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FORMULATION AND INVITRO EVALUATION OF MESALAZINE SUSTAINED RELEASE MATRIX TABLETS

S. Deepa*, Kalyani and Sunitha

Gyana Jyothi College of Pharmacy, Uppal Bus Depot., Hyderabad-500089, Telangana, India.

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***Corresponding Author**
Dr. S. Deepa
Gyana Jyothi College of Pharmacy, Uppal Bus Depot, Hyderabad-500089, Telangana, India.

ABSTRACT

The aim of the present study was to develop sustained release formulation of Mesalazine to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC-K 200 M, Sodium Carboxy Methyl Cellulose, Grewia gum, Almond gum were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. GOhere as from the dissolution studies it was evident that the formulation (F9) showed better and desired drug release pattern i.e., 99.9% in 12 hours. It contains the HPMC-K 200 M 1:1 as sustained release material. It followed Zero order release kinetics mechanism.

KEYGOORDS: Mesalazine, HPMC-K 200 M, Sodium Carboxy Methyl Cellulose, Grewia gum, Almond gum, Sustained release system.

1. INTRODUCTION

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology.[1] Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing

drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.

Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet.[2] A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio.[3,4] Numerous drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® technology) and osmotic pumps with laser drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients.[5,6]

1.8 Biological factors influencing drug release from matrix tablet[16,25]

- ✓ Biological half-life.
- ✓ Absorption.
- ✓ Metabolism
- ✓ Distribution
- ✓ Protein binding
- ✓ Margin of safety

A) Biological half-life

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and

phenytoin are the examples.

B) Absorption

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.

Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

- ✓ Drug should have law half-life (<5 hrs.)
- ✓ Drug should be freely soluble in water.
- ✓ Drug should have larger therapeutic window.
- ✓ Drug should be absorbed throughout the GIT

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

D) Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine.

E) Protein Binding

The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

F) Margin of safety

As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

1.9. Physicochemical factors influencing drug release from matrix tablet[16,25]

Table. No: 1.2: Physicochemical Parameters for Drug Selection.

S. No.	Parameter	Preferred value
1	Apparent partition coefficient	High
2	Molecular weight/ size	< 1000
3	Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
4	General absorbability	From all GI segments
5	Release	Should not be influenced by pH and enzymes

Table. No: 1.3: Pharmacokinetic Parameters for Drug Selection.

S. No.	Parameter	Comment
1	Elimination half life	Preferably between 0.5 and 8 h
2	Elimination rate constant	Required for design
3	Total clearance	Should not be dose dependent
4	Absolute bioavailability	Should be 75% or more
5	Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be the required dose size
6	Intrinsic absorption rate	Must be greater than release rate
7	Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

A) Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

B) Ionization, pKa and aqueous solubility[23-25]

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

C) Partition Coefficient

GOhen a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time.[26] In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

D) Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine.[12] Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug.[21]

2. METHODOLOGY

Material and sources

Name of the material	Source
Mesalazine	SURA LABS
HPMC-K 100 M	Merck Specialities Pvt Ltd, Mumbai, India
Sodium Carboxy Methyl Cellulose	Merck Specialities Pvt Ltd, Mumbai, India
Grewia gum	Merck Specialities Pvt Ltd, Mumbai, India
Almond gum	Merck Specialities Pvt Ltd, Mumbai, India
MCC PH 102	Merck Specialities Pvt Ltd, Mumbai, India
Sodium Stearyl Fumerate	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India

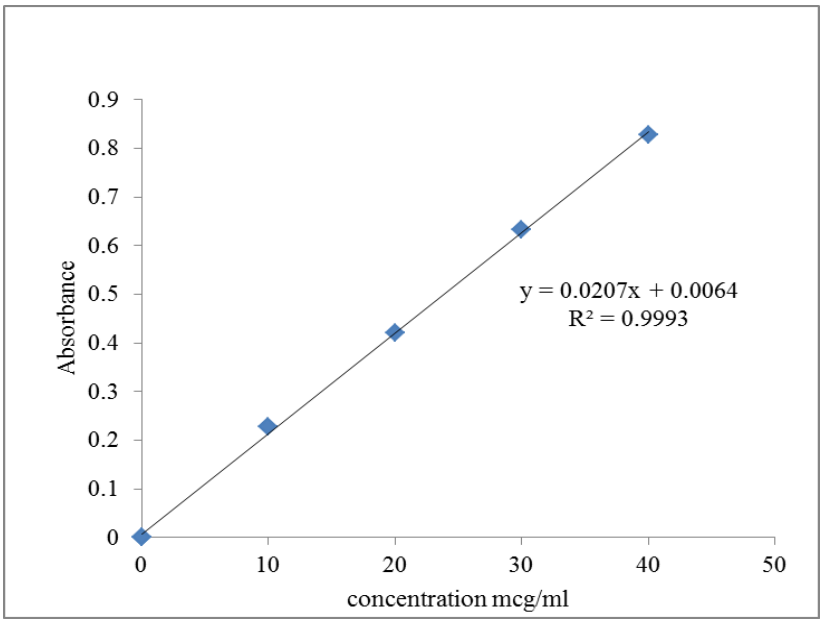
Formulation of Mesalazine release tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Mesalazine	200	200	200	200	200	200	200	200	200	200	200	200
HPMC-K 100 M	100	-	-	-	150	-	-	-	200	-	-	-
Sodium Carboxy Methyl Cellulose	-	100	-	-	-	150	-	-	-	200	-	-
Grewia gum	-	-	100	-	-	-	150	-	-	-	200	-
Almond gum	-	-	-	100	-	-	-	150	-	-	-	200
MCC PH 102	190	190	190	190	140	140	140	140	90	90	90	90
Sodium Stearyl Fumerate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total Œt	500	500	500	500	500	500	500	500	500	500	500	500

RESULTS AND DISCUSSION

Standard curve of Mesalazine in 0.1N HCl

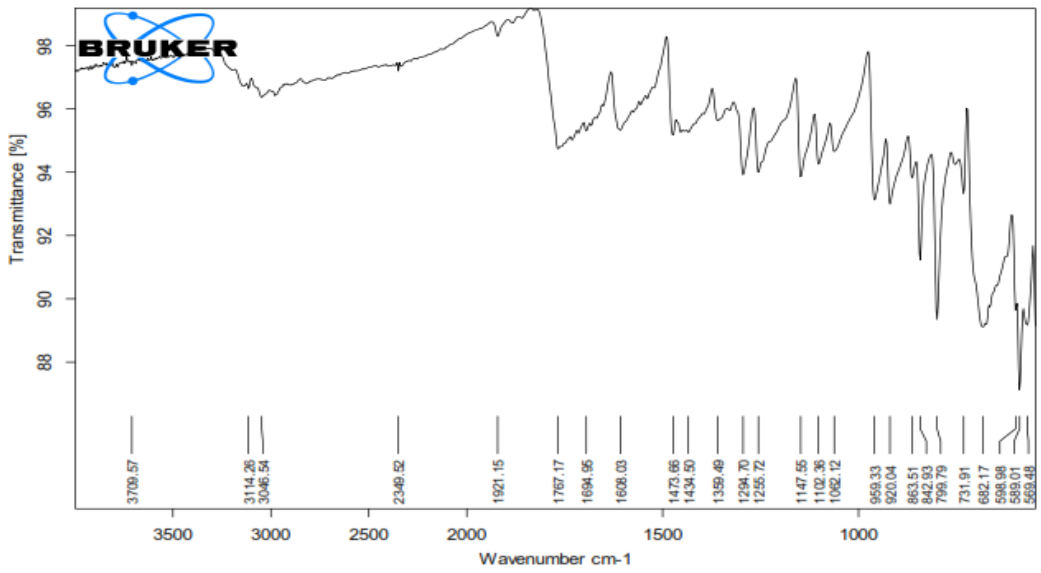
Concentration (µg/ ml)	Absorbance
0	0
10	0.229
20	0.421
30	0.632
40	0.828
50	0.931



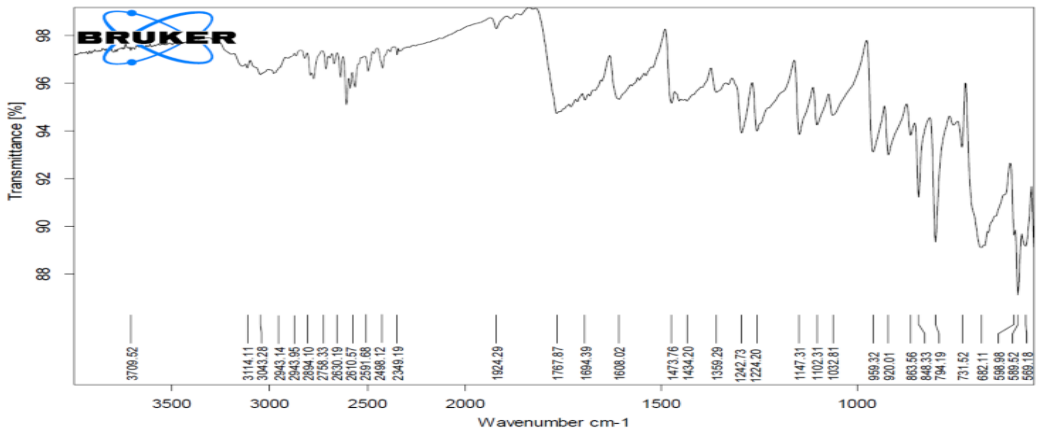
Calibration of Mesalazine in Phosphate buffer pH 6.8

Drug and Excipient Compatibility Studies

FTIR study



FTIR GRAPH OF PURE DRUG



EVALUATION PARAMETERS

Pre-compression parameter

Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.25 ±0.52	0.43 ±0.022	0.61 ±0.033	11.20 ±0.03	1.10 ±0.06
F2	24.16 ±0.68	0.54 ± 0.051	0.64 ±0.013	11.21 ±0.21	1.14 ±0.051
F3	28.38 ± 0.56	0.47 ± 0.08	0.54 ± 0.01	12.96 ± 0.42	1.14 ± 0.031
F4	28.53 ± 0.57	0.48 ± 0.06	0.56 ± 0.08	14.28 ± 0.47	1.16 ± 0.032
F5	25.41 ±0.65	0.52 ±0.091	0.59 ±0.064	14.21 ±0.17	1.25 ±0.022
F6	26.08 ± 0.51	0.55 ± 0.011	0.62 ± 0.06	11.29 ± 0.35	1.12 ± 0.023
F7	26.43 ±0.62	0.56 ± 0.07	0.63 ± 0.012	11.11 ± 0.12	1.12 ± 0.056
F8	25.46 ± 0.57	0.55 ± 0.08	0.62 ± 0.011	11.29 ± 0.57	1.12 ± 0.015
F9	25.15 ± 0.58	0.49 ± 0.01	0.56 ± 0.08	12.5 ± 0.21	1.14 ± 0.012
F10	27.61 ± 0.63	0.53 ± 0.09	0.61 ± 0.071	13.1 ± 0.15	1.15 ± 0.021
F11	26.12 ± 0.1	0.44 ± 0.03	0.50± 0.061	12 ± 0.58	1.13 ± 0.012
F12	27.26 ± 0.56	0.52 ± 0.055	0.59 ± 0.08	11.86 ± 0.57	1.13 ± 0.026

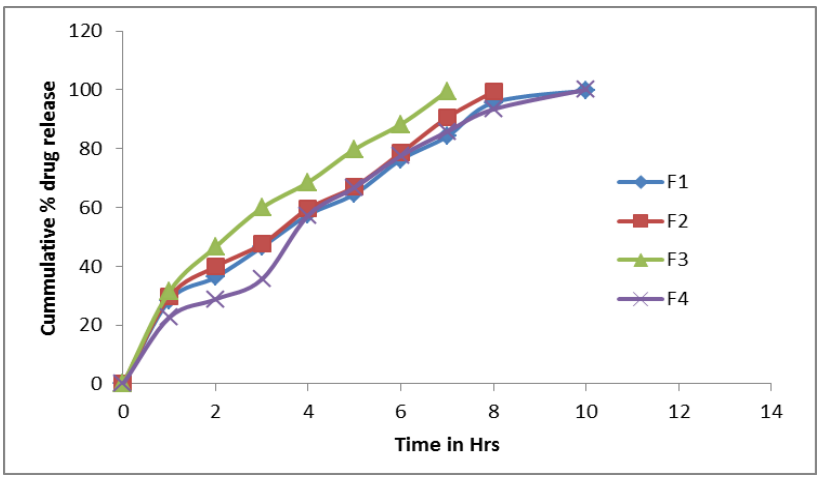
Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	501.5 ± 0.25	4.8±0.04	0.51±0.04	5.6±0.03	102.3 ± 0.21
F2	501.53 ± 0.34	4.5 ± 0.02	0.561±0.03	5.2 ±0.02	99.50 ± 0.22
F3	498.25± 1.15	4.7±0.01	0.45±0.02	5.3 ±0.05	97.2 ± 0.19
F4	502.15 ± 1.31	4.7±0.05	0.54±0.07	5.6±0.04	99.3 ± 0.13
F5	499. 23±0.25	4.6±0.09	0.48±0.08	5.6 ±0.09	104.3 ± 012
F6	503.26 ± 1.25	4.7±0.01	0.45±0.02	5.4±0.05	98.2 ± 0.19
F7	499.5 ± 0.95	4.8±0.07	0.51±0.04	5.3 ±0.03	102.3 ± 0.28
F8	502.5 ± 0.86	4.7±0.04	0.55±0.07	5.3 ±0.05	98.3 ± 0.20
F9	501.36 ± 1.17	4.7±0.04	0.56±0.04	5.7±0.08	100.8 ± 0.17
F10	499.95 ± 1.72	4.8±0.01	0.45±0.05	5.4 ±0.05	98.8 ± 0.14
F11	502.26 ± 0.81	4.5±0.01	0.55±0.02	5.6±0.06	98.2 ± 0.15
F12	500.25 ± 2.02	4.8±0.03	0.52±0.03	5.7±0.04	103.5 ± 0.14

***In Vitro* Drug Release Studies**

Dissolution Data of Mesalazine Tablets Prepared with 1:0.5 (Drug : polymer) Ratios of polymers like HPMC-K 100 M (F1), Sodium Carboxy Methyl Cellulose (F2), Grewia gum(F3), Almond gum (F4).

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED			
	F1	F2	F3	F4
0	0	0	0	0
1	28.4	29.6	31.4	22.6
2	36.3	39.9	46.6	28.8
3	46.6	47.6	59.9	35.6
4	57.5	59.6	68.6	57.3
5	64.6	67.1	79.8	66.8
6	76.3	78.6	88.3	77.6
7	84.2	90.6	99.5	85.8
8	95.7	99.4		93.4
10	99.8			100.1
12				



Dissolution study of Mesalazine Sustained tablets (F1 to F4).

Dissolution Data of Mesalazine Tablets Prepared with 1:0.75 (Drug : polymer) Ratios of polymers like HPMC-K 100 M (F5), Sodium Carboxy Methyl Cellulose (F6), Grewia gum(F7), Almond gum (F8).

TIME (hr)	Cumulative percent of drug released			
	F5	F6	F7	F8
0	0	0	0	0
1	19.7	24.2	27.9	16.8
2	29.2	33.3	41.6	22.7
3	42.1	42.6	48.2	30.5
4	53.4	54.3	60.4	49.1
5	61.9	61.8	66.8	61.7
6	70.6	72.6	78.6	68.8

7	76.8	81.8	87.3	73.4
8	81.6	94.2	98.7	81.1
10	97.3	99.1		98.2
12	100.2			

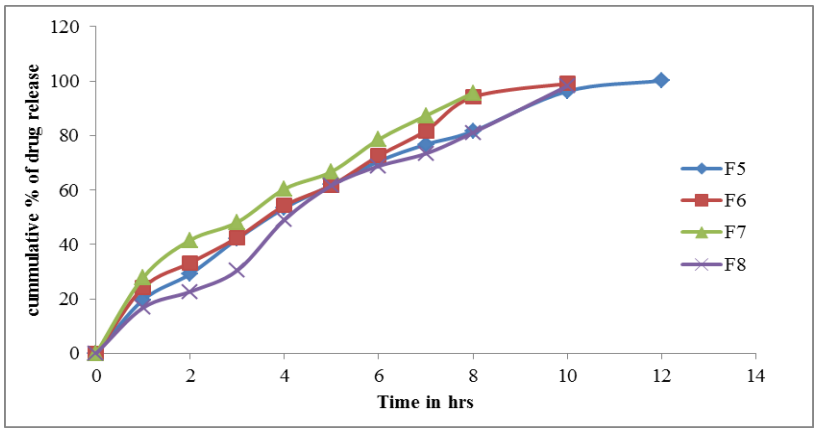


Figure 9.6: Dissolution study of Mesalazine (F5 to F8).

Dissolution Data of Mesalazine Tablets Prepared with 1:1 (Drug : polymer) Ratios of polymers like HPMC-K 100 M (F9), Sodium Carboxy Methyl Cellulose (F10), Grewia gum(F11), Almond gum (F12).

TIME (hr)	Cumulative Percent of Drug Released			
	F9	F10	F11	F12
0	0	0	0	0
1	17.2	18.7	15.6	11.9
2	22.6	28.6	26.8	17.6
3	33.8	39.6	33.9	26.3
4	44.3	51.2	49.8	33.3
5	52.8	57.8	62.5	51.8
6	65.9	64.6	72.1	58.2
7	73.3	79.8	83.6	68.3
8	79.7	89.8	92.5	78.8
10	90.5	96.9	98.6	91.9
12	99.9	100.1	100.3	98.9.

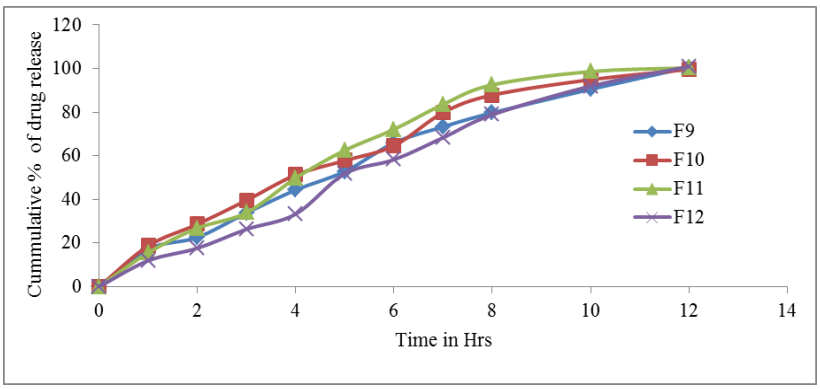


Figure 9.7: Dissolution study of Mesalazine (F9 to F12).

Release kinetics data for optimized formulation (F9)

TIME (T)	CUMULATIVE (%) RELEASE Q	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	% Drug Remaining
0	0	0			2.000		100
1	17.2	1.000	1.236	0.000	1.918	17.200	82.8
2	22.6	1.414	1.354	0.301	1.889	11.300	77.4
3	33.8	1.732	1.529	0.477	1.821	11.267	66.2
4	44.3	2.000	1.646	0.602	1.746	11.075	55.7
5	52.8	2.236	1.723	0.699	1.674	10.560	47.2
6	65.9	2.449	1.819	0.778	1.533	10.983	34.1
7	73.3	2.646	1.865	0.845	1.427	10.471	26.7
8	79.7	2.828	1.901	0.903	1.307	9.963	20.3
10	90.5	3.162	1.957	1.000	0.978	9.050	9.5
12	98.9	3.464	1.995	1.079	0.041	8.242	1.1

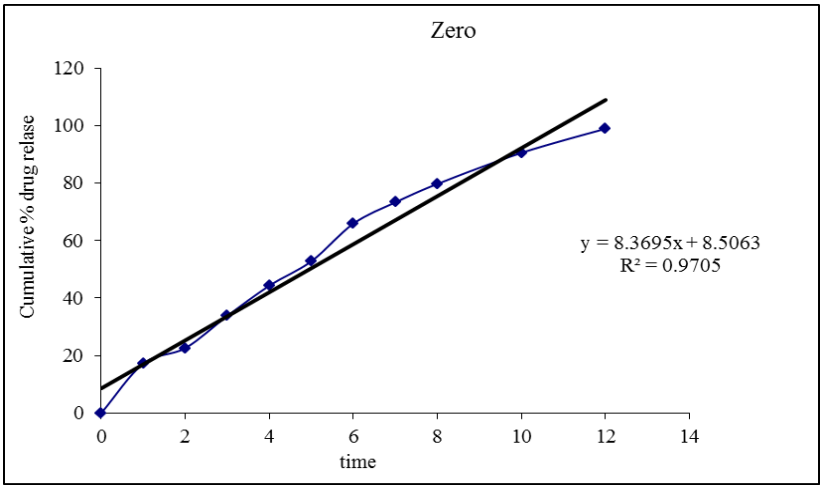


Figure 9.8: Graph of zero order kinetics.

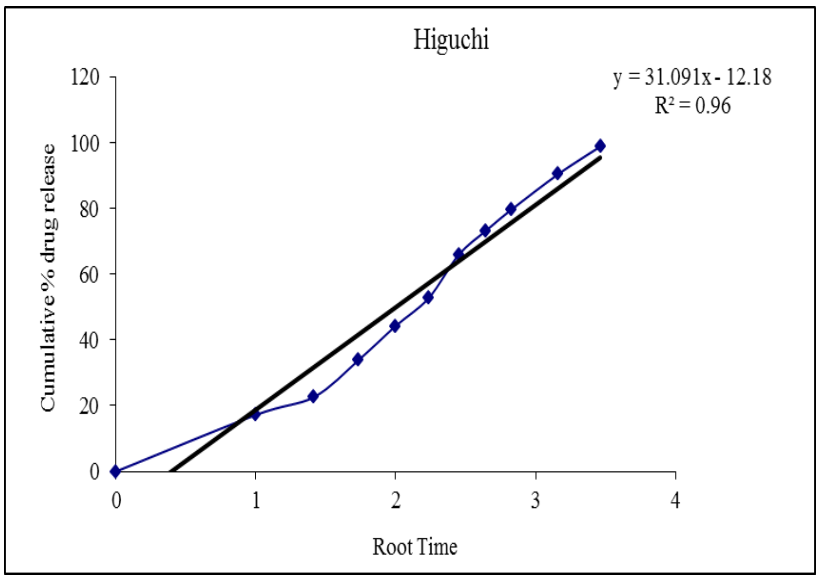


Figure 9.9: Graph of higuchi release kinetics.

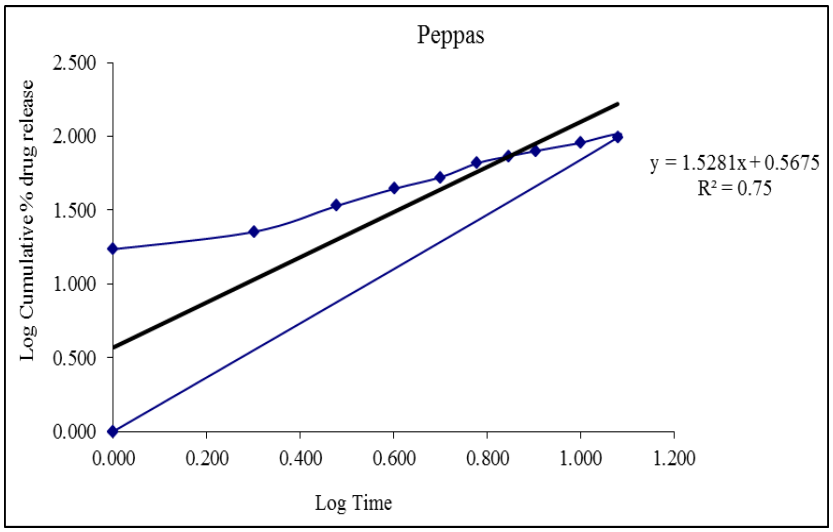


Figure 9.11: Graph of peppas release kinetics.

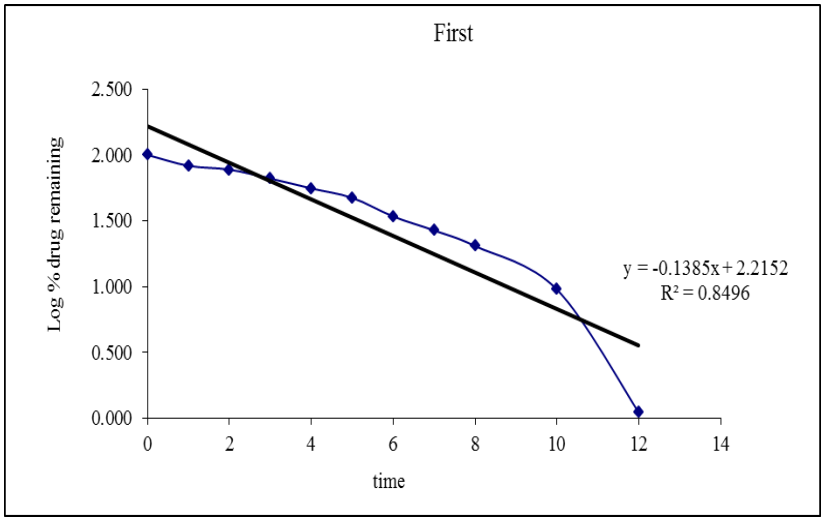


Figure 9.12: graph of first order release kinetics.

CONCLUSION

Results of the present study demonstrated that SR matrix of Mesalazine prepared with polymers like synthetic polymer HPMC K200 M and Natural polymer Almond Gum could proved to control the drug release for 12hr. The formulations contain same concentration polymers like sodiumcarboxy methyl cellulose and Grewia Gum are not retard the drug release upto 12Hrs. The optimized formulation kinetic parameters were evaluated it follows the zero release kinetics.

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