

Available online on 15.08.2022 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

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Research Article

## Formulation, Evaluation and Comparison of Mesalamine compression coated tablets by using Natural and Semi synthetic polymers

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### Article Info:



#### Article History:

Received 19 June 2022

Reviewed 26 July 2022

Accepted 02 August 2022

Published 15 August 2022

### Cite this article as:

Joshna B, Janaki Devi Sirisolla, Formulation, Evaluation and Comparison of Mesalamine compression coated tablets by using Natural and Semi synthetic, Journal of Drug Delivery and Therapeutics. 2022; 12(4-S):33-39

DOI: <http://dx.doi.org/10.22270/jddt.v12i4-s.5606>

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### Abstract

The main objective of this research paper is to formulate, evaluate and compare compression-coated tablets of Mesalamine using natural and synthetic polymer. The natural polymers used were pectin and Xanthan gum and the synthetic polymer used was HPMC E50 LV. Initially tablets were prepared by direct compression method using different polymers and both pre-compression and post-compression evaluation was conducted. Using the same polymers compression coated tablets of mesalamine were prepared by compression coating method using Cellulose acetate phthalate as the enteric polymer. These tablets were also subjected to pre-compression and post-compression evaluation and all the values obtained were in acceptable limits. Dissolution studies were conducted in different media having pH 1.2, 6.8 and 7.4. The dissolution results showed the drug release of uncoated tablet of HPMC E50 LV was 108.42% at 480 minutes, Pectin was 100.53% at 300 minutes and Xanthan gum was 108.73% at 90 minutes. The drug release of coated tablets of HPMC E50 LV was 100.42% at 680 minutes, Pectin was 102.31% at 580 minutes and Xanthan gum was 100.42% at 300 minutes. Hence the study showed that the compression coated tablets of mesalamine using HPMC E50 LV showed delayed release of the drug in 680 minutes.

**Keywords:** Mesalamine, Colon targeting drug delivery system, Compression coating method, Delayed release, Cellulose acetate phthalate.

## INTRODUCTION

Oral route of the administration is the most widely used and convenient way of drug administration. Conventional oral dosage forms such as immediate release tablets after administration rapidly disintegrates, followed by dissolution and absorption in GI tract <sup>1, 2</sup>. The main drawback of conventional dosage forms is they cannot protect the drug from the hostile environment of upper GI tract, where local targeted drug delivery is required.

The drug delivery systems with colon targeting have several advantages ranging from improved local drug concentrations at the site of action and minimizing unnecessary drug absorption at upper GI tract and also reducing systemic side effects <sup>3,4</sup>. The major objective of developing drug delivery systems with site specificity is to deliver a therapeutic dose of active to the site of action, to achieve and maintain the active concentrations within the therapeutic window.

Targeted delivery systems prevent degradation or inactivation of active components while passing to GI tract and protects the drug candidate till it reaches the target site of action. Thus, reducing drug dose and dosing frequency by reducing unintended drug disposition to non-targeted organs/ tissues with reduced systemic side effects. An optimal target drug delivery system shall be made with biocompatible polymers and also biodegradable once the drug is release from the system. Any ideal drug delivery system shall be cost effective,

reproducible, easy and simple to commercially manufacture at larger scales <sup>5,6,7</sup>

In recent times oral colon specific drug delivery systems (CSDDS) have achieved great importance for their ability to deliver therapeutic peptides and proteins. In comparison to small intestine, large intestine (colon) has negligible brush boarder membrane and very less enzymatic activity pancreatic enzyme <sup>8</sup>. Drug delivery to colon has very wide advantages such as reduced dose and dosing frequency, minimized adverse effects <sup>9</sup>. Several chronic and serious ailments of the colonic region can be treated using CSDDS more effectively than the conventional dosage forms <sup>10,11</sup>

The main aim of this research is to target the delivery of the drug to the colon without degradation in the GIT by using natural and synthetic polymers like pectin, xanthan gum and HPMC E50 LV respectively and then using cellulose acetate phthalate as an enteric polymer.

## MATERIALS AND METHODS

### Materials

Mesalamine, pectin, xanthan gum, HPMC E50 LV, microcrystalline cellulose, talc, magnesium stearate.

### Methods

#### Preparation of calibration curve of Mesalamine

Stock solution of Mesalamine was prepared by dissolving 10 mg of drug in 10 ml (1000 $\mu$ g/ mL) of 0.1N HCl. From this solution working standard was prepared by pipetting out 1 mL of stock solution in 10 mL volumetric flask and the volume was made upto 10 mL with 0.1 N HCl <sup>19</sup>. From the working standard drug solution (100 $\mu$ g/mL) different solutions of concentrations 10,20,30,40,50  $\mu$ g/ mL was prepared by taking into a series of volumetric flask. The working standards of mesalamine were observed against 0.1N HCl as blank at 330 nm. <sup>12-15</sup>

**Table 1 Absorbance of mesalamine observed against 0.1N HCl**

| Concentration ( $\mu$ g/ mL) | Absorbance |
|------------------------------|------------|
| 0                            | 0          |
| 10                           | 0.004      |
| 20                           | 0.009      |
| 30                           | 0.013      |
| 40                           | 0.019      |
| 50                           | 0.023      |

#### Preparation of Mesalamine core tablets using direct compression method

The core tablets of mesalamine were prepared by direct compression method. Mesalamine, HPMC E50 LV, Microcrystalline cellulose, Magnesium stearate and talc were weighed accurately. All the dry ingredients were mixed properly in mortar and pestle. Finally, the mixed blend was compressed using M/S Rimek mini press 2 machine. <sup>18</sup>

#### Formulation of mesalamine core tablets using HPMC E50 LV, pectin and xanthan gum prepared by direct compression method

##### HPMC E50 LV

| Ingredients | Weight in mg per tablet |
|-------------|-------------------------|
| Mesalamine  | 200                     |

|                            |     |
|----------------------------|-----|
| HPMC E50 LV                | 100 |
| Microcrystalline cellulose | 47  |
| Magnesium stearate         | 4   |
| Talc                       | 4   |

#### PECTIN

| Ingredients                | Weight in mg per tablet |
|----------------------------|-------------------------|
| Mesalamine                 | 200                     |
| Pectin                     | 100                     |
| Microcrystalline cellulose | 47                      |
| Magnesium stearate         | 4                       |
| Talc                       | 4                       |

#### XANTHAN GUM

| Ingredients                | Weight in mg per tablet |
|----------------------------|-------------------------|
| Mesalamine                 | 200                     |
| Pectin                     | 100                     |
| Microcrystalline cellulose | 47                      |
| Magnesium stearate         | 4                       |
| Talc                       | 4                       |

#### PREPARATION OF MESALAMINE COMPRESSION COATED TABLETS USING CELLULOSE ACETATE PHTHALATE

In this method 50% of the cellulose acetate phthalate was placed in the die cavity and the core tablet was placed in the center of the die. Remaining 50% of the cellulose acetate phthalate was added and compressed. Compression was done using round punches having punch size of 12 mm sufficient to provide a compression force of 5-6 Kg/cm<sup>2</sup>. <sup>16,17,20</sup>

**Table 2 Formulation of Mesalamine coated tablets using Cellulose Acetate Phthalate**

| Ingredients per tablet in mg | HPMC E50 LV (HCT) | Pectin (PCT) | Xanthan Gum (XCT) |
|------------------------------|-------------------|--------------|-------------------|
| Core tablet                  | 355               | 355          | 355               |
| Cellulose acetate phthalate  | 200               | 200          | 200               |
| Total weight                 | 555               | 555          | 555               |

## EVALUATION OF MESALAMINE TABLETS

### PRECOMPRESSIONAL STUDIES

#### BULK DENSITY:<sup>8</sup>

Bulk density was determined by placing the powder containing the drug and other excipients into a graduated cylinder and measuring the volume and weight as it is. It was calculated by using formula

$$\text{Bulk density} = \text{Mass} / \text{volume} \quad 1$$

#### TAPPED DENSITY:<sup>8</sup>

Weighed powder was transferred to a graduated cylinder and was tapped for a fixed number of taps (100). Tapped density was calculated by formula given in equation

$$\text{Tapped Density} = \text{Weight of granules} / \text{Tapped volume} \quad 2$$

#### HAUSNER'S RATIO<sup>8</sup>

The Hausner's ratio measures the flowability of a powder or granular material.

It is calculated by formula given in equation

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density} \quad 3$$

**COMPRESSIBILITY INDEX<sup>8</sup>**

It is a simple test to evaluate bulk density and tapped density of granules and the rate at which it is packed down. The formula for Carr's index was given in equation

$$\text{Carr's Index (\%)} = \frac{[(\text{Tapped density} - \text{Bulk Density}) \times 100]}{\text{Tapped Density}} \quad 4$$

**ANGLE OF REPOSE<sup>8</sup>**

The angle of repose of the drug mixture was determined by using the fixed funnel method. The accurately weighed granules were passed through the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder. The mixture was allowed to flow through the funnel freely onto the surface. The diameter of the powder was measured and angle of repose was calculated using the formula given in equation

$$\tan \theta = h/r \quad 5$$

**HARDNESS<sup>8</sup>**

The tablet hardness, is the force required for breaking in a diametric compression force. The hardness of the tablets was studied using Monsanto hardness tester, which applies force to the tablet diametrically with the help of inbuilt spring and expressed in kg/cm<sup>2</sup>.<sup>8</sup>

**UNIFORMITY OF WEIGHT<sup>7</sup>**

Weight variation test was done with 20 tablets. It is the variation of individual tablet weighed from the average weight of 20 tablets.

| Average weight of tablet           | % Deviation |
|------------------------------------|-------------|
| 80 mg or less                      | ±10         |
| More than 80 mg or less than 125mg | ±7.5        |
| 125 mg or less                     | ±5          |

**FRIABILITY<sup>7</sup>**

The friability of prepared tablets was measured using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes or 100 revolutions. The tablets were again weighed and the percentage of weight loss was calculated.

$$F = \frac{W(\text{initial}) - W(\text{final}) \times 100}{W(\text{initial})} \quad 6$$

**IN - VITRO DISSOLUTION RATE STUDIES**

The *in-vitro* dissolution rate studies of mesalamine core tablets were performed using 8 stage dissolution test apparatus (Electrolab TDT-08L) fitted with baskets (50 rpm) at 37 ± 0.5°C, using HCl buffer 1.2, phosphate buffer 7.4 and 6.8 (900 ml) as a dissolution media.<sup>18,19</sup> At the predetermined time intervals, 5 ml samples were withdrawn, filtered through 0.45µ membrane filter, diluted and assayed at 330 nm using a shimadzu UV/Visible double beam Spectrophotometer. Cumulative percentage release was calculated by using standard absorbance from the calibration curve. All the dissolution experiments were conducted thrice (n = 3)

**KINETICS OF DRUG RELEASE**

The *in-vitro* dissolution profile of selected formulations was fitted to Zero order, first order, Higuchi model and Korsmeyer-Peppas model to ascertain the kinetic modelling of drug release. Correlation coefficient (R<sup>2</sup>) values were calculated for linear curves obtained by the regression analysis of the above

plot.<sup>10</sup>

- Zero-order kinetic model – Cumulative % drug released Vs time.
- First-order kinetic model – Log cumulative % drug remaining Vs time.
- Higuchi model - Cumulative % drug released Vs square root of time.
- Korsmeyer-Peppas model - Log cumulative % drug released Vs log time.

**ZERO-ORDER KINETICS**

Zero order release can be predicted by the following equation:<sup>16</sup>

$$A_t = A_0 - K_0 t \quad 7$$

A<sub>t</sub> - Drug release at time 't'

A<sub>0</sub> - Initial drug concentration

K<sub>0</sub> - Zero-order rate constant (hr<sup>-1</sup>)

When the data plotted as cumulative % drug release Vs time and the plot is linear, then the data obeys zero-order equal to K<sub>0</sub>.

**FIRST ORDER KINETICS**

First order release can be predicted by the following equation:

$$\log C = \log C_0 - \frac{K_1 t}{2.303} \quad 8$$

When the following data is plotted as log cumulative % remaining Vs time results a straight line and then the release obeys first order kinetics. The constant 'K' obtained by multiplying 2.303 with the slope values.

**HIGUCHI'S MODEL**

Drug release from the matrix by diffusion has been described by following Higuchi's classical diffusion equation:

$$Q = [D\varepsilon/\tau (2A - \varepsilon CS) CST]^{1/2} \quad 9$$

Q - Amount of drug released at time 't'

D - Diffusion coefficient of the drug in the matrix

A - Total amount of drug in unit volume of matrix

CS - It is the solubility of drug in the matrix

ε - Porosity of the matrix

τ - Tortuosity

T - Time at which amount of drug released

When the data obtained is plotted as Cumulative % drug released Vs square root of time it results in a straight line, which means that drug release follows diffusion mechanisms. The slope obtained is equal to 'K'.

**KORSMEYER - PEPPAS MODEL**

To study the mechanism of drug release, the invitro release data were fitted to the well-known exponential equation (Korsmeyer - Peppas model), which is often used to describe the drug release behavior from polymeric systems.<sup>17</sup>

$$\frac{M_t}{M_\infty} = K t^n \quad 10$$

K - Constant incorporating structural and geometrical characteristics of the drug/polymer system

N - Diffusion exponent which is related to the mechanism of drug release

## RESULTS AND DISCUSSION

**Table 3 Precompression studies of mesalamine core tablets**

| Formulation | Bulk density<br>g/cc | Tapped density<br>g/cc | Hausner's ratio | % Compressibility<br>carr's index | Angle of repose<br>(Degrees) |
|-------------|----------------------|------------------------|-----------------|-----------------------------------|------------------------------|
| HT          | 0.5                  | 0.625                  | 1.25            | 1.25                              | 18.17                        |
| PT          | 0.52                 | 0.55                   | 1.057           | 15.45                             | 19.24                        |
| XT          | 0.5                  | 0.62                   | 1.24            | 19.35                             | 22.34                        |

The above table indicates that precompression studies of mesalamine core tablets have passed all the precompression parameters and the values are within lim

**Table 4 Evaluation of mesalamine core tablets**

| Formulation | Hardness<br>(kg/cm <sup>2</sup> ) n± S. D | Weight variation<br>(mg/tab) n± S. D |
|-------------|-------------------------------------------|--------------------------------------|
| HT          | 5± 0.02                                   | 355±0.013                            |
| PT          | 5.5 ± 0.01                                | 354±0.012                            |
| XT          | 5 ± 0.03                                  | 355±0.014                            |

The above table shows that all the mesalamine core tablets have passed the hardness and weight variation test, all the values are within acceptable limits.

**Table 5 Evaluation of mesalamine compression coated tablets**

| Formulation | Weight variation<br>(mg) | Hardness<br>(Kg/cm <sup>2</sup> ) |
|-------------|--------------------------|-----------------------------------|
| HCT         | 554±2.54                 | 5.5±0.11                          |
| PCT         | 553±2.91                 | 5±0.15                            |
| XCT         | 555±.07                  | 5.5±0.13                          |

The above table indicates that all the mesalamine compression coated tablets have passed the evaluation parameters and the values are within acceptable limits.

**Table 6 Zero order, First order, Higuchi and Peppas**

| Formulation | Zero order     |                | First order    |                | Higuchi        | Peppas         |       |
|-------------|----------------|----------------|----------------|----------------|----------------|----------------|-------|
|             | R <sup>2</sup> | K <sub>0</sub> | R <sup>2</sup> | K <sub>1</sub> | R <sup>2</sup> | R <sup>2</sup> | N     |
| HCT         | 0.698          | 0.341          | 0.987          | 0.0009         | 0.885          | 0.864          | 0.689 |
| PCT         | 0.389          | 0.341          | 0.987          | 0.011          | 0.873          | 0.61           | 0.623 |
| XCT         | 0.919          | 0.577          | 0.859          | 0.029          | 0.976          | 0.970          | 0.542 |

The table shown above contains the values of the drug release kinetics

**Table 7 FTIR values of mesalamine and other compounds.**

| S. No | Functional group      | Mesalamine               | Mesalamine + HPMC E50<br>LV + Cellulose Acetate<br>Phthalate | Mesalamine + Pectin +<br>Cellulose Acetate<br>Phthalate |
|-------|-----------------------|--------------------------|--------------------------------------------------------------|---------------------------------------------------------|
| 1.    | -CH <sub>2</sub>      | 3570.8 cm <sup>-1</sup>  | 3496.1 cm <sup>-1</sup>                                      | 3568 cm <sup>-1</sup>                                   |
| 2.    | -OH                   | 3001.42 cm <sup>-1</sup> | 3001.42 cm <sup>-1</sup>                                     | 3001.42 cm <sup>-1</sup>                                |
| 3.    | -CH                   | 1610.56 cm <sup>-1</sup> | 1617.7 cm <sup>-1</sup>                                      | 1617.7 cm <sup>-1</sup>                                 |
| 4.    | -OH bending vibration | 1446.36 cm <sup>-1</sup> | 1448.1 cm <sup>-1</sup>                                      | 1448.1 cm <sup>-1</sup>                                 |
| 5.    | CH-O-CH               | 1349.28 cm <sup>-1</sup> | 1353 cm <sup>-1</sup>                                        | 1353 cm <sup>-1</sup>                                   |
| 6.    | N-H                   | 1131.07 cm <sup>-1</sup> | 1125.7 cm <sup>-1</sup>                                      | 1136cm <sup>-1</sup>                                    |

The FTIR interpretations in the above table indicates that there is no interaction of the polymers and excipients with the drug

Table 8 FTIR interpretation of Pectin.

| S. No | Functional group      | HPMC E50 LV                   | Pectin                      |
|-------|-----------------------|-------------------------------|-----------------------------|
| 1.    | -CH <sub>2</sub>      | -                             | 1460 cm <sup>-1</sup> range |
| 2.    | -OH                   | -                             | 3402 cm <sup>-1</sup> range |
| 3.    | -CH                   | -                             | 2932 cm <sup>-1</sup> range |
| 4.    | -OH bending vibration | -                             | 1377 cm <sup>-1</sup>       |
| 5.    | -CH-O-CH              | -                             | 1017 cm <sup>-1</sup>       |
| 6.    | N-H                   | -                             | 1584 cm <sup>-1</sup>       |
| 7.    | -C-O                  | 1051 cm <sup>-1</sup> range   |                             |
| 8.    | Aromatic ring         | 1543 cm <sup>-1</sup> range   |                             |
| 9.    | Aliphatic chain       | 2899.9 cm <sup>-1</sup> range |                             |

The above table indicates the FTIR values of HPMC E50 LV and Pectin.

Table 9 FTIR interpretation of Xanthan Gum and other polymers.

| S. No | Functional group | Xanthan gum                         | Mesalamine+ Xanthan Gum + Cellulose Acetate Phthalate | Mesalamine + Xanthan Gum               |
|-------|------------------|-------------------------------------|-------------------------------------------------------|----------------------------------------|
| 1.    | -CH <sub>2</sub> | 2900.56 cm <sup>-1</sup>            | 2797.27 cm <sup>-1</sup>                              | 2974.41 cm <sup>-1</sup>               |
| 2.    | COO <sup>-</sup> | 1749.57-1612 cm <sup>-1</sup> range | 1651.97 cm <sup>-1</sup>                              | 1622.66-1622.20 cm <sup>-1</sup> range |
| 3.    | C-O              | 1049.60 cm <sup>-1</sup>            | 1084.56 cm <sup>-1</sup>                              | 1085 cm <sup>-1</sup>                  |

The above table shows that there are no interactions between the drug mesalamine and other polymers.

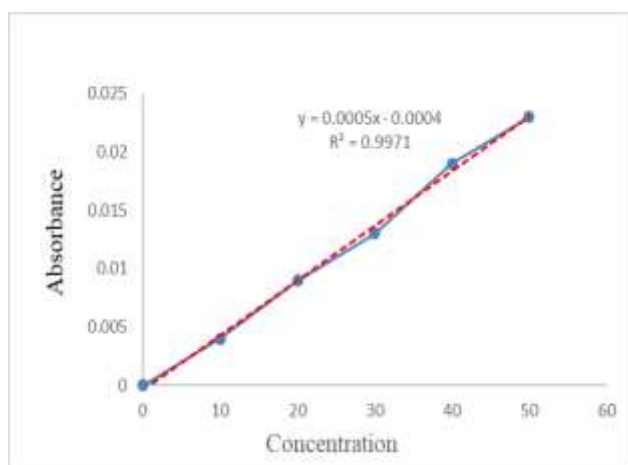


Fig 1 Calibration curve of Mesalamine

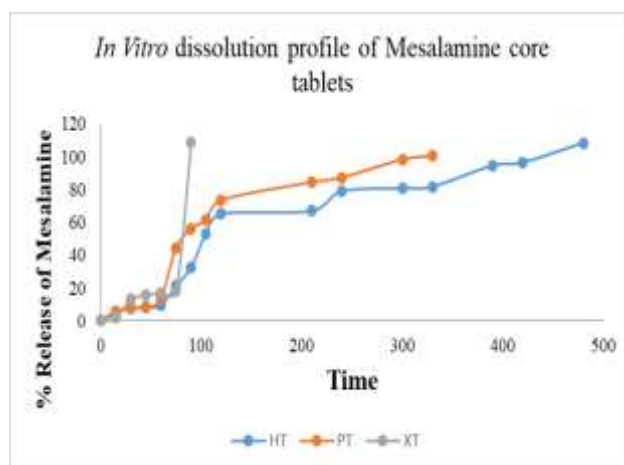


Fig 2 In Vitro dissolution profile of Mesalamine core tablets

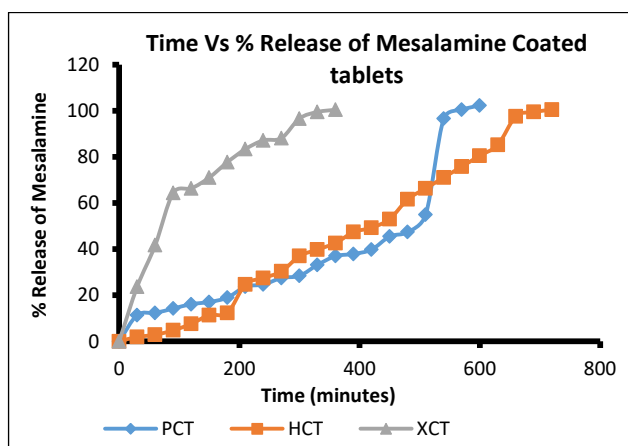


Fig 3 Zero order plot of mesalamine coated tablets

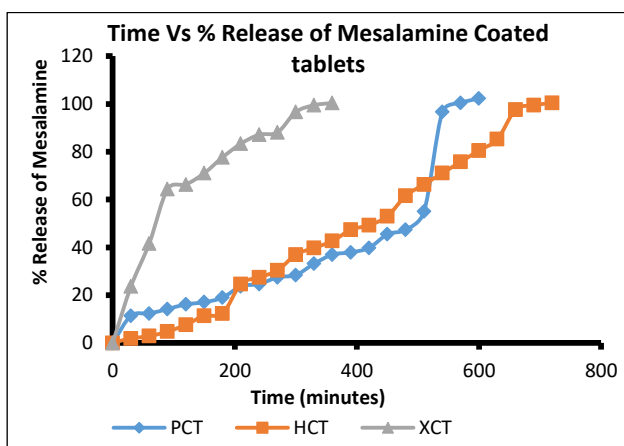


Fig 4 First order plot of mesalamine coated tablets

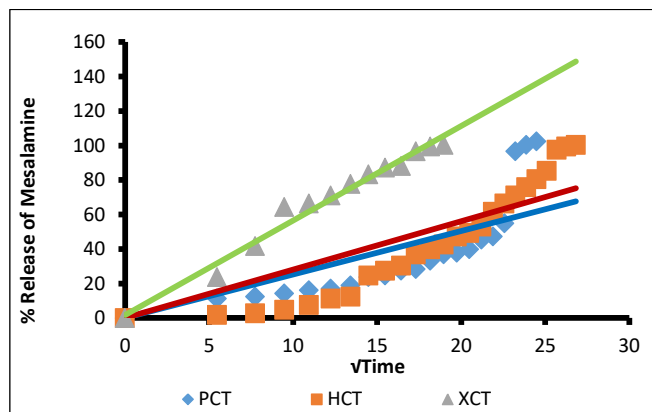


Fig 5 Peppas plot of Mesalamine coated tablets

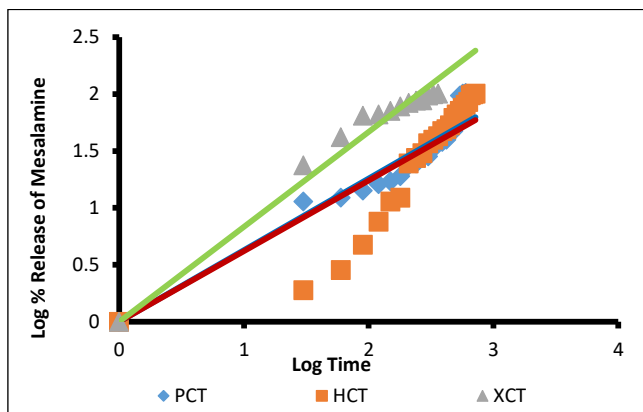


Fig 6 Higuchi plot of Mesalamine coated tablet

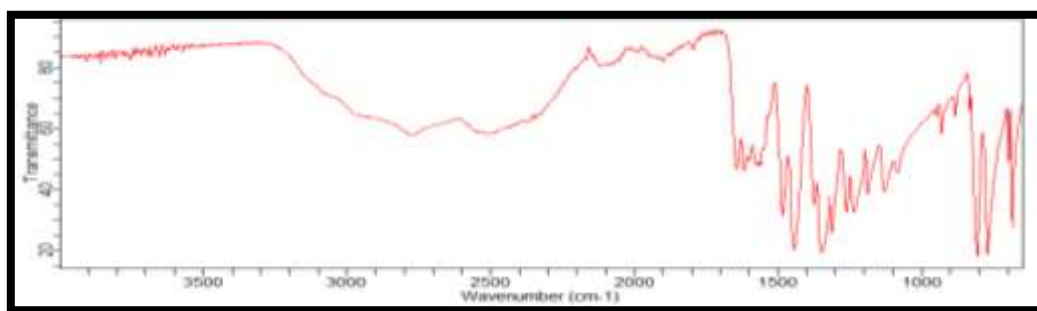


Fig 7 FTIR spectrum of Mesalamine

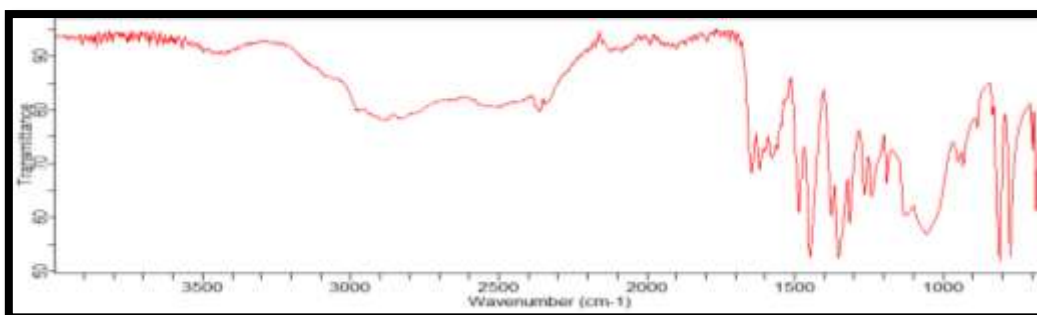


Fig 8 FTIR spectrum of Mesalamine + HPMC E50 LV + Cellulose acetate phthalate

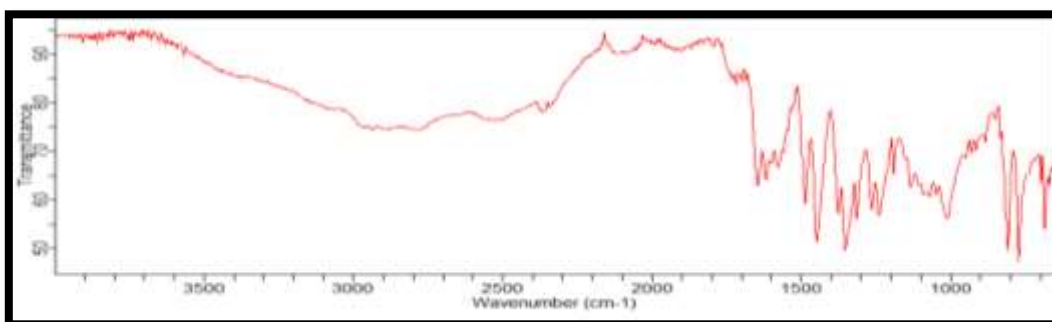


Fig 9 FTIR spectra of Mesalamine + Pectin + Cellulose acetate phthalate

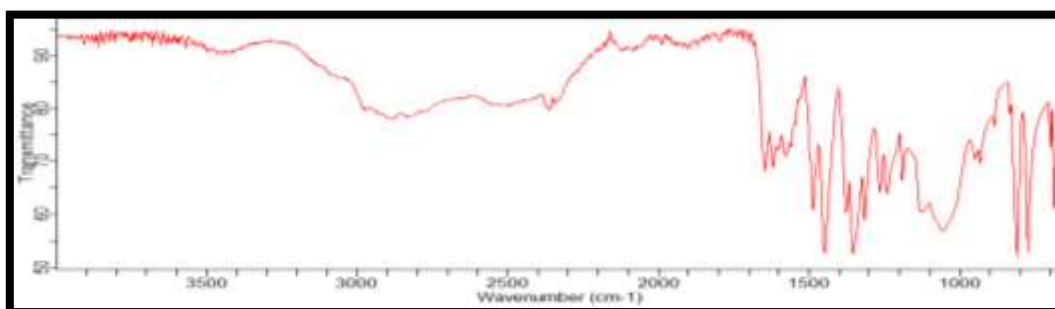


Fig 10 FTIR spectrum of Mesalamine + HPMC E50 LV + Cellulose acetate phthalate

## CONCLUSION

The present work involves the formulation of colon targeted matrix tablet of Mesalamine by using direct compression method. Literatures regarding, Mesalamine tablet dosage form preparation, excipients selection, manufacturing method, etc., has been collected and reviewed. In this work, selection of various excipients was done based on a literature review.

Excipients include HPMC E50 LV, Pectin, Xanthan gum Talc, Magnesium stearate. The amounts of excipients were selected by performing FT-IR method. Various Preformulation studies have also been performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies.

The result showed that the API was compatible with all the excipients selected. The tablets were formulated by using direct compression method using the selected excipient in different quantities. The formulated tablets were tested for both pre-formulation parameters and post compression parameters as per requirements of standards.

The formulated Mesalamine matrix tablets were coated with enteric polymer Cellulose acetate phthalate by compression coating method. The tablets prepared were evaluated for weight variation, thickness, hardness, friability, drug content, disintegration time and in-vitro dissolution studies. All these parameters were found to be within the required standard limits.

Comparative studies of coated mesalamine tablets and uncoated mesalamine tablets are evaluated for the hardness, thickness, in-vitro dissolution studies and disintegration time. HPMC E50 LV coated tablet showed 100% drug release nearer 12 hrs. Since it protects the core under acidic condition while at the same time show the fastest drug release under intestinal pH.

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