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## Formulation and in Vivo Evaluation of Sulfasalazine Tablets for Colon Targeting Using Design of Experiment

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### ABSTRACT

The aim of the study was to develop colon targeted tablets of Sulfasalazine (SSZ) by wet granulation method using  $3^3$  Response surface method with design of experiment software and Eudragit RS 100, Eudragit RL 100-55, Ethyl cellulose and PVP K-30 as pH dependent polymers. All the formulations (F1 to F27) were evaluated for the physicochemical parameters and were subjected to *in vitro* drug release studies. The amount of Sulfasalazine released from tablets at different time intervals was estimated by UV spectrophotometer. The formulation F17 shown  $98.21 \pm 1.15$  of Sulfasalazine after 24 h, whereas marketed product drug release was  $96.21 \pm 1.87$  after 1 h. The results of the study showed that formulation F17 is the best formulation on the basis of drug release and other evaluation parameters. From *in vivo* bioavailability studies, after oral administration of colon targeted tablet containing 500 mg Sulfasalazine, the  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-\infty}$  of optimized formulation and marketed product was found to be  $684.31 \pm 4.03$  ng/mL,  $6.01 \pm 0.04$  h,  $4525.12 \pm 2.02$  ng\*h/ mL and  $702.26 \pm 3.23$  ng/mL,  $1.50 \pm 0.01$ h,  $3335.18 \pm 2.02$  ng\*h/mL respectively.  $C_{max}$ ,  $T_{max}$  and AUC values of optimized formulation were found to be significantly higher than of marketed product. The pH dependent system is a promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of Sulfasalazine in the effective management of colon related diseases.

**Keywords:** Sulfasalazine, Colon targeting, Crohn's disease, Eudragit, pH dependent polymers, Pharmacokinetic parameters.

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## INTRODUCTION

Today, colon specific drug delivery is challenging task to pharmaceutical technologists. Therapeutic advantages of targeting drug to the diseased organ include a) The ability to cut down the conventional dose b) Reduced the incidence of adverse side effects and c) Delivery of drug in its intact form as close as possible to the target sites [1].

The most critical challenge in Colon targeted drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine [2, 3]. To develop a reliable colonic drug delivery system, the transit time of dosage forms through the gastrointestinal (GI) tract needs to be understood very well. The transit of per orally administered formulation through the GI tract is highly variable and depends on various factors. For example, factors like disease state of the lumen (diarrhea, diabetes, peptic ulcer etc) concomitant administration of other drugs (domperidone, cisapride, metoclopramide etc), body posture (vertical or supine) and food type (fat and protein content) can influence the gastric emptying rate [4].

Sulfasalazine, sold under the trade name Azulfidine among others, is a medication used to treat arthritis, ulcerative, and Crohn's disease [5]. It is often considered as a first line treatment in rheumatoid arthritis [6]. It is taken by mouth. It belongs to a class of drugs called sulfa drugs and is used in the treatment of rheumatoid arthritis (RA) and some other autoimmune conditions. Sulfasalazine is in the disease-modifying antirheumatic drugs (DMARDs) family of medications. It is unclear exactly how it works but is broken down into sulfapyridine and 5-aminosalicylic acid [7]. The present work deals with the preparation and *in vivo* evaluation of colon targeted delivery systems containing Sulfasalazine using pH dependent systems with different grades of polymers.

## MATERIALS AND METHOD

Sulfasalazine was generous gift sample from Valens molecules Pvt. Ltd, Hyderabad. Eudragit RL 100, Eudragit RL 100-55, HPMC K4M and EC were obtained from Aurobindo Pharma Ltd, Hyderabad. All other chemicals and solvents are of analytical grade.

### **Preparation of colon tablets of sulfasalazine**

Twenty seven formulations (F1-F27) were prepared by wet granulation method using 3<sup>3</sup> Response surface methods (3 variables and 3 levels of polymers) by using Design of experiment software with polymers like Eudragit RS 100, Eudragit RL 100-55 and Ethyl Cellulose (Table 1). All the formulations were varied in concentration of polymers, magnesium stearate constituted in all the formulations. All the ingredients were passed through sieve no. 85# and were mixed uniformly.

Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in Isopropyl alcohol). The wet mass was passed through sieve no. 12# and dried at 45<sup>0</sup>C for 2 h. Dried granules were sized by sieve no.18# and add magnesium stearate and talc [8]. Granules obtained were compressed with 10 mm flat punch (Cadmach, Ahmedabad, India).

**Table 1: Composition of Sulfasalazine tablets**

S.NO	Sulfasalazine	Eudragit RS 100	Eudragit RL 100-55	EC	PVP K-30	DCP	Mg Stearate
F1	500	35	28	63	16	51	7
F2	500	49	28	63	16	37	7
F3	500	35	42	56	16	44	7
F4	500	42	28	63	16	44	7
F5	500	35	42	63	16	37	7
F6	500	49	28	56	16	44	7
F7	500	35	42	56	16	44	7
F8	500	35	42	63	16	35	7
F9	500	35	42	49	16	53	7
F10	500	49	35	63	16	31	7
F11	500	42	28	49	16	58	7
F12	500	42	42	49	16	44	7
F13	500	42	35	63	16	37	7
F14	500	42	35	56	16	44	7
F15	500	42	35	49	16	51	7
F16	500	42	28	49	16	58	7
F17	500	49	42	56	16	30	7
F18	500	42	42	56	16	37	7
F19	500	49	28	49	16	51	7
F20	500	42	42	63	16	30	7
F21	500	49	35	63	16	30	7
F22	500	49	35	49	16	44	7
F23	500	49	42	49	16	37	7
F24	500	35	35	49	16	58	7
F25	500	49	35	49	16	44	7
F26	500	49	42	63	16	23	7
F27	500	42	35	56	16	44	7

**\*Total weight of the tablet is 700mg**

### Introduction to Design of Experiments (DOE)

DOE is an essential piece of the reliability program pie. It plays an important role in Design For Reliability (DFR) programs, allowing the simultaneous investigation of the effects of various factors and thereby facilitating design optimization. This article introduces the concept of DOE. Future articles will cover more DOE fundamentals in addition to applications and discussion of DOE analyses accomplished with a ReliaSoft software product [9, 10].

## Evaluation Tests

### Evaluation of post compression parameters

Different evaluation parameters like Weight variation [11], Thicknesses [12], Hardness [13], Friability [14], Content Uniformity [15] and *In Vitro* Swelling Studies [16] were conducted.

### *In Vitro* Drug Dissolution Study

*In vitro* drug release studies for developed sulfasalazine tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml of acidic buffer pH 1.2 (first 2 h), Phosphate buffer pH6.8 (next 4 h) and Phosphate buffer pH 7.2 at  $37 \pm 0.5^{\circ}\text{C}$  temperature with 100 rpm. The amount of drug release was determined at different time intervals upto 24h by UV visible spectrophotometer (Shimadzu UV 1800) at 246nm [17].

### Stability studies

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

### Pharmacokinetic studies of Sulfasalazine

#### Animal Preparation

Male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature  $25^{\circ}\text{C}$ , Relative Humidity 45% and 12 h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee NO: 1970/PO/RE/S/17/CPCSEA.

#### *In vivo* study design

The rabbits were randomly divided into two groups each group contains three animals. The group A was received prepared Sulfasalazine optimized tablets (500 mg), marketed product (500 mg) was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24 h post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5 min to 10 min and stored frozen at  $-20^{\circ}\text{C}$  until analysis [18].

### HPLC study

The estimation was carried out by using Qualisil BDS C18 (250×4.6 mm, 5µm) column with mobile phase containing separation was achieved using a reversed–phase column (4.6 x 150 mm, 5 µm) C18, a mobile phase comprising Acetonitrile: Methanol: 20 mM phosphate buffer (0.2 % TEA, pH 4.5) (50:10:40, v/v/v) and UV detection at 210 nm. Internal standard methotrexate was used. The peaks obtained were sharp with retention times of Sulfasalazine and methotrexate were 4.2 min and 2.3 min respectively. Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature.

### Pharmacokinetic analysis

The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with  $p < 0.05$  was considered statistically significant.

## RESULTS AND DISCUSSION

### Evaluation parameters of Sulfasalazine tablets

The prepared tablets were evaluated for different physicochemical properties and the results are found to be within the pharmacopoeial limits, which depicted in Table 2.

The Swelling study of colon sulfasalazine tablets was given in Table 2, showed that the swelling index of the tablet increases with increase in time upto 12 h, this may be attributed to the fact that the erosion of ethyl cellulose. This indicates that the drug will remain in intestinal region till drug is released completely from the delivery system and promotes evacuation after its release.

**Table 2: Physico-chemical parameters of sulfasalazine tablets**

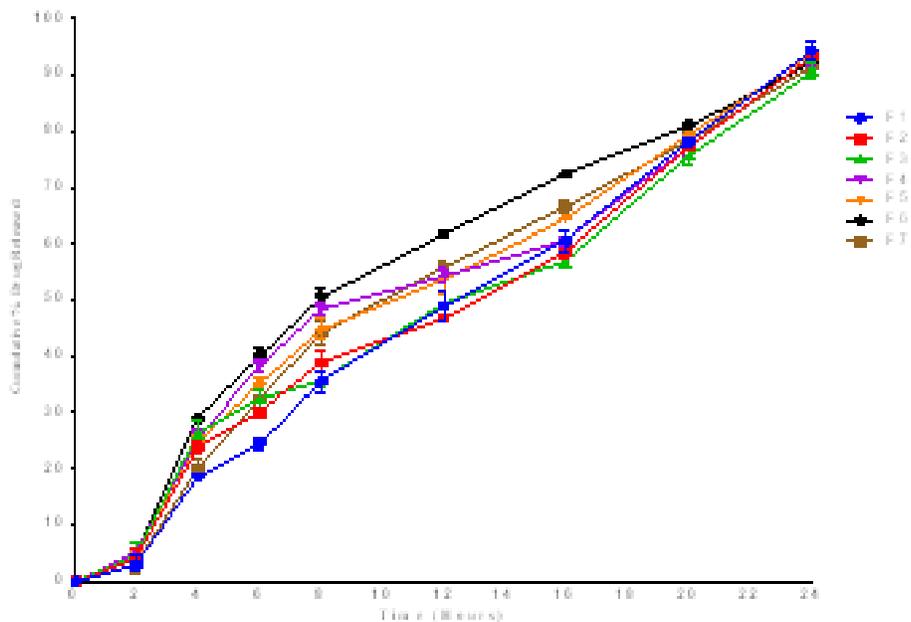
F. No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm <sup>2</sup> )	#Friability (%)	#Content uniformity (%)	#Swelling index (%)
F1	700.12±0.20	8.1±1.04	7.1±0.13	0.51±0.08	97.23±1.23	88±0.27
F2	699.23±0.24	8.0±1.16	7.0±0.33	0.54±0.09	98.04±1.03	87±0.53
F3	698.08±0.15	8.1±1.05	7.3±0.13	0.63±0.07	96.56±0.94	86±0.51

F4	701.09±0.70	8.2±1.09	7.2±0.10	0.56±0.05	97.11±0.63	86±0.93
F5	701.89±0.50	8.1±1.37	7.1±0.10	0.61±0.07	95.23±0.81	85±0.43
F6	700.34±0.20	8.2±1.11	7.2±0.10	0.67±0.09	96.45±0.32	80±1.04
F7	700.23±0.60	8.0±1.61	7.0±0.15	0.54±0.02	95.11±1.17	88±0.64
F8	699.12±0.50	8.2±1.03	7.2±0.15	0.67±0.02	97.23±0.45	80±0.60
F9	700.23±0.48	8.2±0.45	7.2±0.19	0.56±0.02	97.13±1.17	89±0.64
F10	700.24±0.20	8.1±0.25	7.1±0.21	0.77±0.07	96.23±0.49	85±0.65
F11	701.45±0.97	8.1±0.70	7.4±0.10	0.76±0.05	98.97±0.95	84±0.75
F12	702.03±0.54	8.4±0.25	7.6±0.15	0.73±0.08	98.45±0.35	86±0.51
F13	701.04±0.30	8.5±0.60	6.8±0.18	0.52±0.09	96.85±0.24	94±0.78
F14	698.23±0.35	8.1±0.56	7.2±0.10	0.72±0.02	96.18±0.13	81±0.83
F15	699.34±0.25	8.5±0.70	7.6±0.08	0.71±0.20	97.25±1.21	89±0.63
F16	701.12±0.55	8.1±0.40	7.2±0.21	0.78±0.9	97.45±1.30	86±0.43
F17	700.23±0.50	8.3±0.17	7.7±0.04	0.51±0.04	99.94±1.31	97±0.97
F18	701.67±0.30	8.2±0.40	7.6±0.14	0.82±0.03	98.56±1.36	94±0.87
F19	699.13±0.45	8.0±0.17	7.0±0.12	0.84±0.01	97.29±1.31	89±1.13
F20	699.45±0.55	8.3±0.96	7.5±0.10	0.63±0.03	97.18±1.36	88±1.23
F21	698.12±0.70	8.2±0.50	7.3±0.12	0.66±0.03	96.27±1.30	90±1.27
F22	701.45±0.80	8.0±0.63	7.0±0.10	0.72±0.015	96.34±1.16	91±0.83
F23	700.23±0.55	8.3±0.78	7.8±0.17	0.76±0.04	96.14±1.46	87±1.21
F24	700.12±0.60	8.4±0.86	7.7±0.14	0.73±0.06	97.16±0.56	91±0.93
F25	699.14±0.75	8.1±0.57	7.6±0.15	0.67±0.07	96.23±0.84	93±0.92
F26	700.18±0.15	8.3±0.63	7.7±0.18	0.72±0.03	97.34±1.16	95±0.18
F27	700.23±0.75	8.4±0.98	6.9±0.05	0.89±0.04	97.10±1.11	93±1.25

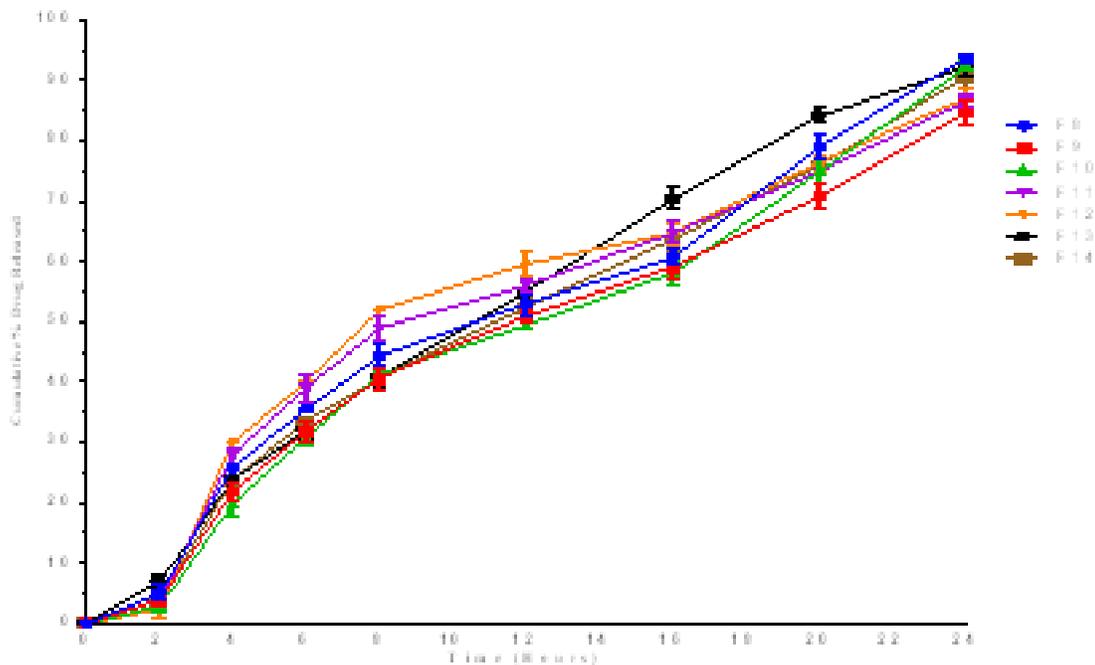
\*Values are expressed in mean± SD :( n=20); #Values are expressed in mean± SD :( n=3)

### ***In vitro* dissolution studies of Sulfasalazine colon targeted tablets**

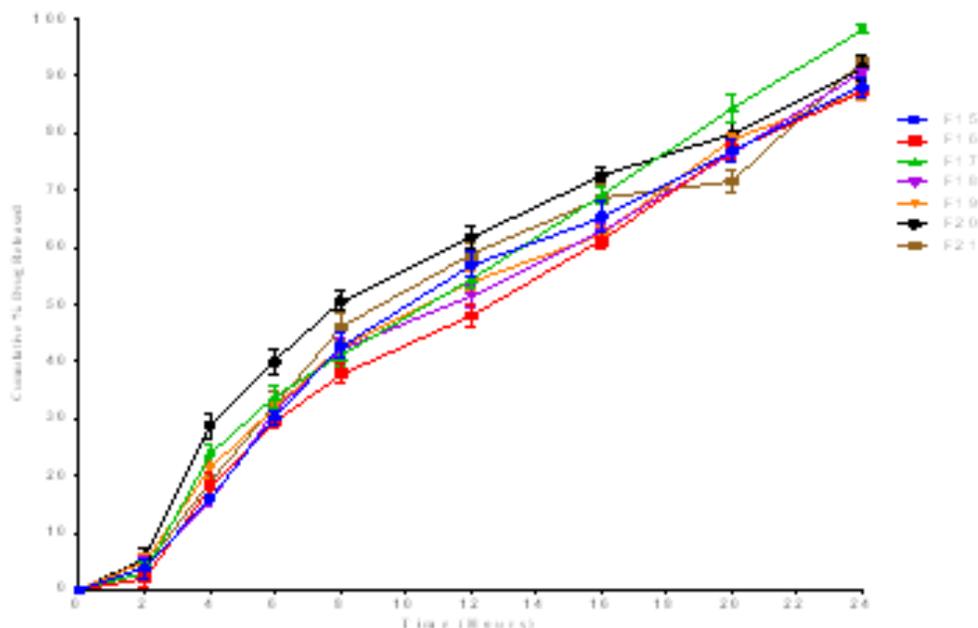
The *in vitro* drug release studies of 27 different formulations of Sulfasalazine along with marketed product were carried out and the results are depicted in Figure 1, 2, 3, 4. The highest drug release was found in the formulation F17 i.e. 98.21±1.15% within 24 h. F17 was found to be optimized formulation based on the dissolution and other evaluation parameters. The *in vitro* drug release profile from marketed conventional tablet was found to be 96.21±1.87% within 60 min.



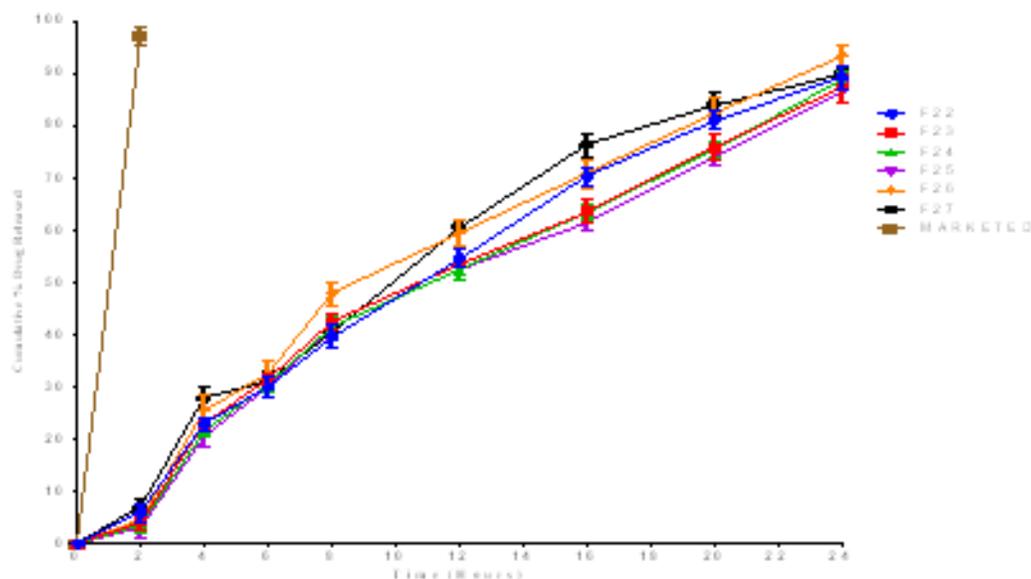
**Figure 1:** *In vitro* Drug Release Profile for colon Sulfasalazine tablets F1-F7



**Figure 2:** *In vitro* Drug Release Profile for sulfasalazine tablets F8-F14



**Figure 3: *In vitro* Drug Release Profile for sulfasalazine tablets F15-F21**



**Figure 4: *In vitro* Drug Release Profile for Sulfasalazine tablets F22-F27 with marketed product**

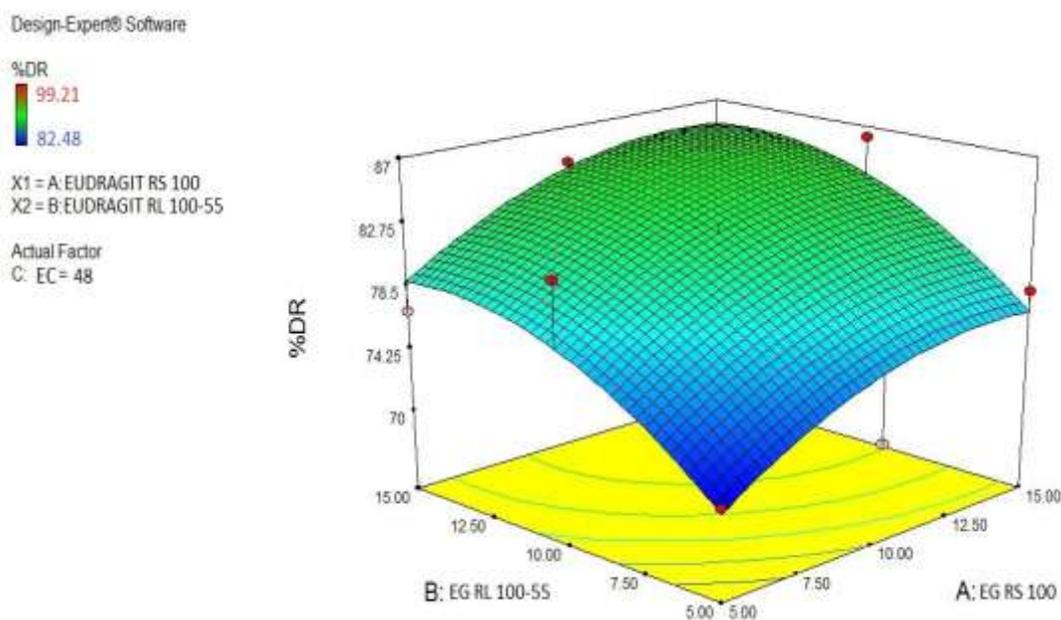
### Design of Experiment

This method is mainly used to explain the effect of one factor on other factor, to know whether this effect is significant or not, if significant how it influence the response. In this present work the effect of one factor (Ethyl Cellulose) on other two factors (Eudragit RS 100, Eudragit RL 100-55) was studied.

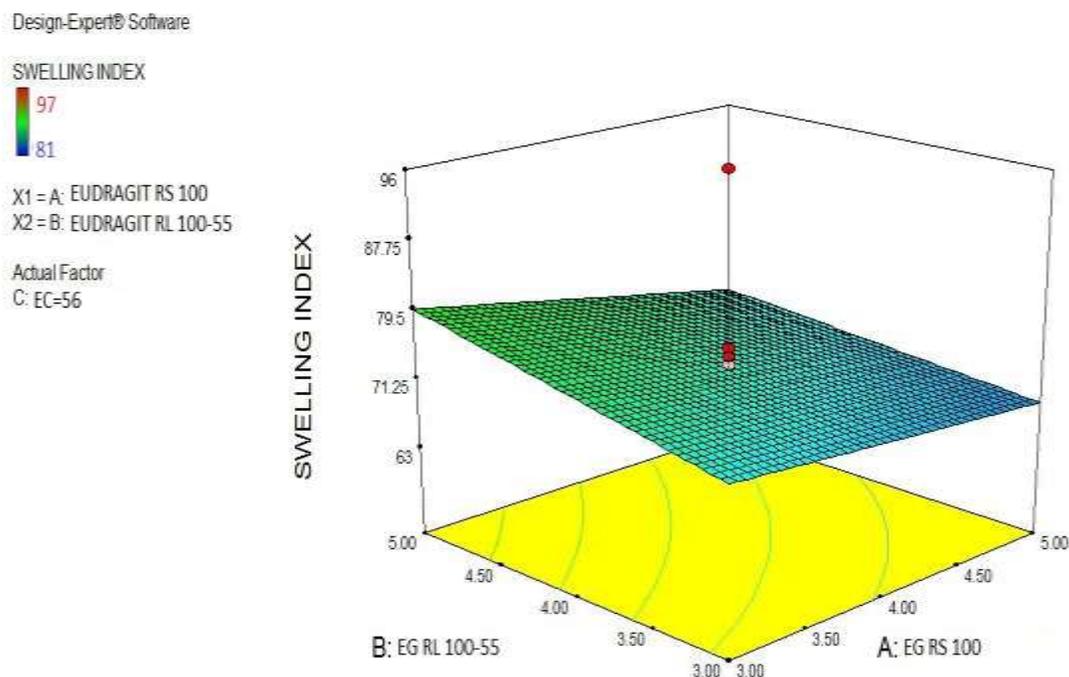
In the above graph the effect of ethyl cellulose on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of ethyl cellulose on % cumulative drug release. The formulations with all 3 factors shown % cumulative drug release in between 82.48-98.21 but when ethyl cellulose is in low concentrations from the formulations the maximum % CDR is near 82.48. This is the effect of factor (Ethyl Cellulose) on response (Figure 5).

There is a negligible effect on Swelling Index of formulations because all formulations have excellent Swelling property and there is slightly influence on Swelling Index by ethyl cellulose (Figure 6).

After subjecting the optimized formulation (F17) to the accelerated stability studies, there were no major changes observed in drug content, *in Vitro* drug release, Swelling index and hardness of the formulation, hence the formulation was found to be stable.



**Figure 5: Response surface plot showing the influence of amount of polymer on the release profile of sulfasalazine colon tablets for Cumulative % Drug Released.**



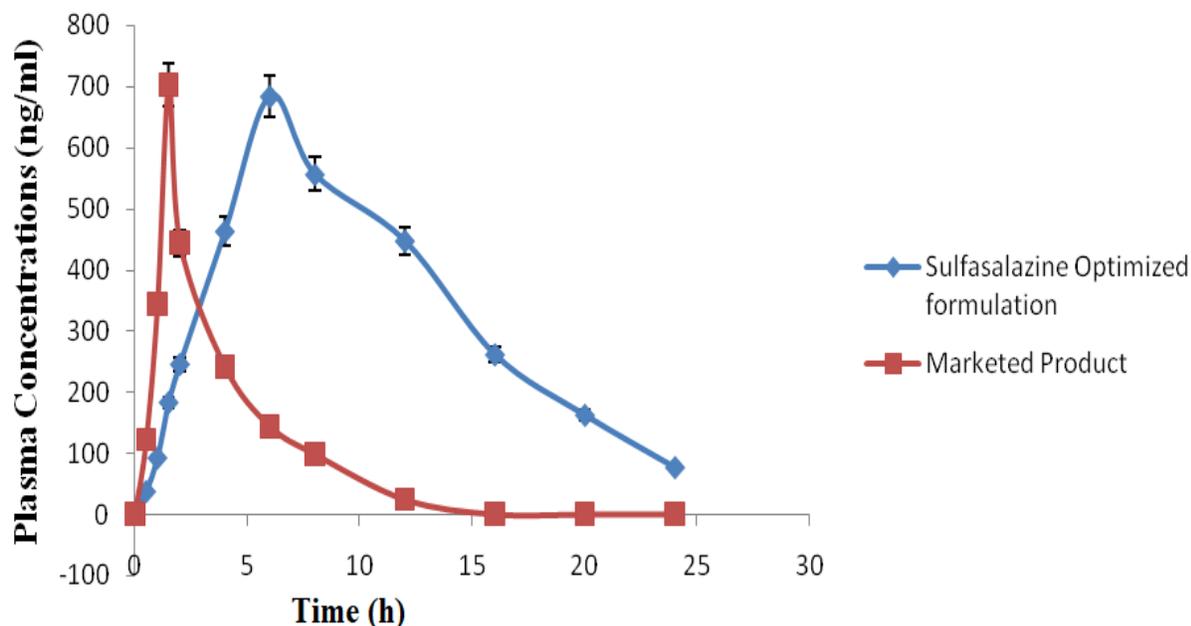
**Figure 6: Response surface plot showing the influence of amount of polymer on Swelling Index of sulfasalazine colon matrix tablets**

### Bioavailability Parameters

Mean plasma concentration profiles of prepared Sulfasalazine optimized formulation and Marketed product are presented in Figure 7. Sulfasalazine optimized formulation exhibited as sustained release *in vivo* when compared with Marketed product. All the pharmacokinetics parameters displayed in Table 3. Sulfasalazine reference drug was available in plasma within in 2 h after its oral administration. The  $T_{max}$  of the optimized formulation was significantly different ( $p < 0.05$ ) from that of the marketed product. Low  $T_{max}$  value for the reference drug ( $1.50 \pm 0.01$  h) indicates rapid absorption while the higher  $T_{max}$  of the test drug ( $6.01 \pm 0.04$  h) suggests slower absorption. This delayed absorption of test preparation is most likely due to the sustained release of the drug. On the other hand, the  $C_{max}$  of reference formulation was significantly different from the test preparation. The half-life of the reference preparation was low which indicates rapid removal of the drug from plasma. This was also supported by the high elimination rate constant value. On the other hand, the test formulation exhibited higher half-life and low elimination rate constant values indicating slower drug disposition and prolonged effect. However, the  $AUC_{0-\infty}$  values for the two formulations were significantly different.

**Table 3: Comparison of pharmacokinetic parameters of Sulfasalazine Optimized formulation and Marketed product**

Parameters	Sulfasalazine optimized formulation	Marketed product
$C_{max}$ (ng/ml)	684.31±4.03	702.26±3.23
$AUC_{0-t}$ (ng*h/ml)	3286.12±1.01	2784.19±1.01
$AUC_{0-\infty}$ (ng*h/ml)	4525.12±2.02	3335.18±2.02
$T_{max}$ (h)	6.01±0.04	1.50±0.01
$t_{1/2}$ (h)	11.25±0.004	4.12±0.05
$K_{el}$ ( $h^{-1}$ )	0.0616±0.05	0.168±0.05

**Figure 7: Plasma Concentrations of Sulfasalazine optimized formulation and Marketed Product at different time intervals**

## SUMMARY AND CONCLUSION

In present work attempt was made to formulate and evaluate colon tablets of sulfasalazine. Twenty-seven formulations (F1-F27) were prepared by wet granulation method using  $3^3$  response surface method. All the physico-chemical properties of the formulations were within the limit. The formulation F17 was selected as optimized formulation because it showed minimum release in stomach (Acidic buffer pH 1.2) and small intestine (Phosphate buffer pH 6.8) and a maximize release in proximal colon (Phosphate buffer pH 7.2).

Among 27 formulations the formulations containing less amount of ethyl cellulose (EC) concentrations shown minimum amount of drug release as it retards the drug release and maximum drug was released from the formulation F17 within 24 h (98.21±1.15). From in vivo bioavailability

studies, after oral administration of colon targeted tablet containing 500 mg Sulfasalazine, the  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-\infty}$  of optimized formulation and marketed product was found to be  $684.31 \pm 4.03$  ng/mL,  $6.01 \pm 0.04$  h,  $4525.12 \pm 2.02$  ng\*h/ mL and  $702.26 \pm 3.23$  ng/mL,  $1.50 \pm 0.01$  h,  $3335.18 \pm 2.02$  ng\*h/ mL respectively.  $C_{max}$ ,  $T_{max}$  and AUC values of optimized formulation were found to be significantly higher than of marketed product. The pH dependent system is a promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of Sulfasalazine in the effective management of colon related diseases. From this study it can be concluded that the colon tablets of Sulfasalazine formulations can be an innovative and promising approach for the delivery of sulfasalazine for the treatment of ulcerative colitis and Crohn's disease.

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