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# Studies on Design, Development and Characterization of Colon Targeted Drug Delivery of Mesalamine using Coexcipient polymer

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**Abstract:- The aim of this study was to develop a colon-targeted drug delivery system using a co-excipient prepared by the spray drying technique. The co-excipients used in the formulation containing blend of polymers for colonic release, the drug used in the study was Mesalamine, which is a non-steroidal anti-inflammatory drug commonly used in the treatment of various inflammatory conditions. Mesalamine was directly compressed with spray dried Coexcipient. In vitro dissolution studies of Tablets were shown that more than 20 % drug release takes place in first 5 hours. Hence to maintain lag time and to minimize drug release in upper GIT Tablet was further coated with functional enteric coating with Instacoat EEN which is a dry powder for reconstitution of methacrylic acid copolymer in a hydroalcoholic solvent system which provide enteric protection at minimum weight gain to maintain less than 10 % drug release with lag time of 5 hours. Tablets prepared according to optimum Coexcipient concentration and coated with Instacoat EEN to achieve lag time of 5 hr with drug release less than 10 % of mesalamine. The in vitro drug release studies were carried out in simulated gastric and intestinal fluids and a pH 7.4 phosphate buffer. The release profile of the formulation showed a sustained drug release in the intestinal fluid, indicating the colon-targeted drug delivery of the formulation. Overall, the co-excipient-based formulation prepared by the spray drying technique showed promising results in terms of its physicochemical properties and colon-targeted drug delivery. This study provides a foundation for the development of novel drug delivery systems for the treatment of various inflammatory conditions affecting the colon.**

***Keywords:-*** *Colon targeting, pH dependent polymers, Spray drying, Coexcipient, Mesalamine.*

## I. INTRODUCTION

Colon-targeted drug delivery has been the subject of extensive research owing to its numerous advantages over conventional drug delivery systems. The major benefit of colon-specific drug delivery is that it enables the delivery of drugs specifically to the colon, thereby reducing the dose and frequency of drug administration, and minimizing systemic side effects. In addition, colon-targeted drug delivery is useful for the treatment of various diseases such as ulcerative colitis, inflammatory bowel disease, colorectal cancer, and other gastrointestinal disorders. Coexcipient polymers are an emerging class of polymers that have attracted attention in colon-targeted drug delivery. Coexcipient polymers act as a carrier or matrix for the drug, and they can also modify the drug release properties by controlling the swelling and erosion of the polymer matrix. The use of Coexcipient polymers in colon-specific drug delivery systems has several advantages such as improved drug stability, enhanced drug bioavailability, and reduced toxicity. Considering these findings, the current study aims to develop and evaluate a CTDDS formulation using Coexcipient by the spray drying technique. The coexcipients will be carefully selected based on their physicochemical properties and their ability to enhance drug release in the colon region. The developed formulation will be evaluated for its physicochemical properties, in vitro and drug release, and pharmacokinetic parameters, to assess its potential for targeted delivery to the colon region. Overall, the findings of this study have the potential to contribute to the development of effective CTDDS formulations using Coexcipient by spray drying technique, which can improve therapeutic outcome and reduce premature drug release. Several studies have reported the successful formulation and evaluation of colon-targeted drug delivery systems using Coexcipient polymers. For example, Chen et al. (2020). Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that affects millions of people worldwide. The two major forms of IBD are Crohn's disease and ulcerative colitis, which are characterized by symptoms such as abdominal pain, diarrhoea, rectal bleeding, and weight loss. The treatment of IBD typically involves the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as mesalamine, which is effective in controlling the inflammation associated with IBD. However, the oral delivery of mesalamine is associated with several limitations, including poor bioavailability, low solubility, and a short residence time in the colon. Therefore, the development of an effective colon-targeted drug delivery system for mesalamine is essential for the treatment of IBD. Several approaches have been explored to achieve colon-targeted drug delivery, including pH-sensitive coatings, time-dependent coatings, and microbial-triggered systems. However, these approaches have several limitations such as variable colonic pH, unpredictable transit times, and variations in the microbial population of the colon. To overcome these limitations, the use of co-excipients has been investigated as a means of achieving colon-specific drug delivery. Co-excipients are typically polymers that are mixed with the drug to form a matrix that

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can control drug release by modulating the diffusion of the drug through the matrix. In this study, we aimed to develop a colon-targeted drug delivery system for mesalamine using a co-excipient polymer prepared by the spray-drying technique. The co-excipients used in the formulation included Eudragit RSPO, hydroxypropyl methylcellulose K15 (HPMC), PVP K 30, and MCC. These co-excipients were chosen based on their ability to provide pH-independent and time-dependent release of mesalamine in the colon. The spray-drying technique was chosen as the method of preparation because it is a simple and cost-effective technique that can produce uniform particles .The co-excipient was and mesalamine were directly compressed into tablets in one step.

## II. MATERIALS AND METHODS

### *A. Materials*

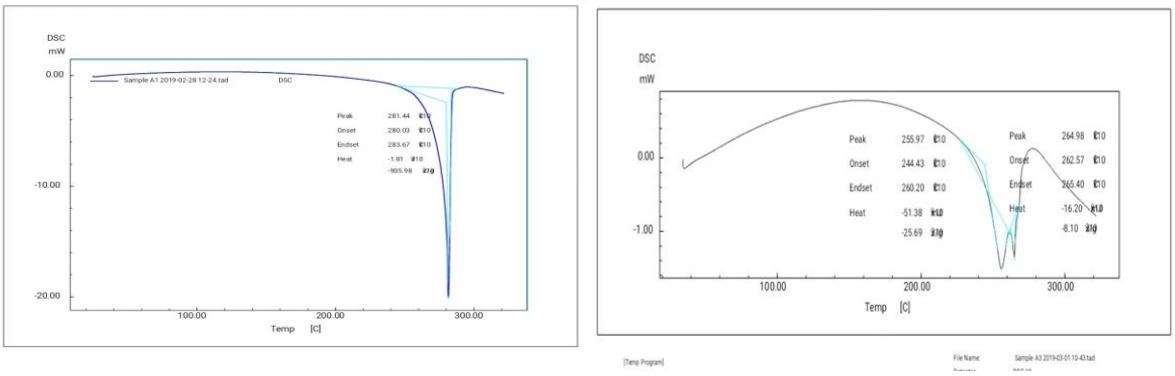
Mesalamine is obtained from the Lupin Pharma , Aurangabad, India.as a gift sample. All other chemicals were of analytical grade purchased from local suppliers.

### *B. Methods of Preparation of controlled release Coexcipient by spray drying*

- **Co-excipient by spray drying**: The co-excipient was prepared by the spray drying technique using Eudragit, HPMC, PVP and MCC in predetermined ratios. The ingredients were mixed well and dissolved in a suitable solvent system consisting of acetone and water. The solution was then sprayed using a spray dryer (Labultima) with the inlet temperature set at 60 °C and outlet temperature at 40 °C. The obtained co-excipient powder was stored in an airtight container for further use.
- **Preparation of Mesalamine tablets**: The optimized co-excipient was directly compressed with Mesalamine powder in a suitable ratio using a tablet compression machine. The tablets were then subjected to hardness testing and friability testing to ensure their mechanical strength and durability.
- **Enteric coating of Mesalamine tablets**: To achieve colon-specific drug delivery, the optimized tablets were coated with an enteric coating using Instacoat EEN, which is a dry powder for reconstitution of methacrylic acid copolymer in a hydroalcoholic solvent system. The coating was applied using a spray gun with the inlet temperature set at 50°C and outlet temperature at 30°C.
- **In vitro dissolution studies**: The in vitro dissolution studies were carried out using a dissolution apparatus in simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8), and pH 7.4 phosphate buffer. The dissolution profile of the tablets was analysed spectrophotometrically at 320 nm using a UV-visible spectrophotometer. The study was conducted for a period of 24 hours, and samples were collected at regular intervals.
- **Characterization of the formulation**: The optimized formulation was characterized for various parameters such as hardness, thickness, weight variation, friability and dissolution study. Stability studies were conducted under accelerated conditions of temperature and humidity to ensure the stability of the formulation over a period of 6 months.

Overall, the methodology described above was used to prepare and characterize a colon-targeted drug delivery system using a co-excipient polymer prepared by spray drying. The results obtained from this study provide a basis for the development of novel drug delivery systems for the treatment of various inflammatory conditions affecting the colon

- **Drug excipients compatibility study:** The drug-excipients interaction study was carried out by physical observation and also by using spectroscopy and DSC




( A ) ( B )

Fig. 1: DSC thermograms of A: pure mesalamine and B: drug: polymer physical mixture.

- **Development of directly compressible co-processed excipient by spray drying:** To optimize the spray drying process first three different diluents were selected dispersed in water (20% w/v) and spray dried. Spray drying of diluents was done by using processing parameters of spray dryer. Obtained spray dried diluents was dried and evaluated for micromeritic and post compression study.
- **Characterization of spray dried diluents:** In this stage, diluent for further process of co-excipient was selected among lactose, MCC and DCP. Those spray dried diluents were dried and evaluated for flow properties, moisture content, % yield and for post compression parameters. The results obtained from this evaluation were recorded in table.

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Table 1: Characterization of spray dried diluents

| Diluent | Evaluation parameters* | | | | | |
|---|---|---|---|---|---|---|
| | Spray dried yield (%) | Moisture content | Carr's Index (%) | Angle of repose (°) | Hardness (Kg/cm$^2$) | Friability (%) |
| **Lactose** | **14.44** | **2.41** | **16.39± 0.019** | **Poor** | **4.2±0.015** | **0.312 ±0.014** |
| **MCC** | **19.76** | **1.83** | **21.96± 0.091** | **Good** | **5.9±0.015** | **0.124 ±0.045** |
| **DCP** | **8.97** | **4.67** | **32.06± 0.017** | **Fair to pass** | **5.1±0.015** | **0.137 ±0.031** |

*All values are mean ± SD, n=3,

In this stage it was also found that there was less deposition of spray dried product in case of MCC, hence the spray dried yield was more. While spray dried yield were less in case of lactose and DCP as compared to MCC. Because of sticky nature of DCP and lactose, it got more deposition in drying chamber. High Carr's index reveals a tendency of powders to form bridges. It was also found that spray dried lactose and DCP had poor flow property, low spray dried percentage yield and more moisture content while spray dried MCC had shown good flow property, and less moisture content. Post-compression study was done on all three spray dried diluents. The placebo tablets were prepared and evaluated for friability and hardness. The optimization of the processing parameters of spray dryer was done on the basis of the results obtained in the above parameters and required % spray dried yield, moisture content and compressibility with highest desirability of 0.982 (max. 1). Hence, from desirability optimized spray dried parameters selected were as inlet temperature 100 °C, feed rate 5 rpm and atomization pressure 2 bar and these selected parameters were used for preparation of control release co-excipients for colon targeting . Hence from obtained results spray dried MCC had better flow than spray dried MCC and lactose selected further for development of co-excipient.

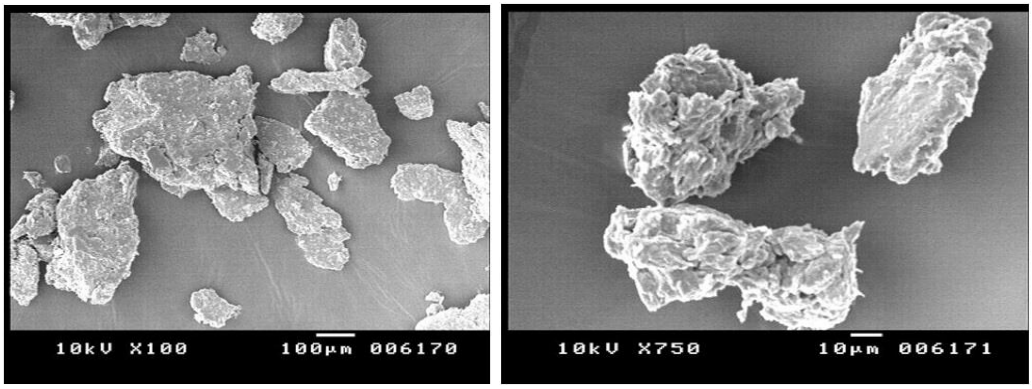


Fig. 2: SEM images Drug and of Co-processed excipient containing MCC, HPMC K15M and Eudragit RSPO.

Formulation of preliminary trial batches of Mesalamine control release matrix tablets using co-excipient for Colonic delivery:

In this step mesalamine was combined with co-excipient (B1-B16) batches to develop tablets by direct compression using rotary tablet compression machine (Karnavati, 8 station, 11 mm circular, concave faced).

Table 2: Post compression evaluation of Preliminary trial batches B1-B16

| Formulation code | Thickness (mm) | Hardness (Kg/cm$^2$) | Friability (%) | Content uniformity (mg) |
|---|---|---|---|---|
| B1 | 6.22 ±0.031 | 4.6±0.156 | 0.087 | 97.61±3.22 |
| B2 | 6.24 ±0.171 | 4.8±0.214 | 0.091 | 97.11±7.54 |
| B3 | 6.32 ±0.031 | 5.7±0.123 | 0.189 | 98.35±4.36 |
| B4 | 6.33 ±0.213 | 5.9±0.125 | 0.134 | 97.15±2.08 |
| B5 | 6.35 ±0.0450 | 4.4±0.135 | 0.165 | 98.36±3.68 |
| B6 | 6.26 ±0.034 | 4.6±0.312 | 0.189 | 98.36±6.26 |
| B7 | 6.23 ±0.098 | 5.3±0.087 | 0.241 | 97.36±2.84 |
| B8 | 6.26 ±0.064 | 5.6±0.324 | 0.197 | 97.36±4.56 |
| B9 | 6.19 ±0.064 | 5.1±0.098 | 0.188 | 98.87±4.21 |
| B10 | 6.33 ±0.014 | 5.2±0.074 | 0.146 | 97.65±5.40 |
| B11 | 6.27 ±0.084 | 6.0±0.068 | 0.219 | 98.87±4.27 |
| B12 | 6.25 ±0.018 | 6.5 ±0.071 | 0.086 | 97.67±4.88 |
| B13 | 6.28 ±0.094 | 5.4 ±0.081 | 0.124 | 98.73±3.58 |
| B14 | 6.22 ±0.031 | 6.1±0.156 | 0.087 | 97.61±4.10 |
| B15 | 6.24 ±0.171 | 6.8±0.214 | 0.091 | 97.11±4.62 |
| B16 | 6.22 ±0.031 | 6.7±0.123 | 0.189 | 98.35±3.24 |

*All values are mean ± SD, n=3,

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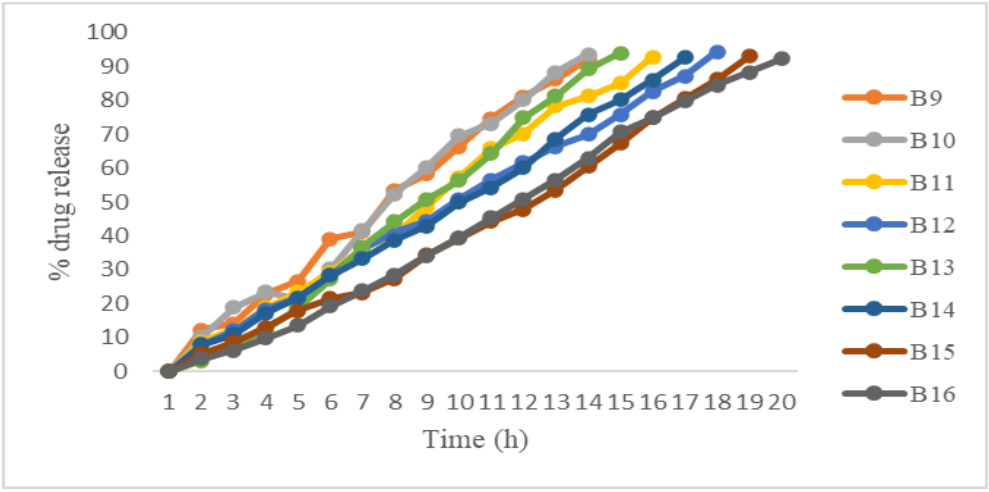
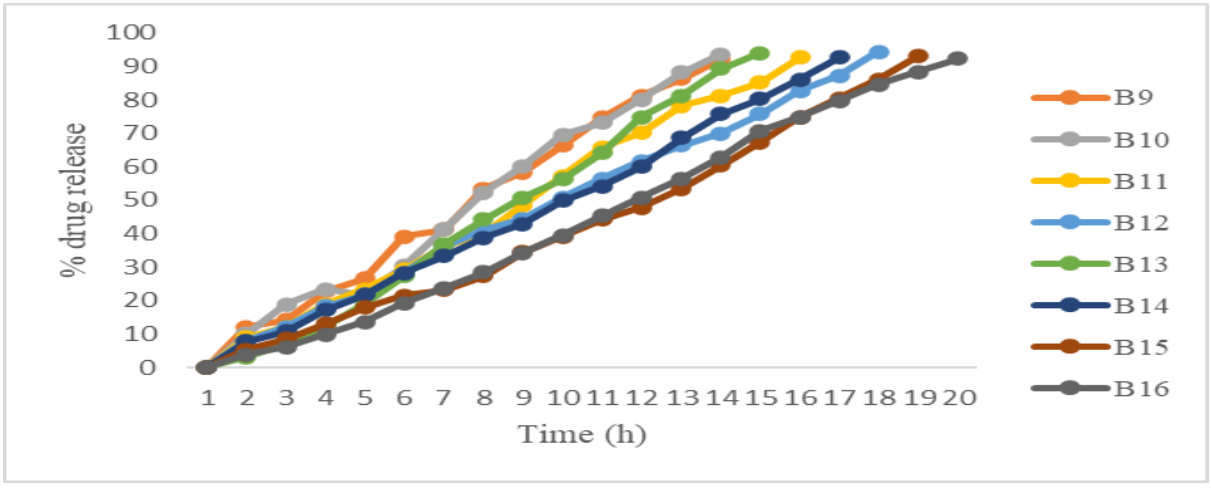



(B1-B8)




(B9-B16)

Fig. 3: % drug release of mesalamine from experimental trial batches

From results obtained as shown in table no 1, it was observed that formulations containing combination of Eudragit RSPO and HPMC K5M in co-excipient B1, B2,B3,B4, B5,B6,B7 and B8 showed complete drug release within 12 hrs. respectively which was not desirable. Trial batches B9, B10, B11 and B13 showed good release up to 14 hours. B12, B14, B15 and B16 showed satisfying controlled release of the drug up to 16, 15, 17, 18 hrs. respectively. This may be due to combination effect of release retardant pH independent polymer Eudragit RSPO and hydrophilic polymer HPMC K15M. The mechanism of drug release may be associated with the erosion and diffusion. Based in vitro drug release result batch B15 showed 90% drug release in 17 hrs. but there was more than 20% drug release takes place within first 5 hrs. Based on the above observations, batches B15 was selected for further study. Batch C1-C5 were developed by coating at different coating weight gain 1,2,3,4 and 5% to achieve less than 10% drug release in upto 5 hrs. and evaluated for in vitro drug release study.

## III. IN VITRO DRUG RELEASE STUDY OF MESALAMINE COATED TABLETS BATCHES (C1-C5):

*In vitro* drug release study of optimization batches was conducted in pH 1.2, 7.4 and 6.8 simulated to stomach, small intestine and colon respectively. Formulation showed lag time of 3, 4, 5, 5 and 6 h for C1, C2, C3, C4, C5 and C6 respectively. Formulation showed 94.36±3.68% drug release within 12 h, 95.64±3.73 drug release within 13 h, 96.48±3.90% drug release within 14 h, 97.32±4.84% drug release within 16 h and 96.32±3.92% drug release within 20 h for C1, C2, C3, C4, C5 and C6 respectively.

From the obtained data it was concluded that mesalamine matrix tablet using co-excipient containing Eudragit RSPO and HPMC K115M with outer functional coating of Instacoat EEN about 5% weight gain shows lag time of 5h and 90% of drug release within 20h which indicates that Instacoat EEN is suitable to maintain lag time and protect drug release in upper GIT. Because patients with IBD may show decrease in the pH value of small intestine and colon. So there might be the chances that the formulation travels down the distal colon and excreted in intact form without releasing the drug. So, it is necessary for

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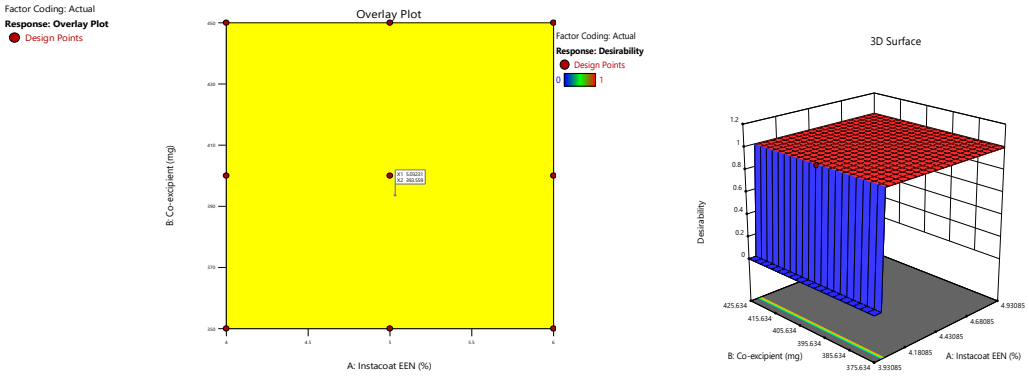
any formulation targeted at the proximal colon region that it should release the drug after a suitable lag time.

## IV. CHECKPOINT FORMULATIONS GENERATED BY SOFTWARE BASED ON DESIRABILITY

Three checkpoint or solution formulations were suggested by the software depending on its desirability factor with highest value (Table ). Checkpoint solution number one with 5.023% Instacoat EEN coating weight gain and 393.55 mg of co-excipient concentration was selected as optimum formulation with high desirability of 0.959 (Figure A & B).

Table 3: Checkpoint formulation generated by software for Mesalamine coated tablets using co-excipient

| Optimized formulation | X1 (%) | X2 (%) | $Q_5$ (Y1) | $Q_{90}$ (Y2) | Desirability | |
|---|---|---|---|---|---|---|
| E1 | 5.023 | 393.55 | 11.398 | 16.80 | 0.959 | **Selected** |
| E2 | 5.79 | 395.43 | 11.3518 | 16.32 | 0.955 | |
| E3 | 4.89 | 400.37 | 11.3025 | 16.40 | 0.954 | |




A: Overlay plot B: Desirab

Fig. 4: Optimized formulation generated by software

The final optimized formulation E1 software suggested solution batch was formulated and subjected for the drug release profile. The tablets prepared according to optimum co-excipient concentration and coated with Instacoat EEN to achieve lag time of 5 h with dru releas less than 10% of mesalamine at pH 1.2 and 7.4 for 2h and 3h respectively. Further in pH 6.8 medium drug release was in controlled manner for about 16 hrs. The drug release profile of suggested optimized batch is shown graphically in Figure .

Table 4: I*n vitro* drug release profiles for an optimized formulation and Marketed formulation

| Medium | Time (h) | % Cumulative drug release | |
|---|---|---|---|
| | | Optimized batch | Marketed |
| **pH 1.2** | 0 | 0 | 0 |
| | 1 | 0 | 5.3±0.42 |
| | 2 | 0 | 11.3±1.60 |
| **pH 7.4** | 3 | 0 | 19.2±1.04 |
| | 4 | 4.82±0.98 | 25.88±1.42 |
| | 5 | 8.48±2.22 | 32.86±2.33 |
| **pH 6.8** | 6 | 12.66±1.08 | 37.83±3.09 |
| | 7 | 18.64±2.66 | 49.36±3.91 |
| | 8 | 26.23±1.70 | 53.39±3.22 |
| | 9 | 32.22±2.28 | 57.22±5.18 |
| | 10 | 41.66±3.88 | 69.8±5.41 |
| | 11 | 48.28±4.30 | 75.19±4.87 |
| | 12 | 52.57±3.70 | 80.36±4.34 |
| | 13 | 57.64±3.98 | 89.87±5.49 |
| | 14 | 65.62±4.17 | 95.9±5.70 |
| | 15 | 74.43±5.80 | |
| | 16 | 82.23±5.18 | |
| | 17 | 88.89±5.20 | |
| | 18 | 93.65±6.08 | |

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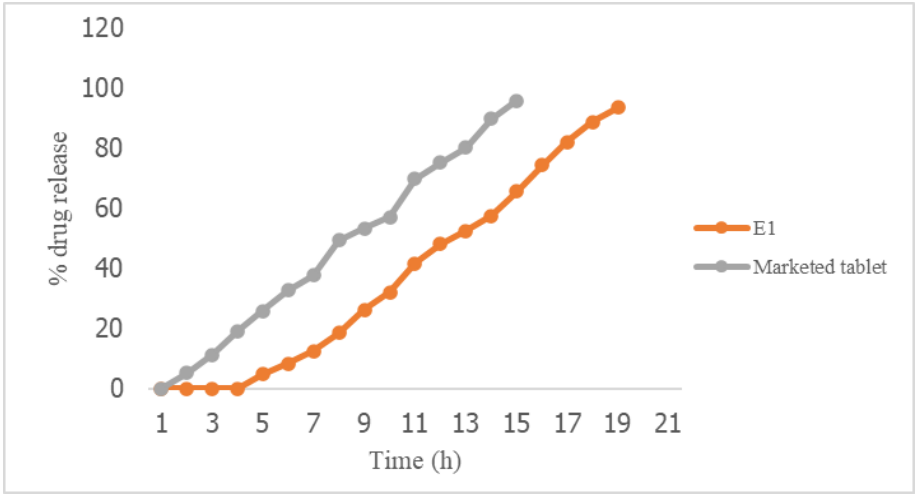


Fig. 5: % drug release profile of mesalamine optimized formulation (E1) and marketed formulation

In order to demonstrate the kinetics study various models investigated for optimized formulation to check the best fitted model. The kinetic study revealed that release data of the optimized batch showed $R^2$ value of 0.907 and 0.832 for the zero order and first order respectively indicating zero order kinetics fit to this model. Likewise the formulation was observed for Higuchi model and $R^2$was found to be 0.765 with fair linearity. Furthermore Korsmeyer-peppas model described drug release kinetics was found to be 0.644. Thus the results clearly point out the prevalence of diffusion mechanism with zero order release. The results are given in the Table.

Table 5: Release kinetics of optimized formulation mesalamine matrix coated tablets

| **Optimized batch code** | **Coefficient of determination ($R^2$) of various Kinetic Models** | | | |
|---|---|---|---|---|
| | **Zero order** | **First order** | **Higuchi release** | **Korsmeyer & Peppas release** |
| **E1** | 0.907 | 0.832 | 0.765 | 0.644 |

## V. CONCLUSION

The optimized batch (E1) and marketed control release tablets (manufactured by Sun Pharma containing 400 mg of same drug,) are studied for comparative evaluation *in vitro* drug release profiles. The optimized batch was identified to provide desired values for percentage cumulative drug released at 18 h i.e. 93.65% and lag time of about 5 hours with less than 10% drug release which is more superior than marketed formulation.The study results showed that the colon targeted drug delivery system formulated using Coexcipient polymer prepared by spray drying technique had improved drug release and bioavailability compared to the commercially available formulations

## CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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