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FORMULATION AND EVALUATION OF COMPRESSION COATED TABLET OF MESALAMINE HYDROCHLORIDE BY SOLID DISPERSION TECHNIQUE.

DR. DASWADKAR SHUBHANGI C.*

Associate professor

Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

Dr. D. Y. Patil Educational Complex, Sec. No. 29, Akurdi, Pune.

SONAVANE SUMIT MANOJ

Dept. Of Pharmaceutical Quality Assurance

Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

Dr. D. Y. Patil Educational Complex, Sec. No. 29, Akurdi, Pune.

Abstract:

The colon targeted drug delivery system is to provide a high concentration of therapeutic agent at the site of action while minimising pre-mature drug release in the upper gastrointestinal tract such as stomach, small intestine, large intestine and thus reducing the emergence of adverse effects to nontargeted areas. In prepared standard marketed formulations such are microsphere, capsule, delayed-release tablet and pellets are mainly used. These formulations are used for reducing the inflammation of colon. The aim of present study was based upon solid dispersion technique and to reducing the frequency of dose administration, to prevent ulcerative colitis by developing compressed coated tablet and this tablet is coating with solid dispersion by using Polyethylene glycol (PEG-4000). We were performed evaluation characteristics of core tablets and compressed coated tablets. The in-vitro drug dissolution study was conducted by using phosphate buffer pH7.4. The result demonstrated that the compressed coated tablet showed a drug release of 98.7% for 12 h. We will investigate the further study for the exact mechanism related to finding of the study.

Keywords: Mesalamine, PEG-4000, Ulcerative colitis and Solid dispersion.

INTRODUCTION:

World-wide, the incidence rates for Ulcerative colitis vary from 0.5 to 24.5 per 1000,000 person-year. In recent year, the colon targeted oral drug delivery system have been investigated extensively to achieve better therapeutic response of anticancer, anti-inflammatory, steroidal and anthelmintic drugs, which are used in various colon related diseases[1-3]. Colon specific delivery system offers several advantages in the treatment of colonic diseases such as Ulcerative colitis, Crohn's disease, Inflammatory Bowel Disease. In additional, several risk factors contribute to its pathogenesis. In last studies have shown that poor adherence has been an important barrier to the successful management of the patients with Ulcerative colitis. Only 40-60% of the patients who are newly diagnosed or have longstanding disease are adherent to therapy[4-6].

Ulcerative colitis is a chronic, long lasting, disease that cause inflammation, swelling and sores called Ulcers on the inner lining of the large intestine. Having Ulcerative colitis puts a patient at increased risk of developing colon cancer[7]. Symptoms include rectal bleeding, bloody diarrhoea, abdominal cramps and pain. Ulcers formed in places where the inflammation has killed the cells of colon, such as bleeding ulcer.

The Mesalamine used in the management of Ulcerative colitis shows comparable ranges of systemic absorption of 5-ASA as measured by plasma pharmacokinetics and 24hr urinary excretion of total 5-ASA. Thus, selection of Mesalamine treatment of ulcerative colitis should be based on other factors such as efficacy, dose response, toxicity of the parent compounds, dosing schedule and cost[8-11].

Mesalamine was found to be prepared marketed formulations such are, delayed release tablets, pellets, Microspheres and capsules are used but still these formulations were not achieved greater effects for ulcerative colitis. In this formulation, the solid dispersion coating offers for reducing the dosing frequency of drug and showing immediate release action. This study was based upon with in-vitro drug dissolution study[12-14]. The aim of present study was formulation and evaluation of compression coated tablet of mesalamine hydrochloride by solid dispersion technique.

MATERIAL AND METHODS:

Mesalamine was obtained from Wockhardt Ltd in Aurangabad, Maharashtra as a gift sample. Polyethylene glycol 4000 (PEG-4000) was purchased from Niram chemicals, Mumbai, Maharashtra. Eudragit RLPO and RSPO was purchased from Evonik Industries, Mumbai. All the chemicals and reagents are used were of analytical grades.

Pre-formulation studies[15-20]:

Organoleptic properties:

In organoleptic properties, it can be performed by different parameters and observed properties of drug.

Determination of Melting point:

Open capillary tube method was used for determination the melting point of the drug. This procedure was performed in triplicate and mean of three observations is considered as a melting point.

Solubility study:

The solubility of the drug was performed by placing of a drug in the conical flask by use of different solvents for 24hrs. This practice was performed thrice and a solvent for analysis of drug was finalized.

FT-IR Spectroscopic Determination:

The drug was characterized by using of Infrared absorption spectroscopy. The required quantity of drug was taken and mixed with potassium bromide and packed into the compact disk and spectrum was recorded.

Calibration curve of Mesalamine

10mg of drug was dissolved in 50 ml of distilled water and then volume made up to 50 ml with distilled water to get concentration 50 ug/ml. Stock solution was diluted further to get concentration range between 2ug/ml to 10ug/ml absorbance was measured at 297nm.

Drug polymer compatibility study

A compatibility study was carried out with potential formulation excipients and drug. API and excipients were mixed in specific quantity and placed in sealed vials for 4 weeks at 40℃ ± 2℃/75%±5% RH and 25℃±2℃/75% ±5% RH. After specific time period sample was withdrawn for FTIR study.

Composition of Mes core tablet:

Table No 1. Composition of core tablet

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Mesalamine (mg)	400	400	400	400	400	400	400	400	400	400	400
Eudragit RLPO and RSPO (mg)	1.4	2.7	2.7	1.7	1.4	2.7	4	4.5	4	2.7	2.7
Crosprovidone (mg)	12	21	12	16	20	16	20	16	12	12	16
MCC (mg)	120	109	118	116	115	116	109	112	117	120	115
Magnesium stearate	Q. s	Q. s	Q.s	Q. s	Q. s	Q. s	Q. s	Q. s	Q.s	Q.s	Q.s

PREPARATION OF CORE TABLET:

All the ingredients were weighed separately and prepared granules by Wet granulation method. The wet mass was passed through 16# sieve and the granules were dried in a oven at 50 ºC. Perfectly granules were mixed uniformly with 2% of talc and 1% magnesium stearate to compressed a core tablet.

EVALUATION OF CORE TABLETS:

Bulk Density (gm/ml)[24-30]:

The bulk density is obtained by adding a known mass of powder to a granulated cylinder.

Bulk Density = weight of lubricated granules / Volume of lubricated granules

Tapped Density (gm/ml):

The tapped density is obtained by Mechanical tapping method to a granulated cylinder containing the sample until little further volume change is observed.

Tapped Density = Weight of lubricated granules / Volume of Tapping

Car's Index:

Based on the bulk density and tapped density, the percentage compressibility of the granules was computed using the car's compressibility index by the formula.

Car's Index = Tapped density – bulk density/ Tapped density*100

Hausner's Ratio:

It is measurement of fractional resistance of the drug. The ideal range should be 1.5 it was determined by ratio tapped density and bulk density.

Hausner's Ratio = Tapped density / Bulk density

Angle of Repose:

The angle of repose of blend was determined by the fixed funnel method. The diameter of the powder cone was measured and angle of repose was calculated using the formula given in equation. $\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone

PREPARATION OF SOLID DISPERSION OF MESALAMINE

Measured quantity of Polyethylene glycol 4000 (PEG-4000) were taken and heated in water bath until they get melted. Then measured quantity of mesalamine was added in the molten base of PEG-4000 at the same temperature with stirring until both form homogenous mass. Melted mixture was then solidified rapidly in an ice bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved and stored in desiccator. Polyethylene glycol 4000 formulation were prepared in the ratio of 1:0.5, 1:1 and 1:1.5.

PREPARATION OF COMPRESSION COATED TABLET

Core tablet were first dedusted then placed in 12mm die cavity of a rotary tablet compression machine. Depending on design the solid dispersion (1:1) were used for the outer shell compression the coat weights were 400 mg. Tablets evaluation parameters were carried out.

EVALUATION OF COMPRESSED COATED TABLETS[31-38]

Weight variation:

Twenty tablets of each of formulations were weighed individually using an electronic balance. The average weighed was calculated and individual tablet weight was compared with average value and the deviation was recorded.

Friability:

The tablets had any dust removed before testing. Tablets were accurately weighed together, and friability was tested using a friability tester after 4 minutes of rotation at 25 rpm, any loose dust from the tablets was removed before accurately weighing again. If friability was not more than 1%, it was considered acceptable. The friability was calculated by equation.

Friability = Weight (Before Test) – (After Test) / Weight (Before Test)

Thickness:

Ten tablets from each batch was determined using Vernier calliper. The thickness variation limits allowed are ± 5% of the size of the tablet.

Hardness:

The tablet to be tested by using Monsanto hardness tester. The held between the fix and a moving jaw and reading of the indicator was adjusted to zero.

Disintegration time:

Six tablets were tested by a disintegration tester following the United State Pharmacopeial method, and water was used as the disintegration medium at 37^{o}C. Disintegration time of each tablet was recorded in minutes.

***In vitro drug release study*:**

The in vitro drug release from coat tablets was carried out using USP paddle apparatus at 50 rpm and 37^{0}C ± 0.5^{0}C.pH 7.4 buffer by using dissolution medium. 10 ml of dissolution medium was withdrawn at predetermined time intervals and fresh dissolution medium was replaced. The samples were withdrawn at regular intervals and analysed by UV spectrophotometer at 297 nm for the presence of the drug.

RESULT AND DISCUSSION

Pre-formulation studies

Organoleptic properties:

The Organoleptic properties are showed in below table.

Table No 2. Organoleptic properties of drug

Sr. No.	parameter	Observed properties
1	Appearance	Solid
2	Colour	White pinkish
3	Odour	Odourless
4	Taste	Tasteless

Melting point Determination

The Melting point of Mesalamine API was found to be 283± 2^{o}C.

Solubility study

Mesalamine was sparingly soluble in Methanol and ethanol, highly soluble in HCL, slightly soluble in acetone and water.

Fourier Transformed Infra-red Spectroscopy

From the FTIR study characteristics of Mes, amine group obtain at 1580 cm^{-1}, C-H bend at 686 and 699 cm^{-1}, C-OH stretching at 1137 cm.

Calibration curve of Mesalamine

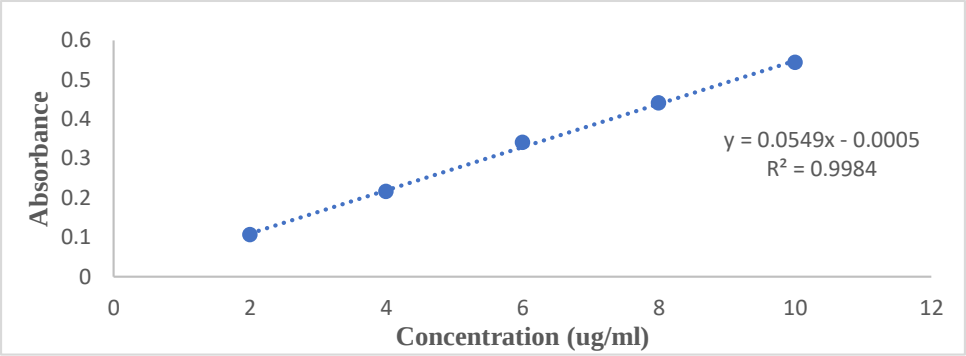

Fig. 1 Calibration curve of Mesalamine in water at 297nm.

Drug excipient Compatibility Study

Table No 3. API compatibility study

Composition	**Parameter**	**Initial**	**1st Month**		**2nd Month**		**3rd Month**	
Ratio			40℃ ±2℃/ 75%±5% RH	25℃±2℃/ 75% ±5% RH	40℃ ±2℃/ 75%±5% RH	25℃±2℃/ 75% ±5% RH	40℃ ±2℃/ 75%±5% RH	25℃±2℃/ 75% ±5% RH
API Alone	Appearance	Pinkish white	As initial	As initial	As initial	As initial	As initial	As initial
	Colour change	No	No	No	No	No	No	No
API+CROSS (1:1)	Appearance	White powder	As initial	As initial	As initial	As initial	As initial	As initial
	Colour change	No	No	No	No	No	No	No
API+E.RSPO &RLPO (1:1)	Appearance	White powder	As initial	As initial	As initial	As initial	As initial	As initial
	Colour change	No	No	No	No	No	No	No
API+MCC (1:1)	Appearance	White powder	As initial	As initial	As initial	As initial	As initial	As initial
	Colour change	No	No	No	No	No	No	No

The compatibility studies between the drug and polymer was evaluated using FTIR spectrophotometry. There was no any significance interaction in IR spectra of drug and excipients.

EVALUATION OF CORE TABLETS:

The preformulation studies of Mes were evaluated for various physical properties and the results were shown in the **Table No 4.** The bulk density showed good character for the Mes tablet. The car's index of F2 was found to be below 15% which indicated excellent flow properties. The Hauser's ratio for all the formulation was less than 2% which also indicates good flow property and packaging characters of powders. Angle of repose observed was within the range of 23-35 and showed that the flow property of the powder was excellent and within the acceptable limit.

Table No 4. Evaluation parameters of core tablets

Formulation code	Bulk density (gm/ml) ± S.D	Tapped density(gm/ml) ± S.D	Car's index (%) ± S.D	Hausner's ratio ± S.D	Angle of repose ± S.D
F1	0.58 ± 0.5	0.63 ± 0.4	15.5 ± 0.4	1.14 ± 0.7	26.0 ± 0.5
F2	0.42 ± 0.2	0.46 ± 0.7	12.7 ± 0.6	1.12 ± 0.2	23.5 ± 0.8
F3	0.55 ± 0.8	0.72 ± 0.7	13.1 ± 0.2	1.15 ± 0.4	24.03 ± 0.3
F4	0.65 ± 0.5	0.55 ± 0.3	12.7± 0.7	1.14 ± 0.1	23.5 ± 0.5
F5	0.54 ± 0.6	0.67 ± 0.8	11.9 ± 0.5	1.13 ± 0.3	24.6 ± 0.6
F6	0.56 ± 0.2	0.52 ± 0.2	15.5 ± 0.5	1.12 ± 0.5	28.01 ± 0.5
F7	0.59 ± 0.4	0.68 ± 0.4	11.3 ± 0.4	1.15 ± 0.8	25.1 ± 1.1
F8	0.63 ± 0.7	0.73 ± 0.5	13.7 ± 0.6	1.16 ± 0.2	26.5 ± 0.5
F9	0.37 ± 0.5	0.45 ± 0.4	15.8 ± 0.3	1.19 ± 0.5	24.4 ± 0.4
F10	0.55 ± 0.8	0.53 ± 0.3	13.2 ± 0.2	1.14 ± 0.1	23.5 ± 0.5
F11	0.56 ± 0.2	0.57 ± 0.2	12.8 ± 0.5	1.15 ± 0.4	24.6 ± 0.3

EVALUATION OF COMPRESSION COATED TABLETS

Tablet were selected randomly from all the eleven batches and physical evaluation of tablets were studied in **Table No 5.** The thickness of tablet was found to be 3.52± 0.05. mg. The hardness was found to be 6.00 ± 0.51 kg and % friability was found to be 0.41 ± 0.02%. The weight variation of the tablet was found to be 527.05 ± 2.23.

Table No 5. Evaluation parameters of coated tablets

Formulation code	Thickness (mm) ± S.D	Hardness (kg/cm^2) ± S.D	Friability (%) ± S.D	Weight variation (mg) ± S.D
F1	3.50 ± 0.02	6.05 ± 0.64	0.38 ± 0.03	528.5 ± 2.60
F2	3.52 ± 0.05	6.00 ± 0.51	0.41 ± 0.02	527.05 ± 2.23
F3	3.52 ± 0.08	6.05 ± 0.79	0.34 ± 0.01	526.63 ± 2.07
F4	3.50 ± 0.04	6.05 ± 0.48	0.32 ± 0.01	528.91 ± 2.65
F5	3.52 ± 0.06	6.05 ± 0.64	0.38 ± 0.03	526.05 ± 2.43
F6	3.52 ± 0.04	6.00 ± 0.44	0.37 ± 0.03	526.95 ± 2.08
F7	3.50 ± 0.07	6.05 ± 0.45	0.38 ± 0.01	527.58 ± 1.85
F8	3.52 ± 0.03	6.2 ± 0.73	0.35 ± 0.05	528.01 ± 1.33
F9	3.52 ± 0.03	6.2 ± 0.64	0.39 ± 0.01	527.58 ± 1.85
F10	3.52 ± 0.05	6.05 ± 0.48	0.38 ± 0.03	526.05 ± 2.43
F11	3.50 ± 0.03	6.2 ± 0.64	0.35 ± 0.01	528.5 ± 1.85

Table No 6. Disintegration time of mesalamine coated tablets

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Time (sec) ± S.D	225± 0.20	221± 0.18	218± 0.15	231± 0.29	232± 0.26	227± 0.12	218± 0.11	231± 0.13	235± 0.15	231± 0.21	225± 0.13

IN-VITRO DRUG DISSOLUTION STUDY OF COMPRESSED COATED TABLET

The dissolution study was carried out using the dissolution apparatus USP-II paddle type. In first stage of drug release obtained in 30 min at range of 58-60% for coated tablet. The coating is made up with Solid dispersion technique. The dissolution profile of mesalamine coated tablet shows total drug release within 12hrs. The coated tablet dissolution profile show in following table.

Table No 8. (%) Drug release of mesalamine coated tablet

TIME (Min)	Formulation ± S.D					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
60	7.66 ±0.577	6.96±1.665	8.6±2.89	8.11±0.577	9.83±2.901	7.2±0.991
120	15.45±1.352	14.9±1.36	17.72±2.91	16.35±1.352	19.13±2.901	14.34±1.034
180	23.6±1.212	24.05±1.83	27.9±2.971	25.57±1.212	29.45±2.882	22.04±1.905
240	31.9±2.438	34.12±2.10	38.4±2.995	35±2.438	40.4±2.967	30.16±2.734
300	40.47±2.51	37.45±2.81	44.32±2.982	45.04±2.516	46.55±2.901	38.42±2.893
360	49.12±1.243	46.55±2.58	53.8±2.884	55.27±1.243	55.6±2.942	47.25±2.935
420	58.05±2.155	55.7±2.73	64.37±2.978	64.5±2.155	64.79±2.79	56.35±2.962
480	67.2±1.501	65.9±2.47	74.9±2.895	74.34±1.501	73.05±2.91	65.67±2.994
540	75.45±2.347	76.47±2.78	85.92±2.794	80.82±2.347	82.07±2.83	74.5±2.982
600	84.2±2.212	85.9±1.90	88.09±2.347	88.54±2.90	89.2±2.84	84.26±0.991
660	91.92±1.34	93.45±2.47	90.09±1.34	90.67±2.882	92.09±2.79	90.6±2.734
720	97.65±2.95	98.45±2.999	97.09±2.982	96.4±2.967	97.6±2.962	95.5±2.99

TIME (Min)	F7	F8	F9	F10	F11
60	7.04±2.212	7.09±1.665	6.96±0.73	7.45±0.73	7.29±2.89
120	14.17±0.65	14.3±1.36	14.07±1.034	15.12±1.034	14.83±2.91
180	21.62±1.34	21.84±1.83	21.37±1.902	22.25±1.902	22.45±2.971
240	29.32±1.28	29.52±2.10	29.12±1.689	29.95±1.689	30.32±2.995
300	37.45±2.30	37.6±2.81	36.672±2.986	38.05±2.986	38.85±2.982
360	45.67±2.76	45.97±2.58	44.62±1.901	46.42±1.901	47.54±2.884
420	54.05±2.94	54.65±2.73	53.05±2.999	54.82±2.999	56.35±2.978
480	62.57±2.95	63.42±2.47	61.55±1.791	63.87±1.791	65.32±2.895
540	71.22±2.85	72.32±2.47	70.4±1.902	72.82±1.902	74.32±2.794
600	80.1±1.665	81.37±2.58	79.5±1.689	82.07±1.902	83.35±2.58
660	89.07±2.47	90.6±2.10	88.15±2.47	91.72±2.81	90.04±2.884
720	96.35±2.73	94.08±2.895	96.02±2.78	95.46±2.999	93.75±2.895

CONCLUSION:

The compressed coated tablet formulation was prepared successfully by using solid dispersion technique. This formulation was evaluated by various evaluation parameters. It can be conducted that from experimental results F2 was best batch. The stability study was revealed for three months that the formulation was stable at specific temperature. The *in-vitro* drug release of F2 formulation was found to be 97 to 99% over 12 hours in controlled manners, hence the present study was a successful attempt to formulation of Mesalamine sustained-release tablet. Further study is necessary to investigate the exact mechanism related to findings of the study.

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