ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

DEVELOPMENT OF A COLON-TARGETED ORAL MATRIX TABLET FORMULATION OF MESALAMINE USING pH SENSITIVE AND BACTERIA-TRIGGERED POLYMERS FOR ENHANCED COLONIC DELIVERY

Rajashree S. Masareddy*, Archana Patil, Sheetal Patil, Shivarajkumar Banachod

Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, Karnataka

*Corresponding author E- mail: rajashreemasareddy@klepharm.edu

ARTICLE INFO

Key words:

Mesalamine,
Matrix tablet,
Sustained release,
Xanthan gum,
Guar gum.

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Background: Approximately two million individuals globally are afflicted with inflammatory bowel disease (IBD), including ulcerative colitis. Mesalamine, a BCS class IV nonsteroidal anti-inflammatory drug utilized for ulcerative colitis, exhibits poor solubility and permeability. Its instability in the stomach leads to rapid absorption in the small intestine and inadequate colonic delivery, resulting in side effects. **Objectives**: To develop and optimize mesalamine matrix tablets for targeted colonic drug delivery, utilizing pH-sensitive and bacterially responsive polymers, respectively, to enhance colonic drug delivery by minimizing premature release in the upper gastrointestinal tract and sustaining drug release with zero-order kinetics, and adherence to compendial standards. **Methodology:** Matrix tablets of mesalamine were developed by incorporating Xanthan gum as a pH-sensitive polymer and Guar gum as a polymer responsive to bacterial enzymatic activity. Compatibility of mesalamine with excipients was verified using FTIR and DSC analyses. Pre-compression tests assessed granule properties, and matrix tablets were manufactured via the tablet-in-tablet method. Post-compression evaluations ensured adherence to compendial standards. A factorial design was employed to examine the impact of polymers concentrations on drug release and physical stability of formulation was demonstrated in short-term stability studies. **Result:** The results indicate the formulated mesalamine matrix tablets, successfully achieved targeted colonic delivery. The optimized formulation released 97.331% of mesalamine over 12 hours, adhering to zero-order kinetics. Compatibility with excipients was confirmed, and the tablets met compendial standards, showing improved drug release and tablet hardness with increased polymer concentrations. The formulation also demonstrated physical stability in short-term stability studies. **Conclusion:** The study proficiently developed mesalamine matrix tablets for precise colonic delivery by incorporating Xanthan gum and Guar gum as key polymers. The formulation complied with all relevant standards and significantly enhanced both drug release duration and tablet mechanical hardness, highlighting its effectiveness as a targeted colonic drug delivery strategy.

INTRODUCTION:

Ulcerative colitis is a chronic, idiopathic inflammatory bowel disease that primarily targets the mucosal layer of the colon and rectum. It usually manifests in the rectum and spreads proximally in a continuous pattern, potentially affecting localized segments or the entire colon. This disease is characterized by persistent mucosal irritation, inflammation, and ulceration of the large intestine, leading to significant gastrointestinal distress.[1] The prevalence of ulcerative colitis (UC) is notably higher in Northern Europe and North America

© Journal of Global Trends in Pharmaceutical Sciences

compared to Asia, with global incidence rates escalating, particularly in rapidly industrializing regions. In Japan, the incidence of UC has progressively risen since the 1960s, reaching 133.2 per 100,000 by 2014 and potentially climbing to 300,000 cases by 2022.[2] In India, UC prevalence is estimated to range between 5.4 and 6.0 per 100,000 individuals.[3] Treatment typically involves several pharmacological approaches, with anti-inflammatory agents like 5-aminosalicylates and corticosteroids being commonly used to reduce inflammation. Additionally, immune system suppressors, such as cyclosporine and tofacitinib, are employed to modulate the immune response and mitigate flare-ups. Advances in therapeutic strategies continue to enhance the management of this debilitating condition.[4] A colon-targeted drug delivery system is designed to modulate drug release specifically within the gastrointestinal tract (GIT), ensuring that the drug is accurately delivered to the colonic lumen, which significantly improves oral bioavailability. This approach is especially beneficial for pharmaceuticals that are unstable or susceptible to enzymatic degradation in the upper GIT. Various strategies for colon-targeted drug delivery have been developed, including pH-sensitive polymer-coated systems, time-controlled release mechanisms, microbially triggered release technologies, pressure-controlled systems, and osmotic-controlled delivery methods.[5] For instance, drugs such as Naproxen[6], Ibuprofen[7], Budesonide[8], Nicotine[9] Acetylharpagide[10], Metronidazole[11], Bumadizone calcium[12], Aceclofenac[13], and Mesalamine[14] are formulated as colon-targeted matrix tablets utilizing advanced synthetic polymers. These formulations are engineered to ensure that drug release is precisely controlled and optimized for therapeutic efficacy, enhancing drug stability and minimizing adverse effects associated with premature release or degradation in the upper gastrointestinal tract. Matrix systems are meticulously engineered to prolong and modulate drug release, thereby sustaining therapeutic efficacy over extended durations. These systems employ a synergy of dissolution and diffusion mechanisms, augmented by release-retardant materials. These materials encompass hydrophobic matrices, lipid-based matrices, hydrophilic matrices, biodegradable matrices, and mineral matrices, each playing a crucial role in achieving controlled and sustained drug delivery.[15] Mesalamine is chemically 5-Aminosaliculic acid hydrochloride which belongs to BCS class IV showing low solubility and low permeability with oral bioavailability of 20-30%, elimination half-life of 7-12 hrs. & pKa value 6.0. It is a Nonsteroidal anti-inflammatory drug used for treatment of both acute & Chronic Ulcerative colitis and Crohn' diseases.[16] This study aims to develop the advanced colon-targeted oral matrix formulation, meticulously engineered for precise Mesalamine delivery specifically to the colon. Utilizing state-of-the-art pH-sensitive and microbial-triggered polymers, the formulation is designed to achieve highly accurate targeted release. Given Mesalamine's instability in the acidic environment of the stomach and its rapid absorption in the small intestine, this formulation effectively addresses the challenge of ensuring therapeutic levels at the colonic site. The innovative matrix system is engineered to resist the conditions of the upper gastrointestinal tract, incorporating natural polymers selected for their safety, non-toxicity, cost-effectiveness, and outstanding chemical compatibility. Consequently, this advanced system ensures controlled and sustained Mesalamine release within the colon, thereby significantly enhancing therapeutic efficacy and improving overall patient outcomes.

© Journal of Global Trends in Pharmaceutical Sciences

2. MATERIAL AND METHOD:

2.1. Materials: Mesalamine was obtained as a gift sample from Selleckchem Pvt Ltd, Mumbai, Arabic gum purchased from Loba Chemie Pvt Ltd, Mumbai, Guar gum and Xanthan gum were purchased from HiMedia Laboratories Pvt Ltd, Mumbai.

2.2. Standard calibration curve of mesalamine in 1.2 pH 0.1N Hcl, 6.8 pH and 7.4 pH phosphate buffer: To prepare a stock solution with a concentration of 1000 µg/ml, 100 mg of Mesalamine was accurately weighed and transferred to a 100 ml volumetric flask containing 100 ml of buffer. 10 ml from the above-mentioned stock solution was pipetted into a 100 ml volumetric flask and volume was made up with buffer to get the concentration of 100µg/ml. Concentrations of 2,4,6,8 and 10 µg/ml were prepared by withdrawing 0.2, 0.4, 0.6, 0.8 and 1.0 ml from second stock solution into 10 ml volumetric flask and the volume was made up with buffer. The absorbance of the prepared dilution was measured at 223 nm using UV spectrophotometer and average of triplicates were noted. Concentration of the solution was plotted against absorbance using Microsoft Excel software

2.3. COMPATIBILITY STUDIES:

2.3.1 FTIR Spectroscopy: The FT-IR spectrum of the obtained mesalamine sample was compared with the standard FT-IR spectrum using a Shimadzu FTIR instrument to assess compatibility with excipients. For accurate analysis, the sample must be completely dry. The solid sample was mixed with powdered potassium bromide (IR grade, thoroughly dried) at a 1:100 ratio using a mortar and pestle. The spectrum was recorded by placing the mixture in the sample cell, with a blank disc of pure potassium bromide serving as the reference. The IR spectra of the physical mixture of the drug and excipients were compared with that of the pure drug to check for any potential interactions.

2.3.2 Differential Scanning Calorimeter: Aluminium crucibles with lid were used to seal the weighed quantity of physical mixtures of drug and excipients. Shimadzu model DSC-60 thermos analytical system was used to obtain DSC thermograms. Analyses has been performed in the presence of nitrogen (nitrogen flow rate 50ml/min) at a standard heating rate of 10 ^{o}C/minute over a temperature range of 30 ^{o}C-350^{o}C. Thermograms having melting point ranges and other transitions of the drug and each excipients obtained previously were retained and compared with thermograms of physical mixture.

2.4 Preparation of Mesalamine core tablets by direct compression method:

The core tablets of Mesalamine were prepared by direct compression method. The formula for the core tablet formulation is given in the Table no. 01. Mesalamine, Acacia and sodium starch glycolate were sieved and weighed and mixed in the geometric ratio. The mixture was lubricated with Magnesium stearate and talc. Then the mixture was compressed using 8 mm punch using single station tablet punching machine.

2.5 Preparation of coating granules by wet granulation method: Coating material prepared by wet granulation. Firstly, Guar gum and Xantum gum were sieved by # 44. Add required quantity of starch paste to the mass and pass it through # 14. Dry the granules at 50^{o}C for 2 hours. The granules were sieved with # 22. Lubricate the granules using Talc and Magnesium.

2.6 Preparation of coated matrix tablet of mesalamine: Preparation of coated matrix tablet done by tablet in tablet method. In this method, firstly the 50% of coating granules were placed in a die, on that core tablet is placed in a center then the remaining 50% of coating granules are placed and tablet is punched in 10 mm punch.

2.7 Experimental Design: Optimization of matrix tablets of Mesalamine was carried using Experimental Design using design

© Journal of Global Trends in Pharmaceutical Sciences

expert 13.0.11.0 version software. A 32 randomized full factorial design was used for optimization of Matrix tablets. In this model 2 factors were evaluated, each at 3 levels using design expert 13.0.11.0 version software to study the effect of critical independent variables/factors on the product quality attributes/response like in-vitro % drug release. Guar gum and Xhantan gum amounts are obtained by software are used to prepare the above 9 formulations. Experimental methods are used to determine the response variable % drug release. Experimental results are compared with projected results produced by software. One way ANOVA at 0.05 was used to analyse response variables. Software generates optimized solutions based on optimization results for independent variables X1 and X2, as well as for response variables Y1 and Y2. [17]

3. EVALUATION OF FORMULATIONS

3.1 Pre-Compression Parameters [18]

3.1.1 Bulk Density (B.D.): Bulk density was measured by transferring the weighed amount of powder into a measuring cylinder and the volume is noted. Average values of triplicates were noted and expressed in g/ml.

Bulk Density (g/ml) = Mass of the Powder/ Bulk Volume.

3.1.2 Tapped density (Dt): The tapped volume was measured by tapping the powder to constant volume. Average values of triplicates were noted and expressed in g/ml.

Tapped Density (g/ml) = Mass of the Powder / Tapped Volume.

3.1.3 Compressibility Index (CI): Carr's compressibility index was used to determine the compressibility index of powder blend. Percentage compressibility of the blend was determined based on the apparent bulk density and tapped density, using the following formula

% Compressibility = [(Tapped density – Bulk density) / Tapped density] X100.

3.1.4 Hausner's ratio: The ease of powder flow is shown by Hausner's ratio. It is given by the equation: Hausner's ratio= Tapped density/ Bulk density.

3.1.5 Angle of Repose: The angle of repose is the maximum angle that can be formed between the surface of a pile of powder and the horizontal plane. The tangent of the angle is equal to the co-efficient of the friction between the particles.

$$\text{Tan } \theta = h/r \text{ or } \theta = \tan\text{-}1h/r$$

Where, h= height of the pile, and r = Radius of the pile. Angle of repose is determined by funnel method. Weighed granules were poured into a funnel fixed on a stand with the tip of funnel closed. The granules form a heap on the surface when allowed to flow freely. The diameter of heap is noted when the tip of funnel touches tip of heap formed.

4. Physical Evaluation of Tablet

4.1 Thickness: The thickness of the tablets for all the formulations (F1-F9) was measured using Vernier calliper in triplicate. Average value was noted and Standard deviation calculated and expressed in mm.

4.1.2 Diameter: The diameter of the tablets for all the formulations (F1-F9) was measured by Vernier calliper in triplicate. Average value was noted and Standard deviation calculated and expressed in mm.

4.1.3 Hardness: Monsanto hardness tester is used to determine the hardness of tablets. The equipment comprises of anvil, adjustable scale, spindle attached to a compressible ring, knurled knob. The tablet is positioned between the spindle and the anvil. The knurled knob turned so that the tablet sufficiently fits into the space. The scale is adjusted to zero. The knurled knob further turned to increase the pressure on the tablet until the tablet breaks. This force is measured from the scale in kilograms. The mean and Standard deviation were computed and expressed in Kg/cm2.

4.1.4 Friability: Friability of the tablets was determined using Roche friabilator. Twenty tablets were taken as sample and pre-weighed accurately on a digital weighing balance and transferred to the drum of Roche

© Journal of Global Trends in Pharmaceutical Sciences

friabilator. The friabilator is rotated for 100 revolutions at 25 rpm. The tablets are taken out from the drum and dusted and weighed again. The difference between the initial weight of the tablets (W1) and weight of the tablets after friability test (W2) gives the friability of the tablet. The mean and Standard deviation were computed and expressed in %.

% Friability = (W initial-W final) / W initial* 100.

4.1.5 Weight variation: Twenty tablets from each batch were randomly selected as sample and weighed individually and the average weight was measured. The average weight and standard deviation of 20 tablets were calculated. Not more than 2 tablets deviate from the average weight and no tablet should deviate by more than twice of that percentage.

5. Drug content: 7.4 pH Phosphate buffer were used to measure the drug content of matrix tablets. Randomly chosen five tablets were weighed and crushed. Mesalamine equivalent to 40 mg of powder was poured into a volumetric flask and dissolved in 100 ml of buffer. In a volumetric flask, 10ml of the above-mentioned stock solution was diluted to 100ml. A further 1ml of the aliquot was added to a 10ml volumetric flask. Using a UV spectrophotometer, the solution's absorbance at 223nm was determined. The readings were noted in triplicate. Average value was noted and standard deviation was calculated.

6. *In-vitro* Dissolution study: *In-vitro* drug release study of prepared formulation batches of tablets was performed using USP dissolution apparatus type II (paddle type). For first 2 hrs the dissolution study was performed in 1.2 pH 0.1N HCl,3hrs study in 6.8 pH Phosphate buffer and the rest in 7.4 pH Phosphate buffer. The temperature of dissolution medium was maintained at 37±0.50˚C with constant stirring of paddles at a rate of 50 rpm. 10ml of the sample was withdrawn from the dissolution media at the time intervals of 1hr for time period of 12 hrs and the fresh dissolution medium of same volume was replaced. The samples withdrawn were analysed by UV Spectrophotometer at 223 nm. The readings were noted in triplicate. Average value was noted and standard deviation was calculated.

7. Drug Release Kinetics: PCP DISSO V3 software is used to analyse release kinetics. The obtained in-vitro data was Fitted into the Peppa's model, Higuchi matrix, zero order model, and first order model in order to determine the mechanism for the drug release and rate of release kinetics of the dosage form. The best fit model was selected by comparing the R values obtained.

8. Stability Studies: Stability studies were performed at accelerated temperature. The amber coloured bottles were used to store tablets and the bottles were tightly plugged with cotton and capped. KESAR control systems humidity chamber was used to perform accelerated stability studies. Prepared tablets were exposed at temperature of 40 ± 2^{o} and relative humidity of 75±5% for 3months and then they were examined for hardness, friability, drug content, and in vitro drug release. [19]

9. RESULT AND DISCUSSION:

9.1 Preformulation studies of mesalamine tablets:

9.1.1 Identification of the pure drug Identification of the pure drug

Description: white to off-white amorphous powder.

Melting point: Melting point of the drug was found to be $280^{o}C \pm 0.77^{o}C$.

9.1.2 DRUG ANALYSIS (Spectrum & Standard calibration curve):

a) Scanning of Mesalamine (Spectrum- λ_{max}): The absorption spectra of Mesalamine showed only one peak at 302 nm in 1.2 pH, 300 nm in 6.8 pH and 223 nm in 7.4.

FTIR Studies:

FT-IR spectra of both pure Mesalamine and its combination with excipients showed all

© Journal of Global Trends in Pharmaceutical Sciences

distinctive drug peaks, confirming compatibility between the drug and excipients.

9.2.2 Differential Scanning Colorimetry (DSC) Analysis: The DSC thermograph of the drug showed a sharp peak at 287°C, while the drug-excipient mixture (Mesalamine with excipients) exhibited a distinct sharp peak at 285°C, indicating drug-excipient compatibility, as shown in Figures 4 and 5.

10.1. Pre-formulation studies of mesalamine tablet: The pre-compressed Mesalamine core tablet blends were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. The corresponding results are presented in the following table, demonstrating that the Mesalamine core tablet blends exhibited good flow characters and compressibility.

10.2. Evaluation of post-compression parameters of mesalamine core tablets: Mesalamine core tablets were evaluated for different post-compression parameters, including diameter, thickness, weight uniformity, hardness, friability. All formulations exhibited results within standard range. The corresponding results are presented in following table.

10.3. *In-vitro* drug release: The in-vitro drug release results for formulations F1-F9 are shown in Table 9 and Figures 6, 7 & 8. The data indicate that higher concentrations of Xanthan gum lead to decreased drug release by prolonging the release duration.

11.RELEASE KINETICS: PCP DISSO V3 software analyzed the release kinetics by fitting in-vitro data to First Order, Zero Order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. Correlation coefficients determined that all formulations followed a Zero Order release pattern with Peppa's Fickian diffusion mechanism. Results are in Table 21.

12. Comparison of Dissolution Profile of Optimized Formulation with Marketed Formulation: The optimized formulation's In-vitro drug release profile was compared to the marketed formulation Zintasa 400 mg, The F1 formulation was selected as an optimized formulation. The data of *in-vitro* release study of the marketed formulation and optimized formulation have been tabulated in Table No. 10 and depicted in Figure Nos.9, 10 & 11 counter plots, repose surface plots & drug release profile**.**

13. STABILITY STUDIES: Stability studies were performed for the optimized formulation F1 and results have been tabulated in following table:

DISCUSSION

This study successfully formulated a mesalamine matrix tablet for targeted colonic delivery, demonstrating sustained drug release by following zero-order kinetics. The incorporation of Xanthan gum and Guar gum proved effective in modulating the release profile, with increased polymer concentrations yielding prolonged drug release and enhanced tablet hardness. The formulation's physical stability in short-term studies indicates promising commercial viability. The strength of this research lies in its rigorous pre-formulation analysis, where compatibility between mesalamine and excipients was confirmed through FTIR and DSC techniques. Furthermore, the innovative employment of pH-sensitive and microbial-degradable polymers, such as Xanthan gum and Guar gum, underscores the precision of the drug targeting strategy aimed at colonic delivery. However, the formulation's long-term stability remains to be fully evaluated under diverse environmental conditions, and the variability in patients' colonic microbiota may influence the degradation of Guar gum, potentially impacting the consistency of drug release. Aligned with existing literature, this work contributes to the expanding field of matrix-based colonic drug delivery systems by providing deeper insights into the use of specific polymer combinations to optimize drug release.

© Journal of Global Trends in Pharmaceutical Sciences

Table no. 1: Mesalamine core tablet formulation:

Ingredients	F
Mesalamine	100
Acacia	50
Starch	3
Talc	1.5
Magnesium stearate	0.5

Weight of each Mesalamine core tablet = 155mg

Table no. 2: Mesalamine coated tablet formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet	155	155	155	155	155	155	155	155	155
Guar gum	50	50	50	100	100	100	150	150	150
Xanthan gum	100	150	200	100	150	200	100	150	200
Starch paste	20	20	20	20	20	20	20	20	20
Mg. stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Lactose	220	170	120	220	120	70	120	70	20

Weight of each Mesalamine coated tablet = 550mg

Table no. 3: Concentration of polymer generated by the software to be added in formulation of mesalamine matrix tablets.

Run	Component 1- Amount of Guar gum (mg)	Component 2 -Amount of Xhantan gum (mg)
	50	100
	50	150
	50	200
	100	100
	100	150
	100	200
	150	100
	150	150
	150	200

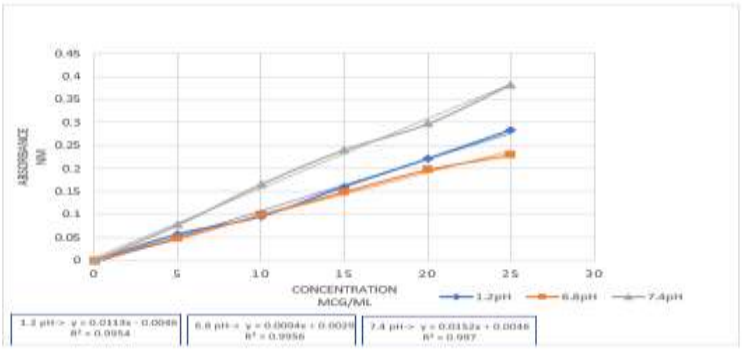

Fig .1: Standard calibration curve of Mesalamine in 1.2 pH (0.1N HCl), 6.8 pH and 7.4 pH phosphate buffer.

© Journal of Global Trends in Pharmaceutical Sciences

Table no. 4: Standard calibrations curve of mesalamine

Concentration (µg/ml)	Absorbance (nm)		
	1.2 pH	6.8 pH	7.4 pH
	Average±SD	Average±SD	Average±SD
0	0	0	0
5	0.544±0.004	0.045±0.003	0.075±0.006
10	0.082±0.082	0.091±0.007	0.162±0.006
15	0.149±0.009	0.140±0.007	0.193±0.046
20	0.200±0.074	0.190±0.005	0.269±0.028
25	0.201±0.066	0.220±0.007	0.366±0.016

UV absorbance values are expressed in mean ± standard deviation (n=3)

c) Solubility: The Mesalamine 's solubility profile results have been tabulated in Table No.5

Sr. No	Name of Compound	Solubility range
1.	Water	0.84g/L at 20 ^{0}c
2.	Methanol	Poorly soluble
3.	NaOH (0.1N)	Soluble
4.	DMSO	Soluble
5.	Acetonitrile	Poorly soluble
6.	Chloroform	Poorly soluble
7.	Alcohol	insoluble

9.2 Drug- Excipient Compatibility Studies:

9.2.1 FT- IR Spectroscopy: FT- IR spectrum of the pure drug Mesalamine ranges between 3484.31-1791.58 cm^{-1} and drug with excipients shows 3083.34-1789.84 cm^{-1}.

Table no. 6: Compatibility study of mesalamine and excipient

Sr. No.	Functional group	Mesalamine pure peak	Mesalamine and excipient mixture peak
1	N-H	3484.31	3083.34
2	O-H	3062.43	3065.98
3	C=C	1662.14	1659.02
4	Alkyl C-H	2941.57	2937.76
5	Alkene C=C	1791.58	1789.84

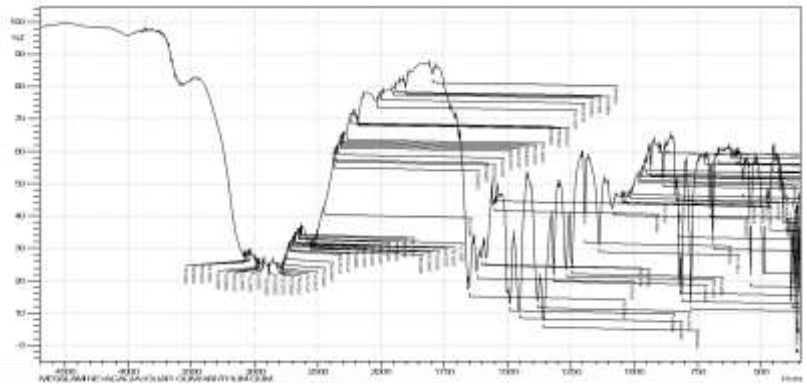

Fig .2. FT-IR Spectrum of Mesalamine

© Journal of Global Trends in Pharmaceutical Sciences

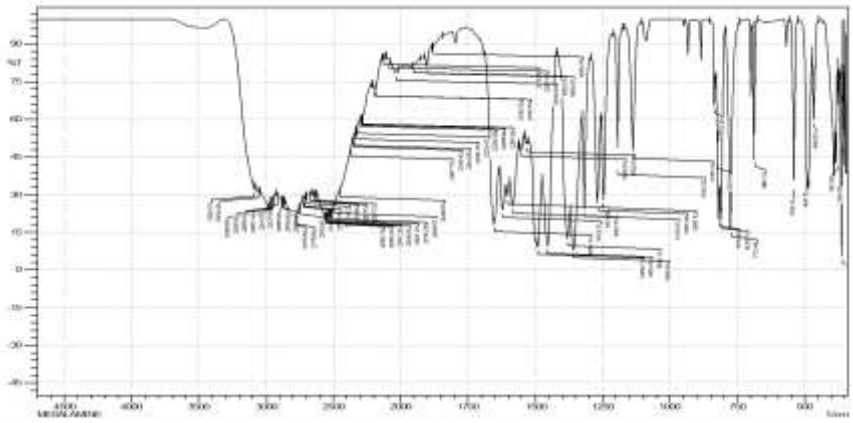

Fig.3: **FT-IR spectrum of Mesalamine +Guargum+Xanthan gum+ Acacia gum**

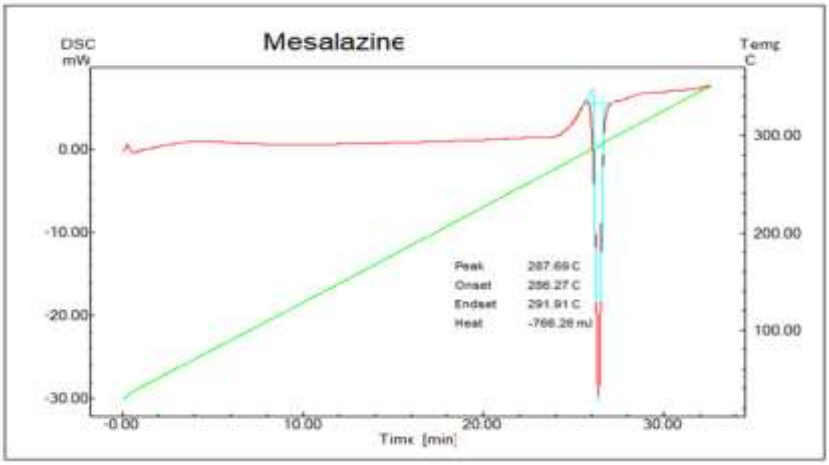

Fig.4: DSC of Mesalamine

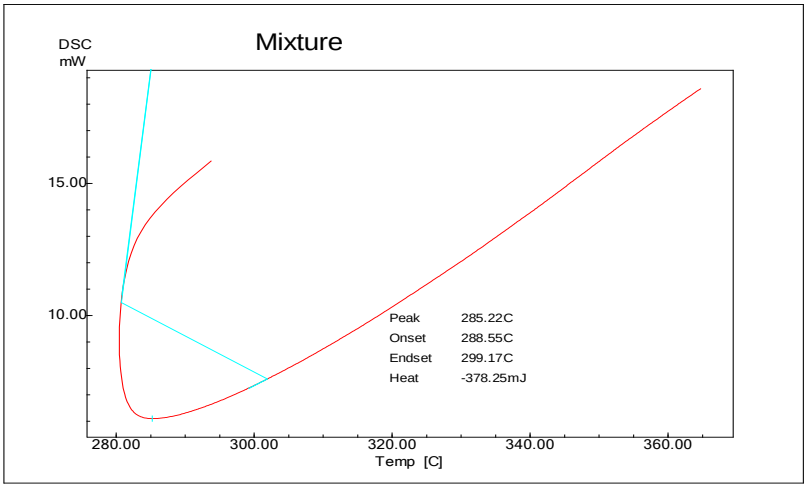

Fig.5: DSC of MESALAMINE +Guargum+Xanthan gum+ Acacia gum

© Journal of Global Trends in Pharmaceutical Sciences

Table no.7: Pre-formulation studies of mesalamine tablet

Formulation batch code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compress ibility (%)	Angle of repose (θ)	Hausner's ratio
F1	0.72±0.06	0.78±0.01	7.6±0.12	$34^{o}.2'$±0.12	1.08±0.07
F2	0.81±0.01	0.84±0.11	3.5±0.21	$35^{o}.3'$±0.17	1.03±0.01
F3	0.88±0.03	0.96±0.04	8.3±0.11	$42^{o}.3'$±0.21	1.09±0.02
F4	0.71±0.01	0.76±0.08	16.9±0.1	$41^{o}.3'$±0.23	1.20±0.08
F5	0.84±0.07	1±0.04	9.2±0.17	$39^{o}.0'$±0.28	1.25±0.07
F6	0.78±0.05	0.86±0.07	6.8±0.24	$38^{o}.3'$±0.27	1.8±0.04
F7	0.82±0.04	0.92±0.09	10±0.26	$36^{o}.1'$±0.13	1.12±0.03
F8	0.91±0.03	1±0.04	10±0.24	$34^{o}.21'$±0.2	1.09±0.04
F9	0.91±0.07	0.95±0.07	7.8±0.21	$31^{o}.3'$±0.29	1.07±0.07

Table no 8. Post-compression parameters of mesalamine core tablets

Formulation batch code	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)
F1	10.0±0.03	5.5±0.04	6.0±0.07	0.36±0.003	548±0.07
F2	10.3±0.02	5.1±0.01	6.1±0.04	0.36±0.007	541±0.03
F3	10.1±0.01	5.3±0.07	6.0±0.07	0.99±0.003	551±0.06
F4	10.2±0.08	5.2±0.06	6.02±0.03	0.78±0.004	539±0.05
F5	10.0±0.07	5.3±0.01	6.0±0.01	0.9±0.003	550±0.09
F6	10.1±0.04	5.6±0.03	5.5±0.03	0.9±0.004	549±0.08
F7	10.4±0.06	5.4±0.04	5.0±0.07	0.30±0.003	553±0.07
F8	10.2±0.01	5.4±0.01	5.5±0.01	0.99±0.007	551±0.03
F9	10.3±0.07	5.5±0.07	5.0±0.08	0.99±0.001	544±0.01

Table no.9: *In-vitro* drug release of formulated mesalamine matrix tablets (F1-F9)

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	1.101	1.101	1.101	1.0125	1.101	1.101	1.002	1.101	1.101
2	2.478	2.478	2.478	2.327	2.478	1.968	2.256	2.478	1.735
3	21.482	7.711	4.682	16.224	4.711	2.682	15.365	2.711	1.682
4	39.411	25.640	7.986	36.415	22.64	4.986	33.587	20.640	1.986
5	53.760	39.990	23.98	49.658	36.99	20.988	47.236	34.990	17.988
6	65.107	51.337	35.33	61.258	48.33	32.335	59.365	46.337	29.335
7	74.471	60.701	44.69	70.589	57.70	41.699	67.325	55.701	38.699
8	80.751	66.980	50.97	76.956	63.98	47.979	75.214	61.980	44.97
9	85.047	71.276	55.27	81.587	68.27	52.275	79.847	66.276	49.275
10	89.867	76.096	60.09	85.674	73.09	57.095	83.896	71.096	54.095
11	93.612	79.84	63.84	89.874	76.84	60.840	87.754	74.842	57.840
12	97.331	83.56	67.55	93.876	80.56	64.558	90.847	78.560	61.558

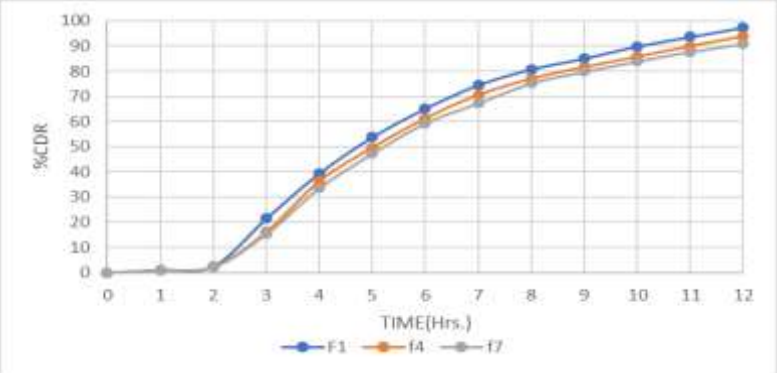

Fig.6: In-vitro drug release of Mesalamine matrix tablet of F1, F4 and F7

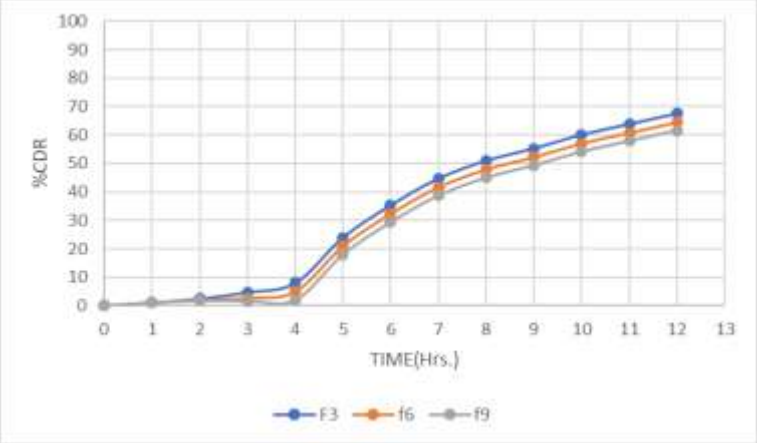

Fig.7: *In-vitro* drug release profile of Mesalamine matrix tablet of F3, F6 and F9

© Journal of Global Trends in Pharmaceutical Sciences

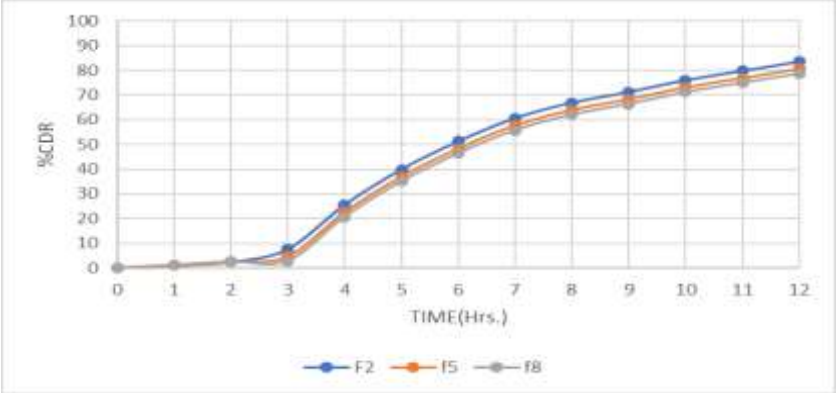

Fig.8: *In-vitro* drug release profile of Mesalamine matrix tablet of F2, F5 and F8

Table no. 10: Release kinetics of formulated mesalamine matrix tablets

Formulation Code	Zero Order Plot	First Order Plot	Higuchi Matrix	Korsmeyer Peppas		Best Fit Model
	R^2	R^2	R^2	R^2	N	
F1	0.949	0.850	0.780	0.923	2.212	Zero order
F2	0.951	0.802	0.788	0.920	2.091	Zero order
F3	0.953	0.885	0.783	0.92	2.137	Zero order
F4	0.951	0.832	0.777	0.951	2.090	Zero order
F5	0.950	0.924	0.782	0.937	2.121	Zero order
F6	0.948	0.910	0.779	0.939	2.136	Zero order
F7	0.949	0.849	0.780	0.922	2.075	Zero order
F8	0.941	0.879	0.779	0.920	2.197	Zero order
F9	0.942	0.842	0.710	0.931	2.071	Zero order

Table no. 11: Comparison of *in-vitro* drug release of mesalamine optimized formulation (f1) with marketed product.

Time (h)	% Cumulative Drug Release of F1 Formulation	% Cumulative Drug Release of Marketed Formulation
0	0	0
1	1.101± 0.312	24.2135±0.125
2	2.478±0.141	43.5864±0.047
3	21.482±0.321	65.248±0.321
4	39.411±0.012	75.5879±0.147
5	53.760±0.031	87.254±0.421
6	65.107±0.417	98.345±0.144
7	74.471±0.0245	
8	80.751±0.0472	
9	85.047±0.034	
10	89.867±0.031	
11	93.612±0.013	
12	97.331±0.317	

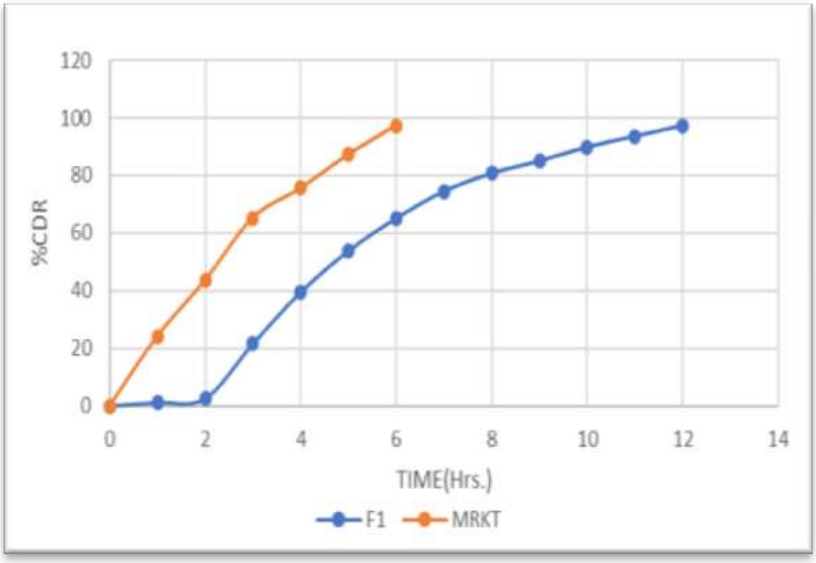

Fig. 9: Comparison of *In-vitro* drug release drug release profile of Mesalamine optimized formulation F1 and marketed formulation.

© Journal of Global Trends in Pharmaceutical Sciences

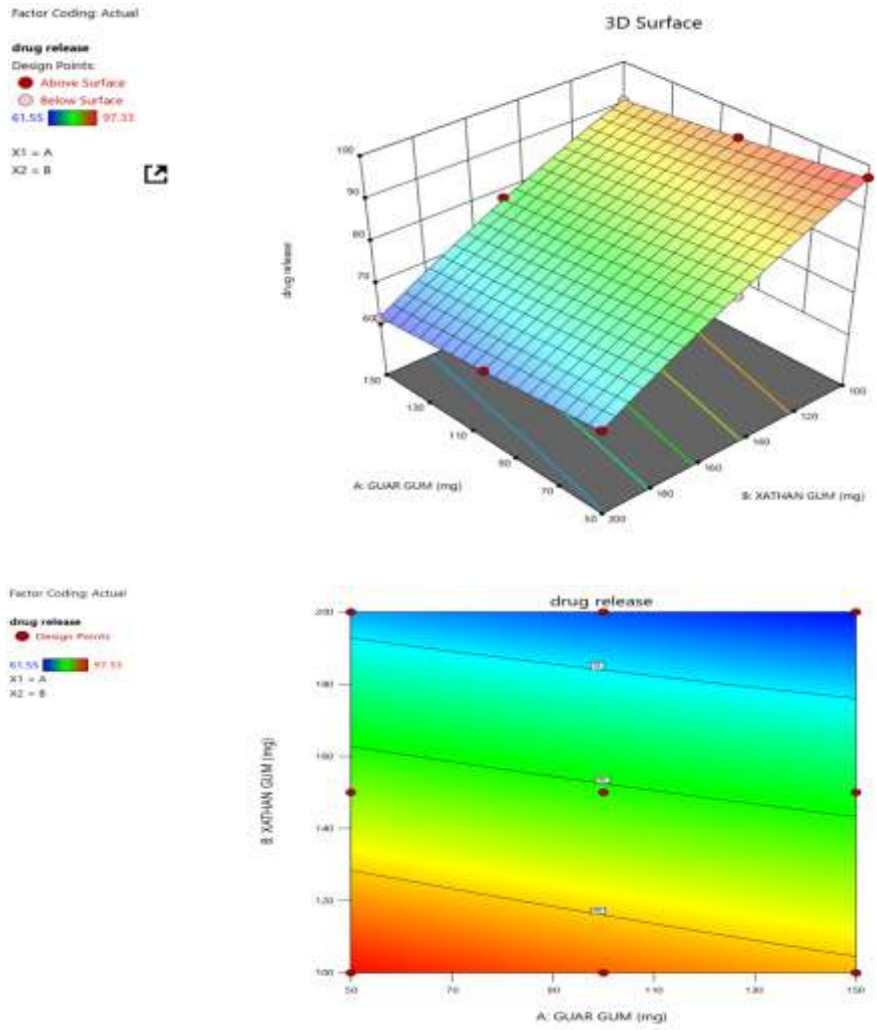

Fig. 10: Contour plot and response surface plot showing the effect of concentration of Guar gum (x1) and Xanthan gum (x2) on In-vitro drug release (y1)

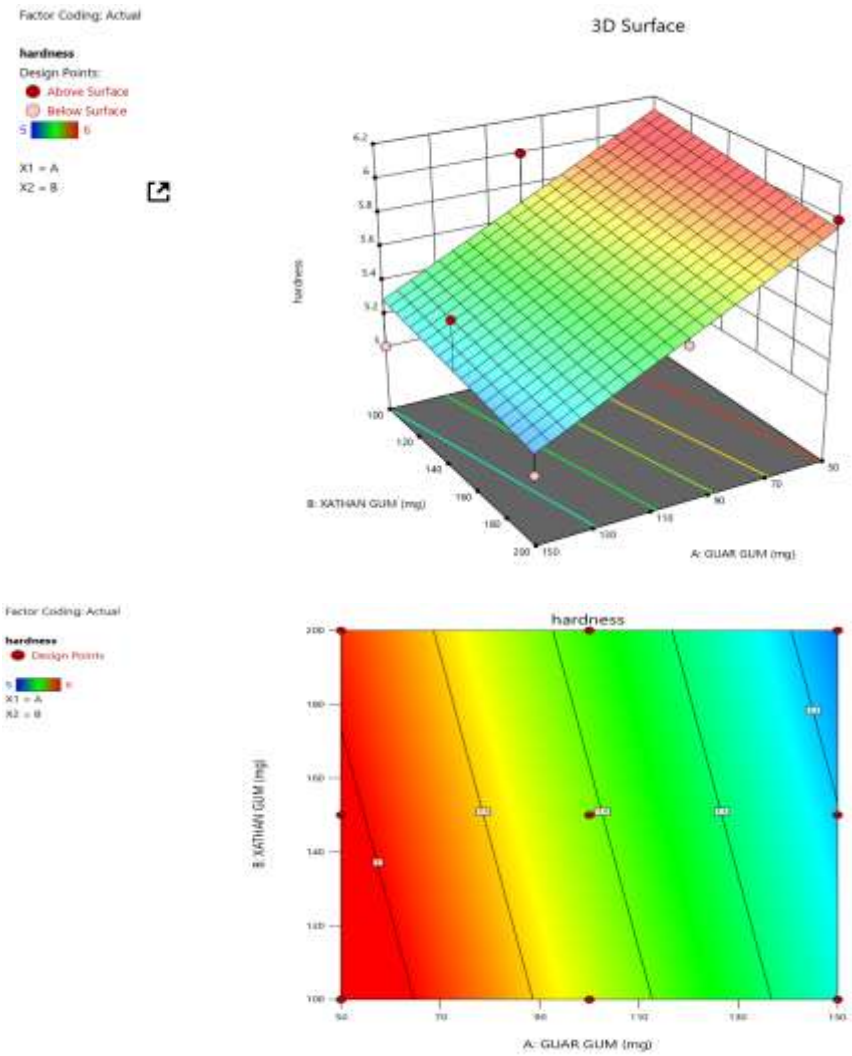

Fig. 11: Contour plot and Response surface plot showing the effect of concentration of Guar gum(x1) and Xanthan (x2) on hardness (y2)

Table no.12: Stability profile of mesalamine optimized formulation (f1)

Parameters	F1 Formulation	
	Accelerated Temperature $40^0C \pm 2^0C$ /RH 75 ± 5% (After 30 days)	
	Initial	30 Days
Hardness (kg/cm^2)	6.0	5.4
% Drug Content in 0.1N HCl	82.21	80.78
% Drug Content in 7.4 pH	89.89	87.01
Cumulative % DR at the end of 12Hrs.	97.33	95.61

© Journal of Global Trends in Pharmaceutical Sciences

Nonetheless, significant regulatory challenges persist, necessitating comprehensive toxicological assessments and extended clinical trials to meet global regulatory standards for new pharmaceutical formulations.

CONCLUSION:

The study proficiently developed mesalamine matrix tablets tailored for exact colonic delivery, by incorporating Xanthan gum (pH-sensitive) and Guar gum (bacteria-sensitive) as key polymers. These polymers efficiently extended the drug release profile, with the optimized formulation attaining a release of 97.331% over a 12-hour period, conforming to zero-order kinetics. The study confirmed the compatibility of mesalamine with the excipients and revealed that higher polymer concentrations substantially enhanced both the release duration of the drug and the mechanical hardness of the tablets. The formulation complied with all relevant standards and exhibited stability during short-term storage, underscoring its promise as an effective strategy for targeted colonic drug delivery.

Acknowledgments: The authors would like to acknowledge the support of KLE's College of Pharmacy for providing the necessary resources to carry out this research. Authors also extend our gratitude to Selleckchem Pvt Ltd, Mumbai, for generously supplying Mesalamine (API) as a gift sample.

Conflict of interest: We do not have any conflict of interest.

REFERENCES:

1. Patel M, Nagarkar R, Mohammed IA, Shah S, Kulal S. Colon targeted drug delivery system: Recent approaches. International Journal of Bioassays. 2021; 10:5763-77.
2. Yamazaki M, Chung H, Xu Y, Qiu H. Trends in the prevalence and incidence of ulcerative colitis in Japan and the US. International Journal of Colorectal Disease. 2023 May 19;38(1):135.
3. Wei SC, Sollano J, Hui YT, Yu W, Santos Estrella PV, Llamado LJ, Koram N. Epidemiology, burden of disease, and unmet needs in the treatment of ulcerative colitis in Asia. Expert Rev Gastroenterol Hepato. 2021 Mar 4;15(3):275-89.
4. Audinarayana N, Srinivasulu A, Sruthikumari V. Colon targeting oral matrix tablets of Mesalamine: Design, development and in-vitro evaluation. International Journal of Novel Trends in Pharmaceutical Sciences. 2020 Jun 17;10(1):18-27.
5. Bhalsing MD, Shekade SV. Formulation and in vitro evalution of colon targeted drug delivery of Aceclofenac. Pharm. Res.2020; 2:2.
6. Pathare VB, Shendge RS, Shinde PS, Pandit SR, Pulate AJ. Formulation and in-vitro evaluation of oral targeted sustained released tablet of Budesonide. International Journal of Health Sciences 2019;20(2); 32:3.
7. Jakate A, McNamee B, Burkindine D. Bioavailability and swallowability of an age-appropriate, delayed-release Mesalamine formulation in healthy volunteers. Clinical Pharmacology: Advances and Applications. 2019; 11:93.
8. Ramanathan M, Subramanian L. Formulation and evaluation of colon targeted matrix tablets of Ibuprofen. Asian Journal of Pharmaceutical Research and Development. 2018 May 28;6(2):9-19.
9. Liu D, Yan H, Kong Y, You Y, Li Y, Wang L, Tong Y, Wang J. Preparation of colon-targeted Acetyl harpagide tablets and its release properties in vivo and in vitro. Frontiers in Pharmacology. 2018 Aug 14; 9:832.

© Journal of Global Trends in Pharmaceutical Sciences

10. Nour, Abdelmalak, Naguib. Novel chewable colon targeted tablets of Bumadizone calcium for treatment of ulcerative colitis: Formulation and optimization. Journal of Drug Delivery Science and Technology. 2016 Oct 1; 35:172-83.
11. Pawar, Gautam. Design, optimization and evaluation of Mesalamine matrix tablet for colon drug delivery system. Journal of Pharmaceutical Investigation. 2015 September 15;46(1):67-78.
12. Solanki, Basuri, Thakkar , Patel. Recent Advances in Granulation Technology. International Journal of Pharmaceutical Sciences and Research. 2015; 5(7): 48-54.
13. Jain, Patel, Kanzariya, Formulation and evaluation of colon targeted matrix tablet of Naproxen. International Journal of Pharmacy and Pharmaceutical Sciences.2014 Aug 8;6(8):183-6.
14. Design Expert [internet] [updated 2014 jan28; created 2009] August, Available from: http://www.statease.com/software/dx 9-trial.html
15. Abraham A, Karakurum A. Acute respiratory failure secondary to Mesalamine-induced interstitial pneumonitis. Case Reports. 2013 Aug 20;2013: bcr2013009834.
16. Sharma M, Joshi B, Bansal M, Goswami. Formulation and evaluation of colon targeted tablets of Mesalamine. Journal of Drug Delivery and Therapeutics. 2012 Sep 15;2(5).
17. Krishnaiah, Reddy PB, Satyanarayana V, Karthikeyan RS. Studies on the development of oral colon targeted drug delivery systems for Metronidazole in the treatment of Amoebiasis. International Journal of Pharmaceutics. 2002 Apr 2;236(1-2):43-55.
18. Guslandi M. Nicotine treatment for ulcerative colitis. British Journal of Clinical Pharmacology. 1999 Oct; 48(4):481.
19. Stability Testing of New Drug Substances and Products. ICH Harmonized Tripartite Guideline, 1993: 2-14.

© Journal of Global Trends in Pharmaceutical Sciences