FORMULATION AND EVALUATION OF MESALAMINE DELAYED RELEASE TABLETS

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ABSTRACT

The most common technique of drug delivery is through oral ingestion, which offers a practical way to efficiently produce both local and systemic effects. It is thought that both local and systemic medication delivery could be accomplished through the colon. Colonic drug delivery is now more significant than ever for the localised treatment of numerous colonic disorders, particularly inflammatory bowel disease (Crohn's disease, ulcerative colitis), and colon cancer. By concentrating the drugs molecules at the site of action, site-specific drug delivery (also known as drug targeting) to lower regions of the GIT improves treatment efficacy and reduces systemic side effects and drug instability problems.

Mesalamine, an effective drug for the treatment of inflammatory bowel disease, faces challenges with targeted delivery to the colon. Various oral and rectal (topical) forms of mesalamine are available, including tablets, micro pellets (granules), suppositories, and enemas. There have been a number of oral formulations created, the majority of which have been built with different mechanisms to delay the release of the active mesalamine ingredient until it reaches the terminal ileum/colon in order to prevent proximal absorption in the small intestine.

This study examines the formulation and evaluation of a colon-targeted drug delivery system for mesalamine using delayed-release tablets prepared by wet granulation. Compatibility studies (40ºc/75% RH) revealed that there were no physical as well as chemical interactions between drug and excipients. Trials of core tablets were carried out with varying proportions of binder (povidone), disintegrant (MCC) and lubricant (talc/Mg-stearate).The research on the development of Mesalamine products has been done using the delayed release polymers Eudragit S100 and Eudragit L100.All the formulations were evaluated for the hardness, friability, thickness, weight variation, drug content, and in vitro drug release studies. The optimized Formulation (CF6)

was placed in an accelerated stability chamber over a period of 3 months. The results of the evaluation tests were satisfactory and within the specified limits.

Key words: Mesalamine,colon targeted drug delivery system, delayed releae, Ulcerative colitis, Eudragit S100 and Eudragit L100,wet granulation,invitro drug release.

INTRODUCTION

Any drug delivery system's principal objective is to deliver a therapeutic dose of medication to a target site such that the required drug concentration can be quickly attained and subsequently maintained. Drugs might be administered locally or systemically at the colon. Topical therapy is possible with local distribution, but drugs that are more effectively used in the colon have less systemic side effects. Multiple severe obstacles to drug distribution are present in the gastrointestinal tract. The possibility for the administration of proteins and peptides has made colonic drug delivery more significant than only the delivery of medications for the treatment of local colon disorders. Due to decreased diversity and intensity of enzyme activities as well as a pH that is close to neutral, the colon presents less unfriendly conditions for medication transport. The colon may also be the optimal location for medication administration due to its extended residence period and low digestive enzymatic activity, which may be beneficial for prolonged drug delivery. Colonic delivery is advantageous for the treatment of colonic disorders like ulcerative colitis, Crohn's disease, colon cancer, and amoebiasis. It also offers the potential to give macromolecular medications orally. The colon is regarded as an adequate place for the absorption of many medications due to the lack of digestive enzymes and the prolonged transit time.

Mesalamine is absorbed in the upper GI tract, yet it has direct anti-inflammatory effects on the irritated mucosa of the colon and rectum. It functions by preventing the body from generating a certain chemical that can induce inflammation. By reducing prostaglandin production in the colon and blocking cyclooxygenase, mesalamine reduces inflammation. To improve its effects, numerous kinds of release-controlled oral formulations of mesalamine have been created. The coating layer of the most popular mesalamine formulation, the pH-dependent release formulation coated with Eudragit-S and Eudragit- L , dissolves at a pH of 7 or above. In the current investigation, mesalamine is created as a compacted coated tablet .Mesalamine is one of the most widely used drugs for treating Crohn's disease and ulcerative colitis, hence it was selected as the drug of choice.

MATERIALS AND METHODS

MATERIALS

Mesalamine was procured from Divi's laboratories, Colloidal silicon dioxide, Eudragit L30D55* , Eudragit L100*, Eudragit S100*, Povidone (Kollidon 30*) was procured from Evonik, Microcrystalline cellulose (Avicel pH 302) from Signet, Talc from Luzenac Pharma, Magnesium stearate (Ligamed MF 2V*)from Peter Grievens, Titanium dioxide , Iron oxide red was procured from Zuhahi Pharma. All other reagents employed were of analytical or pharmaceutical grade.

METHODS

Construction of calibration curve by UV- visible spectrophotometer

Calibration curve of Mesalamine in 0.1 N HCl

Preparation of standard stock solution:

Weigh and transfer about 100mg of Mesalamine and 100ml 0.1NHcl in a 100ml volumetric flask

Preparation of test solution from stock solution:

Take 10ml and dilute to 100 ml with 0.1NHcl stock solution λ max is calculated by using concentration in the range of 200-700 nm.

Standard graph Of Mesalamine

Weigh and transfer about 100 mg of Mesalamine into 100 ml volumetric flask,

add 0.1NHcl solution, make up the volume to 100 ml with 0.1NHcl solution.

From the stock solution, take 10ml and dilute to 100ml with 0.1NHcl, working solution is prepared.

From the stock solution 2,4,6,8 and 10μg/ml were prepared and the absorbance was measured at 232 nm.

Calibration curve of Mesalamine using pH 6.0 Phosphate buffer

10mg of drug was dissolved in phosphate buffer pH 6.0 and final volume was making up to 100ml volumetric flask. The stock solution concentration was 100μg/ml obtained. It was diluted with phosphate buffer pH 6.0 to obtain solution in concentration range 2,4,6,8,10μg/ml. Absorbance of μg/ml solution was measured between 200-400nm by using spectrophotometer.

Calibration curve of mesalamine using pH 7.2 Phosphate buffer

Accurately weighed 10 mg of drug, dissolved in sufficient volume of phosphate buffer pH 7.2 and then made volume up to 100 ml with phosphate buffer pH 7.2 and then working solutions of different concentrations 2,4,6,8,10(μ g/ml) were prepared. The absorbance was obtained at λ max 301nm and calibration curve was plotted between concentration and absorbance.

PREFORMULATION STUDIES

FTIR Studies

FTIR spectrophotometer is used to perform Drug excipient compatibility between drugs and excipients using Brukers Alpha Spectrophotometer. Under high compaction pressure and using the disc method, sample powder was thoroughly combined with potassium bromide at a 100:1 ratio in a glass mortar and pestle. The produced pellets were submitted to IR spectral analysis at wave number ranges of 4000 - 400 cm-1.

PRECOMPRESSION EVALUATION

Bulk density

The mass of the powder divided by the bulk volume is known as the bulk density.

Bulk density = Mass / bulk volume

Tapped Density

It is the ratio of total mass of the powder to the tapped volume of the powder.

Tapped Density = Mass of powder / Tapped volume

Angle of repose

Angle of repose defined as the maximum angle possible between surface of pile of powder and horizontal plane. It is characteristic related to inter particulate friction or resistance movement between particles.

$$\Theta = \tan-1 h/r$$

Hausner's Ratio

Hausner's ratio is correlated to the flowability of a powder or granular material. If it is greater than 1.25 is considered to be indication of poor flowability. H= Tapped density/ Bulk density

% Compressibility

Percent compressibility of powder mix was determined by carr's compressibility index.

Carr's index (%) = TTBD – LBD / TBD x 100 Where ,

BD: Bulk density , TD: Tapped density

PREPARATION OF CORE TABLETS

Mesalamine core tablets were prepared by using wet granulation technique. All the ingredients were weighed separately. Mesalamine USP (API)is passed through #20sieve, lactose monohydrate and povidone k30 passed through #40 sieve and mixed thoroughly in rapid mixer granulator and granulated with purified water. The granules so obtained were dried in rapid fluidized bed dryer until it reaches the LOD. Dried granules were passed through #20sieve. These granules were lubricated with flow promoters like magnesium stearate, talc, sodium starch glycolate and colloidal silicon dioxide. The flow properties of the granules were determined. The lubricated granules were compressed into tablets using a single punch rotary tablet machine.

Table 1: Formulation of Mesalamine core tablets F1-F8

Ingredients(mg/unit)	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
Mesalamine	800	800	800	800	800	800	800	800
Lactose Monohydrate	132	132	198	198	198	198	179	198
Povidone K30	30	30	30	20	20	30	40	30
Purified water (%w/w)	22.4	22.4	22.4	22.4	22.0	18.0	18.0	22.0
Sodium starch glycolate	16	24	24	24	16	16	16	20
Talc	5	5	5	5	5	5	5	5
Colloidal silicon dioxide	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5
Total weight of core tablets (mg)	993	1001	1067	1057	1049	1059	1050	1063

PREPARATION OF COATING DISPERSION

The prepared core tablets were coated with the coating dispersions.

Isopropyl alcohol and purified water were mixed in a ratio of 95:5 before being split into two equal parts in a ratio of 70:30 to create the solvent mixture. On magnetic stirring at 800rpm,Eudragit S100 and Eudragit L100 were gradually added to the majority of the solvent mixture and stirred for 30 minutes. Talc, dibutylsebacate , and colourings agents were gradually added to the second portion of the solvent mixture and homogenized on the Remi homogenizer for 10 minutes at a speed of 6000rpm.Add slowly second portion to the major part of solvent mixture on magnetic stirring and kept for 15min.The prepared solvent mixture passed through the #100mesh.The coating dispersion is prepared and used for coating process.

Table 2: Formulation of Coating trails on core tablets of Mesalamine

Ingredients(mg/unit)	CF1	CF2	CF3	CF4	CF5	CF6
Core tablet	1063	1063	1063	1063	1063	1063
Eudragit S100	58.5	61.9	45.06	41.17	34.11	44.11
Eudragit L100	3.09	-	5.04	7.36	14.92	4.92
Dibutylsebacate	6.2	6.2	5.04	4.92	4.92	4.92
Talc	14.08	14.41	11.78	11.50	11.00	11.00
Ferric oxide Red	1.13	1.13	0.92	0.90	0.90	0.90
Ferric oxide Yellow	0.19	0.19	0.16	0.15	0.15	0.15
Isopropyl alcohol	95parts	95parts	95parts	95parts	95parts	95parts
Purified water	5parts	5parts	5parts8	5parts	5parts	5parts
Total weight of coated tablets(mg/unit)	**1146**	**1147**	**1131**	**1129**	**1129**	**1129**
%Buildup	**8.0%**	**7.0%**	**6.0%**	**5.0%**	**6.5%**	**6.5%**

Table 3: Coating process parameters

Process Parameter	Range
Inlet temperature(°c)	30.4-32.4°c
Product temperature(°c)	22.9-25.6°c
Exhaust temperature (°c)	26.9-28.3°c
Pan rpm	15-30
Spray rate (g/min)	4.40-8.45
Atomization(bar)	0.5-0.2
Pattern air (bar)	0.5-0.2

EVALUATION

The prepared core and coated delayed release tablets were evaluated for following parameters like weight variation (Average weight of 20 tablets by electronic weighing balance, Hardness measured by hardness tester, Friability was examined using USP apparatus (Roche friabilator) at 100 revolutions per minute (rpm), and thickness was measured in millimeters (mm) using a Vernier Calliper. Disintegration in 0.1N in HCL and dissolution studies and results were mentioned in table 6 and 7.

Disintegration Test

One tablet was placed in each tube of the basket for tablet disintegration, and the top half of each tube was covered with a disc. To check for coat damage, tablets were initially tested in 0.1N HCl for 2 hours (simulated stomach transit time) at temperature 37°C±0.5°C

Dissolution studies By carrying out in vitro drug release experiments under circumstances simulating the mouth to colon, it was determined if the tablets of mesalamine had the capacity to remain intact and release the active component in the physiological environment of the stomach, small intestine, and colon. The drug release studies were carried out by using USP dissolution apparatus type 2(paddle) at 100 rpm and 37°±0.5°c. Drug release was first examined in 500mL of 0.1N HCl for 2 hours at 100rpm, then 3hours in 900 mL pH 6.0 at 100rpm, 12hours in 900 mL pH 7.2 at 50rpm. Mesalamine analysis was carried out using UV detection at 232 nm in the acid stage and 301 nm in the buffer stage.

Assay

5mL of 0.25N HCl and 50.0g of the mesalamine standard should be added to a 50mL volumetric flask. Mix after dilution to volume and sonicating to dissolve. To create a 160ppm standard solution, pipette 4 mL of this standard stock solution into a 25 mL volumetric flask, dilution to volume, and mixing. Use a 0.45 m membrane filter to filter. Crush 20 tablets with a weight of about the same to create the sample solution. Fill a 500 mL volumetric flask with precisely weighed powder equal to 800 mg of mesalamine. Add 50 mL of 1N HCl solution, and sonicate for 30 minutes at a temperature below 30 °C while

occasionally shaking. Add 300 mL of water, sonicate it for 20 minutes at a temperature below 30 °C while shaking it intermittently, and then dilute it with water to the desired level. Using a 0.45-m membrane filter, centrifuge a portion of this solution at 3500 rpm for 5 minutes.

Stability studies

The optimized coated formulation was maintained at 40°C with 75% RH , and samples were collected at 30, 60, and 90 days for physical and in-vitro drug release examination.

RESULTS AND DISCUSSION

Construction of calibration curve by UV-visible Spectrophotometer:

Calibration curve of Mesalamine using 0.1N HCL solution

Calibration curve of Mesalamine using 0.1N HCL solution at λ max 232 shown in fig:1 and Calibration curve of Mesalamine using pH 6.0 and 7.2 phosphate buffer at λ max 301 nm shown in fig: 2 and fig:3
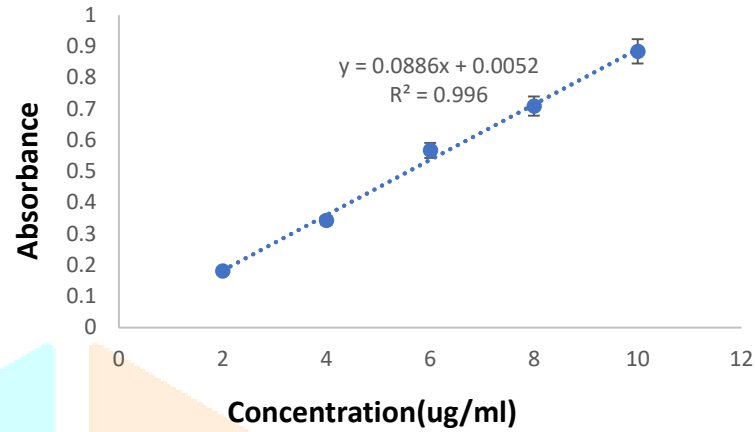
Calibration curve of Mesalamine using 0.1N HCl Solution at λmax 232nm

Figure:1 Calibration curve of Mesalamine using 0.1N HCL solution

Calibration curve of Mesalamine using pH 6.0phosphate buffer λmax 301nm
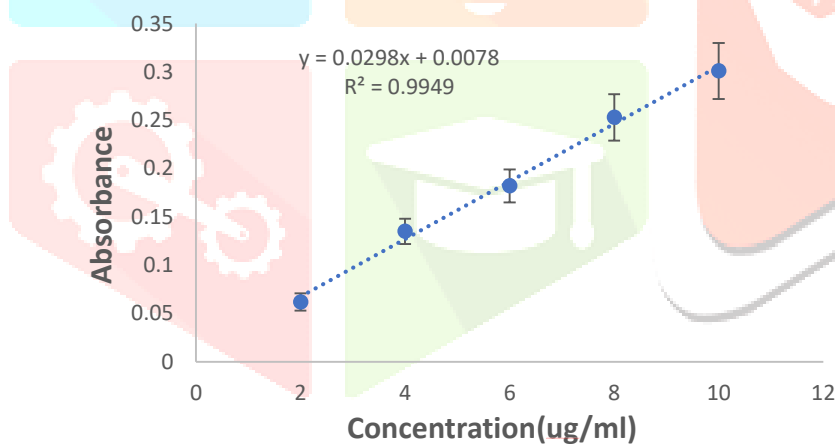
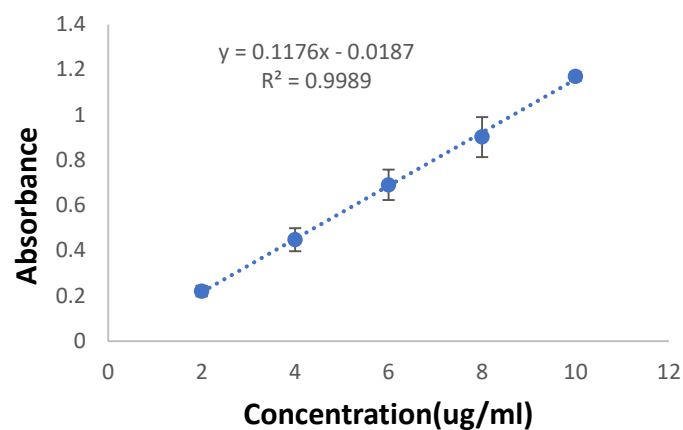Figure:2 Calibration curve of Mesalamine using pH 6.0phosphate buffer solution

Calibration curve of Mesalamine using pH 7.2 phosphate buffer at λmax 301nm

Figure: 3 Calibration curve of Mesalamine using pH 7.2 phosphate buffer solution

PREFORMULATION STUDIES

Drug excipient compatibility studies: According to the drug excipient compatibility studies, there were no significant interactions between the excipients and the drugs.

Drug excipient compatibility studies of Mesalamine pure drug

Figure4: FTIR Spectrum of Mesalamine pure drug

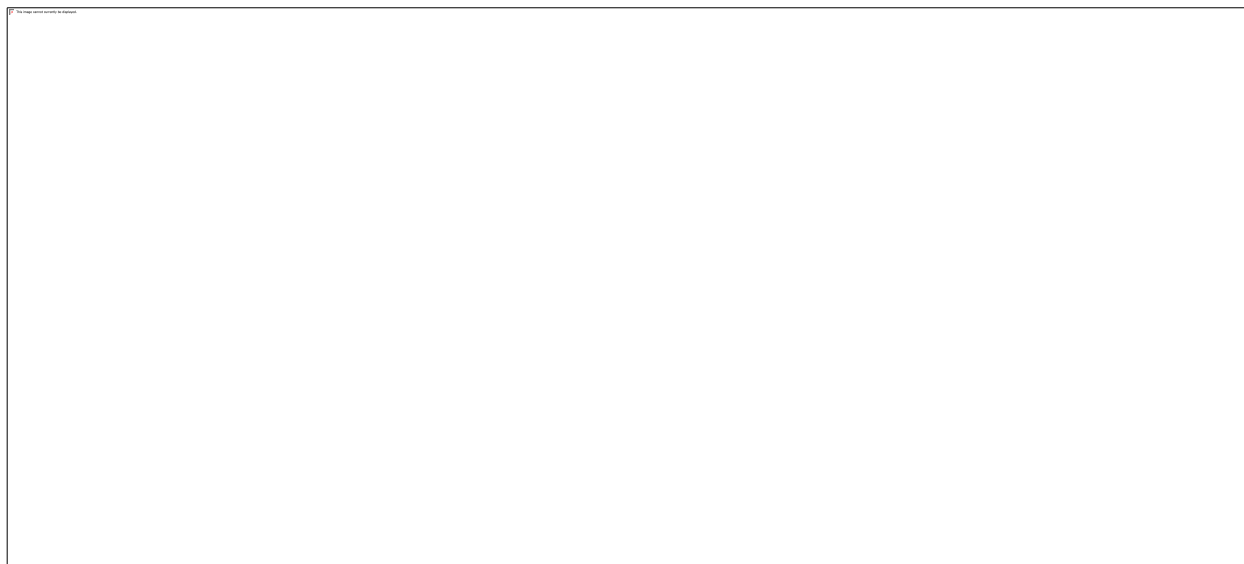Comparison of Mesalamine drug+ all excipients

Figure5: FTIR Spectrum of Drug and Excipients

Table 4 : Interpretation of FTIR Spectra of Mesalamine pure drug and drug+ all excipients

Functional group	Mesalamine pure drug(cm-1)	Mesalamine+ all excipients(cm-1)
C -O	1266.4	1266.4
-NH2	1651.2	1650.2
C=C	1451.1	1450.2
COOH	1796.1	1788.3
O -H	3720.2	3728.8
C-C	1085.4	1086.5

Pure Mesalamine spectra showed sharp characteristic peaks at 1266.4,1651.2,1451.2, 1796.1, 3720.2, 1085.4cm-1. These peaks are also clearly visible in the FTIR spectra of the physical combinations that include Mesalamine and other excipients in the final formula. The excipients chosen for the formulation were thus determined to be compatible with mesalamine.

Preformulation studies

Table 5: Lubricated blend parameters of formulation F1-F8

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (Θ)
F1	0.38±0.06	0.45±0.09	15.56±0.006	1.16±0.002	28.16±0.326
F2	0.48±0.01	0.66±0.013	18.15±0.002	1.20±0.015	30.24±0.211
F3	0.42±0.08	0.50±0.06	14.12±0.015	1.12±0.011	25.96±0.116
F4	0.38±0.05	0.44±0.018	17.77±0.02	1.12±0.006	26.41±0.431
F5	0.45±0.09	0.58±0.03	15.3±0.001	1.21±0.013	30.12±0.315
F6	0.50±0.011	0.65±0.011	18.14±0.031	1.19±0.001	32.05±0.162
F7	0.36±0.03	0.41±0.08	14.34±0.012	1.13±0.012	27.22±0.115
F8	0.41±0.01	0.39±0.006	12.55±0.034	1.10±0.016	29.57±0.576

All values are expressed as mean ± standard deviation, n=3

The granules of mesalamine delayed release tablets were prepared by wet granulation method. Bulk density, tapped density, Carr's index ,Hausner's ratio and angle of repose were used to characterise the granules. The bulk density and tapped density ranged from 0.31- 0.41gm/ml and 0.35-0.46 gm/ml respectively. Carr's index and Hausner's ratio ranged from 112.55 -18.15 % and 1.10-1.21 respectively. The angle of repose of different formulation batches from F1-F8 was found to be from 29.0˚ to 33.6˚. For all of the formulation batches of granules, the angle of repose was less than 30, indicating good flow behaviour.

Evaluation of Mesalamine core tablets formulation F1-F8

Various evaluation tests of weight variation, thickness, hardness, and friability were performed on the uncoated tablets of different formulations.

Table 6: Mesalamine core tablets evaluation of formulationsF1-F8

Formulation	Weight variation(mg)	Thickness(mm)	Hardness (kg/cm2)	Friability
F1	993±0.92	6.22±0.02	15.5±1.02	0.18
F2	1001±0.016	7.32±0.22	16.2±0.45	0.21
F3	1067±0.037	5.89±0.14	17.4±1.11	0.20
F4	1057±0.011	5.90±0.35	17.1±0.06	0.16
F5	1049±0.56	7.25±0.06	15.1±0.17	0.16
F6	1059±0.044	7.51±0.09	18.3±0.13	0.21
F7	1050±0.85	6.34±0.16	19.7±1.18	0.23
F8	1063±0.14	6.39±0.12	14.2±1.14	0.15

All values are expressed as mean ± standard deviation, n=3

Evaluation of Mesalamine coated tablets

A copolymer made of Eudragit S100 and Eudragit L100 is applied in varying amounts to solve the problem of mesalamine's early release. The coated tablets were evaluated for the following parameters including thickness, hardness, disintegration test, weight variation, assay and in-vitro studies.

Table 7:Mesalamine Coated tablets evaluation of formulations CF1-CF6

Formulation	weight variation(mg)	Thickness(mm)	Hardness (kg/cm2)	Disintegration test(min)	Assay(%)
CF1	1145±1.02	7.12±0.09	14.6±0.18	80-92	100.15 ± 0.56
CF2	1146±1.10	7.05±0.01	13.1±1.28	85-98	100.18 ± 0.74
CF3	1131±0.09	6.66±0.15	15.3±1.11	75-79	96.75 ± 0.95
CF4	1129±0.12	6.72±0.74	15.8±1.16	95-102	95.25 ± 0.25
CF5	1129±0.06	6.69±0.31	16.2±1.43	97-109	99.02 ± 0.95
CF6	1129±0.01	6.80±0.57	17.7±1.82	100-115	99.97 ± 0.55

All values are expressed as mean ± standard deviation, n=3

Invitro- drug release studies:

USP Dissolution Apparatus Type II was used to perform the in-vitro release studies. lists The results of the in-vitro drug release studies were listed in Table 8. For all formulations, a graph represents the cumulative percentage release of mesalamine as a function of time.Drug release from all formulations in Buffer Stage II-pH 7.2 (Acceptance criteria- The drug release should not be less than 80% in the phosphate buffer) it was found to be different for all formulations viz. 91.32%, 95.18 %, 94.48%, 96.22 %, 97.31 %, 98.03 %, for CF1,CF2, CF3, CF4, CF5, CF6 respectively.

Table 8: Invitro-drug release studies of Mesalamine coated tablets of formulations CF1-CF6

Dissolution media	Time (hr)	% cumulative drug release					
		CF1	CF2	CF3	CF4	CF5	CF6
%drug release in Acid stage	2hr	0.0	0.0	0.0	0.0	0.0	0.0
%drug release in Buffer stage 1	1hr	0.6	0.0	0.0	0.0	0.0	0.0
%drug release in Buffer stage 2	0hr	0.0	0.0	0.0	0.0	0.0	0.0
	1hr	3.23±0.1	3.89±1.1	4.67±1.6	5.89±1.3	4.21±1.2	5.24±1.3
	2hr	9.76±1.2	10.42±0.9	11.67±1.1	14.56±1.1	11.13±0.9	13.12±1.6
	4hr	11.21±0.6	12.38±0.2	14.29±0.9	15.69±0.3	15.21±0.6	15.87±0.2
	6hr	70.21±0.8	72.39±1.4	74.13±1.2	75.38±1.6	78.18±1.6	68.76±1.1
	8hr	75.31±1.3	77.14±1.1	78.89±1.1	79.19±1.2	82.35±0.8	75.21±1.3
	10hr	86.19±1.6	89.16±0.6	90.12±0.7	92.45±0.8	94.12±1.1	90.23±0.1
	12hr	91.32±0.6	95.18±0.6	94.78±0.2	96.22±0.6	97.31±0.1	98.03±0.6

All Values are expressed as mean ± standard deviation,n=3

Invitro Dssolution studies of Mesalamine Coated tablets
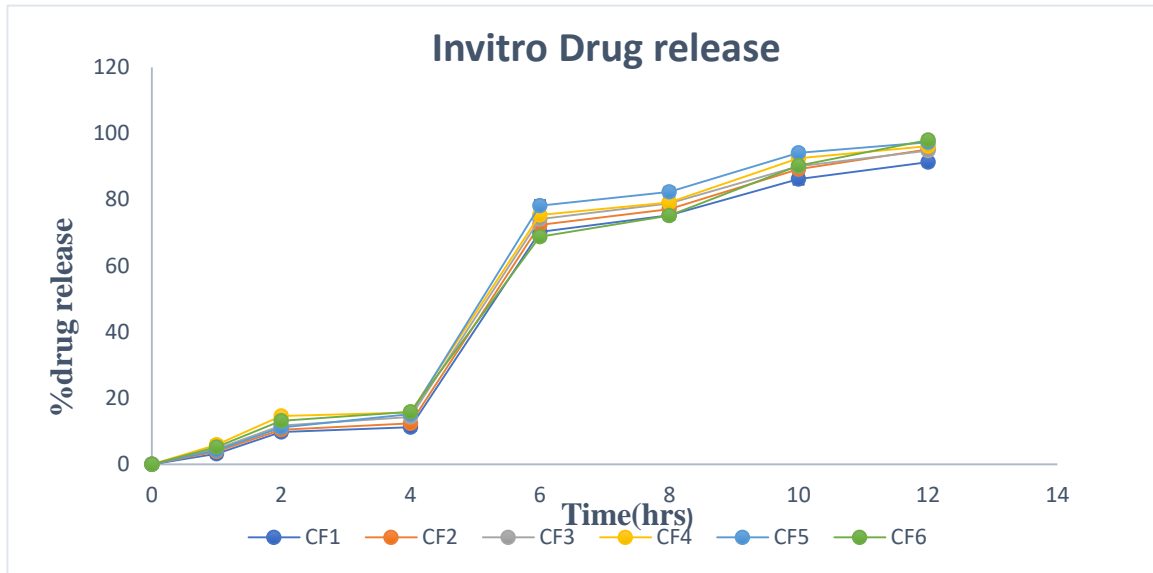

Figure 6: Dissolution profile of Mesalamine coated tablets CF1-CF6

Drug release kinetics of Optimized formulationCF6: Drug release kinetic parameters are performed like zero order kinetic model, First order kinetic model, Higuchi Model, Hixon and crowell Model, and Korsmeyer-peppas model shown in graphs. Kinetic results of optimized formulation followed zero order kinetics as correlation coefficient (R2)value is 0.9393 are higher than that of first order release kinetics. Drug release of optimized formulation is best fitted with Hixson and crowell model as correlation coefficient (R2) value is 0.9491.
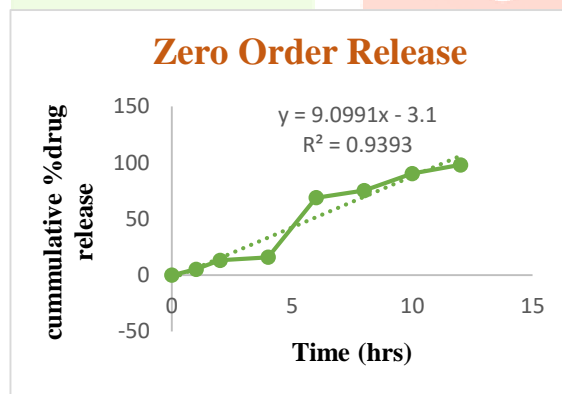

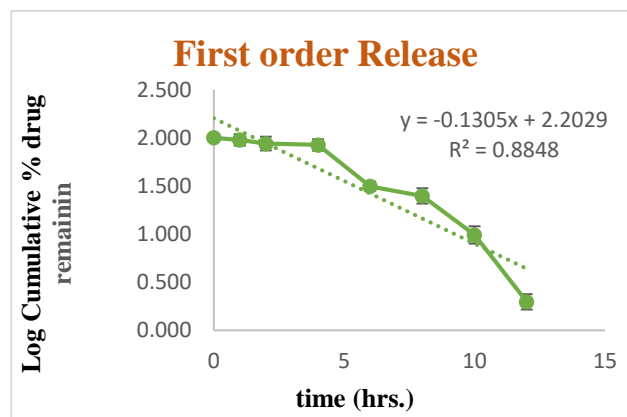Figure 7: Zero order kinetic model
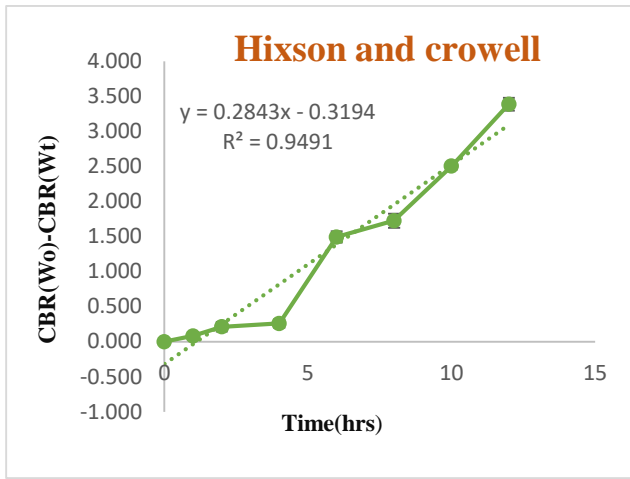

Figure 8: First order kinetic model
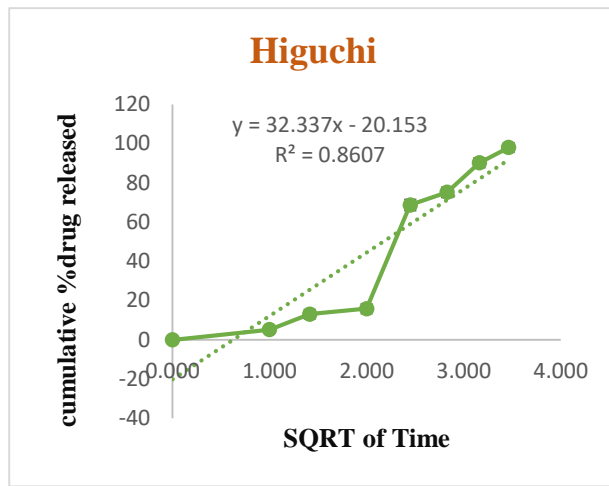
Figure 9: Hixon and crowell model

Figure 10: Higuchi model
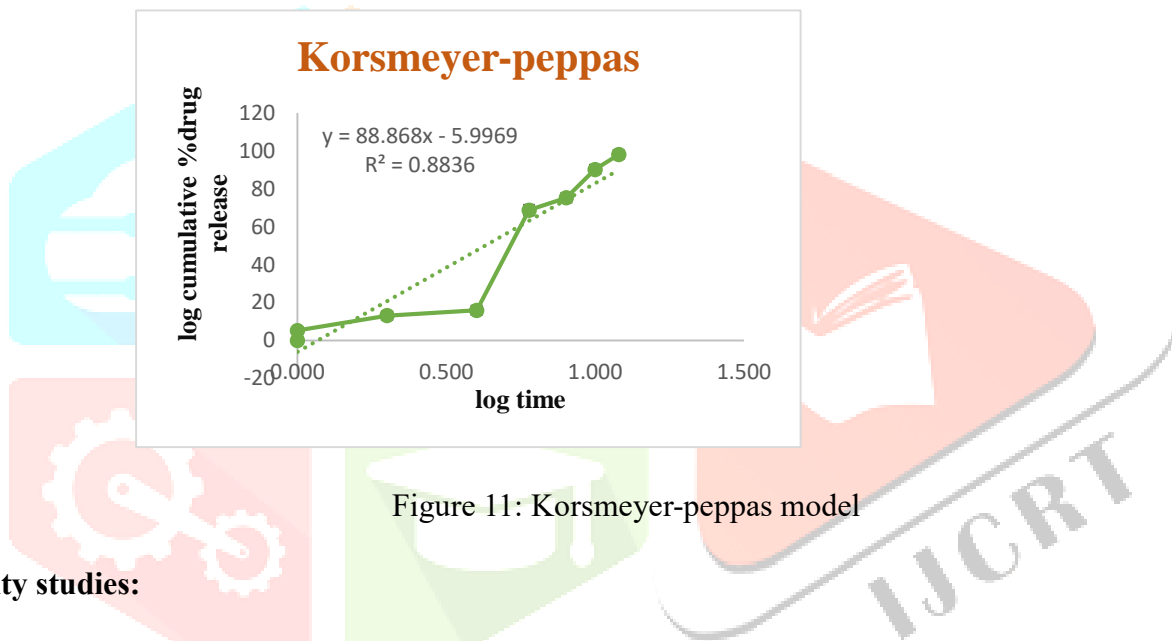

Figure 11: Korsmeyer-peppas model

Stability studies:

According to ICH guidelines, stability study samples of the mesalamine tablet of optimized formulation were stored at 40 ± 2ºc, $75\pm5\%$ RH for three months.

Table 9 : Stability data of the optimized formulation

Time points of loaded sample			Initial	1Month	2Month	3Month
Assay (90-110%)			100.10%	100.20%	98.30%	99.50%
Dissolution	Time	Limit	% Drug release	% Drug release	% Drug release	% Drug release
Acid stage	2hrs	NMT1.0%	0	0	0	0
Buffer stage 1	1hr	NMT1.0%	0	0	0.2	0.1
Buffer stage 2	12hrs	NLT 80%	98.03±0.6	99.8±0.52	99.4±0.12	100.3±0.34

All values are expressed as mean ± standard deviation, n=3

CONCLUSION

Mesalamine is a BCS class IV drug used to treat ulcerative colitis. The present research study was carried out to Formulate and evaluate Mesalamine delayed release tablets by wet granulation method. The nature of the API and its compatibility with excipients were studied by using FT-IR. According to the results, there was no interaction between all of the selected excipients and API.

The core tablets were prepared by using different concentrations of binders and super disinfectants. The prepared core tablets were coated with different polymers like Eudragit S100 and Eudragit L 100. The coating trails are performed with different buildups i.e.,8.0%, 7.0%,6.0%,6.5% and 5.0% without changing the ratios of ingredients in coating composition. From the coating trails, Formulation CF6 displayed a drug release rate of 98.03% after 12hours. Since it offers higher core protection in an acidic environment and exhibits the quickest release of drug in a gut pH environment. So, the trial CF6 was considered as best formulation. The optimized coated formulation (CF6) was charged to stability studies under accelerated storage conditions (40°C/ 75% RH) and the results were compared with initial results shows that there is no effect on Assay, dissolution studies. According to the results, formulation CF6, which contains enteric coated tablets of Mesalamine, would be a promising formulation to achieve the goal of treating inflammatory bowel diseases(ulcerative colitis).

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