# Design and Evaluation of Colon Targeted Dosage Form Containing Mesalazine Using pH Dependent Polymers

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**ABSTRACT**
Colonic drug delivery has gained importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis and irritable bowel syndrome but also for the potential it holds for the systemic delivery of proteins and therapeutic peptides. The aim of the study was to develop colon targeted tablets of Mesalazine by wet granulation method using $3^3$ response surface method with design of experiment software and HPMC K4M, Eudragit RL100, Ethyl cellulose and PVP K-30 used as pH dependent polymers. All the formulations (F1 to F27) were evaluated for the physicochemical parameters and were subjected to *in vitro* drug release studies. The amount of Mesalazine released from tablets at different time intervals was estimated by UV spectrophotometer. The formulation F26 released 98.16% of Mesalazine after 24 h. The results of the study showed that formulation F26 is the best formulation based on the evaluation parameters which provides targeting of Mesalazine for local action in the colon owing to its minimal release of the drug in the first 4 h. The pH dependent tablet system is a promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of Mesalazine for the treatment of disease at colon region.

**Keywords:** Mesalazine, Colon specific, Eudragit RL 100, pH dependent polymers.

## INTRODUCTION
Targeted drug delivery to the colon is mainly for the treatment of colonic diseases, for drugs like proteins and peptides, for the treatment of diseases sensitive to circadian rhythms such as Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon. The advent of slow release technologies increases the chances for a drug to be

released in the colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations. After the several other azo-bonds containing compounds designed to locally release 5-aminosalicylicacid were synthesized bensalazine, balsalazide and olsalazine. In 1986, Saffron and coworkers described the use of azo containing acrylic polymers to the delivery of protein drugs like insulin to the colon. [1] Targeted drug delivery is reliant on the identification and exploitation of a characteristic that is specific to the target organ. In the context of colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure, bacteria and prodrug approach. [2]

The pH gradient in the GIT is not in an increased order and is subjected to both inter- and intra-subject variations. In stomach the pH is 1.5-2.0 and 2-6 in fasted and fed conditions, respectively. The acidic pH is responsible for the degradation of various pH sensitive drugs and enteric coating may prevent it. In small intestine, the pH increases slightly from 6.6-7.0. On entry into the cecum, the pH dropped to 6.8. The pH of colon was found to be increased from 6.8-7.5 and in the rectum, 8.0. [3-4] In the present study it has been aimed at developing pH sensitive matrix tablets of mesalazine for local action in proximal colon, with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of proximal colon with an improved patient compliance, least side effects, better drug therapy and all aspects of an ideal drug delivery system.

Mesalazine is first line drug for the treatment of ulcerative colitis. When administered as a conventional formulation it causes abdominal pain, epigastric distress, stomach pain and acute liver failure. [5] To eradicate these side effects, the release of Mesalazine in the stomach and intestine must be minimized which in turn can be achieved by targeting Mesalazine to its primary site of action i.e. proximal colon. Hence, the present work deals with the preparation and evaluation of colon targeted delivery systems containing Mesalazine using pH dependent systems with different grades of Eudragit L100, Eudragit S100, Eudragit L30D, Eudragit FS 30D, Eudragit L100-55, HPMC K 4M, K 15M and K100M, Pectins, Carbolols, Polyvinyl Acetate Phthalate, Cellulose Acetate Phthalate, Ethyl Cellulose etc.

## MATERIALS AND METHODS

Mesalazine was generous gift sample from Valens molecules Pvt Ltd, Hyderabad. Eudragit RL 100, HPMC K4M and EC were from Aurobindo Pharma Ltd, Hyderabad. All other chemicals and solvents are of analytical grade.

## Preparation of colon tablets of mesalazine

Twenty-seven formulations (F1-F27) were prepared by wet granulation method using $3^3$ response surface method (3 variables and 3 levels of polymers) by using Design of experiment software with polymers like Eudragit RL 100, HPMC K4M and Ethyl Cellulose. All the formulations were varied in concentration of polymers, magnesium stearate constituted in all the formulations (Table 1). All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in Isopropyl alcohol). The wet mass was passed through sieve no 12# and dried at 45°C for 2 hours. Dried granules were sized by sieve no 18# and add magnesium stearate and talc. Granules obtained were compressed with 12 mm flat punch (Cadmach, Ahmedabad, India).

## EVALUATION PARAMETERS
### Weight variation
Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated. [6]

### Thicknesses
Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. [7]

### Hardness
The strength of tablet is expected as tensile strength ($Kg/cm^2$). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted. [8]

### Friability
Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at 6 inches with each revolution. Pre-weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. [9]

### Content Uniformity
20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 10 mg was weighed and dissolved in 100 ml of Phosphate buffer pH 7.2 filtered and drug content analyzed spectrophotometrically in UV spectrophotometer at 227 nm. [10]

### *In vitro* Swelling Studies
The degree of swelling of polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petri dish containing 5 ml of phosphate buffer pH 7.2 in 12 h at regular intervals of time (1, 2, 4, 8, 10 and 12 h), the tablet was taken carefully by using filter paper. [11]

**Table 1: Formulation trials of Mesalazine tablets**

| S. No | Mesalazine | Eudragit RL 100 | HPMC K4M | EC | PVP K-30 | DCP | Mg. Stearate | Total weight |
|-------|-----------|-----------------|----------|-----|----------|-----|--------------|--------------|
| F1 | 400 | 24 | 32 | 64 | 16 | 56 | 8 | 600 |
| F2 | 400 | 40 | 32 | 64 | 16 | 40 | 8 | 600 |
| F3 | 400 | 24 | 48 | 56 | 16 | 48 | 8 | 600 |
| F4 | 400 | 32 | 32 | 64 | 16 | 48 | 8 | 600 |
| F5 | 400 | 24 | 32 | 64 | 16 | 56 | 8 | 600 |
| F6 | 400 | 40 | 32 | 56 | 16 | 48 | 8 | 600 |
| F7 | 400 | 24 | 48 | 56 | 16 | 48 | 8 | 600 |
| F8 | 400 | 24 | 48 | 64 | 16 | 40 | 8 | 600 |
| F9 | 400 | 24 | 48 | 56 | 16 | 48 | 8 | 600 |
| F10 | 400 | 40 | 40 | 64 | 16 | 32 | 8 | 600 |
| F11 | 400 | 32 | 32 | 48 | 16 | 64 | 8 | 600 |
| F12 | 400 | 32 | 48 | 48 | 16 | 48 | 8 | 600 |
| F13 | 400 | 32 | 40 | 64 | 16 | 40 | 8 | 600 |
| F14 | 400 | 32 | 40 | 56 | 16 | 48 | 8 | 600 |
| F15 | 400 | 32 | 40 | 48 | 16 | 56 | 8 | 600 |
| F16 | 400 | 32 | 32 | 48 | 16 | 64 | 8 | 600 |
| F17 | 400 | 40 | 48 | 56 | 16 | 32 | 8 | 600 |
| F18 | 400 | 32 | 48 | 56 | 16 | 40 | 8 | 600 |
| F19 | 400 | 40 | 30 | 56 | 16 | 50 | 8 | 600 |
| F20 | 400 | 32 | 48 | 64 | 16 | 32 | 8 | 600 |
| F21 | 400 | 40 | 40 | 64 | 16 | 42 | 8 | 600 |
| F22 | 400 | 40 | 40 | 48 | 16 | 48 | 8 | 600 |
| F23 | 400 | 40 | 48 | 48 | 16 | 40 | 8 | 600 |
| F24 | 400 | 24 | 40 | 48 | 16 | 64 | 8 | 600 |
| F25 | 400 | 40 | 40 | 48 | 16 | 48 | 8 | 600 |
| F26 | 400 | 40 | 48 | 64 | 16 | 24 | 8 | 600 |
| F27 | 400 | 32 | 40 | 56 | 16 | 48 | 8 | 600 |



**Fig. 1: Mesalazine colon targeted tablets**

### *In vitro* drug release studies

*In vitro* drug release studies for developed mesalazine tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 ml of acidic buffer pH 1.2 (first 2 hours), Phosphate buffer pH 6.8 (next 4 hours) and Phosphate buffer pH 7.2 at 37±0.5°C temperature with 100 rpm. The amount of drug release was determined at different time intervals up to 24 h by UV visible spectrophotometer (Shimadzu UV 1800) at 227nm.

### Analysis of *in vitro* drug release kinetics and mechanism

The *in vitro* release data from several microspheres formulations containing mesalazine was determined kinetically using different mathematical models like Zero order, First order, Higuchi, and Korsmeyer–Peppas model. [12]

DOE is an essential piece of the reliability program pie. It plays an important role in Design for Reliability (DFR) programs, allowing the simultaneous investigation of the effects of various factors and thereby facilitating design optimization. This article introduces the concept of DOE. Future articles will cover more DOE fundamentals in addition to applications and discussion of DOE analyses accomplished with a soon-to-be-introduced ReliaSoft software product. [13-15]

### Drug-excipient compatibility studies
### Fourier transform infrared spectroscopy (FTIR)

The spectral analysis can be used to identify the functional groups in the pure drug and drug-excipient compatibility. Pure Mesalazine FTIR spectra, physical mixtures and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and drug-excipients were taken in the ratio 100:1 and mixed by mortar. The samples were made into pellet by the application of pressure. [16] Then the FTIR spectras were recorded in the wavelength region between 4000 and 400 cm⁻¹.

### Stability studies

Stability testing was conducted at 40°C ± 2°C/75% RH ± 5% RH for 3 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60 and 90 days period according to ICH guidelines. [17] Various *in vitro* parameters like % yield, entrapment efficiency and *in vitro* release studies were evaluated.

### RESULTS AND DISCUSSION
### Physicochemical properties of mesalazine tablets

The evaluation parameters of all the tablets are within the limits (Table 2) and the hardness ranges in between 6-6.5kg/cm². The Friability, weight variation and thickness was found to be within the limits and the results are summarized in table 2. The drug content of all formulation is in between 94.11-99.78%, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches. The Swelling study of mesalazine tablets was given in Table 2, showed that the swelling index of the tablet increases with increase in time up to 12

hours, this may be attributed to the fact that the erosion of ethyl cellulose. This indicates that the drug will remain in intestinal region till drug is released completely from the delivery system and promotes evacuation after its release. Hence all the tablets were subjected to *in vitro* dissolution test to determine the release profiles.

### *In vitro* drug release studies

The In vitro drug release studies of 27 different formulations of mesalazine along with marketed product were carried out and the results are depicted in Table 3, 4, 5 & 6.

**Table 2: Physicochemical parameters of mesalazine tablets**

| F. No | *Weight variation (mg) | #Thickness (mm) | #Hardness (Kg/Cm²) | #Friability (%) | #Drug Content (%) | Swelling index (%) |
|---|---|---|---|---|---|---|
| F1 | 601.65 ± 1.2 | 6.0 ± 0.12 | 6.0 ± 0.12 | 0.52 ± 0.01 | 95.23 ± 0.63 | 83 ± 0.76 |
| F2 | 598.69 ± 0.8 | 6.1 ± 0.06 | 6.1 ± 0.06 | 0.55 ± 0.02 | 97.04 ± 0.06 | 89 ± 0.72 |
| F3 | 598.04 ± 0.5 | 6.1 ± 0.06 | 6.1 ± 0.06 | 0.63 ± 0.03 | 95.56 ± 0.14 | 88 ± 0.64 |
| F4 | 601.05 ± 0.0 | 6.2 ± 0.12 | 6.2 ± 0.12 | 0.72 ± 0.01 | 98.11 ± 1.01 | 88 ± 0.81 |
| F5 | 601.54 ± 0.4 | 6.0 ± 0.00 | 6.0 ± 0.00 | 0.62 ± 0.02 | 94.23 ± 0.8 | 83 ± 1.03 |
| F6 | 600.78 ± 0.4 | 6.3 ± 0.10 | 7.1 ± 0.06 | 0.66 ± 0.01 | 95.45 ± 0.31 | 82 ± 0.84 |
| F7 | 600.65 ± 0.3 | 6.1 ± 0.10 | 6.1 ± 0.10 | 0.58 ± 0.02 | 94.11 ± 0.49 | 80 ± 0.72 |
| F8 | 599.57 ± 0.2 | 6.3 ± 0.25 | 6.3 ± 0.40 | 0.69 ± 0.01 | 97.23 ± 0.51 | 82 ± 0.79 |
| F9 | 600.76 ± 0.35 | 6.3 ± 0.06 | 6.3 ± 0.06 | 0.58 ± 0.02 | 96.13 ± 0.56 | 81 ± 0.80 |
| F10 | 600.49 ± 0.2 | 6.2 ± 0.20 | 6.2 ± 0.42 | 0.79 ± 0.02 | 95.23 ± 0.24 | 87 ± 0.46 |
| F11 | 601.53 ± 0.4 | 6.2 ± 0.06 | 6.3 ± 0.06 | 0.76 ± 0.01 | 97.97 ± 0.21 | 86 ± 0.67 |
| F12 | 602.58 ± 0.3 | 6.3 ± 0.00 | 6.4 ± 0.06 | 0.73 ± 0.02 | 97.45 ± 0.76 | 88 ± 0.93 |
| F13 | 601.34 ± 0.2 | 6.3 ± 0.26 | 6.8 ± 0.35 | 0.72 ± 0.02 | 97.45 ± 0.48 | 96 ± 0.53 |
| F14 | 598.67 ± 0.3 | 6.1 ± 0.21 | 6.4 ± 0.21 | 0.74 ± 0.03 | 96.98 ± 0.23 | 83 ± 1.08 |
| F15 | 599.65 ± 0.2 | 6.4 ± 0.06 | 7.0 ± 0.23 | 0.75 ± 0.02 | 96.45 ± 0.36 | 90 ± 0.91 |
| F16 | 600.65 ± 0.3 | 6.2 ± 0.25 | 6.4 ± 0.23 | 0.78 ± 0.01 | 96.45 ± 0.69 | 88 ± 0.63 |
| F17 | 601.79 ± 0.4 | 6.5 ± 0.15 | 6.8 ± 0.32 | 0.79 ± 0.01 | 96.34 ± 0.35 | 93 ± 0.48 |
| F18 | 601.87 ± 0.1 | 6.5 ± 0.25 | 6.7 ± 0.35 | 0.82 ± 0.01 | 97.56 ± 0.23 | 95 ± 0.90 |
| F19 | 599.67 ± 0.3 | 6.1 ± 0.12 | 6.2 ± 0.12 | 0.84 ± 0.03 | 96.29 ± 0.34 | 90 ± 0.75 |
| F20 | 599.32 ± 0.2 | 6.2 ± 0.12 | 6.5 ± 0.2 | 0.63 ± 0.03 | 97.18 ± 0.81 | 88 ± 0.67 |
| F21 | 598.27 ± 0.4 | 6.2 ± 0.06 | 6.3 ± 0.06 | 0.66 ± 0.02 | 96.27 ± 0.11 | 90 ± 0.54 |
| F22 | 600.27 ± 0.1 | 6.0 ± 0.12 | 6.1 ± 0.12 | 0.53 ± 0.03 | 96.18 ± 0.07 | 98 ± 0.67 |
| F23 | 600.26 ± 0.13 | 6.3 ± 0.17 | 6.8 ± 0.4 | 0.76 ± 0.05 | 96.14 ± 0.76 | 88 ± 0.54 |
| F24 | 600.10 ± 0.5 | 6.3 ± 0.00 | 6.7 ± 0.23 | 0.73 ± 0.08 | 97.16 ± 0.12 | 96 ± 0.86 |
| F25 | 599.12 ± 0.6 | 6.1 ± 0.17 | 6.6 ± 0.12 | 0.67 ± 0.02 | 96.23 ± 0.00 | 93 ± 0.70 |
| F26 | 600.16 ± 0.8 | 6.4 ± 0.10 | 6.7 ± 0.21 | 0.72 ± 0.89 | 99.78 ± 0.23 | 98 ± 0.68 |
| F27 | 600.29 ± 0.15 | 6.5 ± 0.29 | 6.9 ± 0.45 | 0.89 ± 0.03 | 97.10 ± 0.40 | 97 ± 0.75 |

*Values are expressed in mean± SD :( n=20); #Values are expressed in mean± SD :( n=3)

**Table 3: *In vitro* Drug Release Profile for colon mesalazine tablets F1-F7**

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| 2 | 03.13 ± 1.24 | 04.22 ± 1.23 | 04.51 ± 1.21 | 03.27 ± 1.19 | 04.19 ± 0.15 | 04.24 ± 1.78 | 04.65 ± 1.52 |
| 4 | 13.01 ± 1.15 | 12.04 ± 1.34 | 13.71 ± 2.25 | 14.95 ± 2.22 | 12.15 ± 0.88 | 13.95 ± 0.29 | 11.12 ± 1.29 |
| 6 | 28.49 ± 1.44 | 32.05 ± 1.68 | 33.24 ± 1.75 | 28.09 ± 1.78 | 38.18 ± 0.78 | 30.09 ± 1.29 | 28.34 ± 1.82 |
| 8 | 37.32 ± 1.58 | 40.06 ± 1.38 | 38.80 ± 1.52 | 37.72 ± 1.28 | 44.81 ± 1.75 | 39.72 ± 1.16 | 39.12 ± 2.29 |
| 12 | 45.83 ± 2.24 | 47.94 ± 1.24 | 46.50 ± 0.52 | 49.77 ± 1.32 | 52.49 ± 2.28 | 51.77 ± 0.29 | 51.72 ± 1.27 |
| 16 | 63.49 ± 1.78 | 54.88 ± 1.66 | 52.69 ± 0.86 | 67.36 ± 2.26 | 65.57 ± 0.19 | 64.36 ± 0.27 | 65.45 ± 1.19 |
| 20 | 78.28 ± 1.59 | 75.74 ± 1.45 | 66.69 ± 1.77 | 85.23 ± 2.29 | 78.21 ± 0.32 | 74.23 ± 0.27 | 76.56 ± 1.27 |
| 24 | 94.21 ± 1.52 | 92.34 ± 1.32 | 91.88 ± 1.16 | 95.48 ± 1.17 | 93.34 ± 0.25 | 91.34 ± 0.29 | 92.29 ± 1.22 |

Above parameters are communicated as Average ± Standard Deviation: (n=3)

**Table 4: *In vitro* Drug Release Profile for colon mesalazine tablets F8-F13**

| Time (h) | F8 | F9 | F10 | F11 | F12 | F13 |
|---|---|---|---|---|---|---|
| 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| 2 | 05.45 ± 1.23 | 05.82 ± 1.825 | 03.29 ± 1.16 | 05.36 ± 1.48 | 04.26 ± 1.56 | 03.47 ± 1.26 |
| 4 | 13.95 ± 1.96 | 13.89 ± 1.46 | 11.77 ± 2.29 | 12.08 ± 1.28 | 13.15 ± 0.26 | 12.01 ± 0.21 |
| 6 | 32.09 ± 1.44 | 32.35 ± 1.74 | 31.79 ± 1.11 | 29.89 ± 2.28 | 31.18 ± 0.52 | 31.58 ± 0.45 |
| 8 | 40.72 ± 174 | 44.67 ± 1.78 | 42.58 ± 0.75 | 39.87 ± 2.23 | 42.81 ± 0.58 | 45.38 ± 1.78 |
| 12 | 54.77 ± 1.75 | 51.97 ± 1.18 | 50.70 ± 0.56 | 48.97 ± 1.16 | 50.49 ± 1.89 | 53.87 ± 1.89 |
| 16 | 70.36 ± 1.86 | 66.89 ± 1.85 | 67.09 ± 1.86 | 59.76 ± 1.78 | 65.57 ± 1.75 | 61.89 ± 1.16 |
| 20 | 84.23 ± 1.22 | 79.78 ± 2.18 | 75.79 ± 2.22 | 70.69 ± 0.18 | 74.21 ± 1.24 | 73.28 ± 1.89 |
| 24 | 94.86 ± 1.86 | 91.73 ± 2.21 | 93.79 ± 0.85 | 81.21 ± 0.89 | 85.25 ± 1.66 | 94.49 ± 0.88 |

Above parameters are communicated as Average ± Standard Deviation: (n=3)

**Table 5:** *In vitro* **Drug Release Profile for colon mesalazine tablets F14-F20**

| Time (h) | F14 | F15 | F16 | F17 | F18 | F19 | F20 |
|---|---|---|---|---|---|---|---|
| 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| 2 | 03.18 ± 2.09 | 05.24 ± 1.16 | 04.58 ± 1.25 | 05.47 ± 1.18 | 04.46 ± 1.25 | 05.33 ± 1.37 | 04.55 ± 2.33 |
| 4 | 11.77 ± 0.52 | 12.04 ± 2.22 | 13.35 ± 1.14 | 11.05 ± 1.14 | 12.34 ± 1.78 | 10.46 ± 2.24 | 12.12 ± 3.21 |
| 6 | 32.54 ± 1.18 | 31.05 ± 1.17 | 32.64 ± 1.86 | 30.30 ± 1.98 | 36.78 ± 1.28 | 36.97 ± 2.22 | 41.34 ± 2.289 |
| 8 | 41.58 ± 2.22 | 38.06 ± 1.82 | 43.56 ± 1.89 | 42.40 ± 1.82 | 46.78 ± 1.24 | 47.67 ± 1.75 | 57.12 ± 2.41 |
| 12 | 53.28 ± 2.29 | 49.94 ± 1.96 | 50.78 ± 1.75 | 56.50 ± 1.78 | 57.66 ± 1.75 | 59.89 ± 1.96 | 69.72 ± 2.11 |
| 16 | 61.54 ± 2.85 | 63.88 ± 1.48 | 62.69 ± 1.44 | 69.76 ± 1.44 | 63.56 ± 1.22 | 67.67 ± 1.18 | 73.45 ± 2.75 |
| 20 | 73.78 ± 1.86 | 76.74 ± 1.47 | 73.89 ± 2.45 | 77.27 ± 0.47 | 81.65 ± 1.16 | 79.78 ± 2.28 | 84.56 ± 1.78 |
| 24 | 92.78 ± 1.74 | 84.87 ± 1.14 | 83.65 ± 0.85 | 91.43 ± 0.32 | 92.65 ± 1.29 | 92.78 ± 2.23 | 95.45 ± 1.11 |

Above parameters are communicated as Average ± Standard Deviation: (n=3)

**Table 6:** *In vitro* **Drug Release Profile for mesalazine tablets F21-F27**

| Time (h) | F21 | F22 | F23 | F24 | F25 | F26 | F27 |
|---|---|---|---|---|---|---|---|
| 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |
| 2 | 03.12 ± 2.18 | 04.78 ± 1.33 | 04.35 ± 1.22 | 05.22 ± 2.37 | 04.47 ± 2.21 | 03.40 ± 1.28 | 05.12 ± 1.89 |
| 4 | 13.01 ± 1.18 | 14.53 ± 1.11 | 11.66 ± 1.28 | 12.05 ± 2.18 | 13.47 ± 3.14 | 11.05 ± 1.52 | 12.12 ± 1.12 |
| 6 | 34.49 ± 2.22 | 30.68 ± 1.18 | 31.65 ± 1.75 | 33.30 ± 2.22 | 31.78 ± 2.17 | 42.30 ± 1.25 | 36.34 ± 1.75 |
| 8 | 43.32 ± 2.22 | 43.78 ± 1.65 | 42.65 ± 1.72 | 42.40 ± 2.15 | 40.87 ± 2.41 | 59.40 ± 1.19 | 57.12 ± 1.86 |
| 12 | 55.83 ± 1.96 | 52.56 ± 0.18 | 54.32 ± 1.98 | 56.50 ± 1.74 | 51.66 ± 2.44 | 71.50 ± 1.27 | 69.72 ± 1.74 |
| 16 | 66.49 ± 1.58 | 61.08 ± 2.34 | 62.39 ± 1.56 | 63.76 ± 1.74 | 63.86 ± 2.74 | 80.76 ± 1.28 | 73.45 ± 2.28 |
| 20 | 79.28 ± 1.75 | 70.98 ± 2.41 | 76.67 ± 1.42 | 72.27 ± 1.85 | 71.47 ± 2.95 | 89.27 ± 1.58 | 84.56 ± 2.23 |
| 24 | 94.58 ± 2.29 | 81.76 ± 2.77 | 84.45 ± 1.44 | 82.86 ± 1.98 | 83.45 ± 2.14 | 98.68 ± 1.52 | 89.02 ± 2.15 |

Above parameters are communicated as Average ± Standard Deviation: (n=3)

**Table 7: Release kinetics of optimized formulation of mesalazine colon tablets (F26)**

| Formulation Code | Zero Order | | First Order | | Higuchi | | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|---|---|
| | $R^2$ | n | $R^2$ | n | $R^2$ | n | $R^2$ | n |
| F26 | 0.999 | 8.741 | 0.748 | 0.151 | 0.937 | 29.62 | 0.959 | 0.825 |
| Marketed | 0.927 | 8.642 | 0.994 | 0.061 | 0.954 | 24.76 | 0.971 | 0.833 |
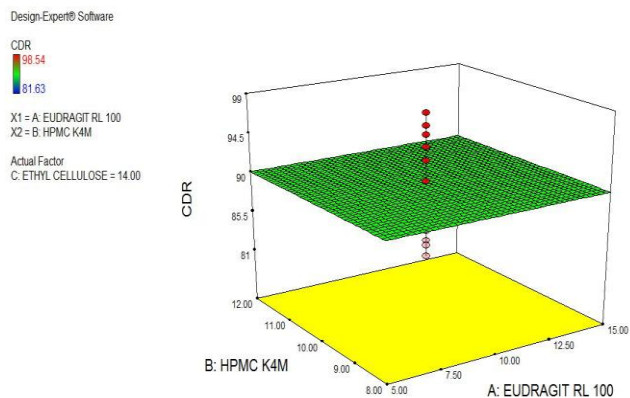


**Fig. 2: Response surface plot showing the influence of amount of polymer on the release profile of mesalazine tablets for Cumulative % drug Released.**
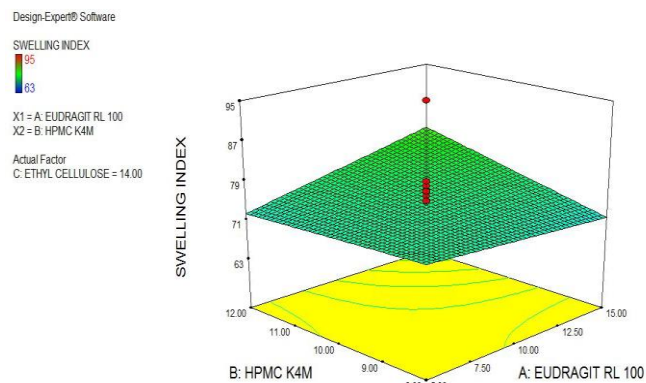


**Fig. 3: Response surface plot showing the influence of amount of polymer on Swelling Index of mesalazine tablets**

The mesalazine tablets extended the drug release up to 24 hours. The highest drug release was found in the formulation F26 i.e. 98.68 ± 1.52% within 24 hours. F26 was found to be optimized formulation based on the dissolution and other evaluation parameters. The in vitro drug release profile from marketed conventional tablet was found to be 96.72 ± 1.56% within 60 min.

**Mathematical modeling of optimized formula (F26) of mesalazine tablets**

In the present study drug release mechanism of optimized mesalazine tablets F26 were best fitting to zero order and Higuchi model because regression coefficient was seen closest to 1 in these models which conforms diffusion assisted mechanism of release. Further the n value obtained from the Korsmeyer-Peppas plots i.e. 0.825 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion. The reference standard release was explained by first order kinetics as the plot showed highest linearity as the drug release was best fitted in first order kinetics. The results are summarized in Table 7.

**Design of Experiment**

This method is mainly used to explain the effect of one factor on other factor. To know whether this effect is significant or not, if significant how it influences the response. In this present work the effect of one factor (Ethyl Cellulose) on other two factors (Eudragit RL 100, HPMC K4 M) is explained. In the above graph (Figure 2) the effect of Ethyl Cellulose on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of Ethyl Cellulose on % cumulative drug release.
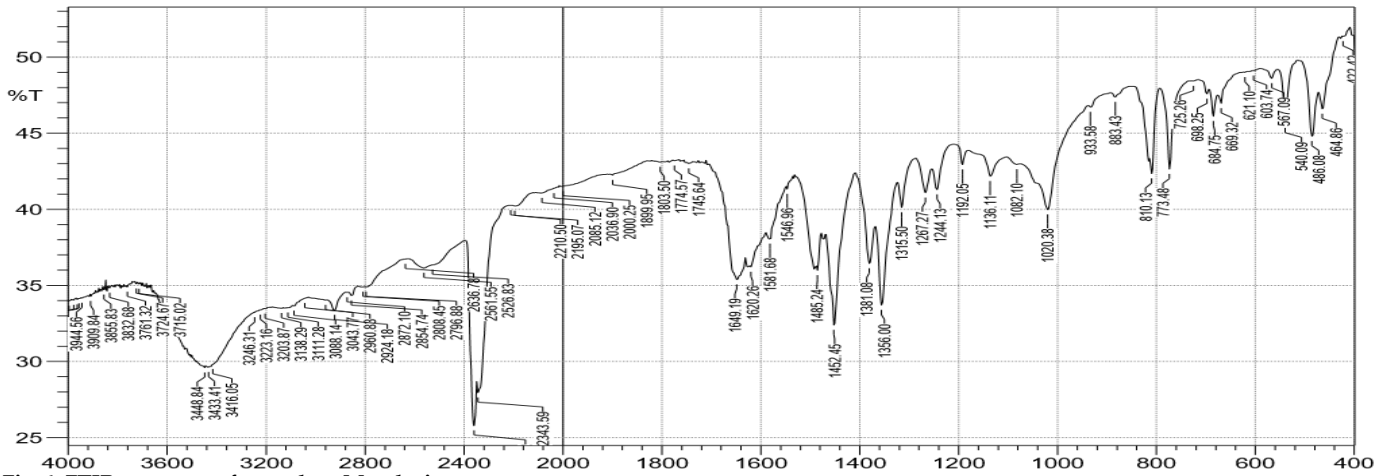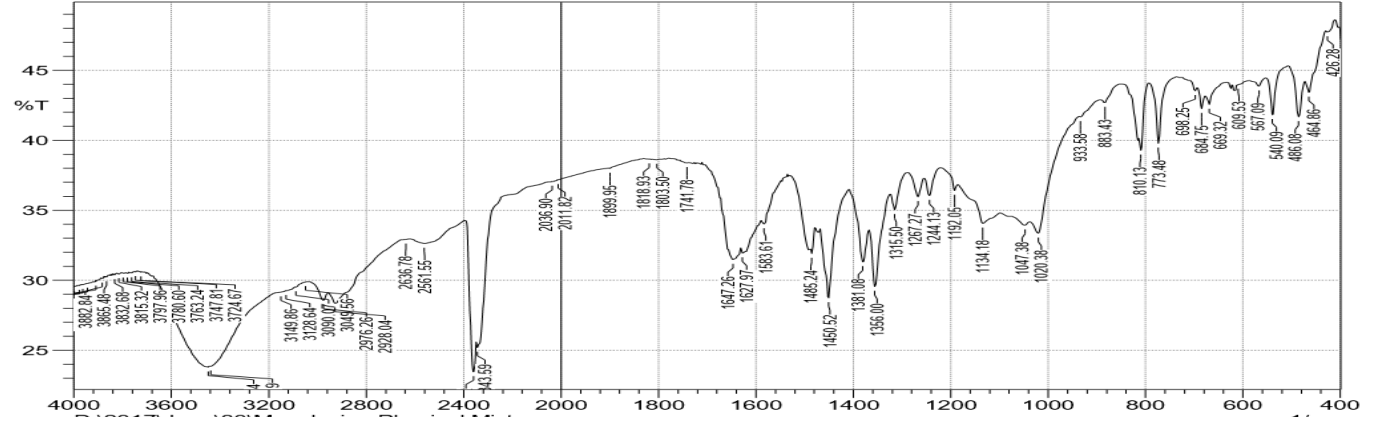
Fig. 4: FTIR spectrum of pure drug Mesalazine


Fig. 5: FTIR spectrum of optimized formulation F26 of Mesalazine physical mixture
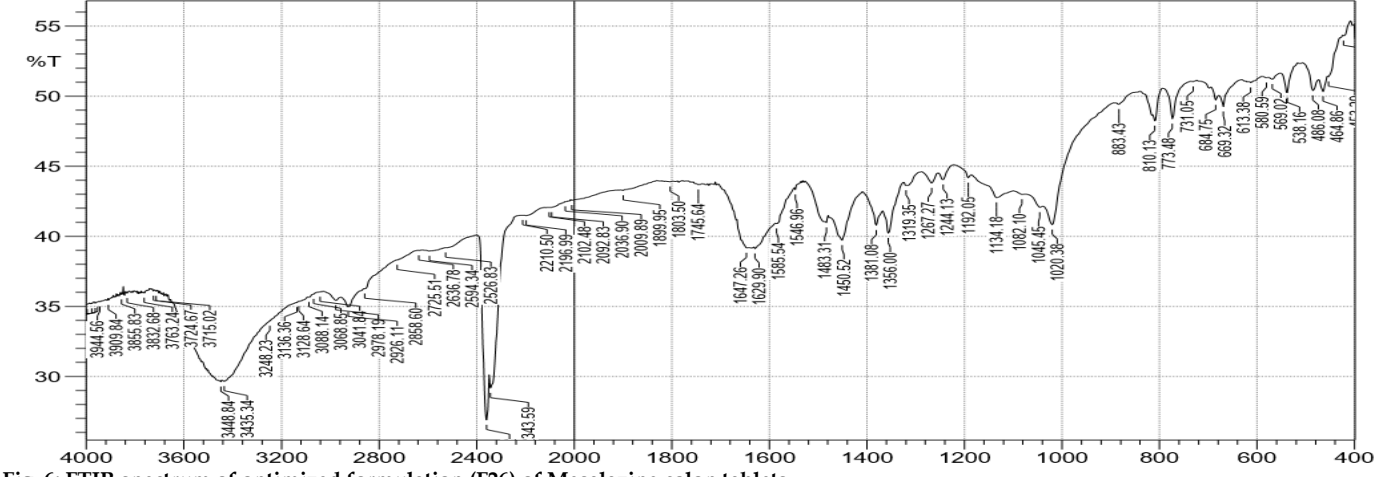

Fig. 6: FTIR spectrum of optimized formulation (F26) of Mesalazine colon tablets

The formulations with all 3 factors shown % cumulative drug release in between 81.21-98.68 but when Ethyl Cellulose is in low concentration the maximum % CDR is near 85.25. This is the effect of factor (Ethyl Cellulose) on response.

There is a negligible effect on Swelling Index of formulations because all formulations have excellent Swelling property and there is slightly influence on Swelling Index by Ethyl Cellulose (Figure 3).

### Drug-excipient compatibility studies
### Fourier transform infrared spectroscopy (FTIR)

The FTIR Spectrum of Mesalazine pure drug, physical mixture and optimized formulation were shown in Figure 4, 5 and 6. The FTIR spectrum of Mesalazine optimized formulation F26 exhibited characteristic bands consistent with the molecular structure of Mesalazine which indicated that no chemical interaction occurred between the drug and excipients used in the formulation.

### Stability study

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (F26) to the Accelerated Stability Studies, the results were shown that there were no major changes in Drug Content, *In Vitro* Drug Release, Swelling Index and Hardness. Hence the formulation was found to be stable and the results are depicted in Table 8.

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**Table 8: Parameters after accelerated stability study of formulation F26**

| Parameters | Temperature Maintained at 40 ± 2⁰C ; Relative Humidity (RH) Maintained at 75% ± 5% RH | | | |
|---|---|---|---|---|
| | Initial | After 1 month | After 2 months | After 3 months |
| **Drug Content (%)** | 99.78 ± 0.14 | 98.76 ± 0.68 | 97.23 ± 0.37 | 97.32 ± 0.22 |
| *In Vitro* **Drug Release (%)** | 98.68 ± 1.15 | 98.09 ± 1.53 | 97.65 ± 1.42 | 97.02 ± 1.35 |
| **Swelling Index** | 98.0 ± 0.64 | 97.0 ± 0.56 | 97.0 ± 0.37 | 96.0 ± 0.23 |
| **Hardness** | 6.7 ± 0.56 | 6.7 ± 0.58 | 6.7 ± 0.15 | 6.7 ± 0.27 |

In present work attempt was made to formulate and evaluate extended drug release colon tablets of mesalazine. Twenty-seven formulations (F1-F27) were prepared by wet granulation method using $3^3$ Response surface method where $3^3$ indicates 3 variables and 3 levels of polymers of different Eudragit RL 100, HPMC K4M and Ethyl Cellulose (low, middle and high concentrations) by using Design of experiment software. FTIR studies results revealed that there was no incompatibility between drug and excipients. The formulation F26 was selected as optimized formulation based on evaluation parameters and in vitro dissolution studies, it showed minimum release in stomach (Acidic buffer pH 1.2) and small intestine (Phosphate buffer pH 6.8) and a maximize release in proximal colon (Phosphate buffer pH 7.2). It can be concluded that the colon tablets of mesalazine formulations can be an innovative and promising approach for the delivery of mesalazine for the treatment of ulcerative colitis.

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