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Formulation, development and evaluation of antiulcerative drug for colon targeting by extrusion spheronization technique

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Abstract
The purpose of study was development of mesalamine colon targeted multiple unit particulate system (Mups). Mesalamine pellets were prepared by extrusion-spheronization process by using microcrystalline cellulose (MCCPH101), povidone K90 and magnesium stearate. The pellets were then coated with ethylcellulose (10 cps 10% w/w) and sodium CMC as retardant. The coated pellets were compressed to form Mups tablet which were subjected for evaluation of various parameters such as bulk density, tapped density, compressibility index, hausner's ratio, friability, hardness, average weight and *in-vitro* dissolution study. The best formulation (F4) was found to be within the acceptable limits with hausner's ratio (1.162-1.327), compressibilty index (20.45-23.51%), average weight range (570-592mg), hardness (140-160 kg/cm^2), friability (0.2-0.18%) and thickness (4.10-4.30 mm). The results of *in vitro* release data indicated that the optimized formulation (F4) showed 100% drug release in 8 h in phosphate buffer (pH 7.2) dissolution medium. A 2^2 factorial design of experiment was applied by Minitab 17 software in which two factors were taken and evaluated at two levels and experimental trials were performed for all four possible combinations.

Keywords: mesalamine, extrusion spheronization, *in-vitro* drug release, colon targeting

Introduction
In recent years, colon targeted delivery systems have been the focus point of formulation laboratories because the colon is considered as a suitable site for the delivery of both conventional and labile molecules, and it is also a site for some specific diseases, such as, ulcerative colitis, crohn's disease, bowel cancer, some infections, and constipation, which require local delivery of the drug (s) [1]. Colonic drug delivery may be achieved by either oral or rectal administration. Rectal dosage forms (enemas and suppositories), are not always much effective due to high variability in the distribution of drug administered by this route [2].
Various approaches have been used for oral delivery of drug(s) to the colon which includes time dependent delivery, pH- dependent systems and bacteria- dependent delivery. The pH dependent systems exploit the generally accepted view that pH of human gastrointestinal (GI) tract increases progressively from the stomach (pH 2-3), small intestine (pH 6.5-7) to the colon (7.0-8.0). Taking advantage of the highest pH value of the colon content, the dosage form containing the active drug in the core is coated with pH dependent material which dissolves at the pH of colon [3, 4].
Ulcerative colitis is the anti-inflammatory disease of the colonic mucosa which is restricted to large intestine and is usually treated with salicylates or glucocorticoids. However, during periods of remission mesalamine is the drug of choice. In this case it is desirable to localize the release of mesalamine to the afflicted site in the colon [5-7]. Thus, mesalamine was used as a model drug in the present study. It is an anti-inflammatory drug, for oral administration in the treatment of diseases of colon (ulcerative colitis, crohn's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption [8].
The multiple unit dosage forms include micro granules/ spheroids, pellets, microcapsules, etc. Pellets for pharmaceutical applications are defined as small, spherical, free-flowing granules with a narrow size distribution, typically varying in diameter between 500 to 1500 µm, in which the active pharmaceutical ingredient (API) is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet or encapsulated or compressed into a tablet. Pellets disperse freely in the GIT. It maximizes drug

absorption, minimize local irritation of mucosa by certain irritant drugs, reduce variations in gastric emptying rates, flexibility in dosage form design, easy to coat; depicting advantages of pellets over tablet [9, 10, 11, 12] The aim of the present study was to formulate, develop and evaluate antiulcerative drug for colon targeting by extrusion spheronization technique and to prepare multi-unit pellet system (MUPS) tablet for colon specific drug delivery systems.

Materials and Method

Materials

Mesalamine drug was obtained as gift sample from Wockhardt, Aurangabad, India, Ethylcellulose (10cps) from Dow Chemicals, and sodium CMC, Microcrystalline cellulose PH101, talc, PVP K-90, syloid 244F were obtained from Signet Chemical, Mumbai. All other chemicals were of analytical grade and used as such.

Method

Extrusion spheronization technique is the most advanced technique of pelletization. The process of extrusion spheronization included dry mixing where the material was dried, mixed to achieve homogeneous powder dispersion; wet granulation using a suitable granulating fluid, powder mixture was transformed into a plastic wet mass. The wet mass thus obtained was extruded to produce rod-shaped particles of uniform diameter that was charged into a spheronizer. The extrudates were rounded off into spherical particles using a spheronizer. The spherical particles were then dried to achieve the desired moisture content and optionally screened to achieve a targeted size distribution. Drying was achieved by tray drying or at room temperature, the specific requirements for a wetted mass to be suitable for extrusion and spheronization [13, 14, 15].

A) Preparation of Pellets by Extrusion Spheronization Technique

The technique selected for the preparation of mesalamine containing pellets of uniform size and shape was wet mass extrusion–spheronization method (Table 1). The procedures used were dry mixing or blending, wet massing, extrusion, spheronization and drying respectively.

Table 1: Ingredients used for forming pellets

S. No.	Ingredients	mg/tablet
1.	Mesalamine	500.0
2.	Microcrystalline cellulose Avicel PH 101	30.0
3.	Povidone K -90	20.0
4.	Magnesium stearate	2.5
5.	Purified water	q.s.
6.	Extrude/ Sphere total wt	552.6

B) Controlled release coating of pellets

The prepared pellets were coated with ethyl cellulose (10 cps, 10% w/w). The coating parameters taken were inlet air temperature (25-35°C), the exhaust temperature (25-45°C), the product temperature (26-30°C), drive speed (40-90), pump rpm (5-9), atomization (1.0), air flow (3-5). The physical parameters taken for compression were description (white grey to pale brown specked round tablet, dimension (12.5mm ± 0.2 mm), tablet weight (570-592mg), hardness was (140-180 N), and thickness (4.10mm), respectively (Table 2).

Table 2: Coating of the prepared pellets

S. No	Controlled release coating	F1	F2	F3	F4
1.	Ethyl cellulose 10 cps	7.5000	10.500	12.500	12.500
2.	Talc	1.000	1.000	1.000	1.000
3.	DBS	1.500	1.500	1.500	1.500
4.	Colloidal silicon Dioxide (syloid)	2.400	2.400	2.400	2.400
5.	IPA	q.s.	q.s.	q.s.	q.s.
6.	Water	q.s.	q.s.	q.s.	q.s
7.	DCM	q.s.	q.s.	q.s.	q.s.
	Total weight of ethyl cellulose coated extrude/sphere	565.000	568.000	570.000	570.00
S. No	**Compression**	**F1**	**F2**	**F3**	**F4**
8.	Sodium starch glycolate	2.00	2.00	2.00	2.00
9.	Colloidal silicon dioxide	2.500	2.500	2.500	2.500
10.	Sodium CMC	15.000	15.000	15.000	12.000
11.	Sodium stearyl fumarate	2.500	2.500	2.500	2.500
	Weight of core Tablet	587.000	590.000	592.000	589.000

Characterization of developed formulation

Standard curve of the drug

Accurately weighed mesalamine (44 mg) was transferred to a 100 ml volumetric flask and dissolved and diluted to the mark with 0.1 N HCl to produce 440µg/ml. 3 ml from 440 µg/ml was transferred to a 50 ml volumetric flask and diluted to the mark with 0.1 N HCl to obtain a standard stock solution having concentration of mesalamine; 26.4 µg/ml. Prepared stock solution was diluted with water to get the final concentrations of 6, 8,10,12,14 and 16µg/ml. The standard solution of Mesalamine was scanned over a range of 200-400 nm U.V. spectrophotometer and λ_{max} was found to be 332 nm. The results obeyed Beer's Lambert law in the concentration range of 6-16µg/ml.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is a technique which is used to obtain an infrared spectrum of absorption or emission of solid, liquid or gas. FTIR studies of pure mesalamine and the prepared formulation was carried out to find any possible interactions between the drug and the polymers during formulation [16]. FTIR spectra were obtained in KBr pellets using a Perkin Elmer model spectrum BX-FTIR spectrophotometer in the ranges 4000- 400 cm^{-1}.

Micromeritics properties [17]

Bulk density is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial

arrangement of particles in the powder bed. The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Hausner's ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the bulk density. Bulk density and tapped density were noted using tapping method using 10 ml measuring cylinder. Angle of repose, Carr's index and Hausner's ratio were calculated to study the flow properties of powder by using following formulas:

Angle of Repose (θ) = $\tan^{-1}$ (h/r)

where, h is height and r is radius of the pile, respectively.

Hausner ratio = Dt/ Db
Carr's index = [(Dt-Db) / Dt] X 100

where, Dt is tapped and Db is bulk density, respectively. An angle of repose of less than 25 degree gives excellent flow and greater than 40 degree gives poor flow. A hausner's ratio of 1.00.to 1.11 gives excellent flow and greater than 1.60 predicts poor flow character. A Carr's index of 5-15 gives excellent flow and greater than 40 degree provides poor flow properties.

Characterization of the prepared tablets

Average weight [18]

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. Deviation should not exceed 10 % (for 80 mg or less tablet weight), 7.5 % (for more than 80 mg but less than 250 mg tablet weight) and 5 % (for 250 mg or more tablet weight), respectively.

Thickness [18]

Tablet thickness was measured using a digital vernier calliper on 3 randomly selected samples.

Friability [18]

It is the measure of mechanical strength of tablet. The preweighed tablets were placed in Roche friabilator apparatus which consists of a plastic chamber that revolves at 25 rpm, so that the tablets fall at a distance of 6 inches in each revolution. At the end of the test, tablets were dusted and reweighed. The friability (F) is determined by the given formula: F = [(Wo-W) / W] X 100 where, F is friability, Wo is the initial weight and W is the final weight of the tablet respectively. Conventional compressed tablets that loose less than 0.5 to 1.0% are generally considered acceptable.

Hardness [18]

Tablets require a certain amount strength or hardness and resistance to friability to with stand mechanical shock of handling in manufacturing, packaging and shipping. The hardness testing of tablet was performed using pfizer hardness tester. Unit of hardness is kg/cm^2. The optimum hardness considered for uncoated tablets is between 4-6 kg/cm^2.

***In-vitro* release studies [19, 20]**

The release rate of Mups tablets were determined using USP dissolution testing apparatus II (paddle type). The test was performed by changing the pH of the medium at 37 ± 0.5°C and 100 rpm. For the first 2 h, the dissolution medium of 350 ml of 0.1 N HCl, pH 1.2 was used, which was followed by raising the pH of the dissolution medium to 4.5 by the addition of 250 ml solution composed of 3.75 g of KH_2PO_4 and 1.2 g of NaOH. At the end of fourth hour pH was raised to 7.4 by adding 300 ml of phosphate buffer concentrate (2.18 g of KH_2PO_4 and 1.46 g of NaOH in distilled water).

The test was performed on six tablets. One tablet was placed in each dissolution vessel containing mentioned ml of water at 37°C ± 0.5° C. Sample (5 ml) was withdrawn at specified time interval, passed through a 0.45 µm membrane filter (Millipore) and the absorbance was measured by UV spectrophotometry at the prescribed wavelength of 332 nm after appropriate dilution and the percentage drug released was estimated. The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution medium after each withdrawal. Perfect sink conditions prevailed during the drug release studies.

Factorial Design

In the present study, a 2^2 factorial design was applied by using Minitab 17 Software containing 2 factors evaluated at 2 levels and experimental trials were performed for all 4 possible combinations. The amount of ethyl cellulose 10 CPS and sodium CMC were selected as independent variables and % drug release as dependent variable. The coded value taken for factorial design for X1 % (Ethylcellulose 10 CPS) range is (7.5-12.5) and for X2 % (Sodium CMC) range is (12.5-18). The value codes of factorial design are represented in table 3.

Table 3: Value codes of factorial design formulation parameter EC and Sodium CMC

Formulation Code	X1 %(Ethylcellulose 10 CPS)	X2 %(Sodium CMC)
F1	7.5	15
F2	12.5	12
F3	10.5	15
F4	12.5	18

Statistical Analysis

The results were expressed in mean ± S.D. One way ANOVA (Analysis of Variance) was performed for studying the statistical significance using Minitab 15 software. Values of $P< 0.05$ were considered to be significant.

Results and Discussion

Identification by FT-IR Spectrophotometer

FTIR studies of mesalamine and formulation was carried out and shows no interaction between the drug and polymer. FTIR studies of mesalamine and prepared formulation are shown in Figure 1 and 2.

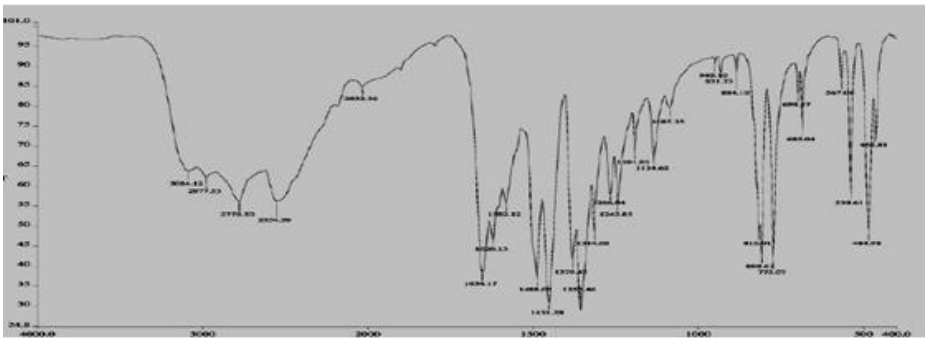

Fig 1: FTIR Spectra of Mesalamine

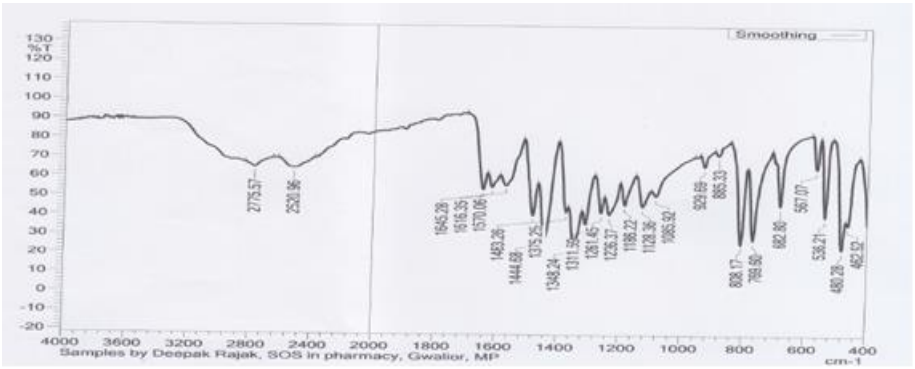

Fig 2: FTIR Spectra of Formulation

Characterization of the Prepared Tablets

The prepared dosage form was evaluated for various parameters such as bulk density, tapped density, hausner's ratio, compressibility index, average weight, hardness, thickness and friability. The angle of repose and hausner ratio of the formulation depicted satisfactory flow properties. The results obtained are presented in the table no 4.

Table 4: Characterization of the prepared mesalamine tablets

Batch	F1	F2	F3	F4
Bulk density(g/ml)	0.495±0.012	0.512±0.022	0.374±0.012	0.363±0.014
Tapped density (g/ml)	0.563±0.018	0.641±0.018	0.434±0.016	0.4360.018
Hausner's ratio	1.137	1.251	1.160	1.201
Compressibility Index (%)	23.51	23.46	20.45	21.52
Angle of repose (in degree)	23.51˚± 1.12	24.62˚± 1.02	25.24˚± 1.18	23.64˚± 1.08
Average weight (mg)	587	570	590	600
Hardness (kg/cm^2)	142	155	140	160
Thickness (mm)	4.10	4.25	4.30	4.12
Friability (%w/w)	0.9	0.12	0.2	0.18

***In-vitro* drug release studies**

All the colon targeted Mups tablet formulations of mesalamine were evaluated for *in vitro* dissolution studies as per the procedure described in above section. In the formulation Batches F4 the highest *in vitro* dissolution profile at the end of 8hrs (100%) was shown by Batch F4 containing ethylcellulose 10 CPS (12.5mg/tab) and sodium CMC in the range of (15mg/tab) which was results near to the innovator marketed formulation where as the batches F1-F3 shows faster release which was not suitable. The results of the *in-vitro* release study are given in table 5 and figures 3 and 4 respectively.

Table 5: Comparative *in-vitro* dissolution profile of the experimental batches

Sampling Interval (Hrs)	% Release of Reference Product	Batch F1	Batch F2	Batch F3	Batch F4
2.0	0.0	0.0	0.0	0.0	0.0
1.0	0.0	0.0	0.0	0.0	0.0
0.5	6.0	20.0	16.0	8.0	4.0
1.0	14.0	32.0	28.0	12.0	10.0
2.0	44.0	68.0	62.0	48.0	38.0
3.0	78.0	95.0	88.0	74.0	68.0
4.0	98.0	-	100.0	96.5	85.0
5.0	100.0	-	-	100.0	92.0
6.0	-	-	-	-	96.0
8.0	-	-	-	-	100.0

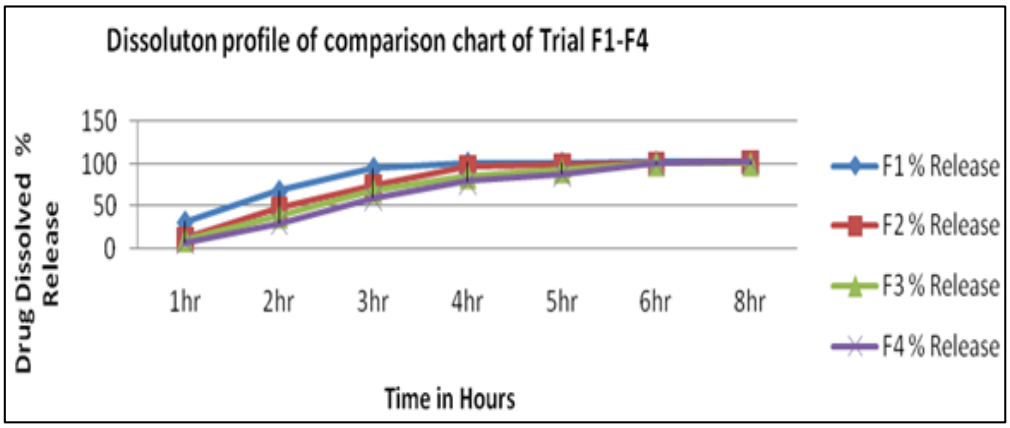

Fig 3: Release profile of the prepared batches F1 to F4.

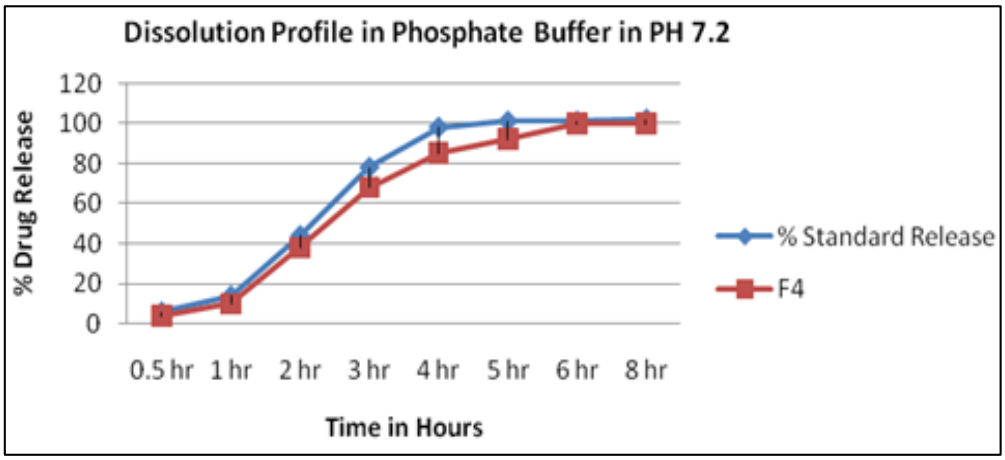

Fig 4: Comparison of marketed formulation and best formulation (F4)

Factorial Design

In the present study, a 2^2 factorial design using minitab 17 software was employed containing 2 factors evaluated at 2 levels and experimental trials were performed for all four possible combinations. The amount of Ethyl cellulose 10 CPS and Sodium CMC were selected as independent variables and % drug release as dependent variable.

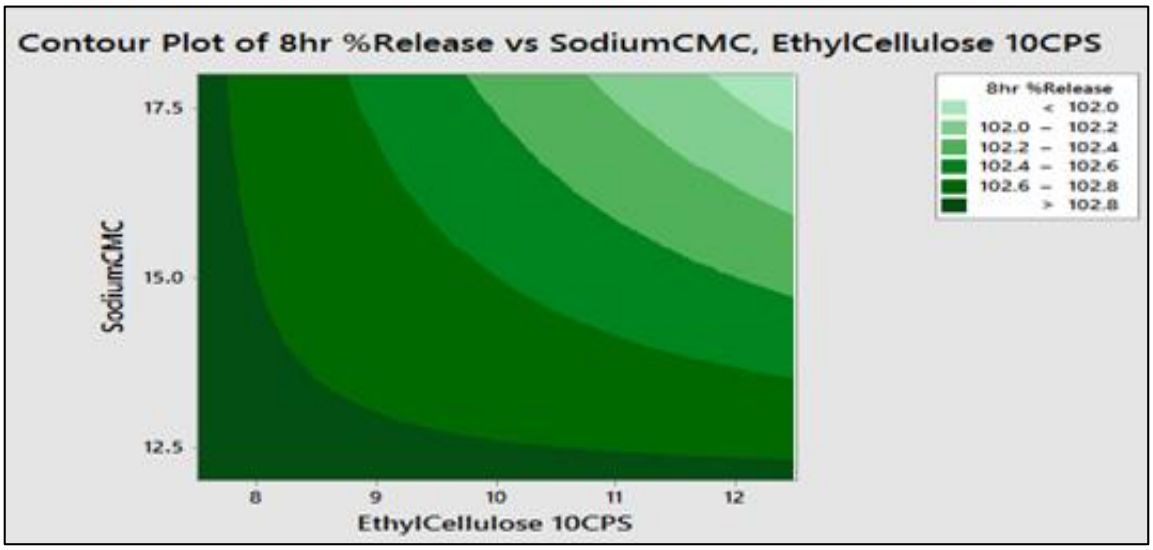

Fig 5: Contour plot between % drug release vs amount of sodium CMC and Ethyl cellulose 10 cps

The contour plot showed the relationship between ethyl cellulose and sodium CMC when taken in the concentration range of (EC-7.5-12.5) and (SodCMC-12.5-18). It shows the interaction and % drug release in 8hr and by applying ANOVA the regression equation of 8Hr release was calculated. Regression Equation in Uncoded Units is given below:

8hr %Release = 99.85 + 0.400 Ethyl Cellulose 10CPS + 0.250 Sodium CMC- 0.0333 Ethyl Cellulose 10CPS* Sodium CMC

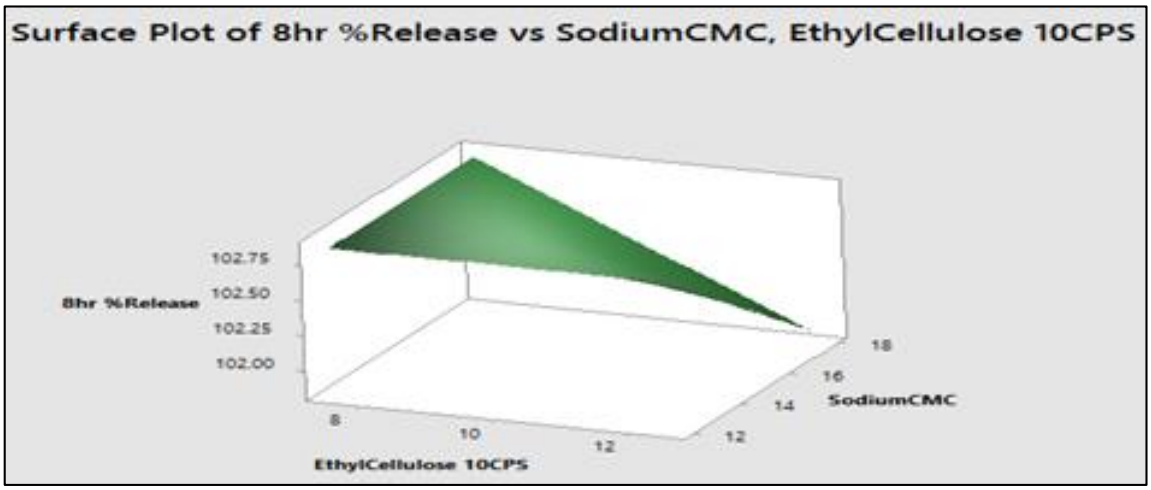

Fig 6: Surface plot between % drug release vs amount of sodium CMC and Ethyl cellulose 10 cps

The surface response plot showed the relationship between the independent factors which are ethyl cellulose 10 cps (7.5-12) and sodiumCMC (12-18) and the dependent factors which is the % drug release in 8hr. It showed good relationship and interaction of both the factors (Figure 5 and 6).

Conclusion

It has been observed that ethyl cellulose 10 CPS and sodium carboxymethyl cellulose are release retardant. So batches from trial were optimized for polymers Ethyl cellulose 10 CPS and Sodium carboxymethyl cellulose in the concentration of different range. In polymers combination Trial 4 batch gives comparative release profile to reference product. All the excipients were compatible with the mesalamine as shown by FTIR studies. The formulated product shows all the properties of slow release Mups tablet dosage form which indicates that combination of polymers at different concentration is not only able to sustain but also control the drug release at desired site. The MUPS tablet was found suitable for colonic release of mesalamine resisting drug release in gastric medium, minimizing release in the upper intestinal region and showing maximum release in the colonic region. Therefore, the developed formulation would prove to be promising for the colon targeted drug delivery of mesalamine and thereby facilitating in the management of ulcerative colitis and Crohn's disease.

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