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# FORMULATION AND INVITRO EVALUATION OF METRONIDAZOLE TABLETS FOR COLON TARGETTED DRUG DELIVERY SYSTEM

**Yalla Karunakar Reddy[1], G. S.Valluri[2], K. Kishore[3], Dr.G.Vijaya Kumar*[4]**

[1,2,3]KGR Institute of Technology and Management, Rampally, Kesara, Rangareddy, Telangana, India,

[4]Professor and Head, Dept. of Pharmacy, KGR Institute of Technology and Management, Rampally, Kesara, Rangareddy, Telangana, India

**Abstract:**

*In the present research work sustained release matrix formulation of Metronidazole targeted to colon by using various polymers developed. To achieve pH-independent drug release of Metronidazole, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.*

**Key Words:** *Metronidazole, Colon targeted tablets.*

**Corresponding author:**

**Dr.Gampa Vijaya Kumar,**

*Professor and Head, Dept. of Pharmacy,*
*KGR Institute of Technology and Management,*
*Rampally, Kesara, Rangareddy, Telangana, India*
*Email ID: vijaytanu71@gmail.com*

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## INTRODUCTION:

**Colon Specific Drug Delivery System (CSDDS)**

The major goal of any drug delivery system is to supply a therapeutic amount of drug to a target site in a body, so that the desired drug concentration can be achieved swiftly and then maintained. Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non target sites. A targeted drug delivery system is preferred in drugs having instability, low solubility and short half life, large volume of distribution, poor absorption, low specificity and low therapeutic index.

Targeted drug delivery may provide maximum therapeutic activity by preventing degradation or inactivation of drug during transit to the target site. Meanwhile, it can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. An ideal targeted delivery system should be nontoxic, biocompatible, and biodegradable and physicochemically stable in vivo and invitro. The preparation of the delivery system must be reasonably simple, reproducible and cost-effective. The targeted drug delivery is dependent on the identification and exploitation of a attribute that is specific to the target organ [1,2]. The colon targeted drug delivery is beneficial for the localized treatment of several colonic diseases mainly inflammatory bowel diseases (IBD), irritable bowel syndrome and colonic cancer. To achieve clinically relevant bioavailability of poorly absorbed drugs from the upper parts of the gastrointestinal tract because of their polar nature and/or vulnerability to chemical and enzymatic degradation in the small intestine specifically for proteins and peptides [3]. The colonic drug delivery provide more effective therapy of colon associated diseases such as irritable bowel syndrome, IBD including Crohn's disease and ulcerative colitis, and also has potential to deliver macromolecular drugs orally [4]. Colon related pathologies range in seriousness from constipation and diarrhea to the incapacitating inflammatory bowel diseases through to colon cancer, the third most widespread form of cancer in both women and men [5].

**Benefits of CSDDS [6]**

1. Target drug delivery
2. Decrease in dose to be administered
3. Decreased side effects
4. Improved drug utilization
5. It is a promising site for a drug which is unstable or poorly absorbed from upper GI tract

**Rationale for Colonic Drug Delivery**

1. Topical application of drugs active at the mucosal level and May reduces adverse effects in the treatment of colonic of colonic disease.
2. It is important in the treatment of colonic diseases like ulcerative colitis, crohn's disease, cancer and infections
3. It also provide opportunity to clarify the mechanism of action of some nonsteroidal anti- inflammatory drugs (NSAID) such as sulfide which get metabolized in the colon to the active moiety and interfere with the proliferation of colon polyps (first stage in colon cancer) probably in local mode.
4. Colon is capable of absorbing some drugs efficiently.
5. Drug absorption enhancer works better in the colon as compare to small intestine.
6. Large intestine is potential site for absorption of protein drugs

**Advantages of Colonic Drug Delivery**

1. Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.
2. The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.
3. The colon targeted drug delivery can also be used for chronotherapy for effective treatment of diseases like asthma, angina and arthritis.

**Disadvantages of Colonic Drug Delivery**

1. There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired site. The pattern of drug release may differ from person to person which may cause ineffective therapy.
2. The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.
3. The major disadvantage of colonic delivery of drug is poor site specificity.
4. Diet and diseases can affect colonic micro flora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In diseased conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
5. Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.
6. Substantial variation in gastric retention time may cause drug release at the undesired site in case of time dependent colonic drug delivery system.

**Strategies for Targeting Drugs to the Colon:**

The approaches for colon specific drug delivery system are prodrug or coated or matrix preparation [7].

**The commonly used approaches are:**

1. pH dependent
2. Time dependent
3. Pressure dependent
4. Bacteria dependent

**Table 1: Materials used in formulations**

| S.no | Name of the material | Purpose | Source | Quality |
|---|---|---|---|---|
| 1 | Metronidazole | Drug | Natco LABS | Lab.Grade |
| 2 | Microcrystalline cellulose | DIluent | Signet Chemical Corporation, Mumbai, India. | Lab.Grade |
| 3 | Sodium starch glycollate | Polymer | SD fine chemicals, Mumbai, India. | Lab.Grade |
| 4 | Cross povidone | Polymer | Merck Specialities Pvt Ltd, Mumbai, India. | Lab.Grade |
| 5 | Croos carmellose sodium | Polymer | Merck Specialities Pvt Ltd, Mumbai, India. | Lab.Grade |
| 6 | HPMC | Polymer | Merck Specialities Pvt Ltd, Mumbai, India. | Lab.Grade |
| 7 | Magnesium stearate | Polymer | SD fine chemicalss, Mumbai, India | Lab.Grade |
| 8 | Talc | Polymer | Merck Specialities Pvt Ltd, Mumbai, India | Lab.Grade |

## METHODOLOGY:

**Analytical method development [8,9]:**

**a) Determination of absorption maxima:**

A solution of containing the concentration 10 µg/ ml was prepared in 0.1N HCl , 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

**b) Preparation calibration curve:**

10mg of drug was accurately weighed and dissolved in 10ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4, 6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N HCl, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 273nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

**Drug – Excipient compatibility studies**

**Fourier Transform Infrared (FTIR) spectroscopy:**

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

**Differential Scanning Calorimetry (DSC):**

DSC scan of samples were obtained in a Perkin Elmer thermal analyzer equipped with a monitor and printer. The instrument was calibrated with indium. Accurately weighed 5 mg of sample were placed in an open, flat bottom, aluminium sample pans. Thermograms were obtained by heating the sample at a constant rate 10 minute. A dry purge of nitrogen gas (20ml/min) was used for all runs sample heated from 35ºC to 400ºC.

**Preformulation parameters**

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

**Angle of repose:**

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$

Tan θ = Angle of repose

h = Height of the cone ,

r = Radius of the cone base

**Table 2: Angle of Repose values ( as per USP)**

| Angle of Repose | Nature of Flow |
|---|---|
| <25 | Excellent |
| 25-30 | Good |
| 30-40 | Passable |
| >40 | Very poor |

**Bulk density:**

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm$^3$. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

$V_o$ = apparent volume of powder

**Tapped density:**

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\textbf{Tap} = \textbf{M} / \textbf{V}$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

**Measures of powder compressibility:**

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\textbf{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

**Table 3: Carr's index value (as per USP)**

| Carr's index | Properties |
|---|---|
| 5 – 15 | Excellent |
| 12 – 16 | Good |
| 18 – 21 | Fair to Passable |
| 2 – 35 | Poor |
| 33 – 38 | Very Poor |
| >40 | Very Very Poor |

**Formulation development of Tablets [10,11,12]:**

Colon targeted tablets were prepared by using compression coating technology. Initially internal core tablet containing drug and super disintegrate was formulated. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit L100 and Eudragit S100 are used as polymers for compression coating.

Tablets are developed in two stages

1) Preparation of core tablet containing drug and super disintegrate.
2) Compression coating of prepared core tablets.

**Formulation of core tablet:**

The core tablets are formulated by using 15mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively. The composition of core tablet was given in below table.

**Table 4: Composition of core tablet**

| Ingredient Name | Quantity (mg) |
|---|---|
| Metronidazole | 200 |
| Sodium starch glycollate | 50 |
| Talc | 2 |
| Magnesium stearate | 2 |
| MCC pH102 | 46 |
| Total weight | 300 |

Total weight of core tablet was fixed as 60 mg. The tablets are prepared by using 5mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

**Formulation of compression coated tablets: [11, 12]**

The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials.the composition of coating layer is given in below table.

**Table 5: Composition of coating layer**

| Ingredient name | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Ethyl cellulose (mg) | 25 | 500 | 100 | | | | | | |
| Eudragit S100 (mg) | | | | 25 | 50 | 100 | | | |
| Eudragit L100 (mg) | | | | | | | 25 | 50 | 100 |
| Magnesium stearate (mg) | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc (mg) | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| MCC pH 102 (mg) | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Total weight | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

Compression coating layer was divided into two equal portions i.e., 100mg of each quantity .Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 9mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm$^2$.Then the prepared compression coted tablets are evaluated for various post compression parameters as per standard specifications.

**Evaluation of post compression parameters for prepared Tablets [11,12,13]**

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

**Weight variation test:**

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

**% Deviation = (Individual weight – Average weight / Average weight ) × 100**

**Table 6: Pharmacopoeial specifications for tablet weight variation**

| Average weight of tablet (mg) (I.P) | Average weight of tablet (mg) (U.S.P) | Maximum percentage difference allowed |
|---|---|---|
| Less than 80 | Less than 130 | 10 |
| 80-250 | 130-324 | 7.5 |
| More than | More than 324 | 5 |

**Hardness:**

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

**Thickness:**

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

**Friability:**

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

**% Friability = [ ( W1-W2) / W] × 100**

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

**Determination of drug content:**

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Metronidazole were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

**Drug release studies of Metronidazole core tablets:**

The core tablets containing 200mg Metronidazole of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

**Drug release studies of Compression coated Metronidazole tablets:**

The release of Metronidazole from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid ( SIF, pH 7.4 ) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid ( SIF, pH 6.8 ) was used upto 12 hours to mimic colonic pH conditions.

Drug release was measured from compression coated Metronidazole tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.

**Application of Release Rate Kinetics to Dissolution Data:**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**Zero order release rate kinetics:**

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and '$K_o$' is the zero order release rate constant. The plot of % drug release versus time is linear.

**First order release rate kinetics:** The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

**Higuchi release model:** To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

**Korsmeyer and Peppas release model:**

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, $M_t/ M_\infty$ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log ($M_t/ M_\infty$) versus log (time) is linear.

**Hixson-Crowell release model:**

$$(100-Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

## RESULTS AND DISCUSSION:

The present study was aimed to developing compression coated Metronidazole formulations for colon targeting using ethyl cellulose and enteric coating polymers like Eudragit L100 and Eudragit S 100. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

**Analytical Method**

Graphs of Metronidazole was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4)

**Table 7: Observations for graph of Metronidazole in 0.1N HCl (275 nm)**

| S.No. | Conc [mg/l] | abs |
|---|---|---|
| 1 | 1 | 0.001 |
| 2 | 3 | 0.075 |
| 3 | 4 | 0.128 |
| 4 | 5 | 0.199 |
| 5 | 6 | 0.280 |
| 6 | 7 | 0.343 |
| 7 | 8 | 0.397 |
| 9 | 11 | 0.557 |
| 10 | 12 | 0.623 |
| 13 | 21 | 0.823 |
| 14 | 22 | 0.87 |

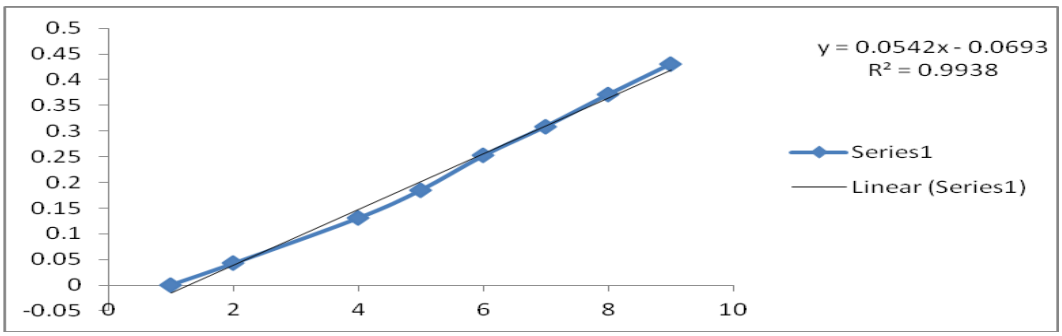


**Fig 1: Standard graph of Metronidazole in 0.1N HCl**

**Table 8: Graph of Metronidazole in 7.4 pH Simulated Intestinal Fluid (319nm)**

| S. No. | Conc [mg/l] | Abs |
|---|---|---|
| 1 | 2 | 0.057 |
| 2 | 3 | 0.129 |
| 3 | 4 | 0.204 |
| 4 | 5 | 0.284 |
| 5 | 6 | 0.372 |
| 6 | 8 | 0.566 |
| 7 | 9 | 0.625 |
| 8 | 10 | 0.709 |
| 9 | 12 | 0.893 |

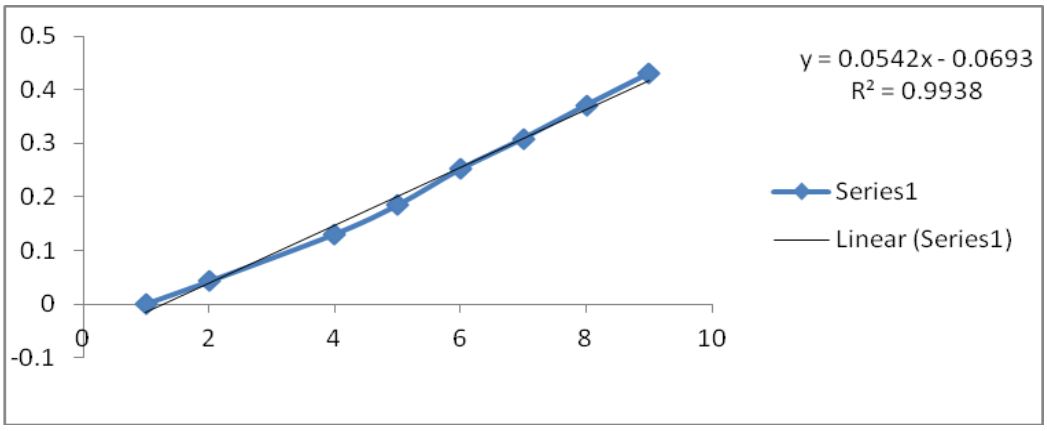


**Fig 2: Observations for graph of Metronidazole in 7.4 pH**

**Table 9: Standard graph of Metronidazole in 7.4 pH**

| No. | Conc [mg/l] | **Abs** |
|---|---|---|
| 1 | 1 | 0.001 |
| 2 | 2 | 0.043 |
| 4 | 4 | 0.131 |
| 5 | 5 | 0.185 |
| 6 | 6 | 0.252 |
| 7 | 7 | 0.309 |
| 8 | 8 | 0.371 |
| 9 | 9 | 0.430 |
| 10 | 10 | 0.504 |
| 13 | 13 | 0.684 |
| 14 | 14 | 0.740 |
| 15 | 15 | 0.799 |
| 16 | 16 | 0.896 |

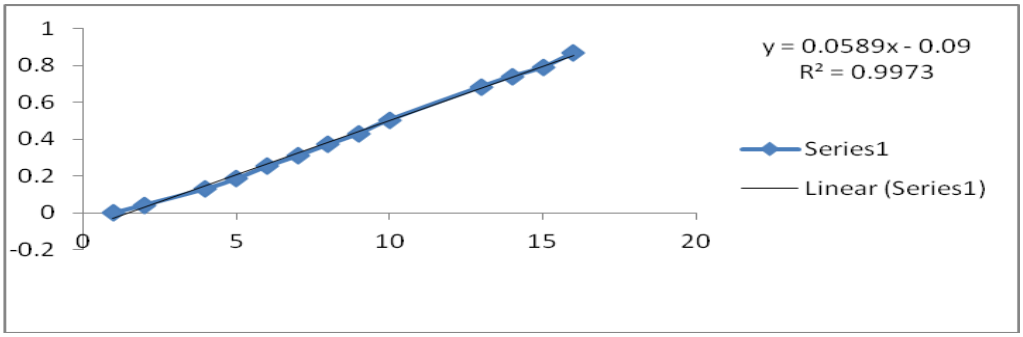


**Fig 3: Standard graph of Metronidazole in 6.8 pH**

**Preformulation parameters of core material**

**Table 10: Pre-formulation parameters of Core blend**

| Formulation Code | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| F1 | 36.01 | 0.55 | 0.645 | 14.72 | 0.85 |
| F2 | 34.8 | 0.57 | 0.66 | 13.63 | 0.86 |
| F3 | 32.74 | 0.53 | 0.606 | 14.19 | 0.858 |
| F4 | 35.33 | 0.531 | 0.613 | 13.37 | 0.866 |
| F5 | 36.24 | 0.549 | 0.641 | 14.35 | 0.856 |
| F6 | 36.12 | 0.564 | 0.666 | 15.31 | 0.846 |
| F7 | 37.08 | 0.581 | 0.671 | 13.41 | 0.865 |
| F8 | 35.12 | 0.567 | 0.654 | 13.12 | 0.845 |
| F9 | 35.45 | 0.571 | 0.689 | 13.28 | 0.855 |

Metronidazole blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Tables 7.4, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

**Quality Control Parameters For compression coated tablets:**

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 300 mg.

**Table 11: *Invitro* quality control parameters for compression coated tablets**

| Formulation codes | Weight variation(mg) | Hardness(kg/cm2) | Friability (%loss) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 312.5 | 4.5 | 0.52 | 4.8 | 99.76 |
| F2 | 305.4 | 4.2 | 0.54 | 4.9 | 99.45 |
| F3 | 298.6 | 4.4 | 0.51 | 4.9 | 99.34 |
| F4 | 310.6 | 4.5 | 0.55 | 4.9 | 99.87 |
| F5 | 309.4 | 4.4 | 0.56 | 4.7 | 99.14 |
| F6 | 310.7 | 4.2 | 0.45 | 4.5 | 98.56 |
| F7 | 302.3 | 4.1 | 0.51 | 4.4 | 98.42 |
| F8 | 301.2 | 4.3 | 0.49 | 4.7 | 99.65 |
| F9 | 298.3 | 4.5 | 0.55 | 4.6 | 99.12 |

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

**In-Vitro Drug Release Studies**

The compression coated tablets containing 12mg of Metronidazole were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of Metronidazole from compression coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid ( SIF, pH 7.4 ) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid ( SIF, pH 6.8 ) was used upto 12 hours to mimic colonic pH conditions.

Drug release was measured from compression coated Metronidazole tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm ,319 and 320 nm respectively. All dissolution runs were performed for six batches.

***In-vitro* Drug Release profile for coated formulations (F1-F9)**

From the dissolution values it was evident that the formulations F3 & F9 were retarded the drug release up to 12 hours, they shown drug release of 98.69 and 96.45 % respectively. Formulations F1 –F3 contains ethyl cellulose alone. As the concentration of ethyl cellulose increases retardation nature was increased.F3 formulation containing 150 mg of ethyl cellulose was show almost negligible amount of drug release in first 3 hours from the 5 $^{th}$ hour onwards it shown drug release as the time proceeds slowly the polymer was undergone erosion and allowed the drug to come out from the dosage form. The formulation was retarded drug release up to 12 hours and it showed maximum drug release in 12 hours i,e., in colon region. Similarly the formulation F9 containing Eudragit L 100 in the concentration of 150 mg also showed similar drug release pattern.

**Table 12: *In-vitro* Drug Release profile for coated formulations (F1-F9)**

| Time(hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5.42 | 0.26 | 0.34 | 2.39 | 1.11 | 1.44 | 8.06 | 2.65 | 1.32 |
| 2 | 12.65 | 0.44 | 0.54 | 17.88 | 1.29 | 12.30 | 20.94 | 7.23 | 2.14 |
| 3 | 23.56 | 4.65 | 1.26 | 30.45 | 11.71 | 24.44 | 30.26 | 18.19 | 2.90 |
| 4 | 66.8 | 17.87 | 2.22 | 40.59 | 30.22 | 36.61 | 45.44 | 30.27 | 8.11 |
| 5 | 86.9 | 29.18 | 3.05 | 55.01 | 40.18 | 47.30 | 63.86 | 42.06 | 17.72 |
| 6 | 98.35 | 35.45 | 18.41 | 73.85 | 54.53 | 55.68 | 72.93 | 51.40 | 30.40 |
| 7 | | 61.04 | 30.05 | 91.92 | 63.88 | 67.53 | 90.23 | 69.13 | 51.64 |
| 8 | | 74.24 | 48.69 | | 80.53 | 78.72 | | 78.45 | 61.59 |
| 9 | | 88.13 | 55.38 | | 95.06 | 83.34 | | 85.67 | 74.97 |
| 10 | | 96.39 | 72.34 | | 95.18 | 90.67 | | 98.45 | 84.18 |
| 11 | | 96.45 | 87.56 | | | 98.12 | | 98.12 | 96.87 |
| 12 | | | 98.69 | | | | | | 96.45 |

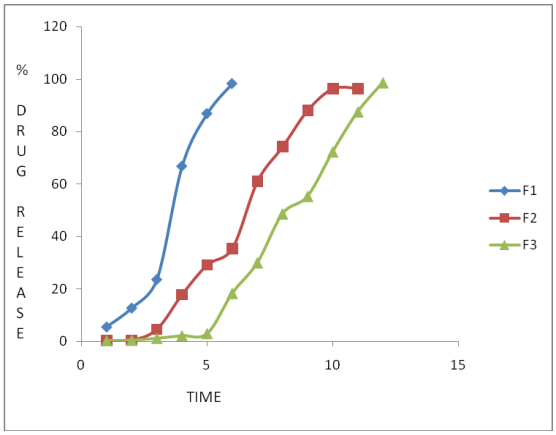


**Fig 4: Dissolution of formulations F1-F3**

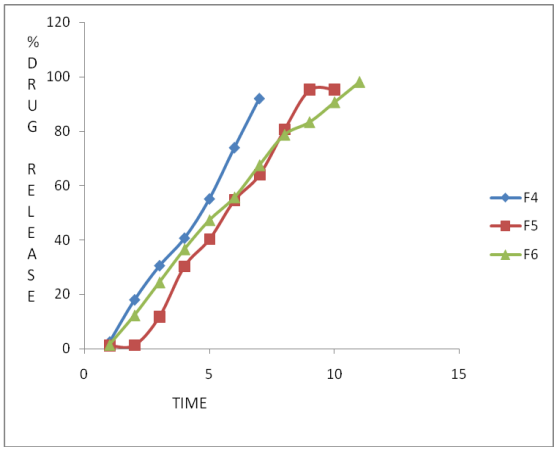


**Fig 5: Dissolution of formulations F4-F6**

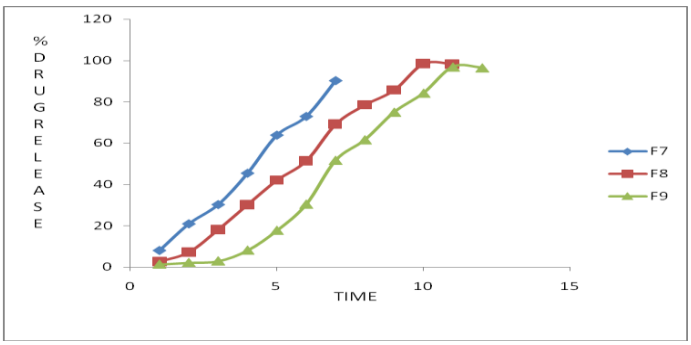


**Fig 6: Dissolution of formulations F7-F9**

**Application of Release Rate Kinetics to Dissolution Data:**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**Table 13: Release kinetics data for optimised formulation**

| CUMULATIVE (%) RELEASE Q | TIME ( T ) | ROOT ( T) | LOG( %) RELEASE | LOG ( T ) | LOG (%) REMAIN | RELEASE RATE (CUMULATIVE % RELEASE / t) | 1/CUM% RELEASE | PEPPAS log Q/100 | % Drug Remaining | Q01/3 | Qt1/3 | Q01/3-Qt1/3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | | 2.000 | 0 | 0 | 0 | 100 | 4.642 | 4.642 | 0.000 |
| 0.34 | 1 | 1.000 | -0.469 | 0.000 | 1.999 | 0.340 | 2.9412 | -2.469 | 99.66 | 4.642 | 4.636 | 0.005 |
| 0.54 | 2 | 1.414 | -0.268 | 0.301 | 1.998 | 0.270 | 1.8519 | -2.268 | 99.46 | 4.642 | 4.633 | 0.008 |
| 1.26 | 3 | 1.732 | 0.100 | 0.477 | 1.994 | 0.420 | 0.7937 | -1.900 | 98.74 | 4.642 | 4.622 | 0.020 |
| 2.22 | 4 | 2.000 | 0.346 | 0.602 | 1.990 | 0.555 | 0.4505 | -1.654 | 97.78 | 4.642 | 4.607 | 0.035 |
| 3.05 | 5 | 2.236 | 0.484 | 0.699 | 1.987 | 0.610 | 0.3279 | -1.516 | 96.95 | 4.642 | 4.594 | 0.048 |
| 18.41 | 6 | 2.449 | 1.265 | 0.778 | 1.912 | 3.068 | 0.0543 | -0.735 | 81.59 | 4.642 | 4.337 | 0.304 |
| 48.69 | 8 | 2.828 | 1.687 | 0.903 | 1.710 | 6.086 | 0.0205 | -0.313 | 51.31 | 4.642 | 3.716 | 0.926 |
| 72.34 | 10 | 3.162 | 1.859 | 1.000 | 1.442 | 7.234 | 0.0138 | -0.141 | 27.66 | 4.642 | 3.024 | 1.617 |
| 98.69 | 12 | 3.464 | 1.994 | 1.079 | 0.117 | 8.224 | 0.0101 | -0.006 | 1.31 | 4.642 | 1.094 | 3.547 |

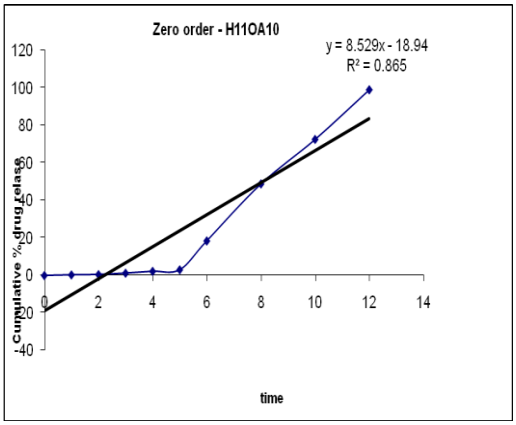


**Fig 7: Zero order release kinetics graph**

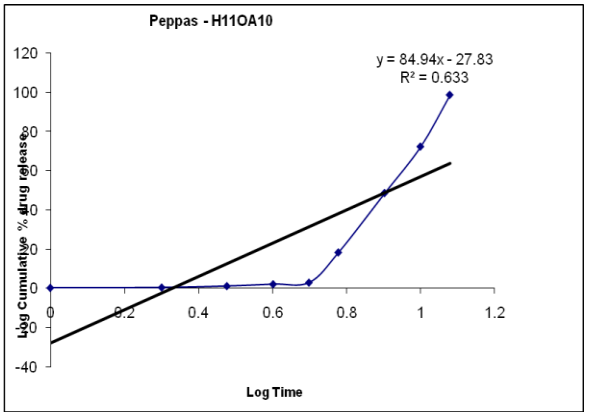


**Fig 8: Korsmayer peppas graph**

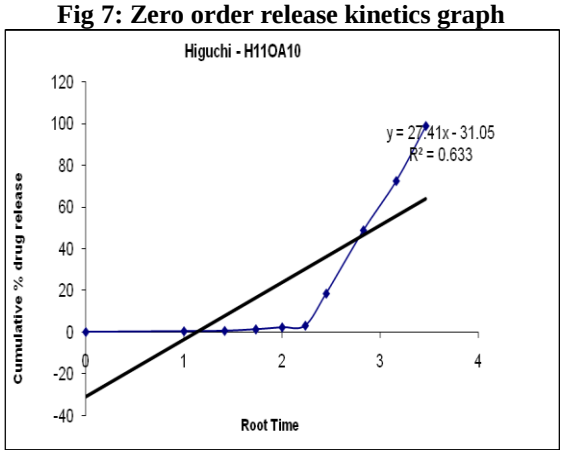


**Fig 9: Higuchi release kinetics graph**

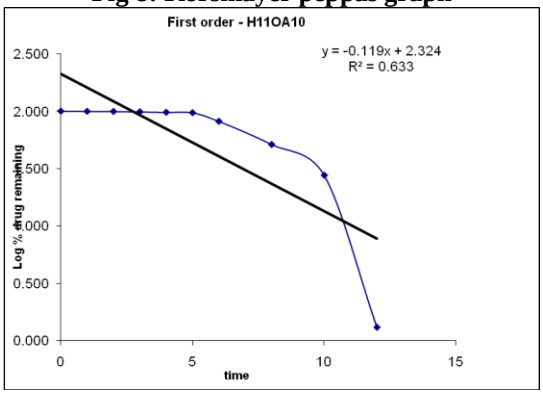


**Fig 10: First order release kinetics graph**

From the above graphs it was evident that the formulation F3 was followed zero order kinetics.

**Compatability studies:**

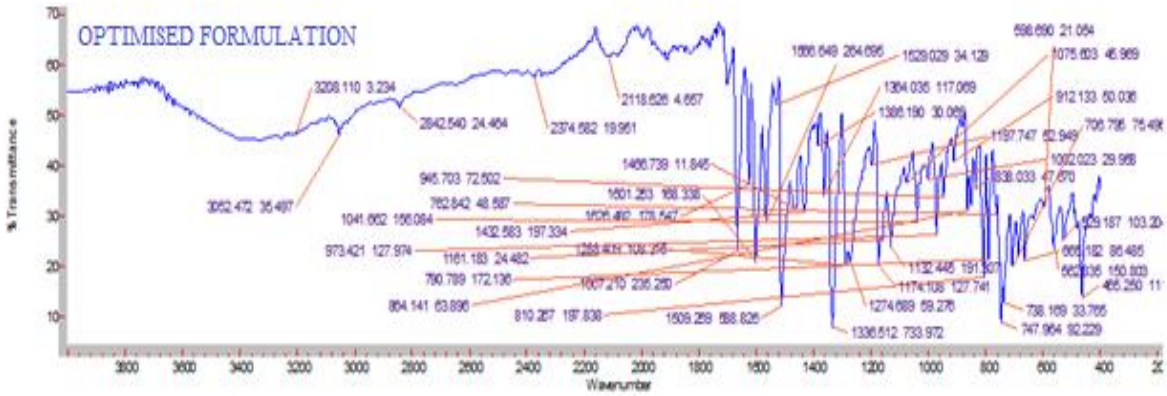


**Fig 11: FTIR spectrum of pure drug**

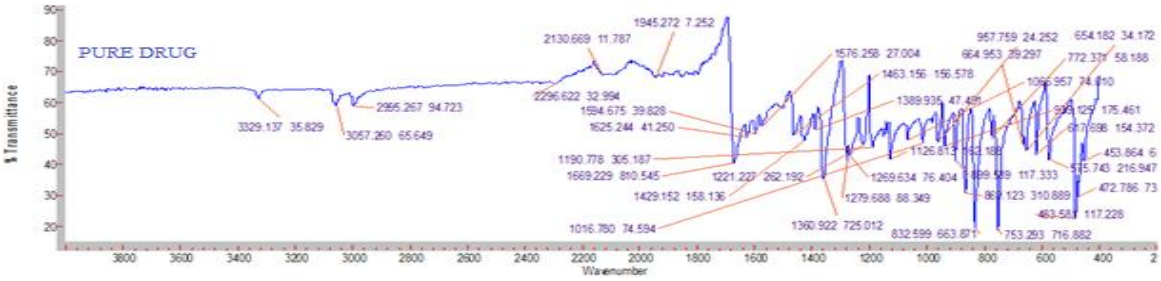


**Fig 12: FTIR spectrum of optimized formulation**

## CONCLUSION:

In the present research work sustained release matrix formulation of Metronidazole targeted to colon by using various polymers developed. To achieve pH-independent drug release of Metronidazole, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.

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