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DESIGN AND EVALUATION OF METHOTREXATE LOADED MULTILAYERED TABLET FORMULATION FOR TREATMENT OF COLON CANCER

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ABSTRACT: The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. The aim of the present research work was to develop sustained release multi-layered formulation of Methotrexate, targeted to colon by using the combination of pH- dependent release, timed release and microbially triggered system. Multi-layered tablets were prepared by wet granulation technique method using starch paste as binder. Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation etc. The influence of core tablet compositions, polymer combination ratios and coating levels on the in vitro release rate of Methotrexate from coated tablets was investigated. The results showed that less than 10% drug was released within %hrs (0.1 N HCl for2 hr and phosphate buffer pH 7.4 for 3hrs), and about 40% of the drug was released in the pH 6.8 phosphate buffer within 10.5 hr.

INTRODUCTION: Most of the conventional drug delivery systems are failed to treat colonic diseases as the drugs do not reach the site of action in appropriate concentrations. Thus, an effective and safe therapy of these colonic disorders, using site-specific drug delivery systems is a challenging task to the pharmaceutical technologists [1, 2]. Colonic delivery can be accomplished by oral or rectal administration [3]. Suppositories are only effective in the rectum because of the confined spread and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore, oral administration is preferred but for this purpose, many physiological barriers have to be overcome [4, 5].

Colon cancer is one of the most common internal malignancies. Colon cancer is one of the most common internal malignancies. Chemotherapy is used to treat advanced colorectal cancer. However, conventional chemotherapy is not effective in colorectal cancer as it is in other cancer, as the drug does not reach the target site in effective concentration [6, 7].

Various approaches available for the poor site specificity of pH dependent systems, because of large variation in the pH of gastrointestinal tract, were well established. The timed-release systems release their load after a predetermined period of administration [8, 9, 10].

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Methotrexate (MTX) is a drug of choice in the treatment of colon cancer and now a day's rheumatic disease. MTX is a folate antimetabolite. It is an analogue of aminopterin, which is also derived from folic acid. MTX has a half-life of 3 to 10 hours (for low doses); 8 to 15 hours (for high doses) and insoluble in water, ethanol, and soluble in dilute solutions of alkaline hydroxides, carbonates and in dilute HCl. The oral bioavailability of MTX is relatively very small i.e. 33%.

In the present study we have used the combination of three approaches i.e. pH dependent approach, timed release approach and microbially triggered approach which provides high or sufficient amount of drug at the colonic site and provides better sustainability. The purpose of this study was to design and evaluate Methotrexate loaded multi-layered tablet formulation for treatment of colon cancer.

This system is designed in such a way to provide complete protection over the entire intestinal section including the small intestine, containing acid resistant coat of Eudragit S100 (outermost), middle hydrophobic coating of HPMC over the inner core containing drug and polysaccharide Xanthum gum, was aimed at releasing most of the drug to the colonic part.

MATERIALS: Methotrexate gifted by Oncare Pharmaceuticals Private Limited, Chandigarh, HPMC supplied by Yarrow chem. Products, Mumbai, Xanthan Gum supplied by SD-Fine Chem. Limited, Mumbai, Eudragit S 100 supplied by Rohm, microcrystalline Cellulose (SD-Fine Chem. Limited, Mumbai). All other chemicals are of analytical grade.

PREPARATION OF METHOTREXATE LOADED MULTI-LAYERED TABLET

Preparation of Core Tablet: Active ingredients along with all the excipients were passed through sieve no. 80. Accurately weighed API (MTX), polysaccharide (Xanthum gum) and other co-formulating agents (except Magnesium stearate and Talc) were mixed properly using mortar and pestle. 10% w/v Starch paste was prepared and add drop wise to form a desired lump, which was passed through sieve no.22.

After that obtained granules was dried in hot air oven at a temperature of less than 50^{o}C. Magnesium stearate and Talc was added over the dry granules and subjected for direct compression using 6mm punch to form core tablet. Totally 4 formulations (FX1 to FX4) were developed and studied. Also, the dried granules of MTX were characterized for rheological properties. After adding lubricant (talc) and anti-adherent (magnesium stearate) to the granule bed, subsequent blending the granules was compressed into tablets. Core tablets (diameter, 6 mm; average tablet weight, 100mg) were compressed within 6 mm of punches on Cadmach 16 station compression machine under a common compression force of 3-4 Kg/cm^2 **(Table 1)** .

Preparation of compression coated tablet (Hydrophobic coating layer): Six mm diameter drug cores were compression-coated into coated tablets. For this accurate quantity of hydrophobic polymer (HPMC) and other co-formulating agents were taken and mixed properl til uniform mixing. Compression coated tablet were prepared by first filling half of the polymer blend in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half of the polymer blend on top, then compressed Cadmach 16 station compression machine with a compression force to obtain tablets with hardness in the range of at 6-7 Kg/cm^2 **(Table 1)**.

Preparation of Enteric coated layer (Acid Resistant Coating Layer): Prepared compressed tablet was coated by using dip coating technique. In this method selected polymer (Eudragit S 100) and other co-formulating agents were dissolved in organic solvent like methylene chloride, isopropyl alcohol, methanol, ethanol, acetone, at various concentration. Compressed tablet were coated using coating pan. Coating procedure repeated until 15% over all weight gain was not observed **(Table 1)**.

TABLE 1 COMPOSITION OF DRUG LOADED MULTI-LAYERED TABLET

Ingredients	FX1 (mg)	FX2 (mg)	FX3 (mg)	FX4 (mg)
Composition of Core				
Methotrexate	7.5	7.5	7.5	7.5

Xanthum Gum	15	22.5	30	37.5
MCC – 101	40	40	40	40
Lactose	32.5	25	17.5	10
Mg. St.	3	3	3	3
Talc	2	2	2	2
Composition of Hydrophobic Coating Layer				
HPMC (K4M)	200	200	200	200
PVP (K30)	45	45	45	45
MCC-101	30	30	30	30
Mg. St.	2	2	2	2
Talc	3	3	3	3
Composition of Acid Resistant Coating Layer				
Eudragit S100	2gm	2gm	2gm	2gm
Methylene chloride : IPA (75:25)	15 ml : 5 ml	15 ml : 5 ml	15 ml : 5 ml	15 ml : 5 ml
Polyethylene glycol (PEG 400) (1% w/v)	0.2 ml	0.2 ml	0.2 ml	0.2 ml
Titanium dioxide (TiO_2) (0.05% w/w)	1 mg	1 mg	1 mg	1 mg

Drug excipients compatibility study: FT-IR spectra of drug and physical mixture of excipients and drug (1: 1) were recorded with a FT-IR spectrophotometer (Shimadzu Corporation, Japan, 8400s) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1: 100 and pressed using a hydrostatic press (Kimaya Engineers, Mumbai, India) at a pressure of 10 tons for 5min. The disc was placed in the sample holder and scanned from 4000 to 500 cm-1 at a resolution of 1 cm^{-1}.

Differential scanning Calorimetry is used to determine drug excipient compatibility studies and also used to observe more phase changes, such as glass transitions, crystallization, amorphous forms of drugs and polymers. Drug and physical mixtures of drug and excipients were analysed by differential scanning calorimeter (Mettler Toledo, USA).The thermo grams of MTX, physical mixture of MTX with excipients were obtained at scanning rate of 20^0C/min conducted over 25-250^0C.

Pre-Compression:

Characterization of Core Granules [11]: The quality of tablet, once formulated by rule, was generally dictated by the quality of physicochemical properties of blends. There were many formulations and process variables involved in mixing steps and all these can affect the characteristics of blend produced.

Bulk Density: Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula

$$\rho b = \frac{M}{Vb}$$

Where M=Mass; Vb = Bulk Volume

Tapped Density: The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The constant minimum volume (Vt) occupied in the cylinder after tapping's and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula

$$\rho t = \frac{M}{Vt}$$

Where M=Mass; Vt = True Volume

Compressibility Index: The simplest way for measurement of flow of the powder was its compressibility, an indication of the ease with which a material can be induced to flow. It is expressed as compressibility index (I) which can be calculated as follows

$$I = \frac{(\rho t - \rho b)\,X100}{\rho t}$$

Where, ρt = Tapped density; ρb = Bulk density.

Hausner's Ratio: Hausner's ratio (HR) is an indirect index of ease of powder flow. It was calculated by the following formula

$$HR = \frac{\rho t}{\rho b}$$

Where, ρt is tapped density and ρb is bulk density.

Angle of Repose: Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula.

$\tan \theta = \frac{h}{r}$; Therefore; $\theta = \tan^{-1} \frac{h}{r}$

Where, θ is angle of repose; h is height of cone; r is radius of cone.

Post compression characterization [12, 13]: After compression of powder blends, the prepared tablets were evaluated for weight variation, tensile strength, thickness, friability and drug content.

Weight Variation: The weight variation test would be satisfactory method of determining the drug content uniformity. As per USP42, twenty tablets were taken and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

Friability: Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Pre-weighed sample of tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F %) was determined by the formula

$$F\% = \left(1 - \frac{Wo}{W}\right).100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

Tablet Hardness: The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness.

Drug Content: The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg of drug was weighed accurately and dissolved in 100ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly and subjected for sonication. The undissolved matter was removed by filtration through Whatmann filter paper No.41. Then dilutions were carried out (if required). The absorbance of the diluted solutions was measured at 303 nm. The concentration of the drug was computed from the standard curve of the Methotrexate in phosphate buffer of pH 6.8 and the drug content was calculated using formula,

$$\text{Drug content} = \frac{\text{Conc.}^n \times \text{vol.} \times DF}{1000}$$

***In vitro* Drug Release Study [14]:** To study how composition of the coat and core to coat ratio interfere drug release profile of tablet. The dissolution test was carried out using the USP XXXIII type II apparatus (Paddle apparatus TDL 08 L; Electrolab India Pvt. Ltd., Mumbai, India) with a rotation speed of 100 rpm and 900 mL medium at 37±0.5°C. In vitro release study for drug loaded multilayered tablets was carried out by keeping the tablets for 2 h in 0.1 N HCl (900 ml), simulated gastric fluid (SGF). The dissolution medium was then replaced with pH 7.4 phosphate buffer solution (900 ml), simulated intestinal fluid (SIF), and tested for 3 h. The time dependent coated tablets were evaluated by exposing them to 900 ml SIF for 3 h which was later replaced by pH 6.8 phosphate buffer solution (900 ml), simulated colonic fluid (SCF), and tested for release.

Kinetics of drug release from Coated Tablet: The release from the different formulations was determined by curve fitting method Data obtained from in vitro release studies were fitted to various kinetic equations. The kinetic models used were:

$Q_t = k_o\ t$ (zero-order equation),

$\ln Q_t = \ln Q_0 - k_1.t$ (first-order equation),

$Q_t = K\ .S.\ \sqrt{t} = k_H\ .\ \sqrt{t}$ (Higuchi eqn. based on Fickian diffusion)

Where, Q is the amount of drug release in time t, Q_0 is the initial amount of drug in the microsphere, S is the surface area of the microcapsule and k_o , k_1 ,and k_H are rate constant of zero order, first order and Higuchi rate equations respectively. In addition to these basic release models, there are several other models as well. One of them is Peppas and Korsmeyer equation (power law).

$Mt / M\infty = k \cdot t^n$

Where Mt is the amount of drug release at time t and M∞ is the amount release at time t = ∞, thus Mt / M∞ is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent.

RESULT AND DISCUSSION: The objective of present study is to develop and evaluate Methotrexate loaded multi-layered tablet formulation for treatment of colon cancer. The system was developed into three steps: first, core tablet was prepared containing Methotrexate; second, core tablet were coated with hydrophobic polymer HPMC (water insoluble polymer) and; third, enteric coating of compressed coated tablet by Eudragit S 100 (enteric polymer).

Drug Excipients Compatibility Study: Fourier Transformed Infrared Spectroscopy: FT-IR spectra of, drug and physical mixture of excipients and drug (1: 1) (**Fig. 1**). The characteristic absorption peaks of Methotrexate were also found in FT-IR spectra of physical mixture.

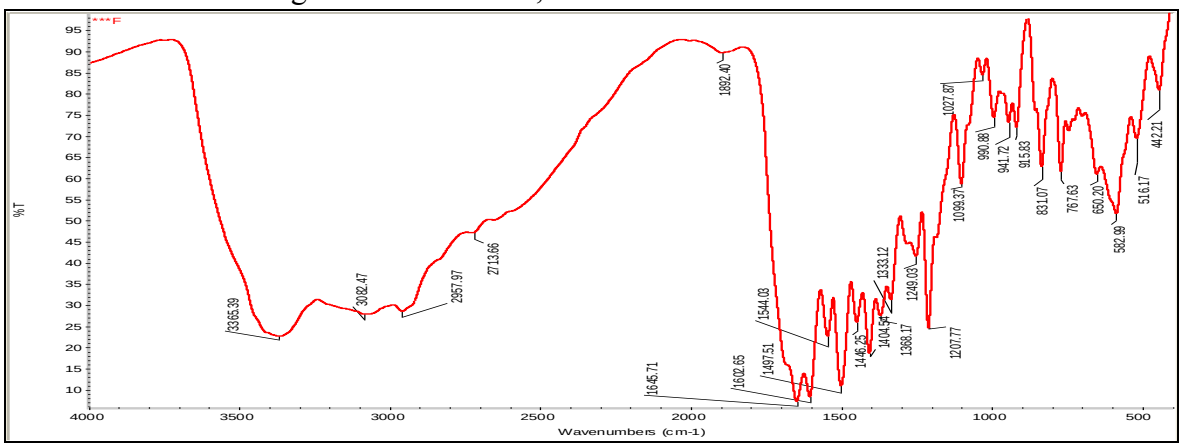

FIG 1(A): FT-IR SPECTRA OF METHOTREXATE

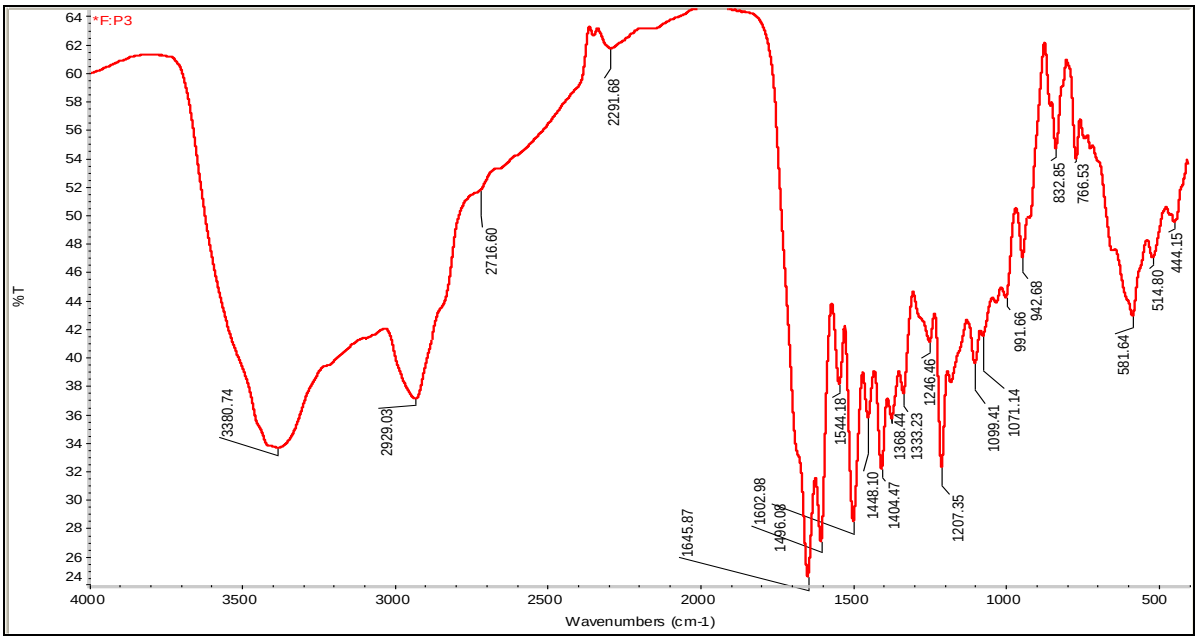

FIG 1(B): FT-IR SPECTRA OF MTX: HPMC

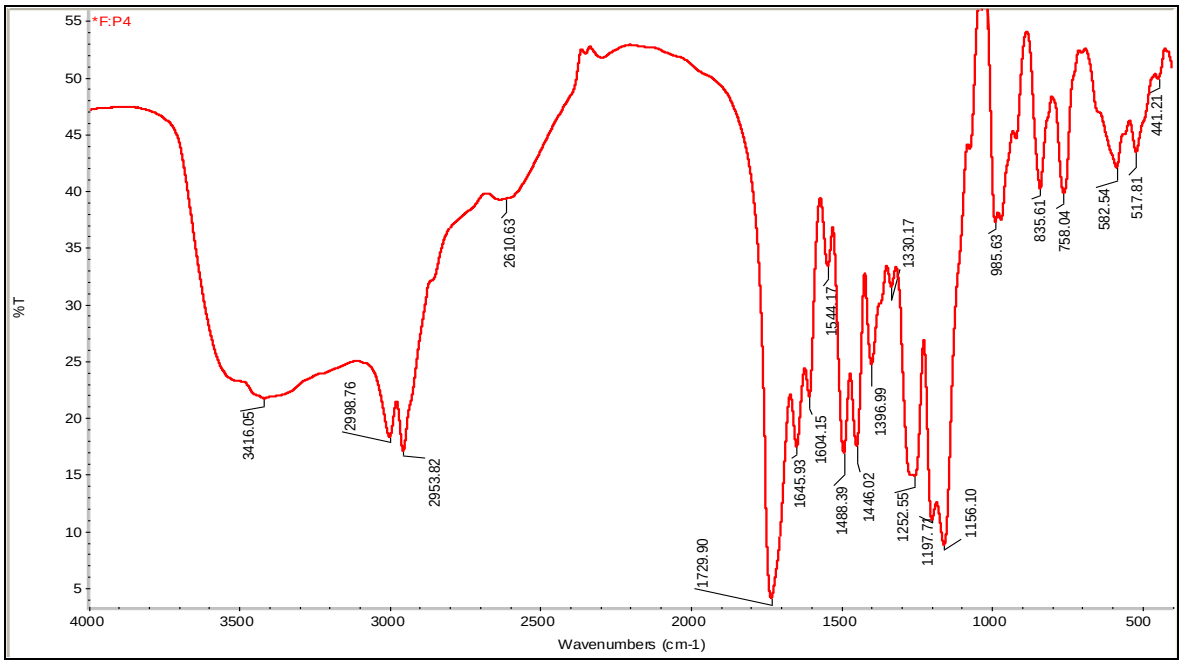

FIG 1(C): FT-IR SPECTRA OF MTX: XANTHUM GUM

The DSC thermograms of various polymers are shown respectively **(Fig. 2)**. These thermo grams indicated that no significant change in peak, shape, and area were found. Therefore this study revealed that there were no interaction between the drug and polymers or may be little interaction.

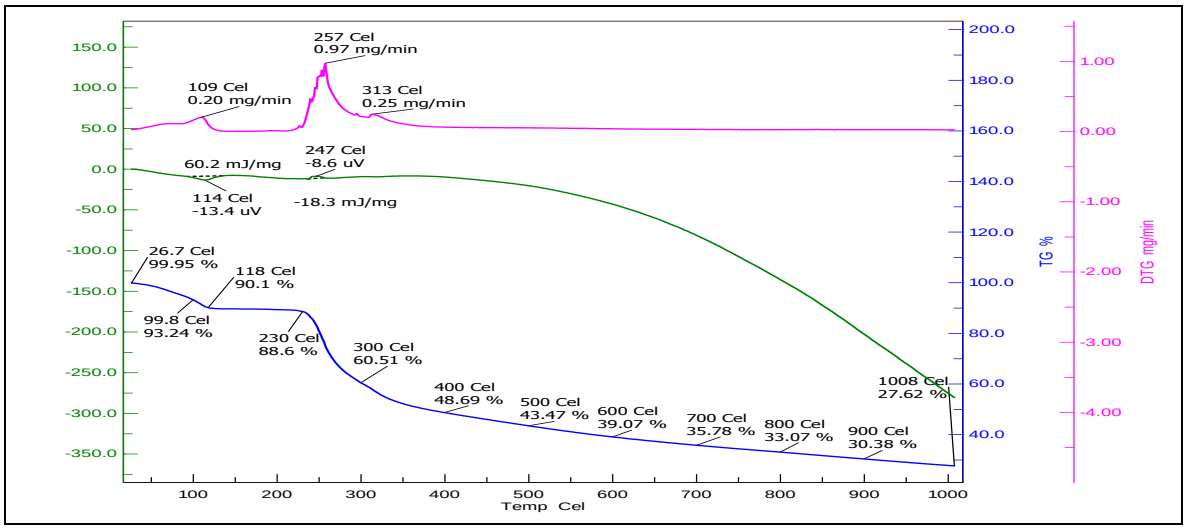

FIG 2 (A) DSC SPECTRA OF METHOTREXATE

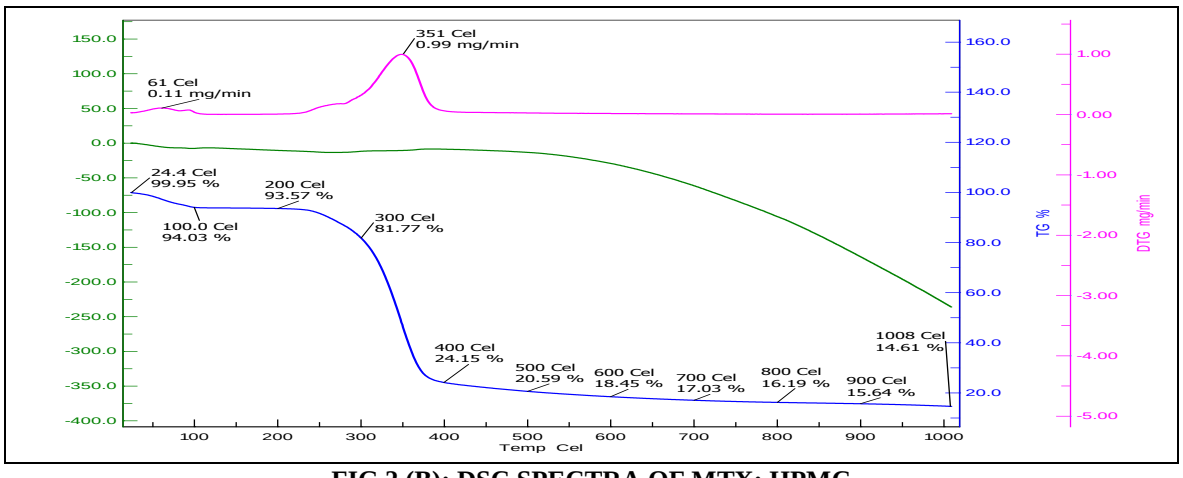

FIG 2 (B): DSC SPECTRA OF MTX: HPMC

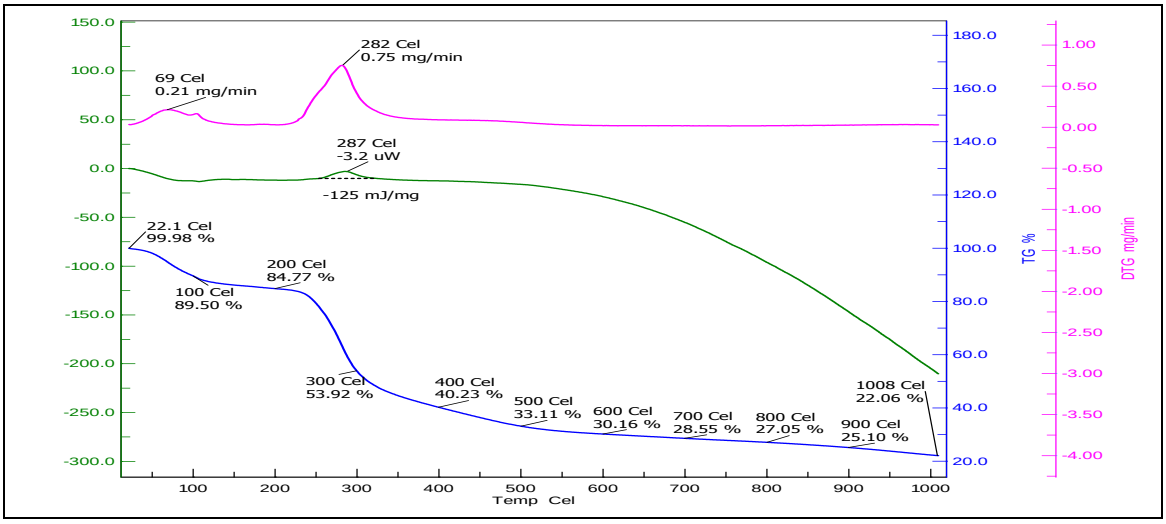

FIG 2(C): DSC SPECTRA OF MTX: XANTHUM GUM

Pre Compression Characterization of Coating Powder Blend and Core Tablet Powder Blend: Pre compression characteristic of the compression coated tablet were evaluated by determining bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose. The bulk density of pre-compression blends was found to be in the range of 0.53 to 0.65 g/cc, tapped density was found to be in the range of 0.61 to 0.74 g/cc, the Carr`s Index values were in the range of 11.12 to 13.43%, the angle of repose was in the range of 24.97to 28.36 and Hausner`s ratio was in the range of 1.122±0.058 to 1.155±0.058. All these pre-compression parameters values were within the pharmacopoeial limit and hence the prepared granules possess good flow ability **(Table 2)**.

TABLE 2: PRE-COMPRESSION PARAMETERS OF METHOTREXATE FORMULATIONS

Formulation code	Angle of Repose (n=3)	Bulk Density (n=3)	Tapped Density (n=3)	Carr`s Index (%)	Hausner`s Ratio
FX1	26.27±1.98	0.57±0.06	0.64±0.05	12.28±1.01	1.122±0.05
FX2	25.42±1.89	0.59±0.03	0.68±0.01	15.25±1.03	1.152±0.04
FX3	24.97±1.86	0.53±0.06	0.61±0.03	13.11±1.02	1.150±0.05
FX4	25.92±1.97	0.56±0.04	0.63±0.02	11.12±1.03	1.126±0.04

Post compression characterization: All the formulated (FX1 to FX4) tablets passed weight variation test as the % weight variation (459±1.78 to 464±2.14) was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of all the formulations ranged between 4.87±0.16 to 5.85±0.11 kg/cm .This ensures good handling characteristics of all batches. The values of friability test were tabulated in above table. The % friability was less than 0.6% in all the formulations ensuring that the tablets were mechanically stable. Thickness of the coated formulation was measured with Digital Vernier calliper. The measured thickness of coated tablets of each formulation ranged between 10.06±0.12 mm to 10.24±0.10 mm. This ensures uniform coating to all batches. The percentage of drug content was found to be between 95.89±1.41% and 98.97±1.42%.

It complies with official specifications and signifies the well entrapment efficiency of prepared formulation **(Table 3)**.

TABLE 3: POST-COMPRESSION PARAMETERS OF METHOTREXATE FORMULATIONS

Formulation code	Weight variation	Hardness	Friability (%)	Thickness	% Drug Content
FX1	463±3.12	5.13±0.11	0.39±0.02	10.24±0.10	96.13±1.23
FX2	462±2.13	5.81±0.13	0.44±0.03	10.18±0.18	95.89±1.41
FX3	458±2.17	4.94±0.15	0.41±0.05	10.21±0.21	96.44±1.70
FX4	461±1.98	5.36±0.12	0.35±0.01	10.06±0.12	98.97±1.42

***In vitro* Drug release study:** The In Vitro release study of prepared colon targeted multilayered tablet formulation was performed using USP type II apparatus. As we are intended to provide a lag

period before drug release and increase the availability of drug at the site of absorption i.e. colon. The formulation should provide less release or no release in 5hrs of time (i.e. 2hrs of average gastric empyting time in 0.1NHCl buffer pH 1.2 and 3hrs of average intestinal transit time im phosphate buffer pH 7.4). As the experimental results revealed all the prepared formulation show less than 10% drug release during 5hrs of study **(Table 4)**.

It proved the effectiveness of acid resistant coating and time dependent coating layer (hydrophobic coating layer). Now as per our formulation aspect the drug should be available at colonic regimen in maximum amount and release the drug effectively with a predetermined rate.

Incorporation of polysaccharides like xanthum gum and guar gum provide a microbially triggered system because these polysaccharides extensively degraded in presence of colonic microflora. As well as this hydrophilic swellable polysaccharide provide a sustained release.

From release data, it was clearly observed that that as we increase the amount of polymer in formulation better sustainability was obtained (i.e. FX4 shows 39.83%, FX3 shows 48.13%, FX2 shows 59.21% drug release after 10.5hrs) **(Fig. 3)**. This may be due to the increased amount of polymeric matrix that reduces the rate of drug diffusion, hence *in vitro* release profile significantly.

TABLE 4 CUMULATIVE % DRUG RELEASE OF DIFFERENT COATED FORMULATION

Time (Min)	Cumulative % drug release			
	FX1	FX2	FX3	FX4
0	0	0	0	0
0.5	0.02	0	0	0
1	0.04	0.05	0.09	0.01
1.5	0.09	0.14	0.12	0.08
2	0.18	0.26	0.26	0.17
2.5	0.26	0.39	0.32	0.34
3	0.39	0.51	0.48	0.49
3.5	0.53	0.96	0.74	0.86
4	0.89	1.43	1.12	1.18
4.5	1.72	3.31	2.93	2.65
5	2.48	6.72	3.86	3.74
5.5	4.97	8.09	5.74	5.92
6	8.81	10.91	8.74	6.45
6.5	12.12	13.19	12.98	12.52
7	15.33	17.42	16.46	13.19
7.5	17.45	21.36	22.51	17.82
8	29.61	28.59	25.98	21.58
8.5	37.89	33.46	28.31	24.42
9	49.38	43.75	32.48	27.88
9.5	53.43	47.69	39.32	31.46
10	64.66	54.51	45.87	35.67
10.5	67.12	59.21	48.13	39.83

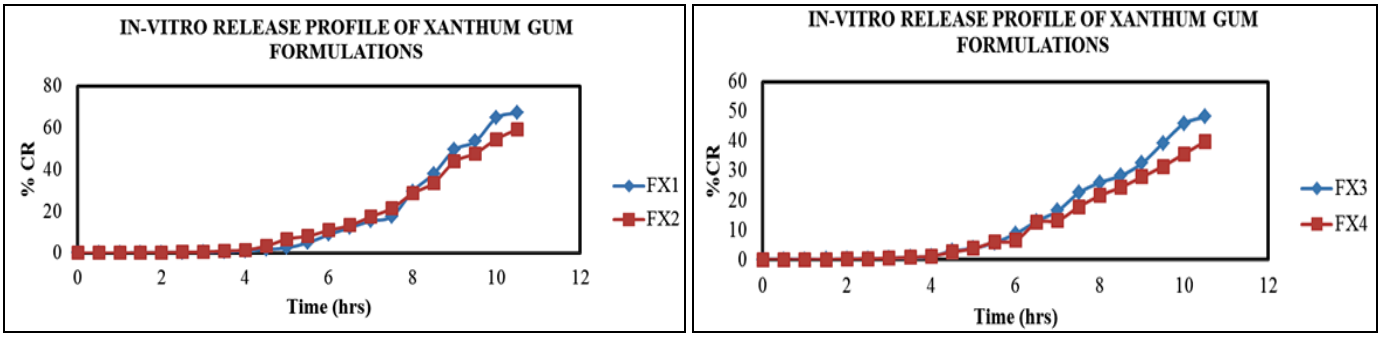

FIG. 3: *IN VITRO* DRUG RELEASE OF MULTI-LAYERED TABLET

Comparison between $T_{50\%}$ and $T_{80\%}$ Value of Prepared Multilayered Formulations: From the graphical representations **(Fig. 4)**, we have concluded that from the various formulations of Xanthum gum, formulation FX4 shows best sustained drug release (i.e. higher $T_{50\%}$ and $T_{80\%}$). This may be due to the prsence of higher or increased concentration of hydrophilic polymer **(Table 5)**.

TABLE 5: COMPARISON BETWEEN $T_{50\%}$ AND $T_{80\%}$ VALUE OF XANTHUM GUM FORMULATIONS

FORMULATION	$T_{50\%}$ (HRS)	$T_{80\%}$ (HRS)
FX1	8.15 ± 0.38	13.03 ± 0.48
FX2	9.09 ± 0.13	14.54 ± 0.71
FX3	10.88 ± 0.27	17.41 ± 0.23
FX4	13.31 ± 0.52	21.29 ± 0.32

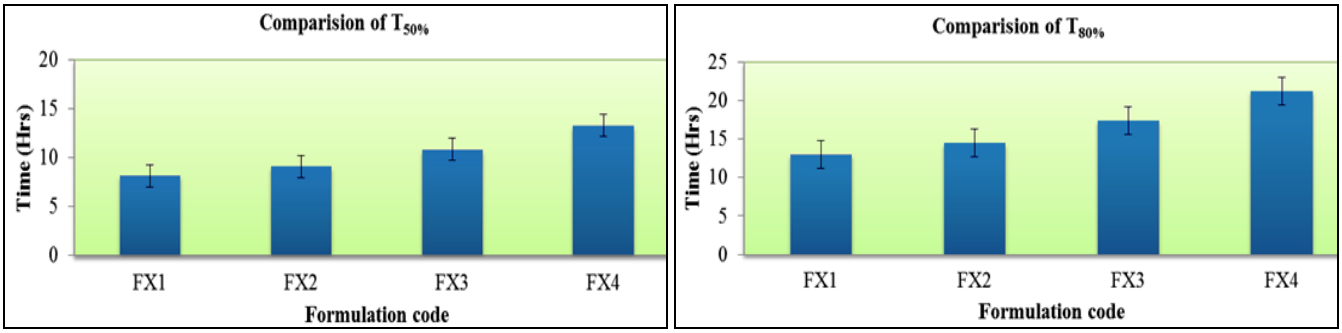

FIG. 4: COMPARISON OF $T_{50\%}$ AND $T_{80\%}$ VALUE OF XANTHUM GUM FORMULATIONS

Swelling Index of Polymers: From the graph **(Fig. 5)**, we concluded that formulation FX4 and FG4 shows higher swelling index, indicating slower or lesser drug release. The better sustained drug release was observed in the formulations i.e. FX4. This may be due to the higher or increased concentration of hydrophilic polymer.

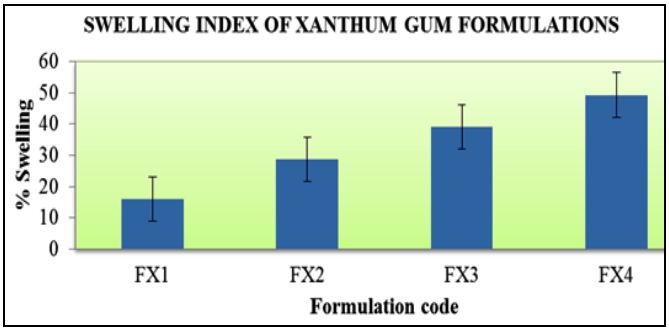

FIG. 5: SWELLING INDEX OF XANTHUM GUM FORMULATIONS

Release Kinetics: From the respective table **(Table 6)** it was observed that the individual formulation having different r^2 value for different model. On the basis of higher value of r^2 we select the best fit model. Now Korsemeyer-Peppas model possess great importance to know the release mechanism of the drug from the formulation. To predict the mechanism of diffusion release, the following equation $Mt/M\infty = kt^n$ was used to analyse data of sustained release of drug loaded formulation. Now n= 0.5 means Fickian diffusion, 0.5< n<1.0 non-Fickian diffusion, and n=1.0 case II diffusion. Considering the n values calculated for the studied loaded multi-layered tablet formulation **(Table 6)**, in all case a super case II transport mechanism is dominant.

The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of diffusion. The release of drug depends on erosion of polymer chain. Generally the perfect zero order release or super case II mechanism was governed by swelling nature of the polymer. Now on the basis of above all experimental results obtained, we have selected the formulation FX4 (i.e. 39.83% drug release after 10.5 hrs).

TABLE 6: RELEASE KINETICS OF OPTIMIZED MULTI-LAYERED FORMULATIONS

Formulation	r^2			Korsemeyer r^2	Peppas plot n
	Zero order plot	First order plot	Higuchi plot		
FX1	0.630	0.640	0.986	0.987	4.474
FX2	0.822	0.760	0.630	0.976	3.593
FX3	0.837	0.795	0.644	0.974	3.722
FX4	0.849	0.821	0.658	0.975	3.486

CONCLUSION: Now as per our formulation aspect the drug should be available at colonic regimen at maximum amount and release the drug effectively with a predetermined rate. Incorporation of polysaccharides like Xanthum gum and Guar gum provide a microbially triggered system because these polysaccharides extensively degrade in presence of colonic environment. As well as these hydrophilic swellable polymers provide a sustained release. Now as we increase the amount of hydrophilic polymers better sustainability is obtained.

On the basis of current research work it had been concluded that formulated multi-layered tablet formulation may be used as an effective tool for colon targeted drug delivery of Methotrexate.

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