ISSN: 0975-766X
CODEN: IJPTFI
Available Online through *Research Article*
www.ijptonline.com

FORMULATION AND EVALUATION OF OLSALAZINE SODIUM ENTERIC COATED TABLETS IN ULCERATIVE COLITIS

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Received on 20-02-2016 *Accepted on 12-03-2016*

Aim: To formulate and evaluate the fabricated olsalazine sodium enteric coated tablets in ulcerative colitis and also compare the In-vitro dissolution profile of optimized Olsalazine sodium enteric coated tablets in the presence of β-glycosidase at targeted colonic region.

Materials: Olsalazine sodium, obtained as a gift sample from Aurbindo Pharmaceuticals Hyderabad, Telangana, and India. Ethyl cellulose, Chitosan, PVP K30, Magnesium stearate, Lactose, Eudragit S-100, Acetone, Triethyl citrate was used as a plasticizer etc. All the above polymers and excipients are obtained from S.D Fine Chemicals, Mumbai.

Conclusion: The present study was fabricated to observe the drug release of Olsalazine sodium enteric coated tablets at targeted site specific colon region. These tablets were formulated from F1-F8 by selecting time dependent and release retard biodegrable polymers such as ethyl cellulose-chitosan composite by combining with different concentrations by wet granulation. This composite was included in this study to control the solubility of premature drug release in gastrointestinal fluid and in this regard, the above formulation F6 was optimized and coated with Eudragit-S 100 as enteric polymer as to retard the drug release at specified site colon by changing suitable concentration as like 1, 3, 5, and7 %. From which F6 containing 5% Eudragit-S 100 was shown only 75.6 % drug release in 24 hrs and also it was compared with dissolution medium containing β-glycosidase. In which enzymatic condition the above formulation enhanced the drug release i.e, 98.3% was found in 24 hrs. Finally the current study was contributed to evaluated all pre, post compressional parameters of optimized formulation with various release kinetic mechanism such as zero order, first order, higuchi plot and peppas mayer equations studies.

Keywords: Olsalazine sodium**,** Ethyl cellulose, Chitosan, Triethyl citrate, Acetone, Lactose, PVP K30, Magnesium stearate and Eudragit-S 100.

1. Introduction:

Ulcerative colitis (UC), is a common, chronic inflammatory disease which affects the gastrointestinal tract especially colon and rectum. Usually, it is mildly active, but it can be life-threatening during severe attacks because of colonic and systemic complications. In addition, patients with long-term ulcerative colitis are at an increased risk of colorectal cancer [1](Ekbom et al., 1990). The exact cause of UC remains unknown, but possible etiological factors, including genetic, immunologic and environmental factors may be involved[2] (Jewell and Patel, 1985). In addition, oxidative stress has been involved in the pathogenesis of ulcerative colitis in experimental animals and in humans[3] (Keshavarzian et al., 1990; Kitahora et al., 1998). It is known that the balance between the antioxidants in the intestinal mucosa is seriously impaired in UC patients compared to normal mucosa, where intestinal inflammation is associated with excessive production of reactive oxygen and nitrogen metabolites[4] (Kruidenier and Verspaget, 2002).Treatment of UC aimed to remission of symptoms and mucosal inflammation. Most of the current therapies for UC involve treatment with corticosteroids and 5-aminosalicylic acid[5] (Podolsky, 1991; Strober et al., 1998).

Topically active olsalazine sodium was, recognizing the need for treating colon cancer (COX-2 may be involved in the adenoma to carcinoma sequence, and that both highly potent and selective COX-2 inhibitors) in a manner that results in a minimal number of systemic side effects, and cognizant of the problem of delivering efficacious levels of drugs to the colonic environment, This research carried out the methods by which therapeutic levels of drugs might be presented to the colonic environment.

2. Materials and Methodology:

2.1. Preparation of matrix coated Olsalazine sodium tablets by wet granulation:

Granules containing Olsasalazine were prepared by wet granulation method. The ingredients were screened through sieve number 26, and then Olsalazine sodium was mixed with various combinations of colon specific combination of polymer composite such as ethyl cellulose, chitosan and lactose**[6]**.

PVP K 30 solution (10%) as binder. Powder mass (each batch weighs approximately 500mg) was moistened with binder solution to get damp mass then it was passed through a 16 number sieve. The granules were dried for 6 hr at 40° C in a

tray drier. Thereafter the granules were mixed with 1% magnesium stearate and talc then compressed into tablet by electric driven tablet press (Riddi, India) using 18 mm punch sizes.

2.2. Preparation of enteric coating polymer solution:

CS: EC composite having different ratios of ethyl cellulose and chitosan were used for coating tablets followed by enteric coating. Eudragit S-100 (250 g) was dissolved in 1000 ml of isopropyl alcohol and TEC (1.25% w/w) as plasticizer. The above tablets were coated by using film coater. Tablets were preheated for 5 minutes and coating of tablets was carried by rotating pan with speed 12 rpm, Outlet temperature with 40^0 C; coating solution feed rate was maintained 8 rpm.

Table-1: Formulation chart for Olsalazine sodium enteric coated tablets (mg/tablet).

Ingrediants	F1	F2	F3	F4	F5	F6	F7	F8
Olsalzine	500	500	500	500	500	500	500	500
Ethyl cellulose (mg)	18	18	18	18	36	36	36	36
Chitosan (mg)	3	6	9	12	3	6	9	12
DEP(Di ethylene pthalate)	6	6.2	7.425	8.25	11	11.55	12.38	13.2
Cetyl alchol	2.1	2.4	2.7	3	3.9	4.2	4.5	4.8
Lactose	108.9	105.4	100.875	96.75	84.1	80.25	76.12	72
Cornstarch	20	20	20	20	20	20	20	20
Binder (PVP-K-30)	30	30	30	30	30	30	30	30
Mg.Stearate(mg)	6	6	6	6	6	6	6	6
Talc(mg)	6	6	6	6	6	6	6	6
Total weight(mg)	700	700	700	700	700	700	700	700

2.3. FTIR compatibility studies:

Drug-polymer interactions were studied by FT/IR spectroscopy .The spectra were recorded for pure drug and different polymer mixtures using FT-IR (Perkin Elmer, Model No.883). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400-4000 cm-1 and the resolution was 2 cm-1.

2.4. Evaluation of pre compressional parameters of olsalazine sodium granules:

The angle of repose (θ) of the granules was determined by using funnel method. Bulk density (BD) and tapped density (TD) were calculated by formula: BD = Bulk mass/Bulk volume; TD = Bulk density = Bulk mass/Bulk volume. Compressibility index and Hausner's ratio of the granules was determined by using the formula: CI (%) = [(TD-BD/BD)] ×100 and HR = TD/BD, respectively[7]. The experiments were performed in triplicate and average values with SD were noted. The results were tabulated in Table 2.

2.5. Evaluation of post compression parameters of Olsalazine sodium enteric coated tablets:

Twenty (20) tablets were randomly selected and weighed. The mean and standard deviation were calculated as described in official standards. The tablets were selected randomly from each batch. Thickness of tablets measured in millimeters (mm) with vernier calipers mean and standard deviation were calculated. The hardness of randomly selected tablets from each batch was measured by using a Monsanto tester. The hardness of 10 tablets was recorded in kilo gram (kg/cm^2), mean and standard deviation were calculated. Twenty (20) tablets were randomly selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Erweka abrasion tester. The tablets were then dusted and weighed again to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

The Olsalazine sodium enteric coated tablets were tested for their drug content. Tablets were finely powdered and quantity of powder equivalent to 500 mg of Olsalazine sodium were accurately weighed and transferred to 100 ml volumetric flask, filled with phosphate buffer (pH 7.4) and mixed thoroughly. The solution was made up to volume and filtered. One milliliter of the filtrate with suitable dilution was analyzed for Olsalazine sodium content at 355 nm using a double beam UV spectrophotometer meter (Elico, India).

2.6. *In-vitro* drug release studies:

The *in vitro* dissolution studies were performed for the Olsalazine sodium enteric coated tablet using USP II dissolution apparatus (Lab India, DS 8000, Mumbai, India) in 900 ml dissolution medium at 100 rpm, 37°C ± 0.5°C. The dissolution media with pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4 were used in order to simulate the pH change along the GIT. The *In vitro* drug release experiments were performed at pH 1.2 for 2 h. Then pH 1.2 buffers were replaced with pH 6.8 phosphate buffer dissolution media for 3 h. After performing the experiments for 3 h with pH 6.8

phosphate buffer, the dissolution media were replaced finally with phosphate buffer pH 7.4 for the next 19 h. At regular time intervals, samples were withdrawn from the dissolution media and filtered with whatman filter paper (0.22 μm).

The absorbance was measured using UV/Visible spectrophotometer (AU-2701, Systronics) at 355 nm[8]. The graph was plotted against cumulative percentage drug release versus time. The experiment was done in triplicate and data were expressed in mean ± SD.

2.7. Kinetic studies:

The rate and mechanism of release of enteric coated of Olasalazine enteric tablets were analyzed by fitting the dissolution data into various kinetics model for the zero-order equation, first order equation, Higuchi's equation and Korsmeyer-Peppas to predict rate release mechanism on the basis of n values[9].

3. Results and Discussion:

Olsalazine sodium enteric coated tablet is one of the approaches for colon specific targated drug delivery system. Attempts have been made for preparation of enteric tablets for site specific release with variable concentration of biodegrable polymers such as ethyl cellulose-chitosan composite. Based on the above various combinations of rate retard polymers a set of formulations for Olsalazine sodium granules were prepared by wet granulation method and fabricated in to selective tablets from F1-F8. There after the above set of tablets were allowed to enteric coating with the help of enteric coat polymer such as Eudragit-S 100 with the different concentrations percentage of Eudragit-S 1, 3, 5and 7% in acetone solution, Tri ethyl citrate was used as a plasticizer and to ensured the optimized formulation for adjusting release pattern according to marketed formulation and USP guidelines of olsalazine sodium enteric coated tablets. In which ethyl cellulose, chitosan used as biodegrable and rate controlling polymer in the stomach, PVP K30 as binder, Mg.stearate and Talc used as lubricant.

FTIR spectra were recorded to assess the compatibility of the drugs and excipients. FTIR spectra of drug (s), physical mixture of drug with different excipients, were recorded and examined. FTIR spectra of Olsalazine sodium showed principal peaks at 1710 and 1740cm^{-1} resulted from C=O stretching and the peak at 2900cm^{-1} resulted from Carboxylic O-H stretching and peaks at 3350, 3020 and 1552 cm^{-1} resulted from aromatic O-H stretching, aromatic C-H stretching and aromatic C=C stretching respectively. The observed FTIR spectrum of drug was matched with reference spectra. Confirming the purity of the drug as per established standards. All characteristic peaks of drug(s) were observed

in the FTIR spectra of physical mixture of drug and different excipients. The results showed there was no appearance or disappearance of peaks in the polymer–drug mixture this confirmed the absence of any chemical interaction between the drug and the polymers. The FTIR spectra of pure drug and physical mixture of drug and different excipients are shown in figure1 and 2 respectively.

Figure: 1 FT-IR spectrum of pure Olsalazine sodium.

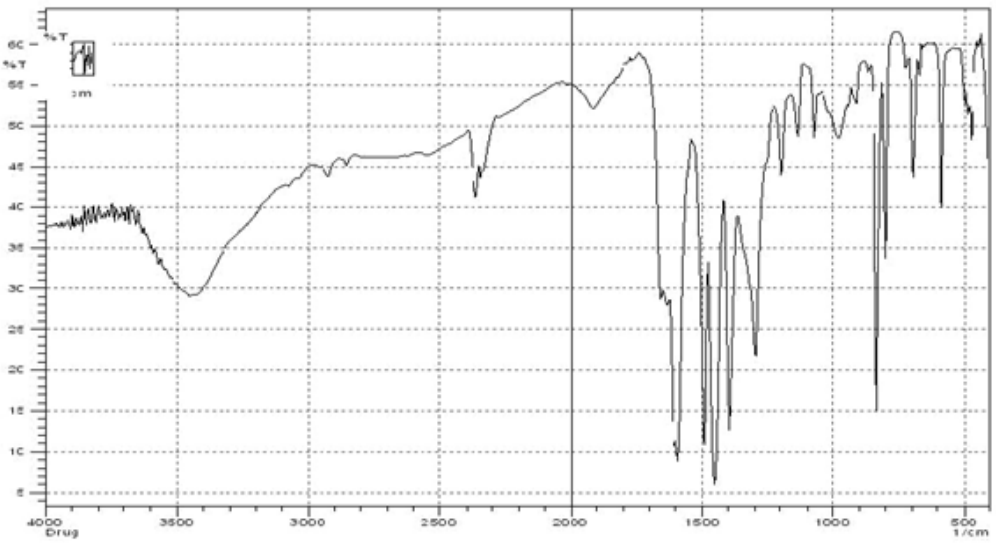
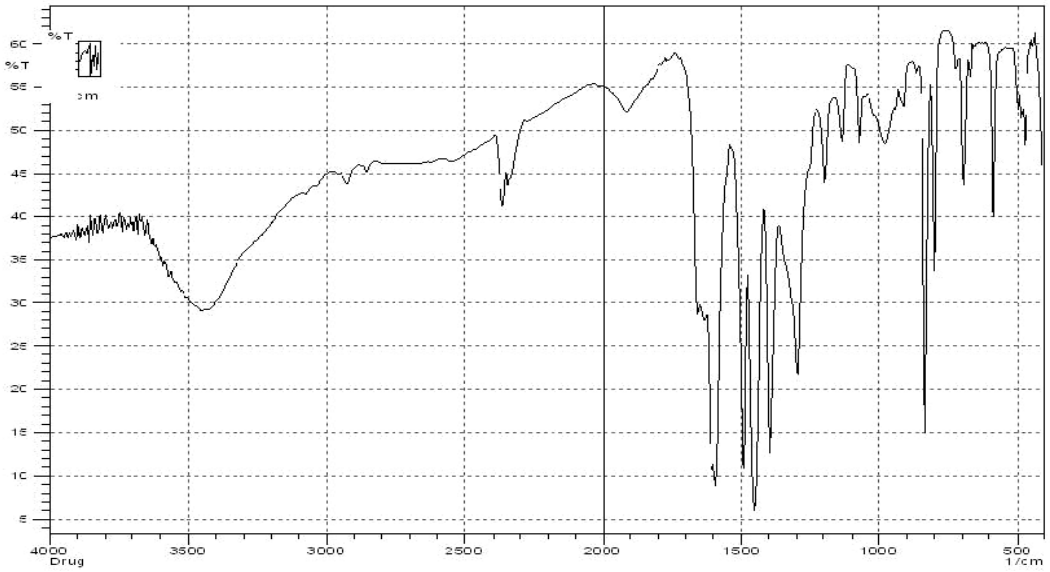


Figure: 2 FT-IR spectrum of optimized Olsalazine sodium enteric coated tablet (F6)



3.1. Evaluation of Olsalazine sodium matrix granules:

The tablets of Olsalazine sodium were evaluated for various physical properties. The bulk densities for the powder blend of various formulations (F1-F8) ranged between 0.311±0.01g/ml and 0.372±0.01g/ml; and tapped density ranged between

0.311±0.22g/ml and 0.371±0.12g/ml as determined by the tap densitometer. These values of bulk density indicated good packing characteristics. The Carr's index (CI) for all the formulations was ranged from 11.21±0.17 to 18.18±0.33, indicating desirable flow properties. The value of Hausner's ration was ranged from 1.10±0.07 to 1.16±0.04. The flow properties of powder blends were further analyzed by determining the angle of repose for all formulations; it ranged between 20.12 and 27.76 **(θ)**. The values indicated satisfactory flow behavior.

Table-2: Evaluation of Olsalazine sodium matrix granules.

Formulation	Bulk Density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's Index	Hausner Index
F1	0.372±0.01	0.321±0.21	24.12±0.21	12.45±0.31	1.16±0.04
F2	0.321±0.06	0.361±0.31	25.24±0.21	14.54±0.43	1.12±0.06
F3	0.341±0.07	0.311±0.22	26.54±0.33	15.23±0.51	1.13±0.03
F4	0.311±0.01	0.371±0.12	22.12±0.43	13.71±0.12	1.14±0.01
F5	0.351±0.05	0.360±0.11	27.76±0.42	18.18±0.33	1.11±0.07
F6	0.321±0.02	0.312±0.32	24.33±0.15	12.33±0.11	1.15±0.05
F7	0.371±0.09	0.341±0.33	20.12±0.44	11.21±0.17	1.12±0.03
F8	0.331±0.08	0.331±0.42	29.23±0.26	15.77±0.27	1.10±0.07

3.2. Evaluation of Olsalazine sodium matrix tablets:

The above formulations (F1-F8) were produced under similar conditions to avoid processing variables. The weight variation, hardness, friability, thickness and content uniformity of all formulations were found to be within acceptable limits as per official specifications. Weight of the optimized ethylcellulose-chitosan coated tablet formulation (F6) was 701.1±0.948mg, hardness was 9.01±0.04 kg/cm2 and thickness was 7.39±0.69. The percentage friability of all the formulations was ranged from 0.52±0.39 to 0.78±0.21 which is less than 1% of their weight. Values of the hardness test and percent friability indicated good handling properties of the prepared tablets. The drug content (assay) uniformity in the Sulfasalazine enteric coated tablets was ranged from 93.29±0.01 to 99.51±0.07%. All the above results were mentioned in Table: 3

Table-3: Evaluation of Olsalazine sodium enteric coated tablets.

Formulation	Thickness (mm)	Average weight(mg)	Hardness (Kg/cm^2)	Friability (%)	Assay (%)
F1	7.40±0.06	698.6 ±0.976	9.12±0.07	0.76 ±0.45	95.20±0.07
F2	7.42±0.46	700.3±0.989	9.11±0.05	0.58±0.23	93.29±0.01
F3	7.38±0.77	700.2±0.955	9.16±0.03	0.78±0.21	97.17±0.02
F4	7.35±0.57	701.5±0.947	9.15±0.01	0.69±0.25	94.35±0.04
F5	7.41±0.88	710.0±0.896	9.21±0.03	0.59±0.17	98.91±0.02
F6	7.39±0.69	701.7±0.948	9.01±0.04	0.69±0.65	99.51±0.07
F7	7.45±0.68	700.1±0.940	9. 29±0.06	0.71±0.72	95.19±0.08
F8	7.36±0.72	699.1±0.987	9.18±0.01	0.52±0.39	96.31±0.05

3.3. *In-vitro* dissolution profile:

The dissolution studies conducted for prepared matrix tablets of olsalazine sodium containing biodegradable polymers and different concentrations Eudragit-S 100 as enteric polymer at different pH conditions for 24 hrs. From the above formulations (F1-F8) F6 formulation contain optimum concentration of ethylcellulose-chitosan composite was shown myrid significant rate release profile.

At pH 1.2 (in the presence of simulated gastric fluid) the F6 formulation was released 3.1%, the same formulation in the presence of intestinal fluid (at pH 6.8) the percentage drug release was 19. 2% observed.

Based on the above released profile, F6 formulation was selected and suitable for enteric coating with different concentrations Eudragit-S 100 to ensure optimum release profile at site specific region of colon.

After the enteric coating, the F6 formulation containg Eudragit-S 100 of 5% shown no drug released was observed in stomach. But in the region of small intestine the percentage was released only 7.9%.

There after the percentage drug released was gradually incresed from large intestine to targeted site, it was found that 15.6% to 75.6% within 24 hrs.

Figure: 3 *In-vitro* dissolution profile of Olsalazine sodium matrix tablets F1-F8.

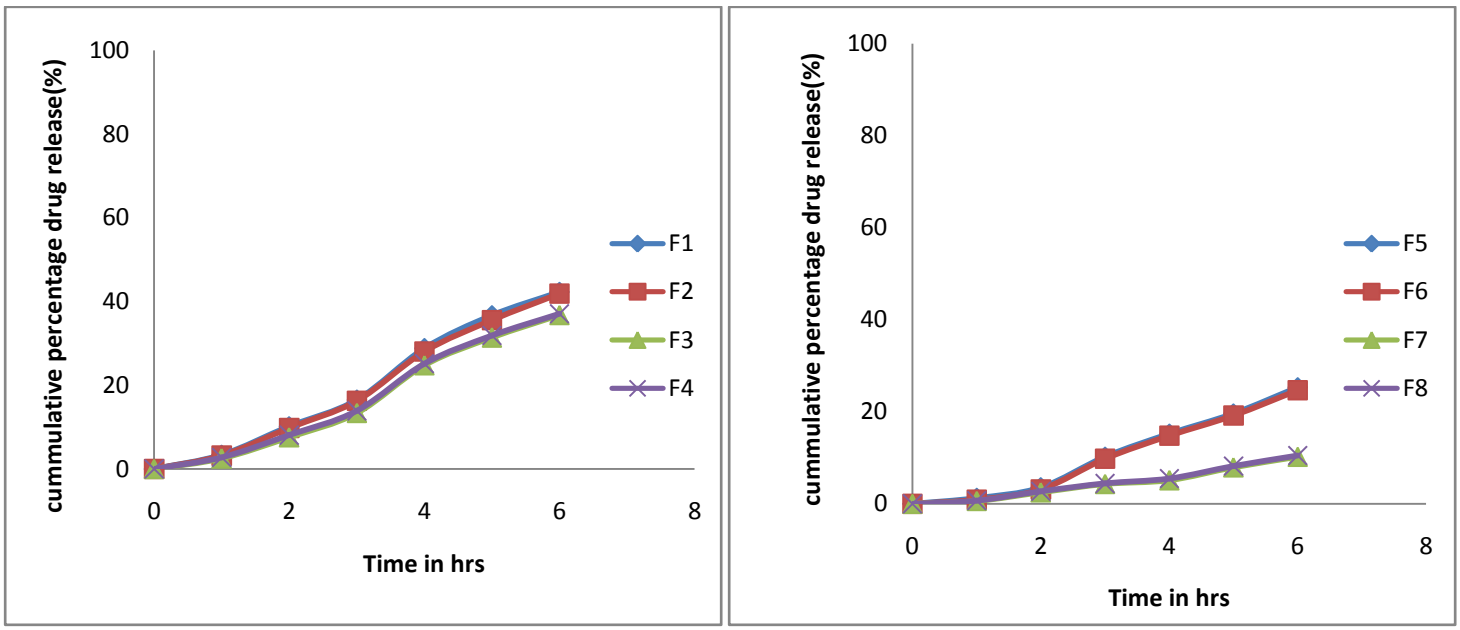
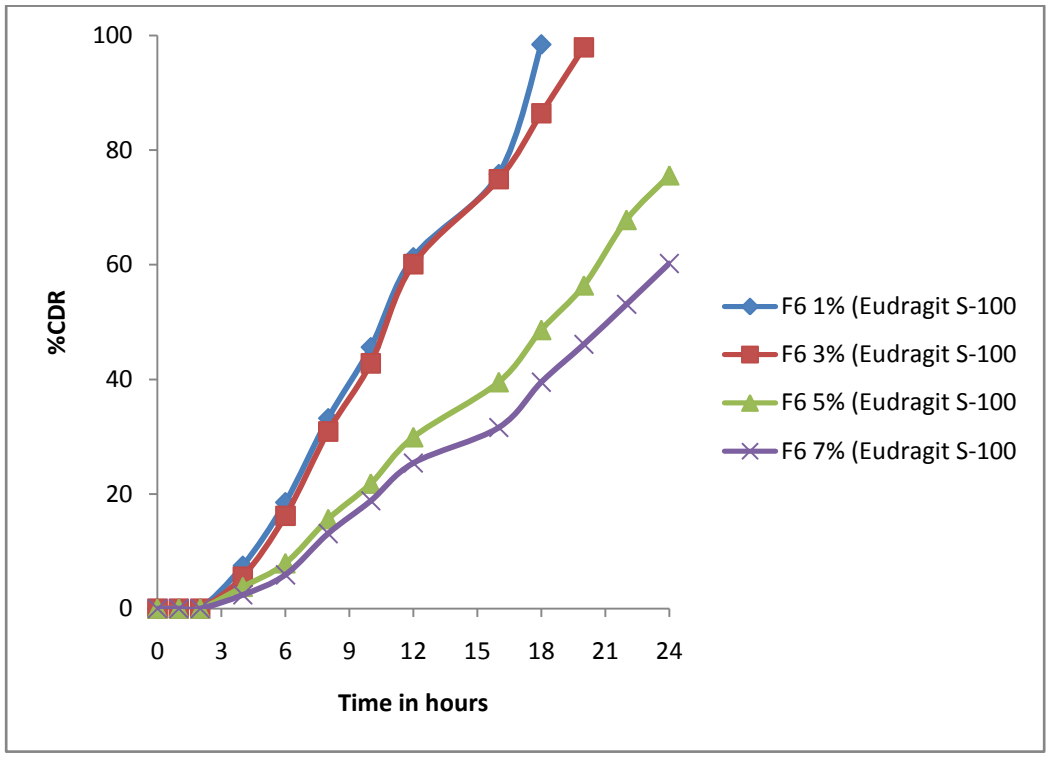
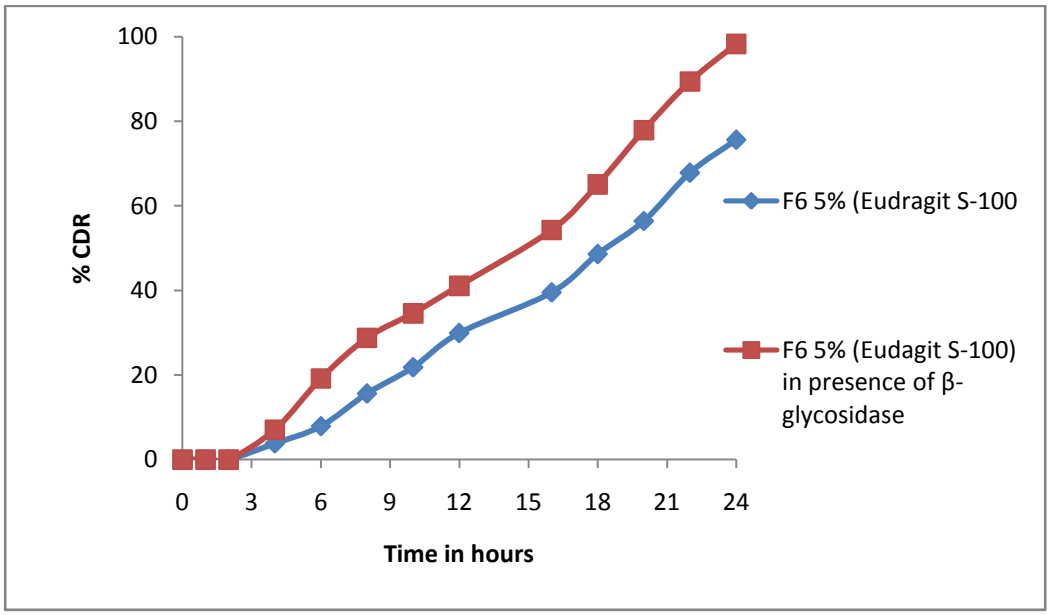


Figure: 4 In-*vitro* dissolution profile of Olsalazine sodium optimized formulation F6 after enteric coating with Eudragit –S 100.



To simulate colonic condition the drug release conducted in presence of β-glycosidase. This enzyme specifically acts on chitosan thus result shown (figure:5) increased release, the composite coated Olsalazine sodium tablets released 75.26 ± 0.51 to 98.3 ± 1.3%, of drug in presence of β glycosidase from optimized formulation (F6) respectively. The result proved that CS:EC composite coated tablets with enteric coating can protect the drug in stomach and intestine and deliver the drug in the colon.

Figure-5: In-*vitro* comparison dissolution profile of Olsalazine sodium optimized formulation (F6) in the presence of β-glycosidase.



3.4. Kinetic studies:

In order to establish the mechanism of drug release, the experimental data were fitted to zero-order, first order, Higuchi and Korsmeyer-Peppas models. The results for kinetics model fitting of the optimized formulation F6 with different concentrations of Eudragit-S 100 were shown in Table 4. The coefficients of regression were in a range between 0.952 to 0.983 (Zero order), 0.688 to 0.945 (First order), 0.839 to 0.863 (Higuchi) and 0.960 and 0.974 (Peppas).

Figure: 6 Zero order plot of Olsalazine sodium optimized formulation (F6).

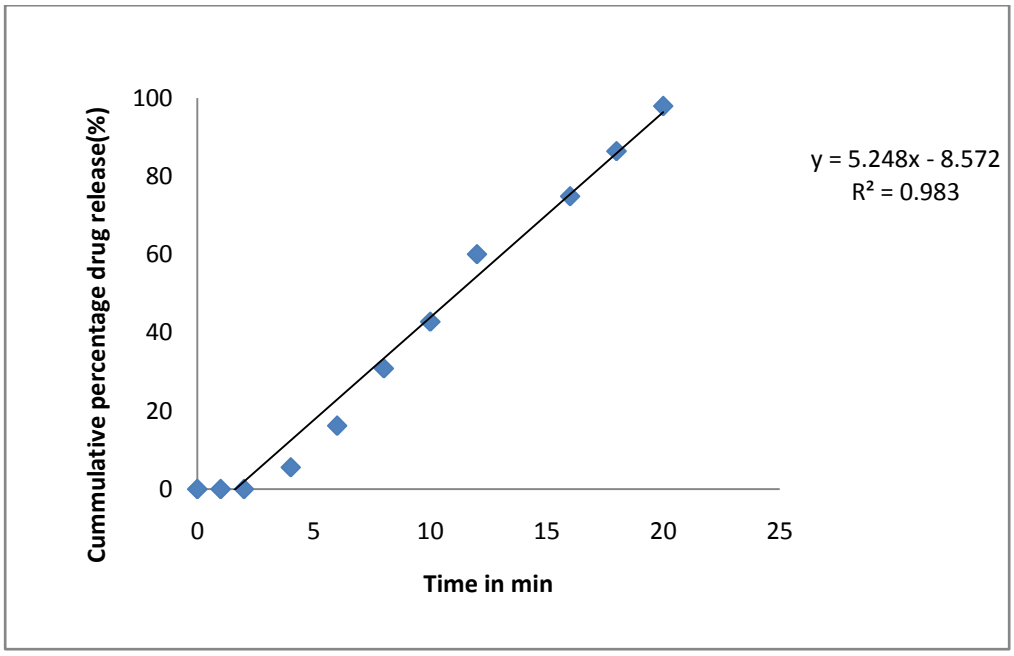


Figure-7: First order of Olsalazine sodium optimized formulation (F6).

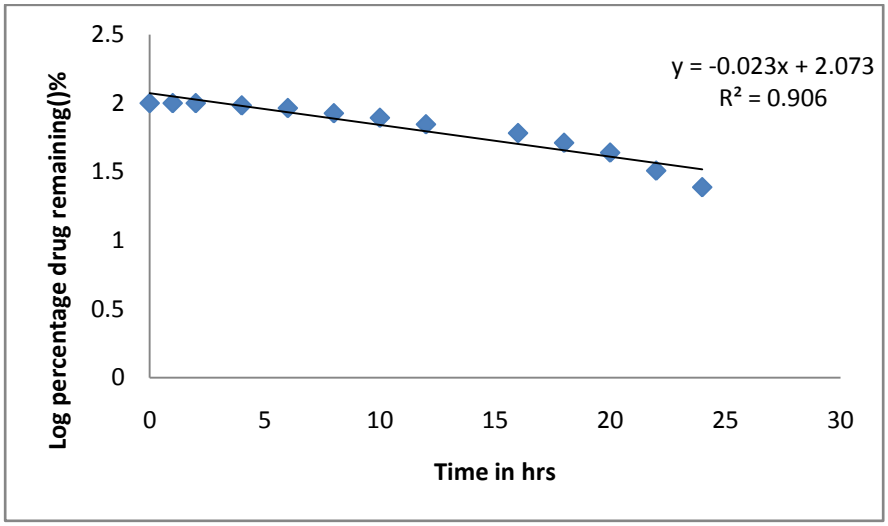


Figure: 8 Higuchi plot of Olsalazine sodium optimized formulation (F6).

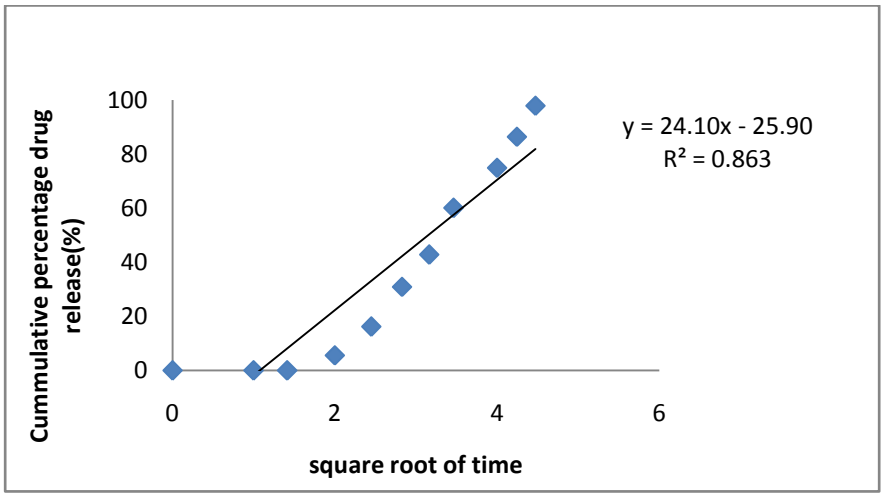
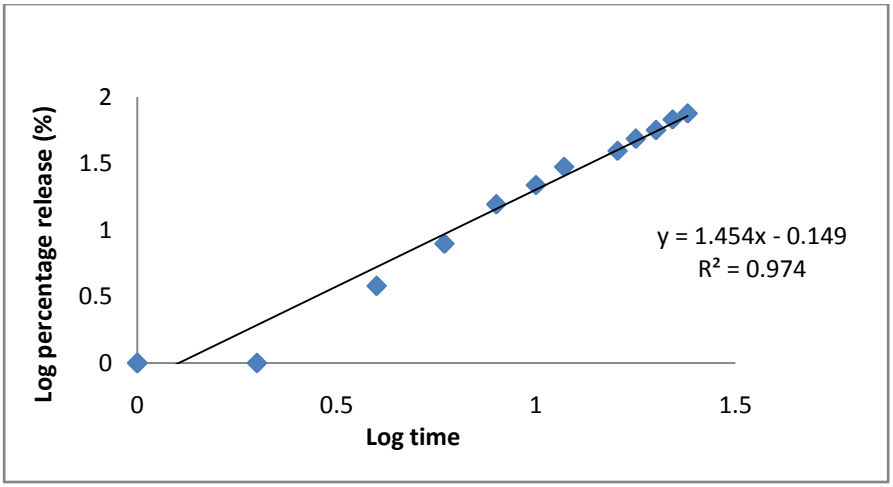


Figure: 9 Korsmeyer peppas of Olsalazine sodium optimized formulation (F6)



The n value for F6 was found to be 0.450, which meant that the mechanism of release for F6 was fickian diffusion and best fit model was Korsmeyer-Peppas. The n value for all formulations was in the range of 0.684 to 0.897 indicating fickian diffusion. Overall, the release mechanisms from these optimized enteric coated tablets of olsalazine sodium can be explained as a result of diffusion of drug through porous matrix in which pores are created by superdisintegrant by disintegrating immediate release layer, thus more contribution of erosion to release mechanism.

Table-4: Regression coefficient values of the formulations in various kinetic models.

Formulation	Zero order	First order	Higuchi plot	Korsmeyer peppas
F6e (1%)	0.977	0.688	0.839	0.964
F6e (3%)	0.981	0.784	0.849	0.966
F6e (5%)	0.983	0.906	0.863	0.974
F6e (7%)	0.952	0.945	0.857	0.960

4. Summary and conclusion:

The present study was carried out to develop colon targeted delivery systems based on the combined approach of a pH-dependent and a specifically biodegradable core matrix tablet. The present work involves the formulation development and *in-vitro* evaluation of enteric coated tablets of olsalazine sodium for colon site specific drug release. Under the pre-formulation studies, drug characterizations, physicochemical evaluation results for the above formulations and drug-excipients compatibility studies were carried out. All the studies showed compliance with the drug characteristics and layer passed the official limits. The enteric coated tablets of olsalazine sodium different formulations (F1–F8) were prepared. All the prepared tablets are evaluated for post compression parameters such as hardness, thickness, weight variation, drug content uniformity and *in-vitro* drug release. The optimized formulation (F6) in the presence β-glycosidase has shown desired release profile of 98.3% in 24 h. The data obtained are fitting to various kinetic models, the optimized formulation (F6) shown (r^2) value of 0.897 and the 'n' value obtained from Korsmeyer-Peppas model showed that the above formulation followed fickian drug release mechanism. Finally all the above results were revealed that F6 formulation has met objective of the present study, drug release, patient convenience and cost effectiveness as a twice a day dose of the drug.

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