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Research

Formulation And *In Vitro* Evaluation Of Mesalazine Sustained Release Matrix Tablets

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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. Where 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 1:1as sustained release material. It followed Zero order release kinetics mechanism.

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

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2, 3]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect[4]. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood levelof a drug often translates into better patient compliance, as well as enhanced clinical efficacyof the drug for its intended use[5, 6].

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms 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.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7, 8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9].

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Rationale for extended release dosage forms

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen[10,11]. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect.

Advantages of sustained release dosage forms

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- 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.

- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- 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.
- Safety margins of high potency drugs can be increased a the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
    - Cure or control condition more promptly
    - Improve control of condition
    - Improve bioavailability of some drugs
    - Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.

Disadvantages of sustained release dosage forms

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor in*vitro* and in*vivo* correlations.

Biological factors influencing drug release from matrix tablet

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

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.

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.

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.

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.

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.

Physicochemical factors influencing drug release from matrix tablet

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.

Ionization, pKa and aqueous solubility

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.

Partition Coefficient

When 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.

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.

MATERIALS

Mesalazine-Procured From Watson Pharmaceuticals Ltd., (Goa, India) Provided by SURA LABS, Dilsukhnagar, Hyderabad, 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.

METHODOLOGY

Analytical method development

Determination of absorption maxima

100mg of Mesalazine pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VISspectrophotometer in the range of 200 – 400 nm.

Preparation calibration curve

100mg of Mesalazine pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 1, 2, 3, 4, and 5ml of solution and make up to 10ml with 0.1N HCl to obtain 10, 20, 30, 40 and 50 µg/ml of Mesalazine solution. The absorbance of the above dilutions was measured at 330nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

Formulation development of Sustained release Tablets

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Mesalazine.

Procedure

In the present work the Mesalazine tablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 12mm punch.

Table 1: Formulation of Mesalazinerelease 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 Wt	500	500	500	500	500	500	500	500	500	500	500	500

RESULTS AND DISCUSSIONS

The present work was designed to developing Sustained tablets of Mesalazine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Mesalazine in 0.1N HCl

The scanning of the 10µg/ml solution of Mesalazine in the ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at λ_{max} as 330 nm. The standard concentrations of Mesalazine (10-50 µg/ml)was prepared in 0.1N HCl showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 2: 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

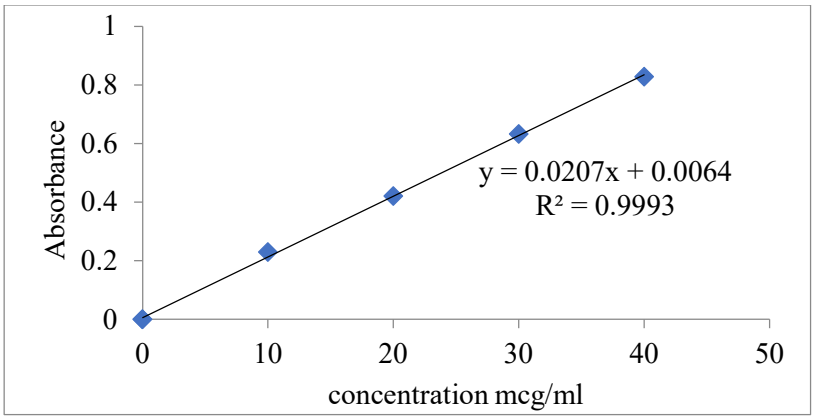

Fig 1: Calibration curve of Mesalazine in 0.1 N HCl at 330nm

Standard Curve of Mesalazine in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Mesalazinein the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 330 nm. The standard concentrations of Mesalazine(10-50µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.997, which suggests that it obeys the Beer-Lamberts law.

Table 3: Standard curve of Mesalazine in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
10	0.219
20	0.428
30	0.639
40	0.836
50	0.981

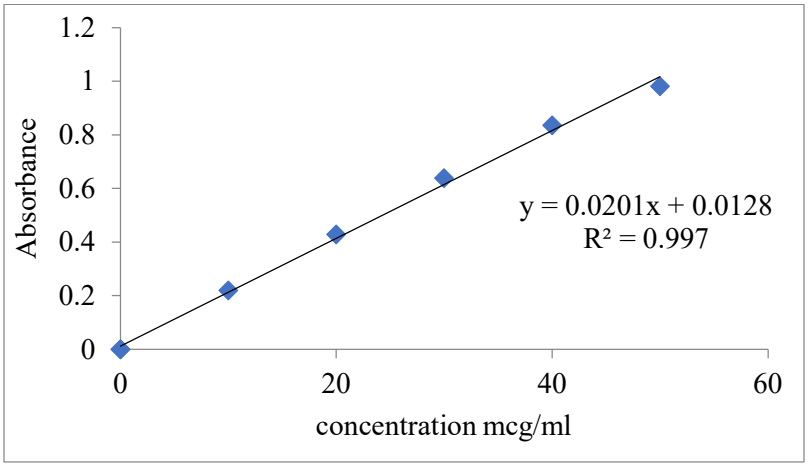

Fig 2: Calibration of Mesalazine in Phosphate buffer pH 6.8

Drug and Excipient Compatibility Studies
FTIR study

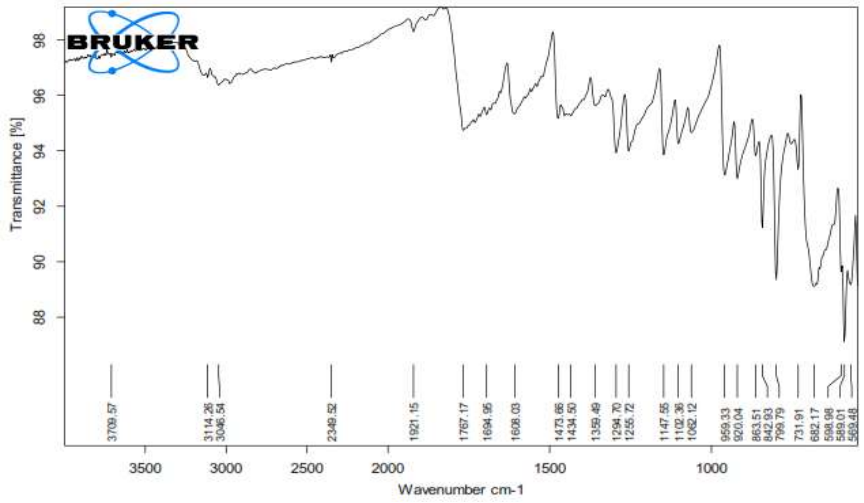

Fig 3: FTIR Graph Of Pure Drug

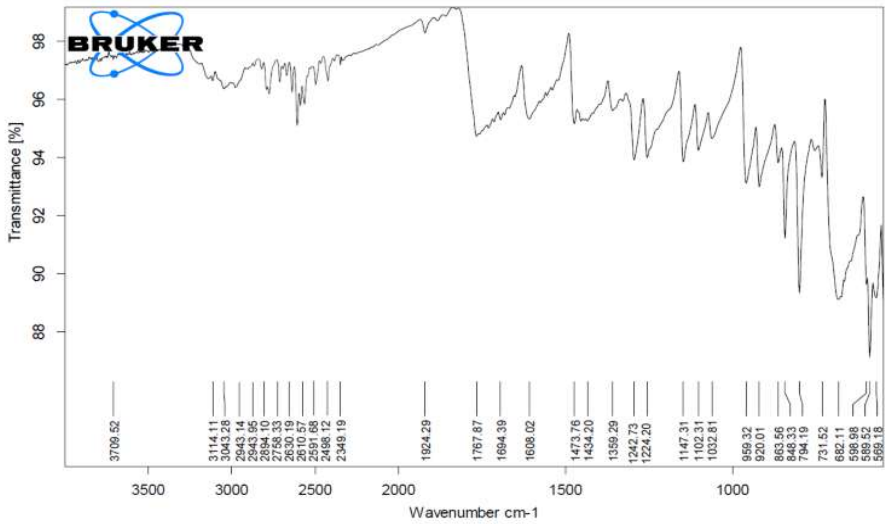

Fig 4: FTIR Graph Of Optimised Formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

Evaluation parameters
Pre-compression parameters

Table 4: 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

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25 to 30; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.44±0.03 to 0.56 ± 0.07 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50± 0.061to 0.63 ± 0.012 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11.11 to 14.28 which showed that the powder has good flow properties.All the formulations were showed the hausner ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Post Compression Parameters For tablets

Table 5: 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

Weight variation and thickness

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 9.5. The average tablet weight of all the formulations was found to be between 498.25± 1.15 to503.26 ± 1.25**.** The maximum allowed percentage weight variation for tablets weighing >250 mg is 5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 5.2 ±0.02 to 5.7±0.08.

Hardness and friability

All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 9.5. The average hardness for all the formulations was found to be between **(**4.5 ± 0.01 **to** 4.8±0.07) Kg/cm^2 which was found to be acceptable. Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 9.5. The average percentage friability for all the formulations was between 0.45±0.04 and 0.56±0.04, which was found to be within the limit.

Drug content

All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 9.5. The drug content values for all the formulations were found to be in the range of **(**98.2 ± 0.15**to** 104.3 ± 012**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In Vitro* Drug Release Studies**

The formulations prepared with different polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 6: Dissolution Data of MesalazineTablets 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				

The % drug release of formulations (F1 to F4) containing 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).depends on the concentration of polymer. The concentration of was1:0.5 ratios was unable to retard the drug release up to desired time. In F1 and F4 formulation was showed maximum % drug release up to 10 hours i.e., 99.8 and 100.1%.

Table 7: Dissolution Data of MesalazineTablets 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			

The % drug release of F5 to F8 formulations depends on ratio of polymer in the solution. The concentration of polymer was unable to retard the drug release up to desired time F6 to F8 Formulations. When polymer formulation

contains HPMC-K 100 M was retard the drug up to desired time period i.e 100.2% at 12 hours. But maximum amount of drug is released with in 10Hrs i.e 97.3% .

Table 8: Dissolution Data of MesalazineTablets 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.

The % drug release of F9 to F12 formulations depends on polymer ratio 1:1. F10 and F11 was unable to retard the drug release up to desired time i.e. Sodium Carboxy Methyl Cellulose (F10), Grewia gum(F11. In F9 and F12 formulations, HPMC-K 100 M and Almond gum **1:1 ratio** showed 99.9 &98.9 % drug release at 12 hours. Hence based on dissolution data of 12 formulations, F9 (HPMC-K 100 M) Synthetic Polymer and F12 Natural polymer (Almond gum) formulation showed better release up to 12 hours. Among these two F9 & F12 F9 shows better within the specified limits. So F9 formulation is optimised formulation.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Mesalazinerelease from Sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyerpeppas mechanisms and the results were shown in below table it follows the zero order kinetics

Table 9: 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

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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