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FORMULATION, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF METHIMAZOLE

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Abstract:
Sustained release tablets are generally taken once or twice a day during a course of treatment whereas in conventional dosage forms there is need to take 3-4 times dosage in a day to achieve the same therapeutic action. The drug was confirmed using FTIR, DSC and UV Spectroscopy, and tested for the stability of drug and polymer interactions. The tablet is formulated using carbopol, Ethyl cellulose and Eudragit, which makes it a matrix tablet, the carbopol is hydrophilic in nature and ramming two are hydrophobic in nature, which controls the release of drug. This formulation was tested for Mucoadhession, Swelling, erosion, adhesion retention, Pre compression and post compression parameters, tested for in vitro drug release as dissolution and tested for stability.

Keywords: FTIR, *Mucoadhession, carbopol, eudragit, ethyl cellulose.*

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INTRODUCTION:

Sustained Release Drug Delivery System (SRDDS) is designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. Any drug or dosage form modification that prolongs the therapeutic activity of the drug. The release of the drug is retarded for a delayed and prolonged period of time in the systemic circulation. Sustained release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug. Sustained release tablets are generally taken once or twice a day during a course of treatment whereas in conventional dosage forms there is need to take 3-4 times dosage in a day to achieve the same therapeutic action. The oral route of drug administration is the most popular and successfully used for conventional delivery of drugs. It offers the advantages of convenience, ease of administration, greater flexibility in dosage form design, ease of production, and low cost. It is probable that almost 90% of all the drugs are administered by oral route. [1-2]

The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration.

Disadvantages of sustained release drug delivery system:

- Increased cost.
- Toxicity due to dose dumping.
- Unpredictable and often poor in vitro-in vivo correlation.
- Increased potential for first- pass clearance.
- Less flexibility in acute dose adjustment. [3]

Advantages of sustained release drug delivery system:

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided. [4]

MATERIALS AND METHODS:

The drug used is methimazole, which is procured form Innova Pharmaceuticals Pvt. Ltd., Nagpur, India. Polymers used are carbopol 934P NF, ethyl cellulose, PVP K30, eudragit RL 100, Magnesium stearate, Lactose, and Talc. All the excipients and drug used are of superior quality and potency.

METHODOLOGY

CONFIRMATION OF DRUG:

Confirmation of drug was carried out by using UV spectroscopy, infrared spectroscopy, and differential scanning calorimetry. [5-6].

UV Spectrophotometer:

The UV spectrum of methimazole in water was scanned at 400 nm to 200 nm. [7]

Infrared Spectroscopy:

The physical mixture was prepared by blending the sample with potassium bromide (1:100) and scanned over range of 4000-400 cm The infrared absorption spectra of pure methimazole was analyzed using FTIR spectrophotometer. [8-11].

Melting Point Determination by DSC:

The melting point of Methimazole was confirmed by differential scanning calorimetry (DSC 1, Mettler Toledo, Switzerland) which was performed at the scanning rate of 10°C/Min with 20 ml/Min of nitrogen spurging. [8-11].

Drug Polymer Interaction Studies:

Drug and excipients were filled in the prewashed ampoules and sealed. The sealed ampoules were kept at 37 ± 0.5°C for 28 days environment stability chamber. After completion of 28 days ampoules were removed from stability chamber and performed the drug-excipients compatibility studies. It was carried out by using Infrared spectroscopy (IR) and Differential Scanning Calorimeter (DSC). [8-11].

FTIR spectroscopy studies

IR spectroscopy was used to determine the molecular interaction between polymer and drug and polymer-polymer. The physical mixtures and drug sample were mixed with dried KBr in ratio 1:100.Then small fraction of mixture was compressed on automatic IR Press at pressure 10 tones to form transparent pellet. Then the IR spectrum of pellet was taken on FTIR spectrophotometer. [8-11].

DSC study:

Drug polymer interaction studies were carried out by using DSC. In this study thermogram of pure drug and with carbopol, ethyl cellulose, eudragit RL 100 and mixtures of drug: carbopol: ethyl cellulose: eudragit RL 100: was taken. Heating was done at a

scan rate of 10°C/min with 20 ml/Min of nitrogen purging. [8-11].

STANDARD CALIBRATION CURVE OF DRUG IN PH 1.2, PH 6.8 AND PH 7.4 BUFFER:
Methimazole (10mg) was dissolved in 100 ml of 1.2, pH 6.8 and pH 7.4 buffer to obtained working standard of 100 µg/ml. Aliquots of 0.5 ml, 1 ml, 1.5ml, 2ml & 2.5 ml from the stock solution representing 5, 10, 15, 2, & 2.5 µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted with respective buffers. Absorbances of the above solution were taken at 252 nm against the blank solution. A graph of absorbance versus concentration was plotted. [12]

SOLUBILITY STUDY OF METHIMAZOLE IN VARIOUS BUFFERS:
The solubility of methimazole in various media with varying pH was studied. Excess amounts of methimazole were placed in water, acidic buffer (pH 1.2), phosphate buffer (pH 6.8 and 7.4), the contents were gently shaken for 24 h at 25 °C in to mechanical shaker. The saturated drug solutions were filtered through 0.45 µm filter and then assayed spectrophotometrically at 252 nm after appropriate dilutions. All experiments were conducted in triplicate. [6]

EVALUATION OF PRECOMPRESSION PARAMETERS OF DRUG AND EXCIPIENTS. [13-16]
Physical properties of drug, polymers and excipients
Drug, polymers and excipients were characterized for their physical properties such as angle of repose, density, compressibility, Hausner'sratio. [13-16]

Angle of Repose
The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. [13-16]
The angle of repose was calculated using the equation.

$$\tan\theta = h/r \quad \ldots\ldots\ldots\ldots (1).$$

Where, 'h' and 'r' are the height and radius respectively of the powder cone.

Table 1: Standard values of angle of repose (θ)

Flowability	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

* May be improved by addition of glidant. (USP 29) Powder Flow (117)

Determination of bulk density:
Previously passed through 20 # sieve weighed 25 g of methimazole (W) transferred in 100 ml graduated cylinder. Carefully leveled the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in g/ml by the following formula. [13-16]

Bulk Density=Wt.of Powder/ Bulk Volume ……. (2).

Determination of tapped bulk density:
Accurately weighed 25 g of drug was taken, previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tapped the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tapped the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volume is less than 2% then final the volume (V2). [13-16]

TappedDensity=Wt.powder/Tapped Volume……. (3).

Compressibility
The compressibility index of all ingredients were determined by following equation [13-16]

Carr's index =[(TBD - LBD)/ TBD× 100]…..……. (4)

Hausner's ratio

Hausner's ratio was determined by following equation [13-16]

Hausner's ratio = TBD / LBD…… (5)

Table 2: Standard values of Carr's index and Hausner's ratio

Carr's index	Type of flow	Hausner's Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-38	Very poor	1.46-1.59
>38	Very, Very poor	>1.60

*May be improved by addition of glidant.

Calculation of Dose of Methimazole:

For sustained drug release up to 24 h, the total dose of drug required was calculated based on the fact that the conventional dose was 10 mg. The loading, maintenance and total doses were calculated by using following equations. [17-18]

Available pharmacokinetic data of drug

Cmax = 300 mcg/ml

Vd =0.5 L/kg = 30 L (60kg)

t1/2=5.5 hrs

Formula:

Loading dose = Cmax × Vd …….(6)

=300 × 30

= 9 mg

Total sustain dose of drug is calculated by using following formula,

Formula:

Dt = Dose [1 +(0.693 ×t/t 1/2)]…….(7)

= 9 (1 + 0.693 × 24/5.5)

= 9 (1 + 3.024)

= 36.21 mg

Preparation of the Swelling Matrix Tablets

The swelling matrix tablets each containing methimazole were prepared by direct compression method and their composition are shown in table 1.PVPK30 was used as binder. Talc and magnesium stearate was used as lubricants. Drug, polymers and binder were mixed using a glass mortar and pestle for about 10 min (passed through 30#). Then magnesium stearate was added as the lubricant (passed through 60#) and thoroughly mixed for 2min. The homogeneous powder mixture was fed through hopper and compressed in to 10 station tablet machine equipped with flat faced die-punch set of 9 mm diameter tooling. [19]

Table 3: Compositions of the different formulation batches for sustained release matrix tablet

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6
Methimazole	36	36	36	36	36	36
Carbopol	75	75	75	75	75	75
Ethyl Cellulose	60	65	70	75	80	85
Eudragit RL100	65	60	55	50	45	40
PVP K30	20	20	20	20	20	20
Lactose	41	41	41	41	41	41
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of Post Compression Parameters:

The different matrix tablets were prepared and evaluated for the following official and unofficial parameters.[7], [12], [17]

Hardness:

The hardness of ten tablets was measured using Monsanto hardness tester. The mean and standard deviation were computed and reported. It is expressed in kg/cm2. [17]

Friability:

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The % friability was calculated using the equation, 8

Friability (%) = (Initial wt-Final wt)/(Initial wt)×100 ……. (8)

Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table 4 and none deviate by more than twice the percentage shown. [7], [12]

Table 4: Weight variation tolerance for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10.0
130-324	7.5
More than 324	5.0

Drug content

Twenty tablets from each batch were weighed and

powdered. The powder equivalent to the 300 mg of tablet was accurately weighed and dissolved in 70 mL of distilled water for 15 min, diluted to 100 mL with distilled water and filtered through the 0.45 µm filters. 10 mL of filtrate was diluted to 100 mL of distilled water. Further dilution was made from 10 to 100 mL with the distilled water. Content of methimazole was determined spectrophotometrically by measuring the absorbance at 252 nm. [19]

Swelling Studies of Swelling Matrix Tablets

The ability of each tablet to swell in pH 1.2 and pH6.8 phosphate buffer medium was determined by swelling them up to their equilibrium. The measurement of swelling rates of carbopol matrix tablets was carried out after immersion of tablet in the test medium to relate the observed phenomena of drug release with rate of polymer hydration. Weighed tablets (W0) were placed in the closed plastic containers and rotated at 150 rpm using environmental orbital shaking incubator (Remi Instruments Ltd, Mumbai, India) with a medium of 0.1 N HCL (pH = 1.2 and pH =6.8) at 37 ± 0.5 °C. After 2, 5, 10, 20 min, and 1, 1.5, 2, 2.5, 3, 4, 6 ,8 and 16 h each swollen tablet was withdrawn from the medium and blotted to remove the surface water and then weighed (W1) on an single pan balance. The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. Percent swelling due to absorbed liquid or water uptake was calculated by equation:

$$\text{Percent swelling}=(W1-W0)/W0\times100 \quad \ldots\ldots\ldots\ldots (9)$$

Where,

W0 indicates weight of the dry tablet before immersion into the test medium and W1indicates weight of the swollen tablet after immersion into the test medium. [19]

The erosion studies of tablets was carried out after immersion of tablet in the test medium pH 1.2 and pH 6.8 phosphate buffer medium to relate the observed phenomena of loss on drying after equilibrium. Weighed tablets (W0) were placed in the closed plastic containers and rotated at 150 rpm using environmental orbital shaking incubator with a medium of 0.1 N HCl (pH =1.2 and pH = 6.8) at 37 ± 0.5 °C. The swollen tablets were placed in hot air oven for the period of 24 h at 80 °C. The wet samples were then dried in oven, allowed cooling in desiccators and finally weighed until constant weight was achieved (W2). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The percentage remaining of tablets after erosion was calculated by equation:

Percent Remaining = 100 - P.E.

Percent erosion was calculated by equation

$$\text{Percent erosion}=(W0-W2)/W0\times100\ldots\ldots\ldots\ldots(10)$$

Where,

W0indicates weight of the dry tablet before immersion into the test medium and W2indicates weight of swollen tablet after keeping into oven for 24 h at 80 °C.59

Mucoadhesion Studies of Carbopol Based Matrix Tablets

A simple apparatus was devised to measure the minimum detachment force shown in (Figure7.1). A piece of Goat stomach (2.0 cm×1.0 cm) removed from newly sacrificed Goat was adhered to a piece of glass, which was fixed on a plank and the plank was assembled with a little crown block. After hydrating the Goat intestine with distilled water, the tablet was by applying little force After hydrating the brought into contact with the Goat intestine by applying little force for minute. After the initial contact, the tablet was encircled by a thread which fastened a light plastic beaker through the crown block. Next, water was dropped into the beaker at a speed of 3.0 ml/minute using peristaltic pump until the tablet and Goat intestine were pulled apart by the gravity of water. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The experiments were performed in triplicate and average values with standard deviation (SD) were reported.60

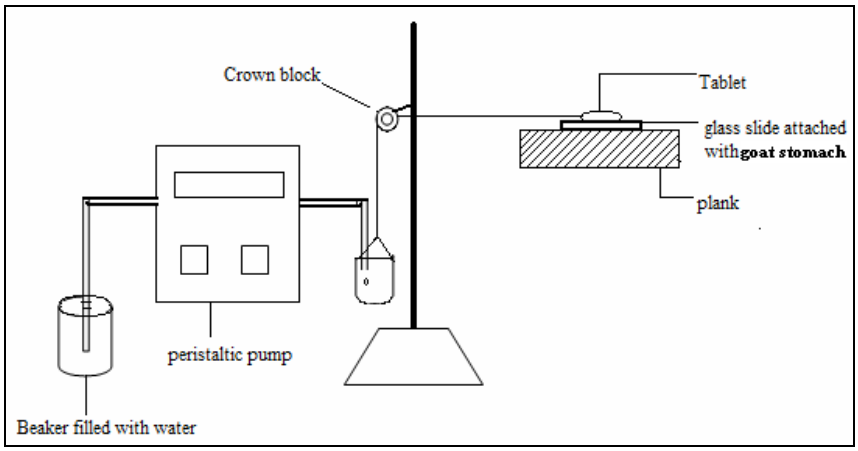

Figure 1: Design of reference assembly for mucoadhession studies

***In Vitro* Tablet Adhesion Retention**

In vitro tablet adhesion retention period the adhesion retention period of the tablets were evaluated by an in vitro method reported for measuring the mucoadhession of some water soluble polymers.[7]

In this an agar plate (1%, w/w) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 50 µl of 0.1 N HCl and attached to the center of agar plate by applying a light force with a fingertip for 20 sec. Five minutes later, the agar plate was attached to a USP disintegration test apparatus (Electrolab disintegration tester. USP) and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5˚C for 3 h.

The adhering tablet on the plate was immersed into the solution at the lowest point and got out of the solution at the highest point. The retention period of the tablet on the plate was noted visually.[8]

***In Vitro* Drug Release Study**

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 24 hours maintained at 37°C ± 0.5°Cusing an eight station USP XXII type 2 apparatus (Lab India, Mumbai, India). The agitation speed was 75 ± 1 rpm. The dissolution medium used in each flask was 600 ml of 0.1N HCl (pH 1.2) for initial 2 hours, after that the dissolution media was changed to 6.8 (or pH was raised by addition of 300 ml of solution of tribasic sodium orthophosphate to each flask (15.2 g in water). The dissolution study was carried out for 24h (initial 2 hours in pH1.2 and rest in pH 6.8) under sink condition. At every 1 hour interval samples of 5 ml were withdrawn from the dissolution medium and the volume was readjusted with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 252 nm by UV spectrophotometer. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard. [17], [20]

Dissolution Data with Different Models [21-23]

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q0-Qt=K0t \ldots \ldots\ldots (11).$$

Rearrangement of equation yields:

$$Qt= Q0+K0t\ldots\ldots\ldots\ldots (12).$$

Where Qt is the amount of drug dissolved in time t,Q0 is the initial amount of drug in the solution (most times, Q0= 0) and K0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some trans-dermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems. [21-23]

First order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$dc/dt=-kc\ldots\ldots\ldots (13).$$

Where K is first order rate constant expressed in units of time-1. Equation (5) can be expressed as:

logC=C0-Kt/2.303……. (14).

Where C0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. [21-23]

Higuchi model

This model is based on the hypothesis that
(1) Initial drug concentration in the matrix is much higher than drug solubility;
(2) Drug diffusion takes place only in one dimension (edge effect must be negligible);
(3) Drug particles are much smaller than system thickness;
(4) Matrix swelling and dissolution are negligible;
(5) Drug diffusivity is constant; and
(6) Perfect sink conditions are always attained in the release environment.
The data obtained were plotted as cumulative percentage drug release versus square root of time

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs. [21-23]

Hixson-Crowell model

Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. To study the release kinetics, data obtained from in vitro drug release studies were plotted as cube root of drug percentage remaining in matrix versus time.

Application: This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. [21-23]

Korsmeyer-Peppas model

To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time. [21-23]

Table 5:Co-relation between 'n' value and transport mechanisms in korsmayars peppa's equation

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.45 < n = 0.89	Non -Fickian transport
0.89	Case II transport
Higher than 0.89	Super case II transport

Stability studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing was to provide evidence on how the quality of a drug substance or drug product varies with time under influence of various environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and self lives to be established. The optimized methimazole formulations were strip packed (Al–Al strip, 0.04mm)and subjected to accelerated stability studies as per ICH guidelines (40 °C± 2°C/75% RH±5% RH). The samples were withdrawn periodically (0, 15, 30, 60, 90, and 180 days) and evaluated for the different physico-chemical parameters viz. appearance, weight variation, thickness, hardness, drug content, and in vitro release studies. [20]

RESULT AND DISCUSSION:

Preformulation study

Confirmation of drug

The drug is identified & Confirmed using following technical methods.

UV spectroscopy

The prepared solution of Methimazole was checked at 400 nm to 200 nm, the λ max absorption was observed at 252 nm which is matched with reported UV spectrum of Methimazole. as shown in fig.2

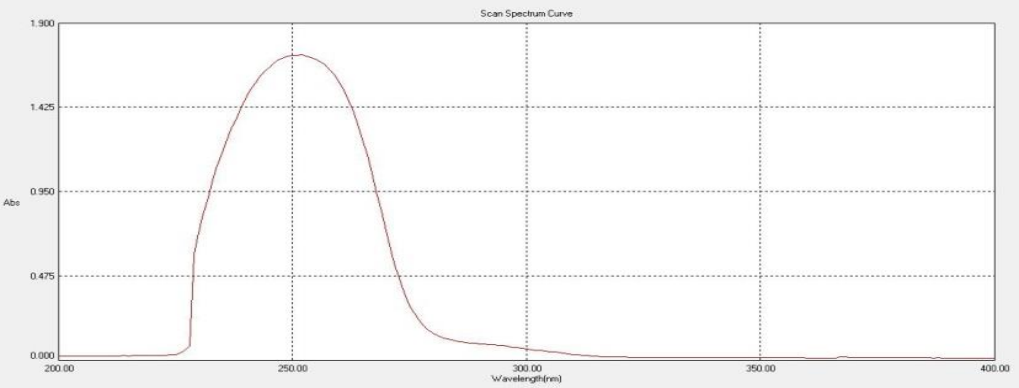

Fig. 2: UV spectrum of methimazole.

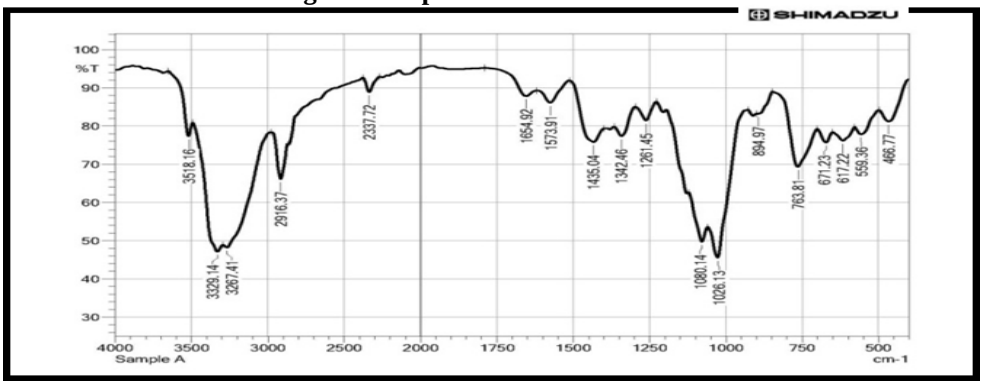

Fig.3: IR spectrum of methimazole

IR spectrum

The IR spectrum was performed in the Kbr dispersion as solid state. The IR spectrum of drug is shown in Fig.3. and interpreted for the confirmation. Spectra shows values of functional group, NH stretching at 3267.41, Aromatic CH stretching at 1573.91, Aliphatic CH stretching at 2916.37, C-H deformation at 1435.04.

Table 6: Interpretation of FTIR spectra of sample A (Pure Drug)

Assignment	Wave Number (cm -1)	Observed (cm -1)
N-H stretching in Amine	3000-3700	3267.41
N-H stretching in Amine	3000-3700	3518.16
N-H stretching in Amine	3000-3700	3329.14
C-H stretching in Alkane	2850-2960	2916.37
C=O stretching in Ester	1680-1760	1654.92
C=C stretching in Aromatic Ring	1500-1600	1573.91
C-H deformation in CH2	1435-1470	1435.04
C-N stretching in Amine	1180-1360	1342.46
C-O stretching in carboxylic acid	900-1250	1080.14
C-O stretching in carboxylic acid	900-1250	1026.13
C-H deformation (ortho-disubstituted)	735-770	763.81
C-Cl stretching	600-800	671.23
C-Cl stretching	600-800	617.22

DSC Thermograph

The DSC was performed for the confirmation of drug at scan rate of 10oC/min. It shows sharp melting endotherm and onset temperature 143 oC .The peak temperature 144oC as shown in Fig. 4. This was matched with the reported melting point of methimazole i.e. 143oC – 147oC.

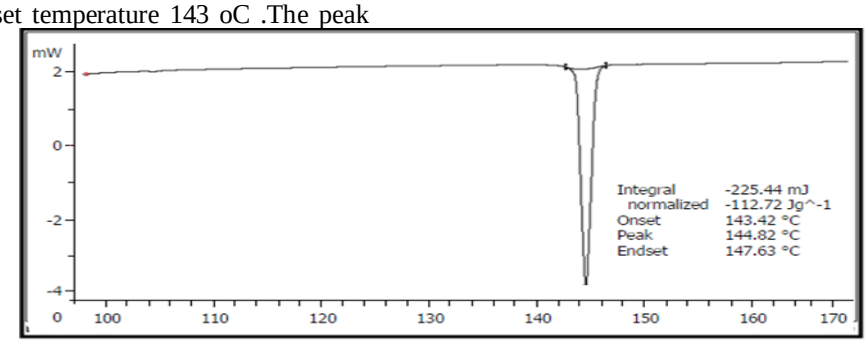

Fig. 4: DSC thermogram of pure methimazole

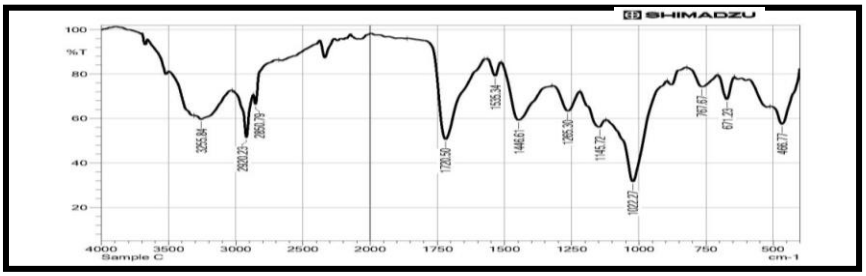

Fig. 5: FTIR spectra of mixture of drug: carbopol: ethyl cellulose: eudragit RL 100 (Drug-Polymer Interaction)

Drug Polymers and Polymer-Polymer Interaction Study

FTIR spectroscopy study

The Physical mixtures of drug and polymers was mixed and checked by FTIR spectral analysis for physical and chemical alteration of the drug with the polymers for characteristic changes. After comparing the spectra's of API – Fig. 3 with mixture of drug and polymer Fig. 5 it shows that there was no interference the functional group of the main principle peaks of the drug, as there are no any alteration found in the spectra of drug and polymer (mixture) Fig. 5 which is compared by spectra of drug and spectra of polymers (polymer interaction study) Fig. 3 & Fig. 6 the above comparison of three spectra shows no change in principal picks , that indicates, the drug and all polymers of the formulation was found to be compatible with each other .

Table 7: Interpretation of FTIR spectra of sample C (Drug-Polymer)

Assignment	Wave Number (cm -1)	Observed (cm -1)
N-H stretching in Amine	3000-3700	3255.84
C-H stretching in Alkane	2850-2960	2920.33
C-H stretching in Alkane	2850-2960	2850.79
C=O stretching in Ester	1680-1760	1720.50
C=C stretching in Aromatic Ring	1500-1600	1535.34
C-H deformation in CH2	1435-1470	1446.61
C-N stretching in Amine	1180-1360	1265.30
C-O stretching in carboxylic acid	900-1250	1145.72
C-O stretching in carboxylic acid	900-1250	1022.27
C-H deformation (ortho-disubstituted)	735-770	767.67
C-Cl stretching	600-800	671.23

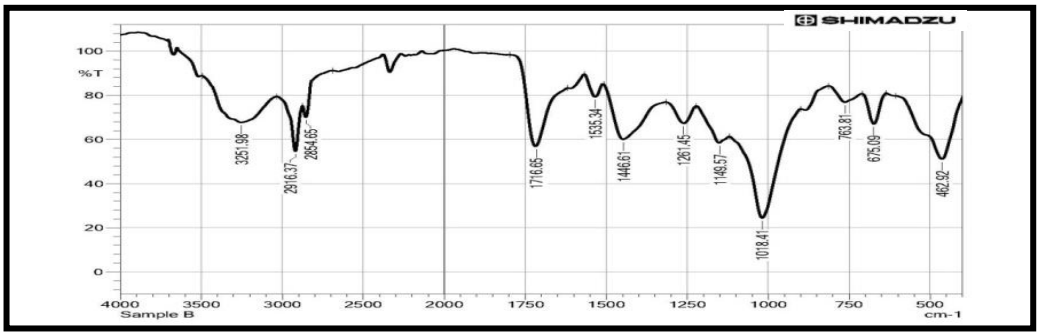

Fig. 6: FTIR spectra of mixture of carbopol: ethyl cellulose: eudragit RL 100 (Polymer Interaction)

Table 13: Interpretation of FTIR spectra of sample B (Polymers)

Assignment	Wave Number (cm -1)	Observed (cm -1)
N-H stretching in Amine	3000-3700	3251.98
C-H stretching in Alkane	2850-2960	2916.37
C=O stretching in Ester	1680-1760	1716.65
C=C stretching in Aromatic Ring	1500-1600	1535.34
C-H deformation in CH2	1435-1470	1446.61
C-N stretching in Amine	1180-1360	1261.45
C-O stretching in carboxylic acid	900-1250	1149.57
C-O stretching in carboxylic acid	900-1250	1018.41
C-Cl stretching	600-800	675.09
C-Cl stretching	600-800	763.81

The FTIR and DSC was very useful in predicting any interaction or changes shown in peak of functional group. so there was no any significant changes in peaks of FTIR spectra during compatibility study. Spectra of drug showed functional group ranges at NH - 3251.98cm-1, aromatic C=C -1535.34 cm-1, aliphatic CH - 2916.37 cm-1, C-N stretching - 1261.45 cm-1.The spectra of mixture of drug and polymer indicating the stable nature of the drug. According to the above interpretation it was found to be the spectra of drug; mixture of drug and polymer; and the spectra of polymers, and all ingradients were compatible with each other.

DSC studies

The endothermic peak near 145oC was observed for the pure drug powder see Figure 4 which shows melting temperature for methimazole. Nearer to 245 °C in Figure 8.6 the broadened endothermic peaks shows the presence of carbopol; Eudragit RL 100.

Near to 160 oC small endotherm shows presence of ethyl cellulose. The DSC thermograms shows there were no any significant difference was seen in onset temperature and peak temperature, as comparing to the pure drug's thermogram Fig.4. It indicates there were no interactions found in drug and polymers selected for the formulation and compatible with each other.

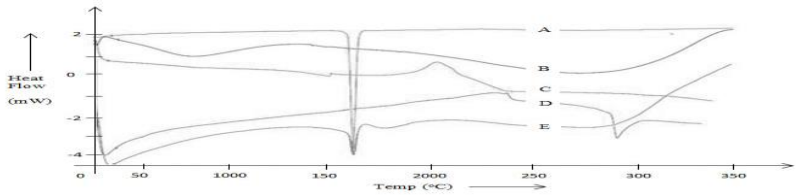

Fig.7: DSC thermogram of (A) pure drug (B) Carbopol 934 (C) ethyl cellulose (D) Eudragit RL100 and (E) formulation

Standard Calibration Curve Of Methimazole In PH 1.2, pH 6.8 And pH 7.4 Buffer

The absorbances are recorded and shown in Table 8 with the concentrations. The results are reported in Fig. 8, Fig. 9 and Fig. 10.

Table 8: Standard calibration curve of methimazole in pH 1.2, pH 6.8 and pH 7.4 buffer

Sr. No.	Concentration (µg/ml)	Absorbance			
		Water	1.2 pH	6.8 pH	7.4 pH
1	5	0.175	0.156	0.161	0.119
2	10	0.321	0.289	0.321	0.215
3	15	0.498	0.424	0.474	0.338
4	20	0.651	0.562	0.614	0.444
5	25	0.833	0.711	0.784	0.564

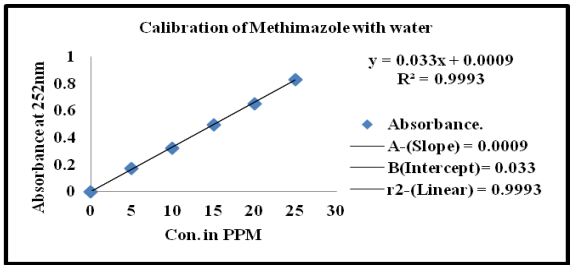

Fig.8 (A): Standard calibration curve of methimazole in Water

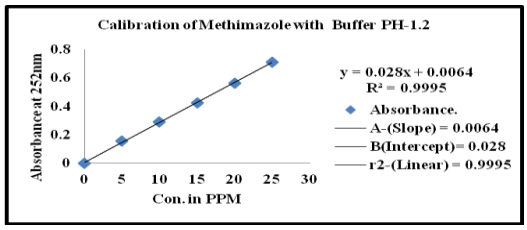

Fig. 8 (B): Standard calibration curve of methimazole in pH 1.2

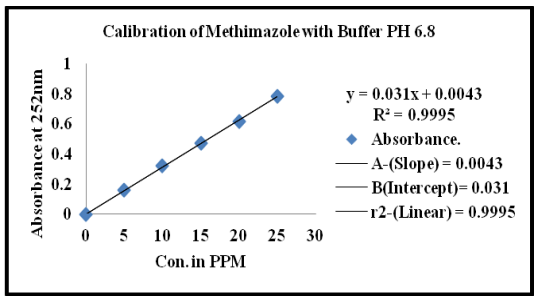

Fig.9: Standard calibration curve of methimazole in pH 6.8

The data was plotted for the Standard calibration curve; Absorbance against concentration; the data was found to be linear; for the concentration of 5 to 25 µg/mL which compiles the Beer's and Lambert's law.

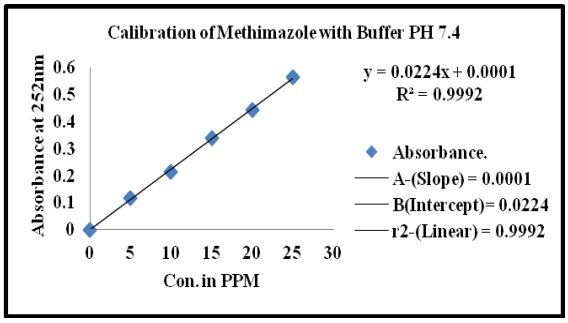

Fig. 10: Standard calibration curve of methimazole in pH 7.4

Solubility Study of Methimazole

The solubility of drug was checked according to the pH and reported in the Table 9, and graph was shown in Fig 11. According to the reported data and graph the pH of the buffer does not have any significant change in the solubility of methimazole.

Table 9: Solubility data of methimazole in various buffers.

Sr. No	Medium	Solubility (mg/ml)
1	Water	185.87
2	1.2 pH Buffer	175.29
3	6.8 pH Buffer	174.55
4	7.4 pH Buffer	173.66

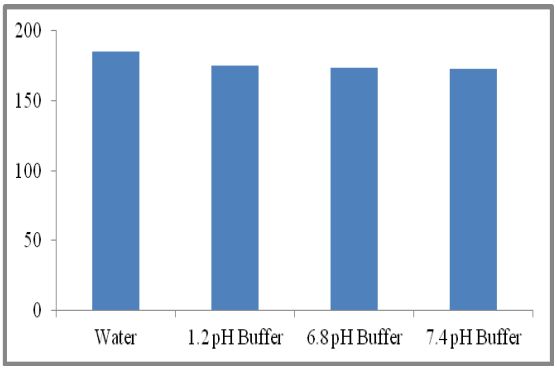

Fig.11: Solubility data of methimazole in various buffers.

Evaluation of precompression parameters of drug, polymers and excipients

Methimazole, excipients and polymers were checked for the physical properties generally which will be checked e.g. Angle of repose, Hausner's ratio, loose bulk density, compressibility index and tapped bulk density and the results were reported in Table 10

Table 10: Physical parameters of drug, polymers and Excipients

Batch	Parameters					
	Angle of Repose (θ)	Loose Bulk Density gm/cm3	Tapped Bulk Density gm/cm3	Hausner's Ratio (HR)	Compressibility Index (%)	Flow Type
Methimazole	31.58 ± 0.011	0.54 ± 0.007	0.62 ± 0.011	1.14± 0.004	0.54 ± 0.007	Good
Carbopol 934P	30.40 ± 0.011	0.56 ± 0.011	0.69 ± 0.007	1.22 ± 0.007	18.06 ± 0.007	Fair
Ethyl cellulose	32.30 ± 0.015	0.48 ± 0.007	0.59 ± 0.018	1.23 ± 0.024	18.74 ± 0.004	Fair
Eudragit RL100	30.66 ± 0.007	0.45 ± 0.031	0.55 ± 0.004	1.23 ± 0.011	18.44 ± 0.011	Fair
PVP (K30)	30.14 ± 0.011	0.43 ± 0.024	0.52± 0.018	1.22 ± 0.011	17.84 ± 0.011	Fair
Lactose	32.59 ± 0.007	0.99 ± 0.004	1.25 ± 0.004	1.26 ± 0.004	20.63 ± 0.007	Passable
Mg stearate	31.20± 0.018	0.53 ± 0.007	0.62 ± 0.011	1.17. ± 0.013	14.38 ± 0.004	Good
Talc	0.50 ± 0.007	0.50 ± 0.007	0.58 ± 0.007	1.17± 0.020	14.51± 0.011	Good

All values are mean ± SD, (n = 3)

Determination of precompression parameters for the matrix sustained release formulation blend:

According to the results of the achieved data the drug and excipients are showing good flow properties and within the normal limits; therefore we can say these drug and excipients are computable with each other and suitable for direct compression method.

Table 11: Precompression parameters of different formulation batches

All values are mean ± SD, (n = 3)

Batch	Parameters					
	Angle of Repose (θ)	Loose Bulk Density gm/cm3	Tapped Bulk Density gm/cm3	Hausner's Ratio (HR)	Compressibility Index (%)	Flow Type
F1	32.88 ± 0.011	0.53 ± 0.004	0.59 ± 0.011	1.12 ± 0.007	10.62 ± 0.011	Good
F2	31.74 ± 0.024	0.45 ± 0.007	0.52. ± 0.007	1.16 ± 0.013	13.98 ± 0.007	Good
F3	32.30 ± 0.011	0.42 ± 0.011	0.48 ± 0.013	1.15 ± 0.013	13.31 ± 0.011	Good
F4	32.02 ± 0.004	0.53 ± 0.018	0.61 ± 0.013	1.15 ± 0.020	12.87± 0.007	Good
F5	31.47 ± 0.011	0.46 ± 0.013	0.53 ± 0.018	1.16 ± 0.024	13.58 ± 0.011	Good
F6	31.20 ± 0.013	0.61 ± 0.011	0.73 ± 0.011	1.16 ± 0.013	17.19 ± 0.013	Fair

Evaluation of post compression parameters of matrix tablet

Post-compression parameters:

All the post compression parameters implies with the USP requirements or meets its requirement; for tolerance of weight variation. The drug content for all the tablet formulations was in between the range of 97.0 to 102.0%. The hardness, diameters, and thicknesses, difference and variation of the individual tablet batches was in the range of ± 3 SD. In the subsequent dissolution studies, the tablets of the same batch follow consistent dissolution behaviors. The tablet properties such as friability, thickness and hardness for the formulations F1 to F6 were determined. The friability of conventionally direct compressed tablet, which lose less than 1% of weight are considered acceptable. In this study the friability of formulation batches was below 1 % that means it is within the limit. It is known that the tablet hardness is not the absolute indicator of strength the hardness for the formulations within the range of 6-7 kg/cm2. All the post compression parameters (physical) was checked and reported as hardness, thickness and friability.

Table 12: Evaluation parameters of close proximity release profile sustained release tablet batches

Parameters	F1	F2	F3	F4	F5	F6
Thickness ±S.D.mm(n=5)	3.33 ± 0.031	3.36 ± 0.024	3.35 ± 0.040	3.33 ± 0.047	3.27 ± 0.036	3.31 ± 0.058
Hardness ±S.D.(kg/cm2)	6.64± 0.029	6.72 ± 0.007	6.65 ± 0.011	6.75 ± 0.013	6.62 ± 0.020	6.63 ± 0.033
Average Weight Variation (n=20) mg	297.35 ± 0.85	296.80 ± 0.85	298.03 ± 0.68	298.43 ± 0.54	298.05 ± 0.67	298.05 ± 0.65
Drug Content (%)	98.92 ± 0.46	98.49 ± 0.35	98.16 ± 0.56	97.87 ± 0.28	97.99 ± 0.27	98.10 ± 0.39
Friability (% w/w)	0.26	0.25	0.26	0.27	0.28	0.23

Swelling and Erosion Study

The best and suitable method for determining the matrix hydration and erosion directly by gravimetrical analysis is very fruitful and for better understanding the mechanism of release.

Table 13: Swelling and erosion study of optimized mucoadhesive matrix tablet

Time (h)	% Swelling ± S.D.	% Erosion ± S.D.
1	10.86 ± 2.32	4.48 ± 1.19
2	15.59 ± 3.23	10.69 ± 2.96
4	20.46 ± 2.84	24.48 ± 2.32
6	33.61 ± 4.59	26.98 ± 3.97
8	49.69 ± 5.65	35.15 ± 4.21
16	68.67 ± 4.92	58.14 ± 3.56

In the entire course of the dissolution the weight loss and gain proceeded throughout the dissolution with matrix hydration. For water retention the high capacity of carbopol matrix is used. The F-6 batch was showing maximum swelling up to 68.67± 4.92 %, which is slightly increased from 1 h to 16 h. As drug release followed by the erosion and diffusion (swelling) both the mechanism, the erosion study shows that till 16 h, 58.14 ± 3.56. erosion (mass loss) takes place.

Mucoadhession Strength Study

According to the discussed method mucoadhession was studied and result was reported in Table 14.

The Tablets which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the drug release from delivery system are called as Mucoadhesive system. The F-6 Batch having the good adjuvant combination and concentrations of drug and polymer such as, ethyl cellulose, Carbopol, Eudragit RL 100 which is having the mucoadhession force of 14.87 ± 0.016 N.

Table 14: Mucoadhession strength study of sustained release mucoadhesive matrix tablet

Formulation Code	Mucoadhession (N)
F 1	8.20 ± 0.007
F 2	8.37 ± 0.016
F 3	10.46 ± 0.013
F 4	10.87 ± 0.016
F 5	14.49 ± 0.011
F 6	14.87 ± 0.016

(n = 3, mean ± S.D.)

***In Vitro* Tablet Adhesion Retention Period**

in vitro mucoadhesive ability and In vitro tablet adhesion retention period test are the representative test of each other for matrix tablets. Like mucus of mucosa, contain the sulfate and carboxyl groups of negatively charged in large numbers of and these are carrier moiety for adhesion of tablet to the mucus membrane. The optimized batch F6 shows adhesion retention time of 10.95 ± 0.10 h. Therefore we can say that tablet has good mucoadhession that release drug for extended time or sustained release mechanism.

***In Vitro* Dissolution Study of Swelling Matrix Tablets**

From the present study the relation and dependency of drug and polymer concentrations, adjuvant type and the rate of drug release from the matrix tablet depended on each other. The formulation batch F6 formulation of Methimazole was found to be optimized and good formulation batch which releases good amount of the drug within 24 h. Generally, sustained release tablet must release the reported quantity of drug with predetermined kinetics in order to maintain an optimum effective drug plasma concentration.

To get this effect, tablet should be compressed and formulated so that it releases the drug in a predetermined and reproducible manner, the physical or morphological observation of the tablets during the dissolution testing which is an indicator that swelling was dominant during the entire course of the dissolution test. According to the theoretical release pattern, calculation shows once daily methimazole SR formulation should release 9 mg in 1 h and 27 mg per hour up to 24 h. This approach involves the use of swelling polymers that could retard the drug release for the period of 24 h in GIT.

Table 15: Dissolution profile of methimazole from

Time (h)	Formulation Batch (% CDR)					
	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	3.33	2.30	8.09	5.77	9.24	12.33
2	14.28	14.14	10.32	17.50	15.47	22.43
3	20.27	17.18	15.77	19.27	28.79	27.56
4	36.45	28.33	27.30	26.32	36.28	35.30
5	41.79	36.71	30.67	32.38	38.54	39.48
6	48.45	38.84	32.25	43.74	43.89	44.71
7	50.52	47.15	43.48	50.79	49.40	48.55
10	61.20	58.21	54.77	60.97	51.60	56.40
12	64.11	62.51	57.64	62.59	54.45	65.45
16	69.98	73.01	67.34	70.26	58.34	67.35
18	75.63	75.20	78.51	76.93	62.00	74.65
20	77.71	83.58	88.57	90.33	69.53	88.42
24	91.24	91.23	90.98	95.58	94.33	91.34

mucoadhesive matrix tablets

As the rate or frequency of stirring increases it will directly proportional the polymer chains detachment from the peripheral surface of the matrix whereas the adjuvant concentration has reached the disentanglement threshold, which ensures and enhancing drug release. Whenever erosion is the predominant part of release mechanism this effect can be more pronounced or collapse under fluid flow shear stress at high agitation rates when the gel structure is weak and likely due to shear stress at high agitation rates. Hence, drug release from Carbopol based swelling matrix tablet was followed by non fickinian diffusion (both due to diffusion as well as erosion). It is discussed and reported in this study that F6 formulation was swells to a large extent, due to which produces a firm gel, and releases the drug mainly and predominantly via swelling/diffusion mechanism.

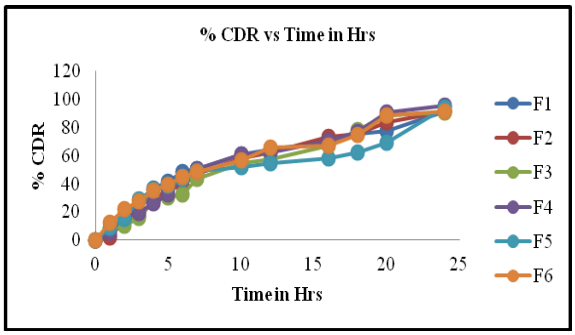

Fig. 12: Dissolution profile of formulation batch F 1 to F 6

Drug Release Kinetics of Dissolution Data

To know the mechanism of drug release from these formulation batches, the data was treated according to Zero order (% cumulative drug release vs time), First order approximation (log cumulative percent drug remaining to be diffused vs. time), Higuchi's approximation (cumulative percent drug diffused vs. square root of time), Korsmeyer-Peppas approximation (log cumulative percent drug diffused vs. log time).

The release of the drug from a matrix tablet containing hydrophilic polymers generally involves the factor of diffusion. Diffusion is related to the transport of drug from the dosage matrix into the in vitro study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases. The in vitro release profiles of the drug from the formulation batches can be expressed by Higuchi's kinetics, as it indicates swelling, Korsmeyer-Peppa's kinetics, as the 'n' value between 0.45 and 0.89 indicates that diffusion is coupled with erosion and hence this mechanism is called anomalous diffusion and Zero order kinetics, as it indicates that the tablets were swollen and the drug release was controlled by swelling.

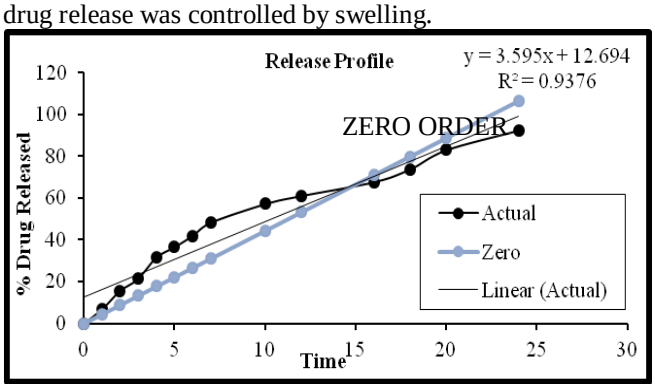

Fig.13: Release kinetic zero order release graph (F6)

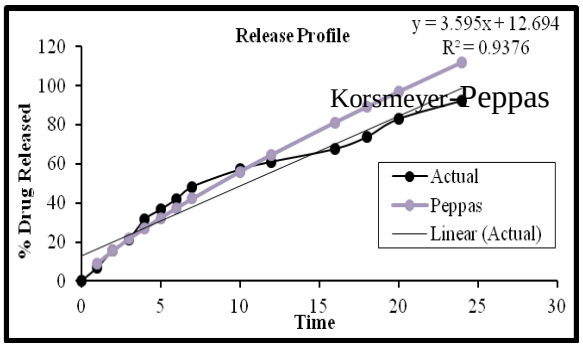

Fig.14: Release kinetic Korsmeyer-Peppas release graph (F6)

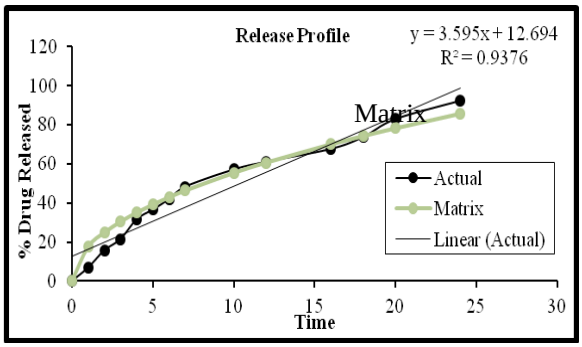

Fig.16: Release kinetic Matrix release graph (F6)

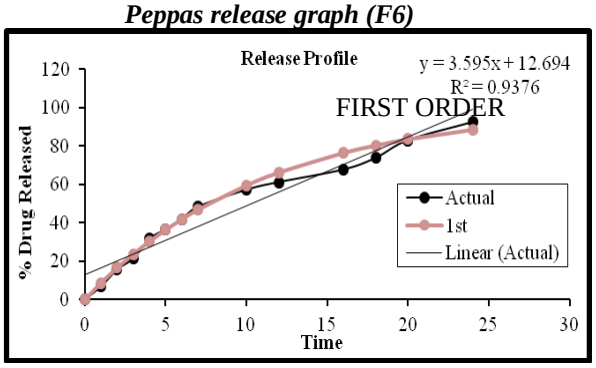

Fig. 15: Release kinetic first order release graph (F6)

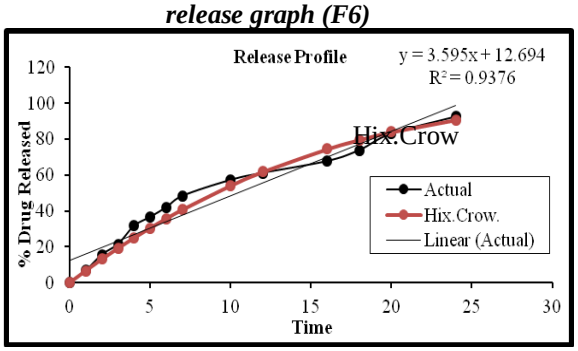

Fig. 17: Release kinetic Hix.Crow. Release graph (F6)

The release exponent (n) was calculated from the slope of the appropriate plots, and the regression coefficient (R2). The in vitro release profiles of the drug from the formulations shows regression coefficient (Higuchi's kinetics) R2=0.9911. Korsmeyer-Peppa's kinetics shows the 'n' value of 0.44 found between 0.44 and 0.89 indicates that diffusion is coupled with erosion and hence this mechanism is anomalous diffusion.

Table 16: Different Kinetics of formulation batches for Dissolution studies

Formulation Code	Zero Order (R2 value)	First order (R2 value)	Matrix (R2 value)	Hix. Crow (R2 value)	Korsmeyer Peppas		Best fitted model
					R2value	N value	
F 1	0.9437	0.9727	0.9778	0.9890	0.9939	0.72	Matrix
F 2	0.8276	0.9883	0.9728	0.9851	0.9724	0.68	1 st Order
F 3	0.9753	0.9451	0.9592	0.9898	0.9934	0.83	Matrix
F 4	0.9383	0.9136	0.9768	0.9744	0.9917	0.69	Matrix
F 5	0.9250	0.9634	0.9841	0.9858	0.9930	0.66	Matrix
F 6	0.7204	0.9587	0.9911	0.9816	0.9938	0.44	Matrix

Effect of hydrophilic polymer on methimazole release:

The Drug release decreased with increase in Carbopol (Main polymer) content and viscosity/molecular weight. According to Siepman and peppas suggested that drug release from matrices is sequently governed as follows;

At beginning, steep water concentration gradient are formed at the polymer/water interface resulting in water imbibition into the matrix, Due to imbibition of water, Carbopol swells resulting in change in polymer and drug concentration and increasing dimension of system. Upon contact with water drug dissolves and diffuses out of the matrix due to concentration gradients. With increasing water

content, the diffusion coefficient of the drug increases substantially. [22]

Thus, Carbopol was found to be dominating excipient controlling the release rate of methimazole in matrix tablets. Formulation batches from F1 to F6 contain the various conc of Carbopol polymer as a main release controlling agent.
After swelling and drug release of system, percent erosion was increased. Due to increase in percent erosion and complete drug release the size of system was reduced to some extent. The optimized formulations (F6) has shown the drug release up to 24 h hence these formulations revealed as sustained release dosage form. For further confirmation it will requires the in vivo bioavailability studies in animals or healthy volunteers and in vitro in vivo correlation.

Effect of hydrophobic polymer on methimazole release:
Use of single polymer may control the release rate but here tried the use of two hydrophobic polymers to ease the more prolong release rate of drug.

The In-vitro release for matrix tablets from the formulation F1 to F6 shows much slower release rate because low water affinity for ethyl cellulose and Eudragit (RL100). The release rate of drug was decreased when proportion of polymer was increases but differed quantitatively different drugs and different matrix materials. As relative concentration of ethyl cellulose and Eudragit is increased in the tablet, retards the penetration of dissolution medium in matrix by providing more hydrophobic environment and thus cause delay in the release of the drug from the tablet. At lower concentration Initial burst effect observed, while at higher concentration much slower release rates takes place.

STABILITY STUDIES
Stability studies were performed According to ICH QC guidelines. Physicochemical parameter was checked at the interval of 30, 60, 90 days are shown in Table 17. Which shows that the optimized tablets of batch F6 is stable even at exaggerated condition of temperature and humidity. After the time interval of 3 month, the optimized batch (F6) was checked for organoleptic properties, appearance, friability, which remains unaffected. The drug content as well as drug release was lies between 98-100%.

Table 17: Evaluation parameters of formulation batch F6 for stability studies

Formulation Code	Time (Days)	Appearance	Hardness (kg/cm2)	%Drug content	%Drug Release
F 6	Initial	White	6.81 ± 0.02	99.33 ± 0.46	98.77 ± 0.01
	After 30 days	White	6.79 ± 0.11	98.80 ± 0.09	98.85 ± 0.04
	After 60 days	White	6.61 ± 0.09	98.89 ± 0.02	98.64± 0.44
	After 90 days	White	6.57 ± 0.08	98.60 ± 0.04	98.67 ± 0.01

CONCLUSION:
The Methimazole matrix sustained release tablet was formulated, with Carbopol; ethyl cellulose and Eudragit RL100. The table is evaluated for mucoadhesion, swelling, erosion , which show the results as in vitro swelling and in vitro mucoadhesion force about 68.67±4.92 % and 14.87 ± 0.016 N, respectively. The optimized batch shows drug release up to 91.34 for 24 h. The batch had adhesion retention time up to 10.95 ± 0.10 h.
From all above findings is was concluded as the Carbopol with Eudragit RL100 and ethyl cellulose in optimum concentrations shows enhanced sustained-release dosage form and the F6 Formulation is found optimum batch. This has mainly Matrix mechanisms of drug release.

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