Int J Pharm Bio Sci 2016 April; 7(2): (P) 90 - 97

Original Research Article **Pharmaceutics**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

DESIGN AND DEVELOPMENT OF COLON SPECIFIC DRUG DELIVERY SYSTEM OF SULFASALAZINE

M. KISHORE[*1], B. VIJAYAKUMAR[2] AND Y. NARASIMHAREDDY[3].

1. Research Scholar Jawaharlal Nehru Technological University Kakinada, Kakinada, A.P, India, PIN: 533001.
2. Jangaon Institute Of Pharmaceutical Sciences, Jangaon, Warangal (D), Telangana, India. PIN: 506167
3. University College of Pharmaceutical Sciences, Warangal, Telangana, India PIN: 506009.

ABSTRACT

The present study was designed to investigate colon targeted and site specific drug release of Sulfasalazine enteric coated tablets was prepared. These tablets were formulated from F1-F8 by selecting time dependent and release retard natural polymers such as guar gum, pectin by combining with different concentrations HPMC(Methocel K100M) and carbopol(Carbopol® 974P NF Polymer) from wet granulation method. This HPMC (Methocel K100M) and carbopol (Carbopol® 974P NF Polymer) was included in this study to control the solubility of Guar gum and pectin premature drug release in the stomach and small intestine. There after the obtained tablets were coated by enteric polymer such as Eudragit-S 100 to retard the drug release at specified site colon by varying with different concentration as like 1, 3, 5, and7 %. This study also included all the evaluated precompression and post compressional parameters of sulfasalazine enteric coated tablets, with various release kinetic mechanism such as zero order, first order, higuchi plot and peppasmayer equations. From these all contributed results the formulation F7, it was pectin based containing Carbopol and enteric coated with the concentration Eudragit-S 100 of was optimized.

KEYWORDS: **Sulfasalazine, Guar gum, Pectin, Eudragit-S 100, HPMC (Methocel K100M), Carbopol(Carbopol® 974P NF Polymer) and Colon.**

M. KISHORE
Research Scholar Jawaharlal Nehru Technological University Kakinada, Kakinada, A.P, India, PIN: 533001.

***Corresponding author**

INTRODUCTION

The design of dosage forms has several objectives one of which is to achieve drug release at sites that will ensure maximum therapeutic benefits. Oral administration of drugs by conventional pharmaceutical formulations is the most convenient and effective delivery system and is preferred over parentral medication. However, not all new drugs can be administered orally possibly because of their sensitivity to gastric acid and their vulnerability to gastrointestinal enzymes[1]. The site-specific delivery of drugs to the target receptor sites has the potential to reduce side effects and to increase pharmacological response. One of the interesting areas to target drugs orally for systemic drug delivery is the colon, the proximal part of the large intestine. In addition there are a number of local pathologies where direct release of drug in the colon would not only improve pharmacotherapy but also reduce potential toxicity and side effects. The treatment of disorders of the large intestine such as irritable bowel syndrome, colitis, Crohn's disease, colon cancer and local infectious diseases where a high concentration of active agent is needed, can be markedly improved using colon-specific delivery systems various systems for specific delivery of drugs to the distal intestine are being developed, taking advantage of the luminal pH in the ileum and the microbial enzymes in the colon, such as pectinase, amylase, dextrase, glycosidase and azoreductase. The selected API of Sulfasalazine was chemically, 2-Hydroxy-5-((4-((2-pyridinylamino)sulfonyl)phenyl)azo)benzoic acid for the treatment of Crohn's disease(ulcerative colitis in colonic region). In addition, delayed-release tablets of sulfasalazine are used to treat rheumatoid arthritis. Sulfasalazine was poorly absorbed from the small intestine (up to 30%), after which it is excreted into the bile. Hence this was taken an account to development of colon targeting systems may permit oral administration of drugs that exhibit poor uptake or degrade in the upper regions of the GI tract. Specific release in the colon also provides a time delay between administration and onset of action which can be useful for diseases with various degrees of severity, such as asthma and arthritis. Sulfasalazine and also helps to reduce joint pain, swelling, and stiffness. Early treatment of rheumatoid arthritis with sulfasalazine helps to reduce/prevent further joint damage and also 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

Sulfasalazine, obtained as a gift sample from Dr. Reddy's Laboratories Limited, Hyderabad, Telangana, India. Guar gum or Pectin, hydrophilic polymer HPMC (Methocel K100M) or Carbopol(Carbopol® 974P NF Polymer), Starch, 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.

METHODOLOGY

Drug–Excipient Compatibility Studies

Drug-polymer interactions were studied by FTIR spectroscopy[3]. 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}.

Preparation of sulfasalazine polysaccharide based granules

Granules containing sulfasalazine were prepared by wet granulation method. The ingredients were screened through sieve number 40, and then Sulfasalazine was mixed with various combinations of colon specific polymers (guar gum or pectin), hydrophilic polymers HPMC (Methocel K100M) or Carbopol (Carbopol® 974P NF Polymer) and lactose. Starch solution (5%) was used as binding agent. Powder mass (each batch weighs approximately 500g) 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 dryer. The dried granules were stored in an air tight container till further processing[4].

Preparation of enteric coating polymeric solution

The enteric coating polymeric solution was prepared by dissolving 50 g of Eudragit S 100 in 1000 ml of acetone. Triethyl citrate was used as a plasticizer with a concentration of 2%.

Preparation of Sulfasalazine matrix tablets

Each batch weighing 500 gr of dried granules in different combination of colon specific polymers (guar gum or pectin), hydrophilic polymers (HPMC or Carbopol) and lactose were mixed with 1% magnesium stearate (Table 1). These granules were compressed into a tablet by tablet compression machine (Riddhi double rotary tablet press RMB4-27). Punch Size: Oval-shaped, 8.74 mm x 18.75 mm. Tablets were stored for further processing[5].

Table 1
Formulation of Sulfasalazine matrix tablets (ingredients in mg/tablet)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Sulfasalazine	500	500	500	500	500	500	500	500
Guar gum	40	80	120	160	**	**	**	**
Pectin	**	**	**	**	40	80	120	160
Lactose	145	105	65	25	145	105	65	25
HPMC(Methocel K100M)	80	40	**	**	80	40	**	**
Carbopol(Carbopol® 974P NF)	**	**	80	40	**	**	80	40
Binder (5%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg.Stearate	10	10	10	10	10	10	10	10
Talc	15	15	15	15	15	15	15	15
Total weight	800	800	800	800	800	800	800	800

Evaluation of pre compressional parameters of sulfasalazine granules

The angle of repose (θ) of the granules was determined by using the funnel method. Bulk density (BD) and tapped density (TD) were calculated by formula: Bulk density=W/V_0, Tapped density=$W/V_{f,}$ [6]. Compressibility index and Hausner's ratio of the granules was determined by using the formula: CI (%) = $[(V_0 - V_f / V_0)] \times 100$ and HR = TD/BD, respectively [7]. The experiments were performed in triplicate and average values with SD were noted. The results were shown in **Table 2.**

Evaluation of post compressional parameters of sulfasalazine matrix tablets

Twenty (20) tablets were randomly selected and weighed. The mean and standard deviation were calculated as described in official standards[8,9]. 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 crushing strength 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 sulfasalazine matrix tablets were tested for their drug content. Tablets were finely powdered and quantity of powder equivalent to 500 mg of sulfasalazine 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 sulfasalazine content at 355 nm using a double beam UV-Visible spectrophotometer (Elico, India).

In-vitro drug release studies

The in vitro dissolution studies were performed for the Sulfasalazine enteric coated tablet using USP II dissolution apparatus (Lab India, DS 8000, Mumbai, India) in 900 ml dissolution medium at 50 rpm, 37°C ± 0.5°C[10,11]. 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 hr. Then pH 1.2 buffers were replaced with pH 6.8 phosphate buffer dissolution media for 4 hr. After performing the experiments for 4hr with pH 6.8 phosphate buffer, the dissolution media were replaced finally with phosphate buffer pH 7.4 for the next 18 hrs[12]. At regular time intervals, samples were withdrawn from the dissolution media and filtered with Whatman filter paper (0.22 mμ). The absorbance was measured using double beam UV-Visible spectrophotometer (Elico, SL-210 India) at355 nm. The graph was plotted against cumulative percentage drug release versus time. The experiment was done in triplicate and data were expressed in mean ± SD.

Kinetic studies

The rate and mechanism of release of enteric coated of Sulfasalazine enteric tablets were analyzed by fitting the dissolution data into various kinetic models[13].

Zero-order equation

Zero-order release kinetics, cumulative amount of drug released vs time and the release rate data are fitted to the following equation: $\mathbf{C = K_0 .t}$

First order equation

First-order release kinetics, log cumulative percentage of drug remaining Vs time and the release rate data are fitted to the following equation:

$$\mathbf{C = 100 \times (1 - e^{-Kt})}$$

Higuchi's equation

The Higuchi release, cumulative percentage of drug released vs square root of time and the release rate data are fitted to the following equation: $\mathbf{Q = Kt^{1/2}}$ Where, K is the constant reflecting the design variables of the system and *t* is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time

Korsmeyer-Peppas equation

log cumulative percentage of drug released vs. log time, and the exponent *n* was calculated through the slope of the straight line. $M_t / M_\infty = Ktn$ Where M_t/M_∞ is the fractional solute release, t is the release time,
K is a kinetic constant characteristic of the drug/polymer system, and *n* is an exponent that characterizes the

mechanism of release of tracers . For matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release [14].

RESULTS AND DISCUSSION

Sulfasalazine enteric coated tablet is one of the approaches for colon specific targeted drug delivery system. Attempts have been made for preparation of enteric coated tablets for site specific release with variable concentration of natural polymers such as Guar gum and Pectin. Based on various combinations of rate retard polymers HPMC(Methocel K100M) and Carbopol(Carbopol® 974P NF) two set of formulations of Sulfasalazine granules were prepared. One set comprising Guar gum based (F1-F4) and another set comprising Pectin based granules (F5-F8). There after the both the sets of granules 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, 5, 7% in acetone solution, Triethyl citrate was used as a plasticizer) and to ensured the optimized formulation for adjusting release pattern according to marketed formulation and USP guidelines of sulfasalazine enteric coated tablets. In which HPMC, Carbopol were used as, Starch as binder, Mg.Stearate and Talc used as lubricant. The characteristics peaks for Sulfasalazine were obtained at 3134.43 cm^{-1} stretching of alkene, 3030.27cm^{-1} stretching of aromatic ring, 2825.81 cm^{-1} stretching of aldehyde, 1280.78cm^{-1}& 1263.42cm^{-1} stretching of aromatic amines, 1004.95cm^{-1}vibrations of aromatic amines, 964.44cm^{-1}, 792.77cm^{-1}, 767.69cm^{-1}& 709.83cm^{-1} are bending of aromatic ring and 574.81cm^{-1} stretching of alkyl halides. Similarly all the characteristics peaks are observed in drug-polymers mixture. This revealed that there was no chemical interaction between drug and polymer. Fig. 1 & 2 demonstrates the FT-IR spectrum of pure Sulfasalazine and Optimized formulation (F7).

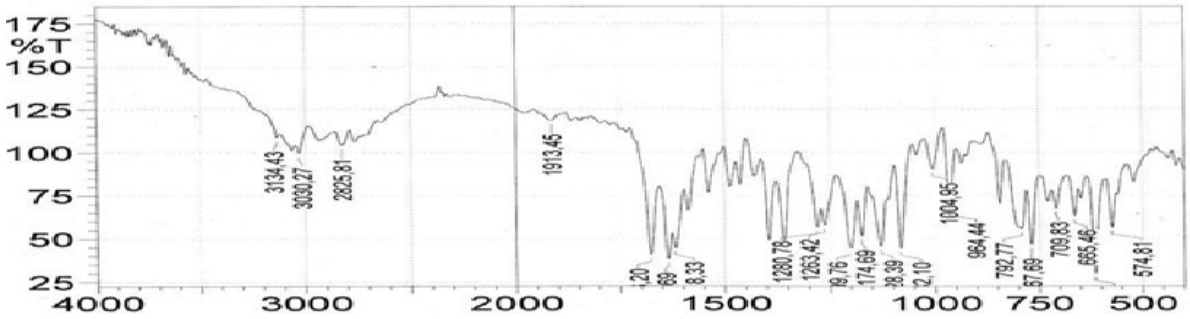

Figure 1
FT-IR spectrum of pure Sulfasalazine

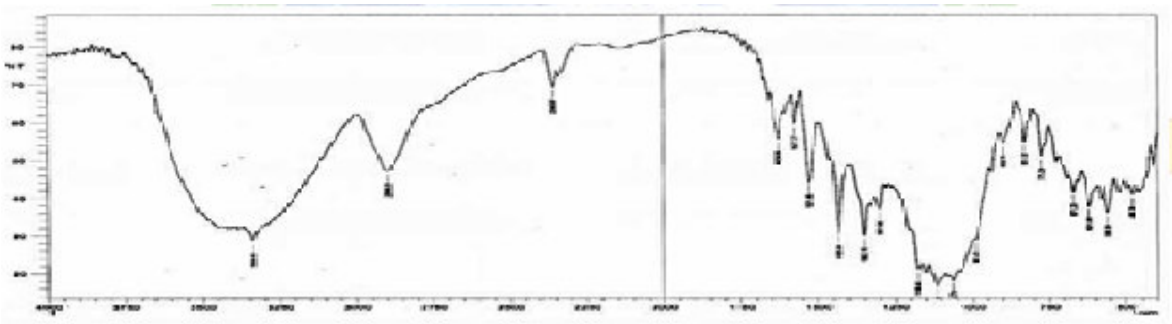

Figure 2
FT-IR spectrum of Sulfasalazine enteric coated optimized formulation (F7)

Evaluation of pre compressional parameters of sulfasalazine matrix granules

The tablets of Sulfasalazine were evaluated for various physical properties. The bulk densities for the powder blend of various formulations (F1-F8) ranged between 0.31±0.01g/cm^3 and 0.37±0.01g/cm^3; and tapped density ranged between 0.31±0.22g/cm^3 and 0.37±0.12g/ cm^3 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 ratio 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±0.44 to 29.23±0.26 **(θ)**. The values indicated satisfactory flow behavior.

Table 2
Evaluation of Sulfasalazine matrix granules

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Angle of repose (θ)	Carr's Index	Hausner's ratio
F1	0.37±0.01	0.32±0.21	24.12±0.21	12.45±0.31	1.16±0.04
F2	0.32±0.06	0.36±0.31	25.24±0.21	14.54±0.43	1.12±0.06
F3	0.34±0.07	0.31±0.22	26.54±0.33	15.23±0.51	1.13±0.03
F4	0.31±0.01	0.37±0.12	22.12±0.43	13.71±0.12	1.14±0.01
F5	0.35±0.05	0.36±0.11	27.76±0.42	18.18±0.33	1.11±0.07
F6	0.32±0.02	0.31±0.32	24.33±0.15	12.33±0.11	1.15±0.05
F7	0.37±0.09	0.34±0.33	20.12±0.44	11.21±0.17	1.12±0.03
F8	0.33±0.08	0.33±0.42	29.23±0.26	15.77±0.27	1.10±0.07

Evaluation of sulfasalazine matrix tablets

All 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 pectin coated tablet formulation (F7) was 800.1±7.5mg, hardness was 9.01±0.77kg/cm^2 and thickness was 7.45±0.31. The percentage friability of all the formulations was ranged from 0.51±0.27 to 0.65±0.22 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 91.29±1.89 to 98.51±2.53%. All the above results were mentioned in Table: 3

Table 3
Evaluation of Sulfasalazine enteric coated tablets

Formulation code	Thickness(mm)	Average weight(mg)	Hardness(Kg/cm^2)	Friability(%)	Assay(%)
F1	7.40±0.21	798.6 ±9.2	9.21±0.51	0.53 ±0.21	96.20±3.15
F2	7.42±0.34	840.3±10.4	9.13±0.72	0.54±0.33	91.29±1.89
F3	7.38±0.38	840.2±8.1	9.61±0.54	0.59±0.20	98.17±2.67
F4	7.35±0.25	841.5±9.8	9.51±0.69	0.63±0.21	97.35±3.48
F5	7.41±0.24	840.0±7.8	9.12±0.75	0.58±0.18	95.91±1.89
F6	7.39±0.22	841.7±8.6	9.92±0.89	0.65±0.22	98.51±2.53
F7	7.45±0.31	800.1±7.5	9.01±0.77	0.51±0.27	97.19±1.98
F8	7.36±0.39	799.1±9.1	9.89±0.92	0.52±0.33	96.31±2.82

In vitro dissolution profile

The dissolution studies conducted for prepared matrix tablets of sulfasalazine containing natural rate retard polymers and different concentrations Eudragit-S 100 as enteric polymer at different pH conditions for 24 hrs. From the above formulations F1-F8, F7 formulation contain pectin based, controlled release polymer Carbopol was shown myrid significant rate release profile. At pH 1.2 (in the presence of simulated gastric fluid) the F7 formulation was released 18.8%, the same formulation in the presence of intestinal fluid (at pH 7.4) the percentage drug release was 28. 2% observed. Based on the above released profile, F7 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 F7 formulation containing Eudragit-S 100 of 5% concentration shown no drug released was observed in stomach. But in the region of small intestine the percentage was released only 5.6%. There after the percentage drug released was gradually increased from large intestine to targeted site, it was found that 24.8% to 95.8% within 24 hrs.

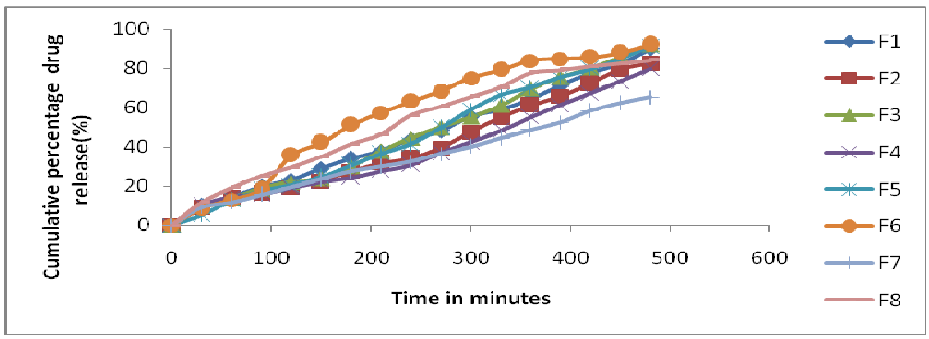

Figure 3
In-vitro dissolution profile of Sulfasalazine matrix tablets (F1-F8) Kinetic studies.

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 F7 with different concentrations of Eudragit-S 100 were shown in Table 4. The coefficients of regression were in a range between 0.961 to 0.976 (Zero order), 0.836 to 0.907 (First order), 0.798 to 0.826(Higuchi) and 0.825 to 0.883 (Peppas).

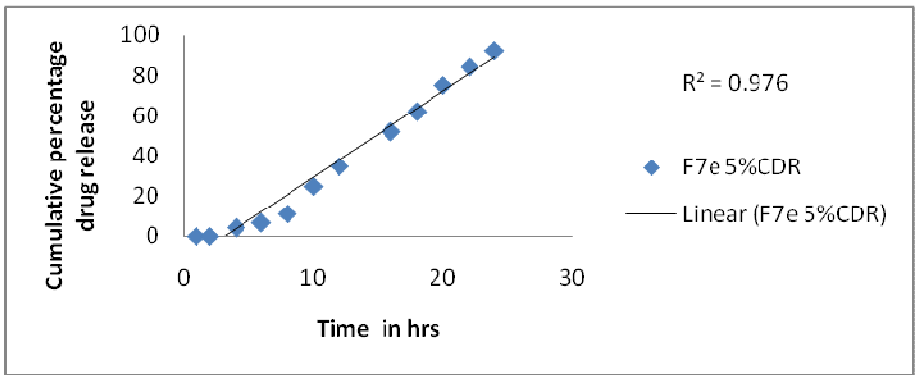

Figure 4
Zero order plot of Sulfasalazine optimized formulation (F7)

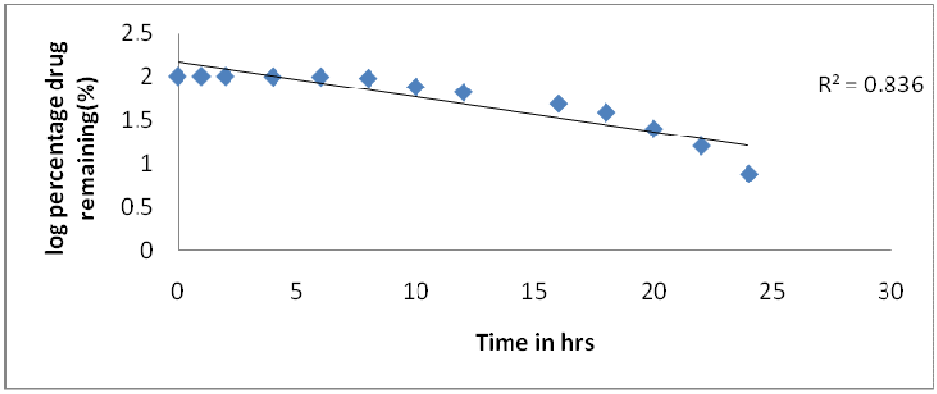

Figure 5
First order of Sulfasalazine optimized formulation (F7)

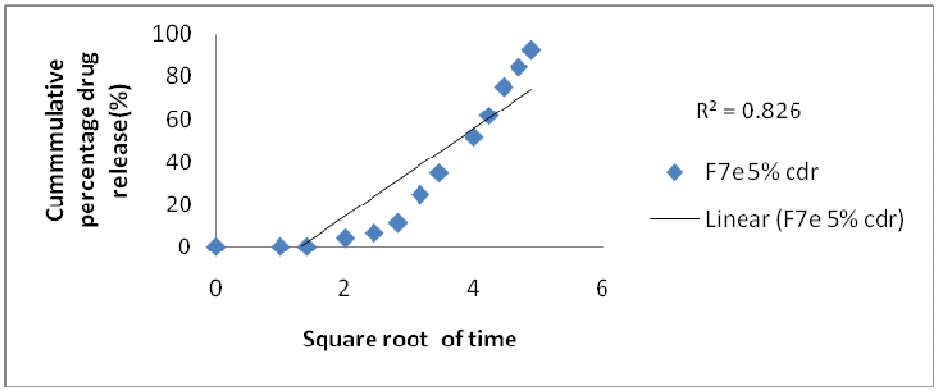

Figure 6
Higuchi plot of Sulfasalazine optimized formulation (F7)

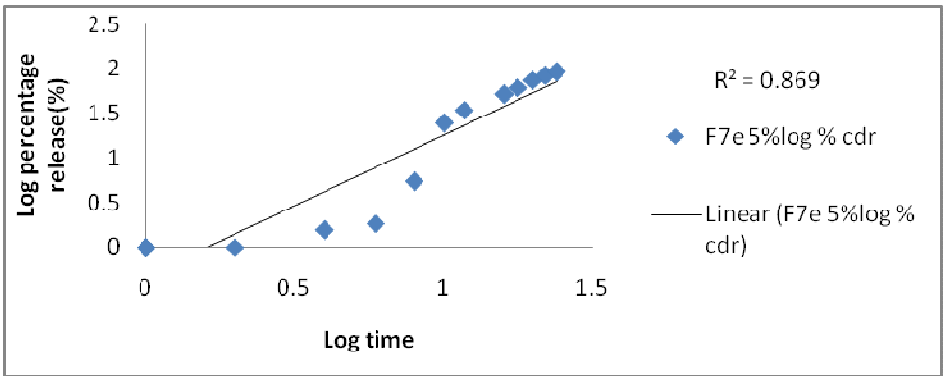

Figure 7
Korsmeyerpeppas of Sulfasalazine optimized formulation (F7)

The n value for F7 enteric coated was found to be >0.89, which meant that the mechanism of release for F7 enteric coated was Super case-II transport mechanism of drug release and best fit model was Korsmeyer-Peppas. The n value for all formulations was in the range of 1.00 to 1.19 indicating Super case-II transport mechanism. Overall, the release mechanisms from these optimized enteric coated tablets of sulfasalazine 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	Korsmeyerpeppas	n values
F7e (1%)	0.961	0.907	0.798	0.825	1.00
F7e (3%)	0.961	0.876	0.798	0.856	1.15
F7e (5%)	0.976	0.836	0.826	0.869	1.19
F7e (7%)	0.965	0.904	0.807	0.883	1.12

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 Sulfasalazine 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 Sulfasalazine different formulations (F1–F8) were prepared. All the prepared tablets were evaluated for post compression parameters such as hardness, thickness, weight variation, drug content uniformity and *in-vitro* drug release. The optimized formulation (F7) has shown desired release profile of 96.2% in 24 h. The data obtained are fitting to various kinetic models; the optimized formulation (F7) shown (r^2) value of 0.991 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 F7 formulation has met objective of the present study, drug release, patient convenience and cost effectiveness as a twice a day dose of the drug.

REFERENCES

1. Ashford M, Fell JT,Attwood D, Sharma H, Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon; Journal of Control Release, 1993; 26:213-220.
2. Krishnaiah YS, Satyanarayana S, Prasad YV. Studies of guar gum compression-coated 5-aminosalicylic acid tablets for colon-specific drug delivery; Drug Development and Industrial Pharmacy. 1999; 25; 651-657.
3. Raghavendrarao N G, Suryakar V B. Formulation and evaluation of montelukast sodium mucoadhesivebuccal patches for chronic asthma attacks; International Journal of Pharma and Bio Sciences. 2010;1(2):1-14.
4. Ahmad MZ, Akhter S, Ahmad I, Rahman M, Anwar M, Jain GK, et al. Development of polysaccharide colon targeted drug delivery system: design and evaluation of Assam Bora rice starch based matrix tablet. Current Drug Delivery. 2011 Sep; 8(5):575-81.
5. Ganesh G.N.K., Sureshkumar R, Jawahar N, Senthil V, Nagasamy Venkatesh D, et al.

Preparation and Evaluation of Sustained Release Matrix Tablet of Diclofenac Sodium using Natural Polymer/ Journal of Pharmaceutical Sciences and Research.2010; 2(6):360-368.

6. Lenaerts VM, Gurny R. Gastrointestinal tract – physiological variables affecting the performance of oral sustained release dosage forms; Bioadhesive Drug Delivery Systems, Boca Raton, FL, CRC Press. 1990.
7. Sharma V. Floating drug delivery system a novel approach to combatregional variability: A Review. International Journal of Pharmacy and Pharmaceutical Science. 2009; 8(2): 134-167.
8. Indian Pharmacopoeia. Government of India, Ministry of Health and Family Welfare, The Controller of Publications, New Delhi. 2007; Vol II, 1358-1359.
9. Lachman L, Liberman HA. The Theory and Practice of Industrial Pharmacy. 3ed, Bombay, Varghese Publications, 1987; 293-294.
10. Ramprasd YV, Krishnaiah YS, Satyanarayana S In vitro evaluation of guar gum as a carrier for colon-specific drug delivery; Journal of controlled release. 1998; 12(59):281-287.
11. Ramprasd YV, Krishnaiah YS, Satyanarayana S Studies of guar gum compression-coated 5-aminosalicylic acid tablets for colon-specific drug delivery; Drug development and industrial pharmacy. 1999; 25(5): 651-657.
12. Krishnaiah YS, Ramprasad YV, Satyanarayana S, Seethadevi A, Nageswarrao L Bhaskar P, Karthikeyan RRS. Guar gum as a carrier for colon specific delivery; Influence of metronidazole and tinidazole on in vitro release of albendazole from guar gum matrix tablets. Journal of pharmaceutical sciences; 2001; 4(3):235-243.
13. Divya A, Kavitha K, Rupesh Kumar M, Dakshayani S, Jagadeesh Singh SD. Bilayer tablets: An overview. Journal of Applied Pharmaceutical Science; 2011: 01(8):43-47.
14. Shirwaikar AA, Srinatha A. Sustained release bi-layered tablets of diltiazem hydrochloride using insoluble matrix system. Indian Journal of Pharmaceutical Sciences; 2004; 6(4): 433-437.