±0.3
F4	0.410±0.05	0.473±0.03	19.7±0.5	1.25±0.01	23.75±0.4
F5	0.450±0.02	0.585±0.04	23.07±0.2	1.30±0.03	25.70±0.5
F6	0.484±0.03	0.415±0.02	21.30±0.4	1.27±0.01	24.89±0.2
F7	0.410±0.04	0.483±0.04	15.11±0.3	1.17±0.04	24.65±0.8
F8	0.541±0.06	0.491±0.01	21.62±0.1	1.27±0.02	23.92± 0.6
F9	0.410±0.05	0.473±0.03	21.30±0.4	1.27±0.01	25.12±0.2

*All values are expressed as mean ± SD, n=3

Table 11: Evaluation of compressed granules of Mefenamic acid.

Batch code	Weight variation (mg	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	488.5±3.5	3.58 ±0.52	5.1±0.51	0.67±0.05	98.3±1.5
F2	495.2±2	3.52±0.16	5.3±0.31	0.52±0.01	99.5±2
F3	503±2.5	3.58±0.48	4.9±0.26	0.54±0.04	97.1±2.3
F4	491.4±3.2	3.48±029	5.5±0.42	0.63±0.09	98.2±1.4
F5	497.1±2.8	3.59±0.28	5.0±0.34	0.71±0.01	98.8±1.9
F6	489.5±3.4	3.56±0.46	4.8±0.65	0.65±0.13	102.3±0.9
F7	500±1.8	3.53±0.65	5.3±0.15	0.55±0.06	97.8±2.6
F8	496.5±6.1	3.50±0.3	5.4±0.23	0.65±0.02	101±2.2
F9	489.5±3.1	3.53±0.65	4.9±0.26	0.71±0.01	101.3±0.9

*All values are expressed as mean ± SD, n=3

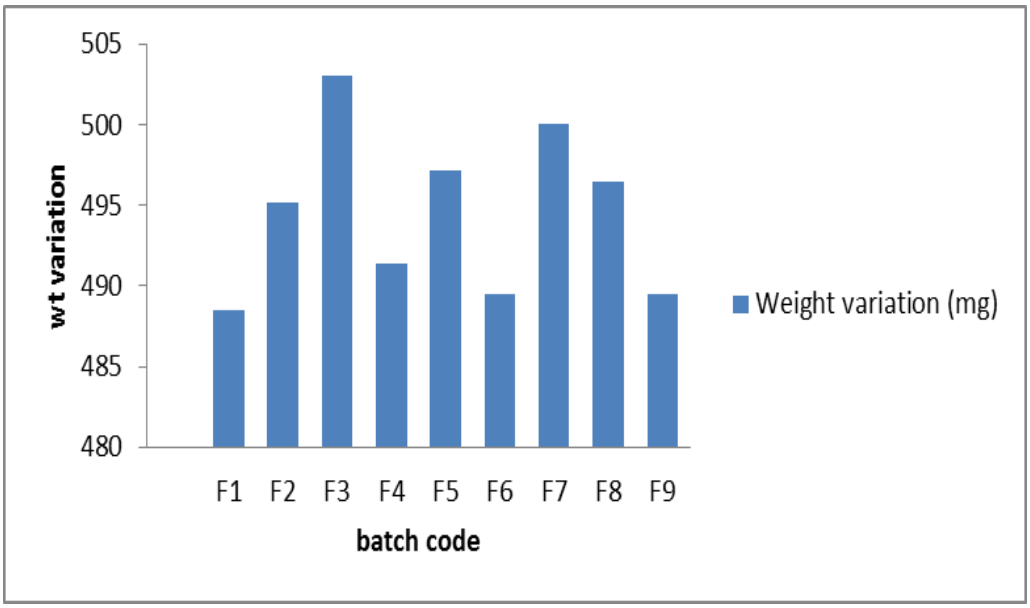


Figure 3: Weight variations Profile of Mefenamic acid tablets (F1 to F9).

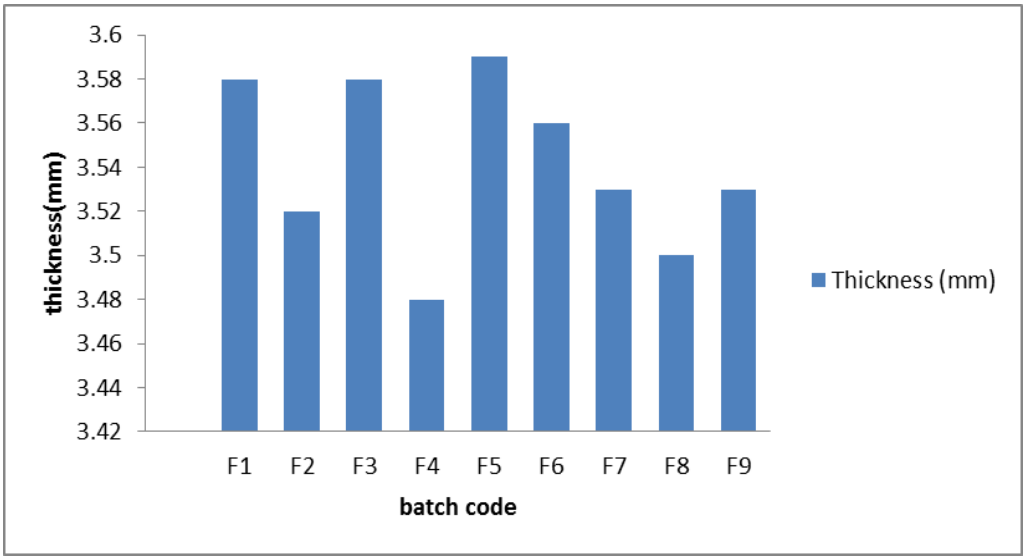


Figure 4: Thickness profile of Mefenamic acid tablets (F1 to F9).

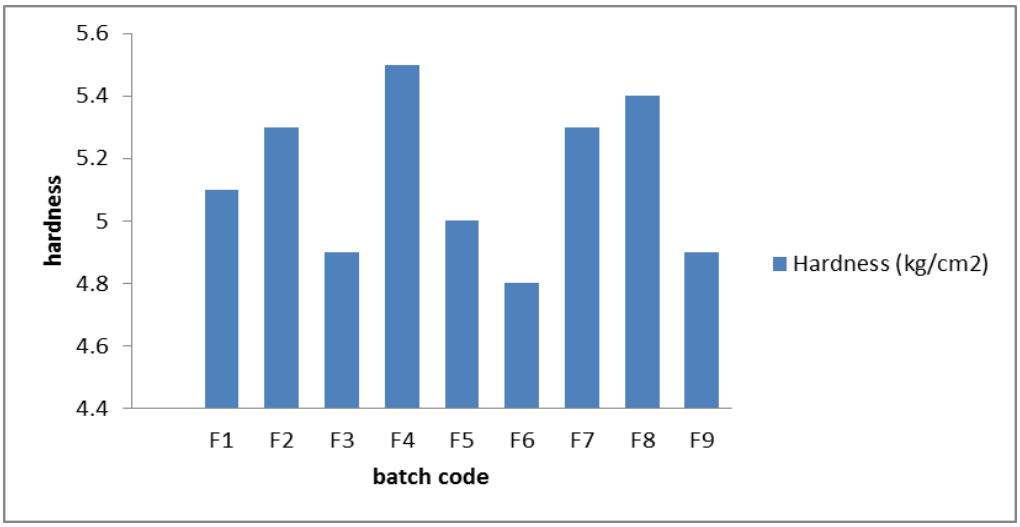


Figure 5: Hardness profile of Mefenamic acid tablets (F1 to F9).

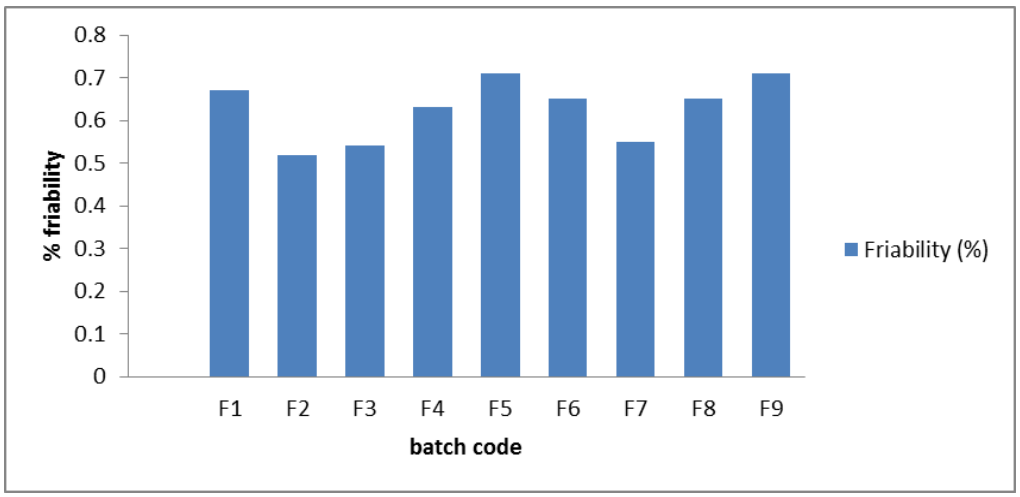


Figure 6: Friability profile of Mefenamic acid tablets (F1 to F9).

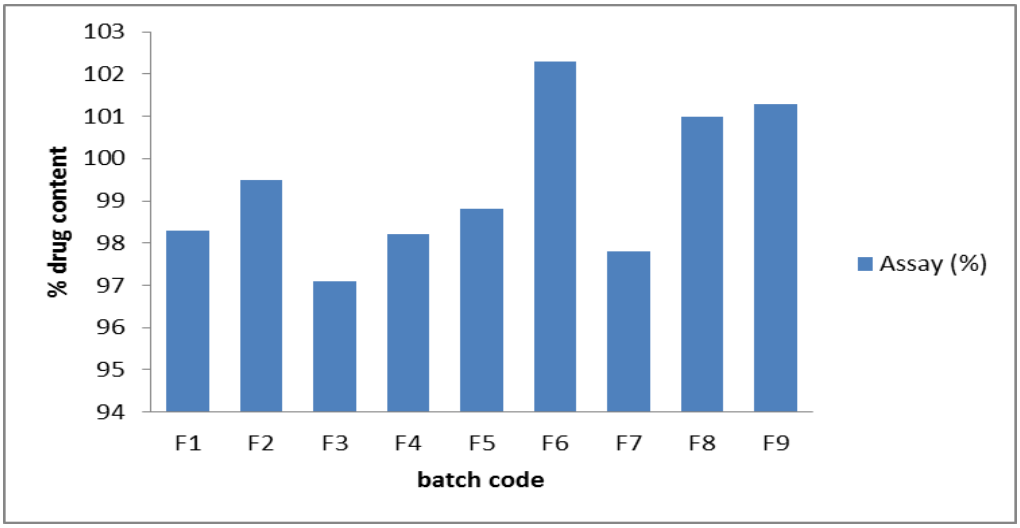


Figure: 7 Drug content profile of Mefenamic acid tablets (F1 to F9).

In vitro dissolution studies

The cumulative percentage drug release of nine formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9 was evaluated by dissolution type-II apparatus using 7.2 phosphate buffers at 50 rpm and samples were collected at different time of intervals for of 1 hour. The data is reported in the table.

Table 12: Results of In-vitro dissolution studies of Mefenamic acid sustained release tablets tablets.

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	0	0	0	0	0	0	0	0	0
1	34.4	20	14.4	16.01	25.14	30.19	26.28	30	16.28
2	47.6	31.2	27.6	34.11	36.99	44.71	40.2	51.2	34.2
3	61.23	44.4	31	47.8	48.81	57.28	54.88	64.4	49.88
4	76.4	55.1	49.4	60.42	58.62	68.40	67.02	71.1	61
6	89.6	69.4	62.6	79.01	69.82	80.31	78.2	87.4	78.2
8	95.3	81.2	78.3	94.54	85.42	92.44	89.3	98.2	98.9
10	99.4	95.08	84.8	99.7	96.3	99.81	97.31		
12		98.2	92.21		100.14		100.33		

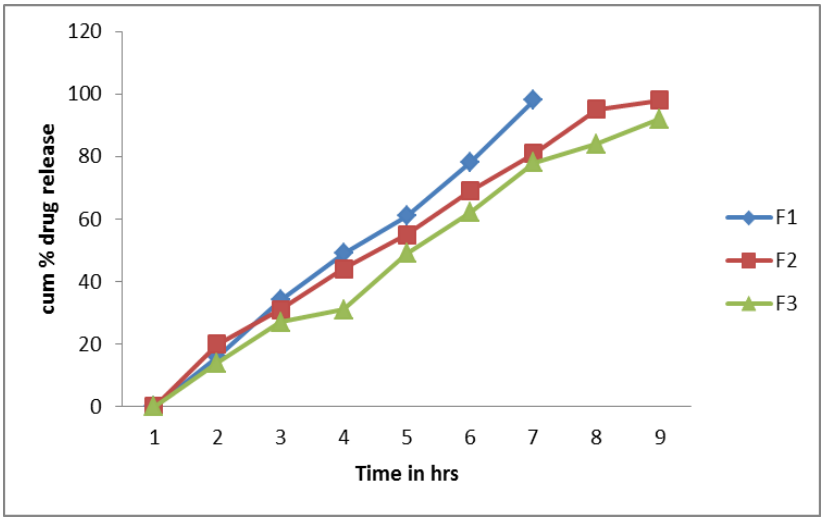


Figure 8: Dissolution profile curve of F1, F2, F3.

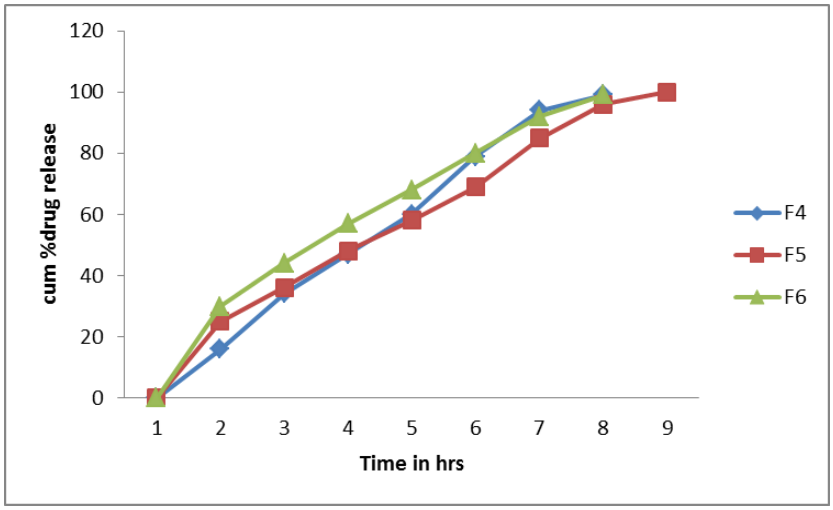


Figure 9: Dissolution profile curve of F4, F5, F6.

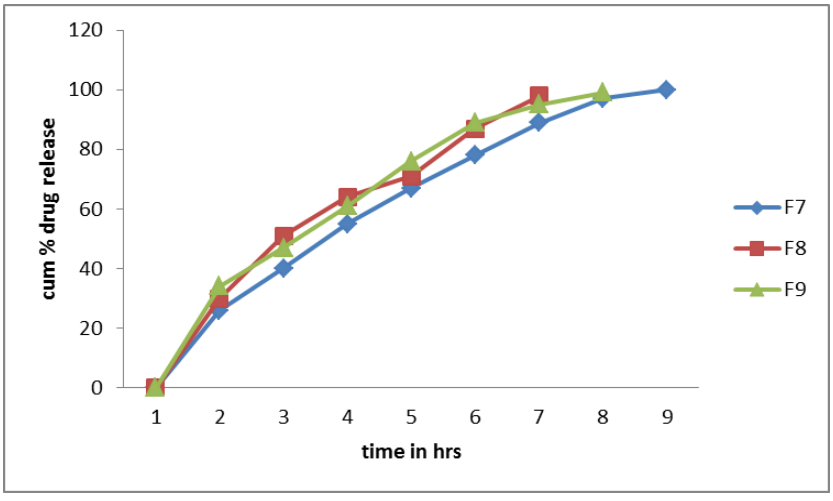


Figure 10: Dissolution profile curve of F7, F8, F9.

Table No.13 Determination of release kinetics.

S.No	Time (hours)	Square root of time	Log time	Cum %drug release	Log cum % drug release	Cum % drug remaining	Log cum % drug remaining
1	**1**	1.000	0.000	16.28	1.212	83.72	1.923
2	**2**	1.414	0.301	34.2	1.534	65.8	1.818
3	**3**	1.732	0.477	49.88	1.690	51	1.708
4	**4**	2.000	0.602	61	1.785	39	1.591
5	**6**	2.449	0.778	78.2	1.892	22	1.342
6	**8**	2.828	0.903	98.9	1.991	2	1.301

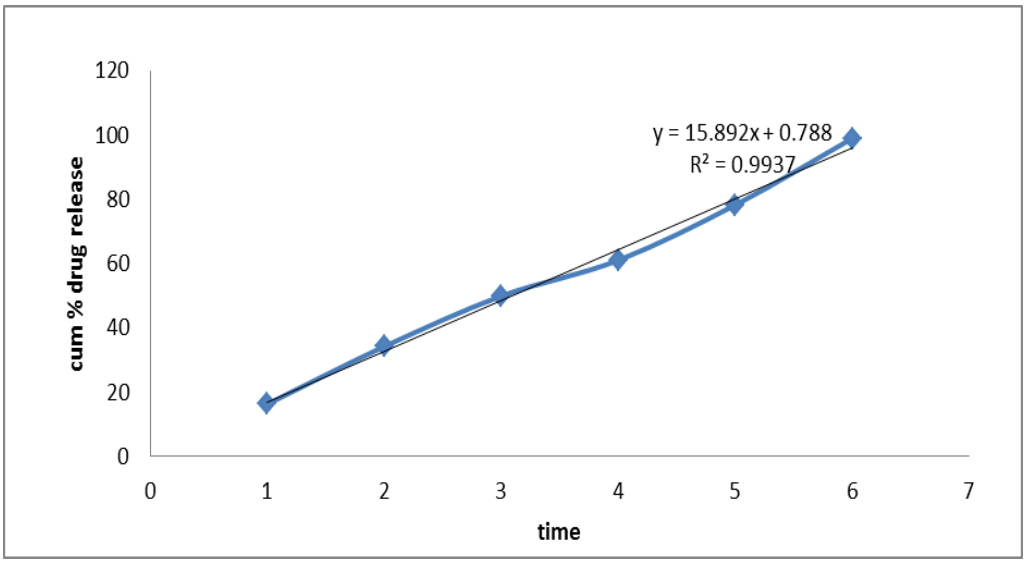


Figure 11: Zero order kinetics for best formulation (F9).

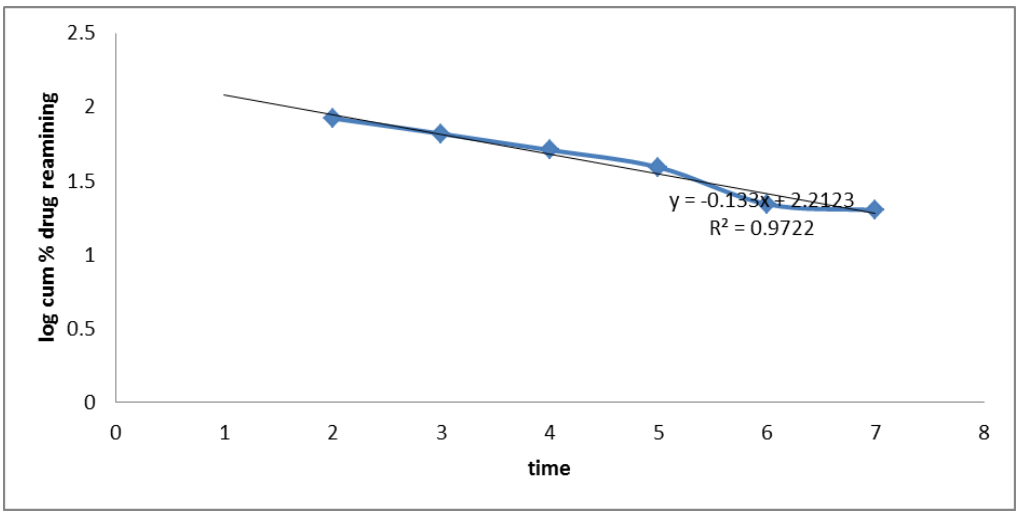


Figure 12: First order kinetics for best formulation (F9).

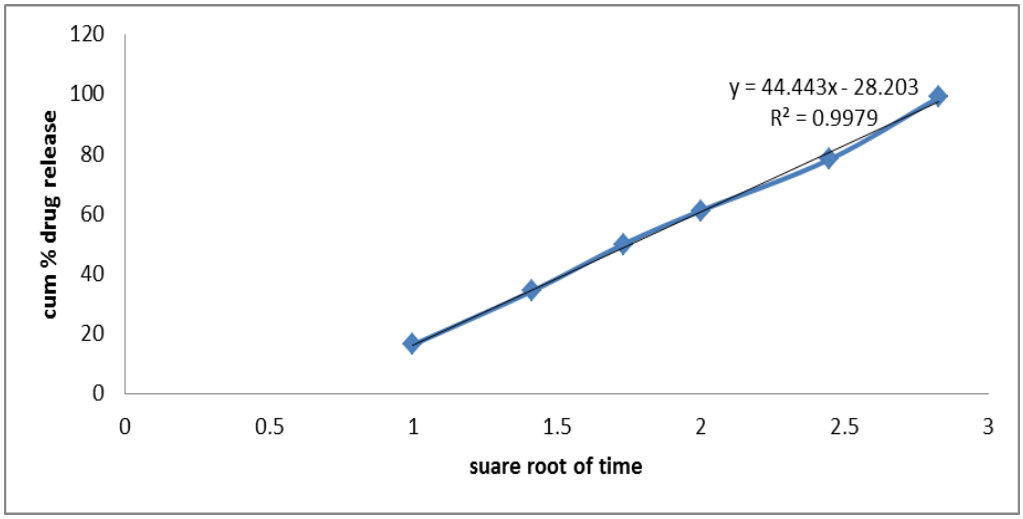


Figure 13: Higuchi model for the best formulation (F9).

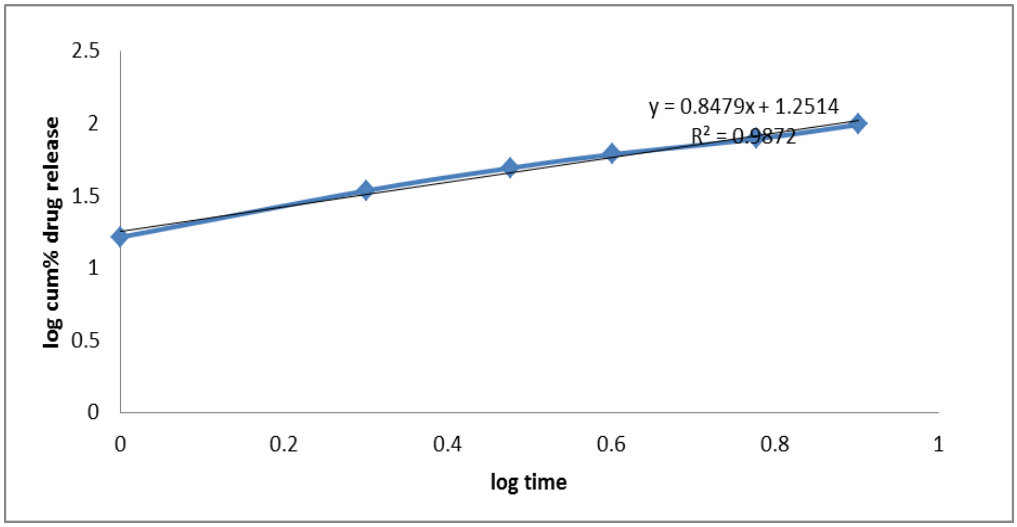


Figure 14: Korsmeyer and pappas model for the best formulation (F9).

DISCUSSION

The objective of the present study is to formulate and evaluate sustained released matrix tablets of Mefenamic acid and study the dissolution profile of the prepared formulations.

Eight formulations (F1 to F9) of Mefenamic acid were developed by preparing the tablets using micro crystalline cellulose as direct compressing agent. Different batches of tablets were prepared using different polymers like HPMC (K15M, K4M, K100M). The tablets were prepared by direct compression method.

Standard calibration curve of Mefenamic acid in 7.2 Phosphate buffer

The calibration curve of Mefenamica cid in 7.2 Phosphate buffer was derived from the concentration and corresponding absorbance. Linear regression analysis gave the equation for

the line of best fit as y = 0.036x - 0.008. Linearity was observed in the concentration range between 5 to30 µg/ml. The values are given in table 9 and graphically represented in figure 2.

Pre compression studies

The pre compression properties of eight formulations (F1 to F9) were studied which includes bulk density, tapped density, compressibility index, hausner's ratio and angle of repose. All the results were found to be with in limits and indicate the free flow. Results are shown in table 10.

Post compression studies

The post compression properties were performed for all the formulations, which include hardness, friability, thickness, weight variation. All the formulations were found to be with in limits according to IP specifications. The results are shown in table 11 and represented graphically in figures 3, 4, 5 and 6, 7.

***In vitro* dissolution studies**

All the prepared batches of tablets were subjected to *in vitro* dissolution studies.

The formulations F1, F2, F3, were prepared by using HPMC K4M as and F4, F5, F6 are prepared by using HPMC K15M the polymer and F6, F7, F8 were prepared by HPMC K100M. The concentration of the polymer was increased in successive manner of 50 mg, 100 mg, 150mg. All the polymers showed effective drug release of which F9 was found to be the best formulation which exhibits 98.9% of drug release at the end of 8 hours. The results are shown in table 12 and represented graphically in figures 8, 9, 10.

Out of all the formulations, F9 was found to be the best formulation as it shows sustained release of the drug with 98.9% throughout 8 hours of the study.

Release kinetics for best formulation

The release kinetics of Mefenamic acid from the sustained release matrix tablets was studied by Zero order, First order, Higuchi model and Korsmeyer- Peppas model. The results explain that the dissolution profile of the Mefenamic acid will follow zero order and obeys Higuchi and Korsmeyer- Peppas model. The n value in the Peppas equation for the best formulation was found to be 0.847. Hence it indicates that release mechanism was non-fickian diffusion. The results are shown in table 13 and represented graphically in figures 11, 12, 13 and 14.

SUMMARY

The present work dealt with the development of sustained released matrix tablet of Mefenamic acid, Mefenamic acid binds the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. As these receptors have a role as a major mediator of inflammation and/or a role for prostanoid signaling in activity-dependent plasticity, the symptoms of pain are temporarily reduced.

The Sustain released matrix tablet form of Mefenamic acid was prepared by Direct compression technique. Various pre compression properties of the prepared formulations were done which include bulk density, tapped density, Carr's index, hausner's ratio and angle of repose which were found to be in limits indicating the free flow.

The post compression properties were performed for all the formulations, which include hardness, friability, thickness, weight variation and the formulations were found to be with in limits.

The *in vitro* drug release profile of the various formulations was performed and compared. The tablets formulated with HPMC K100M polymer shows more sustained action when compared to that of HPMC K4M and HPMC K15M. The high viscosity of the polymers binds the formation of matrix thus sustains the release of drug. It was also observed that the increase in concentration of the polymer decreased the drug release from the polymer matrix.

CONCLUSION

In the present work, efforts have been made to develop sustained released matrix tablets of Mefenamic acid by direct compression technique. The comparison of drug release profile of various formulations showed that usage of HPMC polymer enhances the matrix formation and results in sustained release. Dissolution profile varies with different grades of HPMC.

F9 formulation showed best release profile where the release of drug from the matrix tablet was sustained for 8 hours. All the parametric evaluations were found to be satisfactory.

Hence, it can be concluded that the sustained released matrix tablets of Mefenamic acid was successfully developed and evaluated.

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