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Formulation and Development Matrix Tablets Of Methimazole

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ABSTRACT

Methimazole is active pharmaceutical ingredient effectively utilized in hyperthyroidism. Methimazole inhibits peroxidase as well as iodine interactions with thyroglobulin to produce triiodothyronine with thyroxine. Methimazole shows very low protein binding (1-10%) bounds to plasma proteins and easily metabolized by liver. In this investigation, efforts given to develop a sustained release matrix tablet of Methimazole. Sustained release drug delivery systems are for a maximum of 24 hours clinical effectiveness. Such systems are primarily for the drugs of short elimination half-life. However, drugs with long half-life also qualify if a reduction in steady state fluctuation is desired. Matrix tablets of methimazole were prepared by utilizing direct compression method. HPMC along with Sodium carboxy methyl cellulose used to retard drug release from the dosage form. Matrix tablets of methimazole were evaluated for different quality control test to improve quality of the product. In vitro release study of methimazole matrix tablets shows that polymer percentage used in the formula is enough to extend the release of the drug for at least 12 hr. In dissolution study of matrix of methimazole formulation F2 shows maximum drug release 97.93 % at the end of 6 hours while F1 shows least 83.64 %.

Keywords: Matrix tablet, Methimazole, Sustained Release

INTRODUCTION

In Conventional drug delivery system periodic doses of therapeutic agents are required. Most of the drugs formulated by conventional methods for effective drug administration, but some therapeutic agents are unstable or have narrow therapeutic ranges so require modification. These problems were overcome by developing sustained release drug delivery. Sustained release drug delivery promising approach not only retard the drug release but also minimize the dosing frequency. Sustained release drug delivery effectively improves absorption of the drug due to increase in residence time. Methimazole is absorbed through whole GI tract and bioavailability is 80-95%. Methimazole is biologically active agent widely used in hyperthyroidism. It prevents iodine and peroxidase. Methimazole has a biological half-life of 5 to 6 hours so it requires three-times a day dosing. Hence attempt was made to develop matrix tablets of Methimazole to improve all characteristics.

MATERIALS AND METHOD

Methimazole was purchased from Innova Laboratories, Division of Innova Remedies Pvt. Ltd. Nagpur. HPMC, Na-CMC was procured from Molychem, Mumbai. All other reagent and materials were of analytical grade.

Formulation of Methimazole Floating Matrix Tablets.[1]

The direct compression technique was used to formulate the Methimazole tablets for all batches containing methimazole. Polymers were passed through # 36 sieves. Magnesium stearate was passed through # 60 sieves. Weighed amounts of drug as well all other ingredients were transferred into polythene bag and blended for 10 minutes. The blend was compressed on 10-station rotary press using Round shaped punches. Punches measuring 8 mm were used for compression of the tablets.

Organoleptic Properties:[1,2]

The prepared tablets were evaluated visually for cracks, depressions, pinholes, colour and polish.

Dimensions:

Thickness of the tablets was measured using vernier calipers.

Hardness Test:

The hardness of tablets was tested using Monsanto tester. "Hardness factor", the average of the six determinations, were determined and reported.

Uniformity of Weight:

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage

difference in the weight variation should be within the permissible limits ($\square$7.5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability Test:

Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. It was rotated at a rate of 25 rpm. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula,

$$\text{Friability} = \frac{(W1 - W2)}{W2} \times 100$$

Where,

W1 = weight of the tablets before test

W2 = weight of the tablets after test

Content Uniformity:

Twenty tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately average weighed amount of tablets triturate was taken for analysis. Samples were transferred to different volumetric flasks and were diluted up to the mark using distilled water. The content was shaken well and kept for 30 minutes for dissolving the drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ max 251.5 nm against blank as reference.

In Vitro Drug Release (Dissolution Studies): [1,2]

In vitro drug release study of the samples was carried out using USP – type II dissolution apparatus (Paddle type). The dissolution medium, 500 ml of distilled water , was placed into the dissolution flask maintaining the temperature of 37 + 0.5 0C and rpm of 100. One Methimazole matrix tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 6 hours. Samples measuring 5 ml were withdrawn after every half hour up to 6 hours manually. During sampling, samples were filtered. The fresh dissolution medium (37oC) was replaced every time with the same quantity of the sample. Collected samples were analyzed at 251.5nm using distilled water as blank. The cumulative percentage drug release was calculated using PCP Disso v3 software.

FTIR of Methimazole Matrix Tablet:

The FT-IR spectrum of formulation F2 was recorded using FTIR spectrophotometer (Shimadzu 84005) using KBr pellet technique.

DSC of Methimazole Matrix Tablet:

DSC analysis of formulation F2 was performed using Shimadzu-Thermal Analyzer DSC 60 on 2-5mg samples. Samples were heated in an open aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 300°C under a nitrogen flow of 2 bar pressure.

RESULTS AND DISCUSSION

Organoleptic Properties:

All the prepared matrix tablets were white in color having smooth surface. The thickness of all the formulations was varies with drug: polymer ratio it ranges from 4.6-5.2 mm. The weight variation test was carried out as per official method and the average percentage deviation of all the formulation was found to be less than 5 %. It was found that all batches show percent drug content more than 98%. The tablet hardness of all the formulations was determined and it was found in the range 5.5-5.7 kg/cm^2. Another measure of tablet hardness was the friability. Compressed tablets that lose less than 1 % of their weight are generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable. The absorption bands shown by F2 are characteristic of the groups present in the molecular structure of Methimazole. The presence of absorption bands corresponding to the functional groups present in the structure of Methimazole and the absence of any well-defined unaccountable peaks is a confirmation of the purity of the formulation. The DSC curve of Methimazole shows a sharp endothermic peak at 191.26 ^{0} C corresponding to its melting, and indicating its crystalline nature. Drug release studies were made to determine whether the release of the drug is slow enough for at least 6-7 hr. Matrix of methimazole formulation F2 shows maximum drug release 97.93 % at the end of 6 hours while F1 shows least 83.64 %.

DSC of F2 formulation shows the endothermic peak at 146.20 without any degradation. There is no any shift of the peak but the intensity is less as compared to the pure drug. Peak intensity is less due to less content of the drug in the sample. Heat required for the peak is -1.88J/g. The value of release exponent, n, obtained from Krosmeyer Peppa's equation was greater than 0.5 for all eight formulation i.e.F1, F2, F3, F4, F5, F6, F7 and F8 indicate non-Fickian (Anamolous) diffusion so the final mechanism of drug release was swelling or chain relaxation of polymers followed by diffusion and erosion and the drug releases by first order phenomenon as there was continuous increase in % cumulative drug release up to 6 hours.
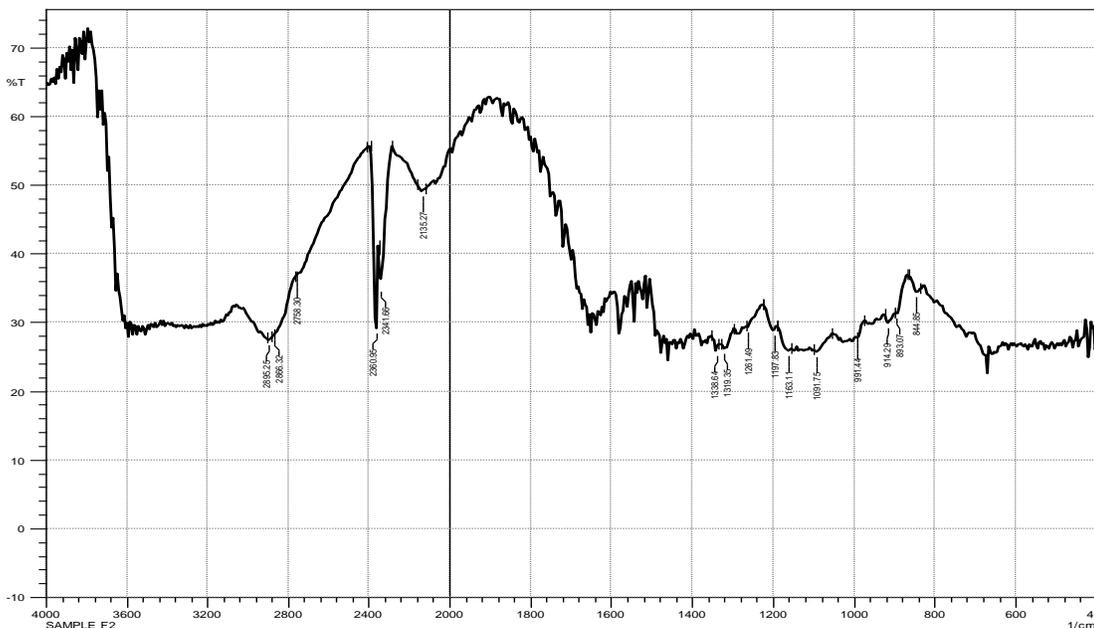
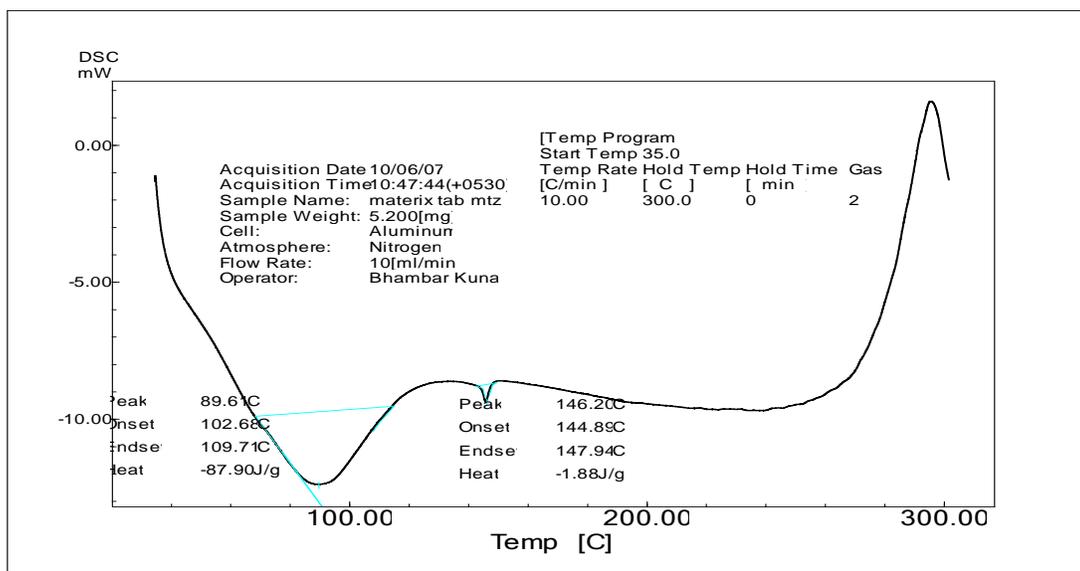**Figure 1: FT-IR Interpretation of Matrix Tablet (F2)**
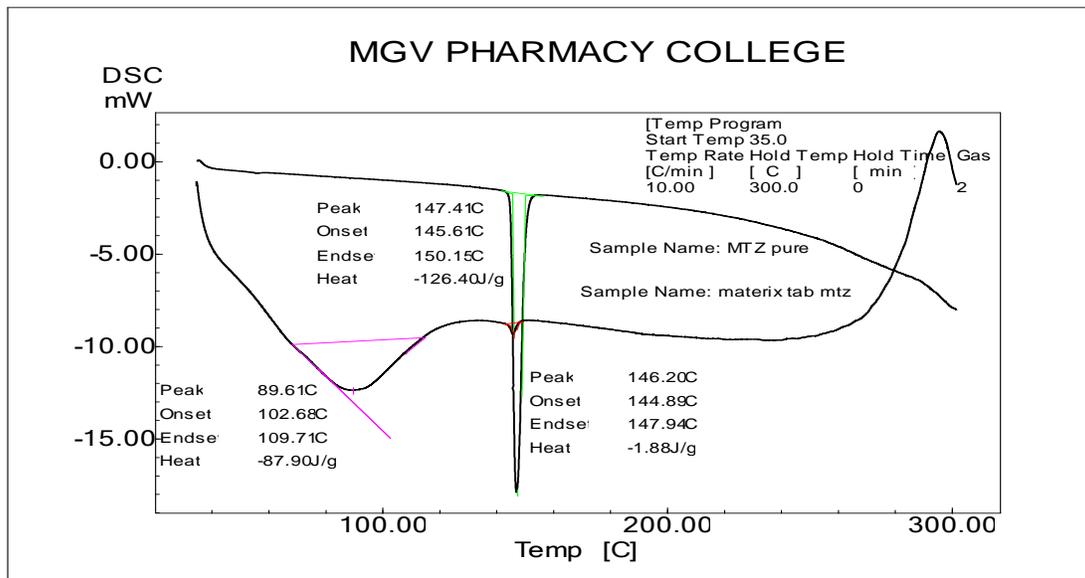

Figure 2: DSC Overlay of F2

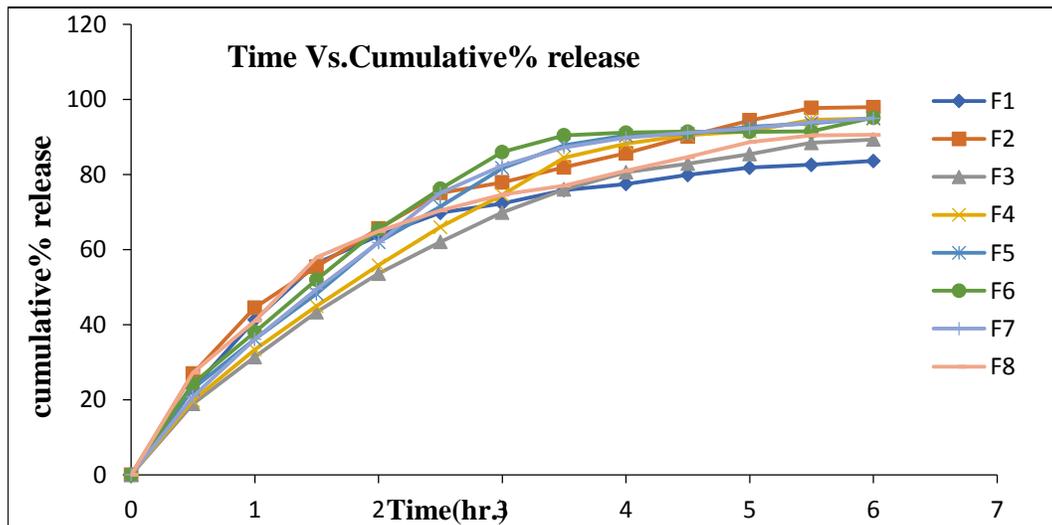**Figure 3: DSC Overlay of F2 and Methimazole**

Figure 4: Comparative Dissolution Profile of Methimazole Matrix Tablets
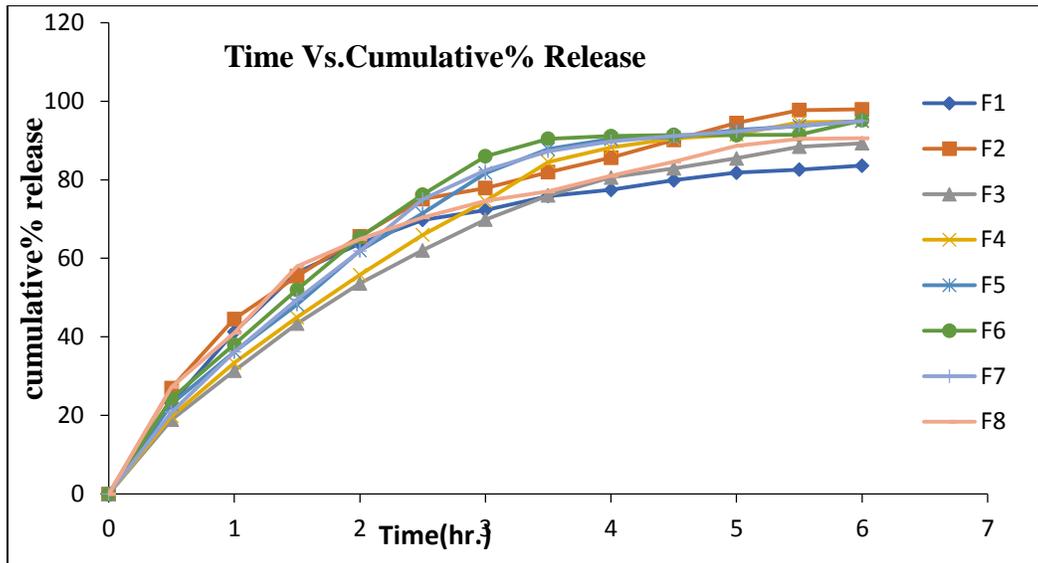
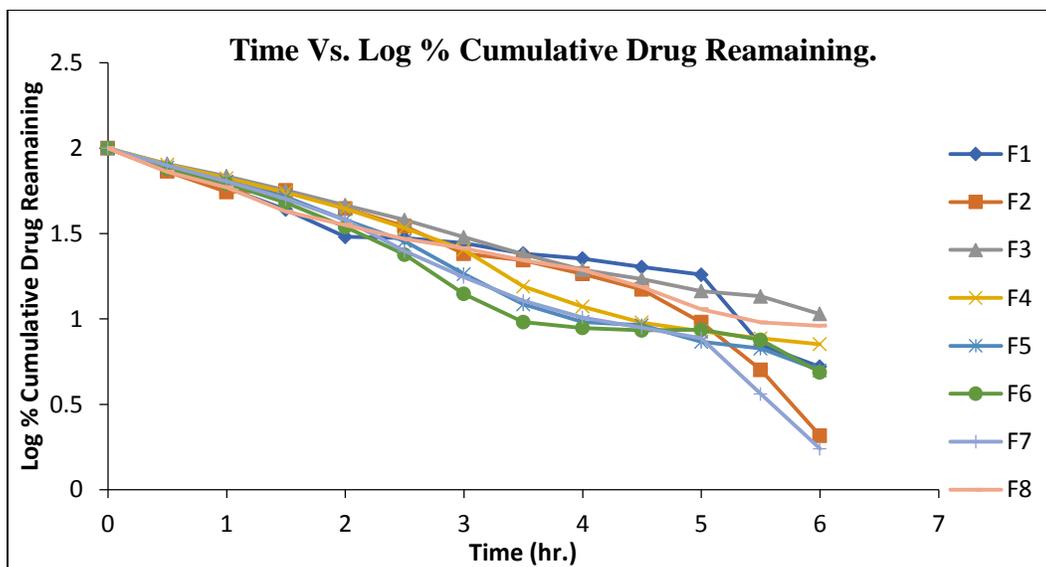**Figure 5: Methimazole Matrix Tablet Combined Zero Order Graph**

Figure 6: Methimazole Matrix Tablet Combined First Order Graph
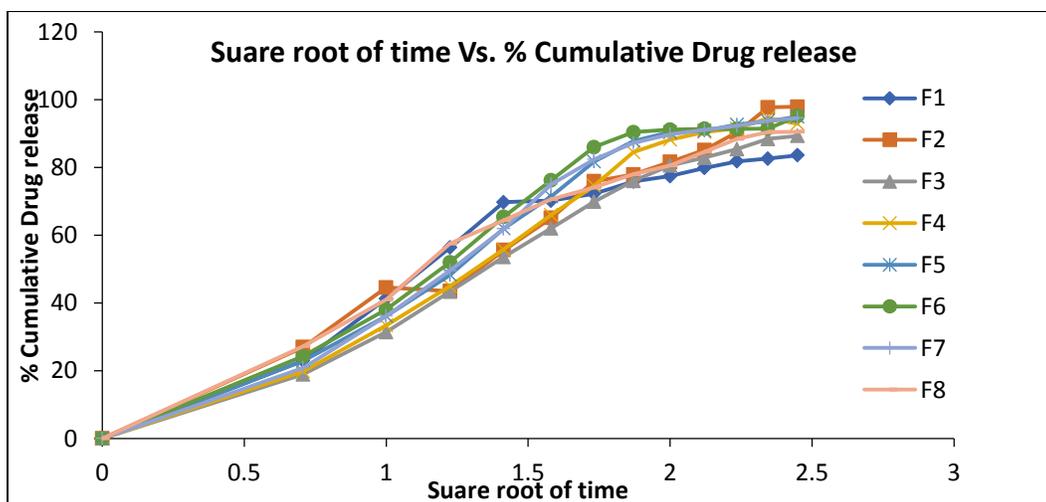
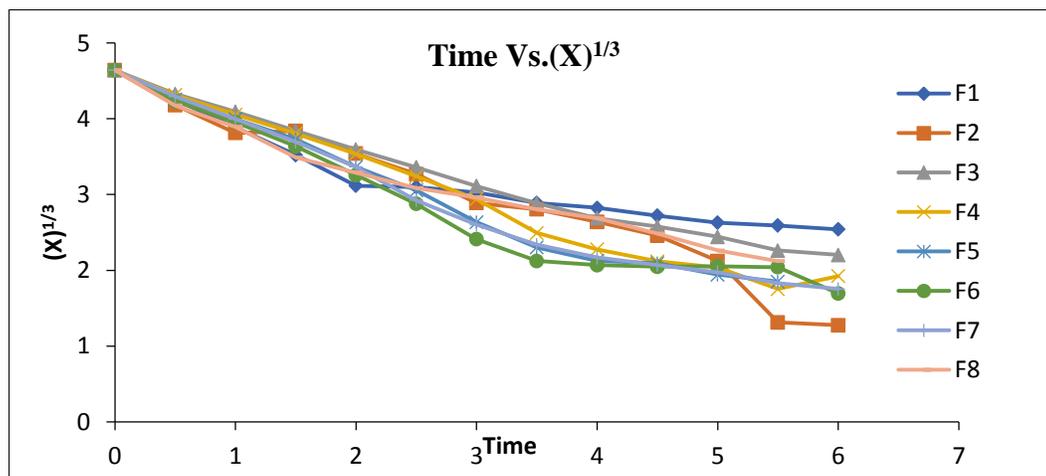

Figure 7: Methimazole Matrix Tablets Combined Higuchi Graph.

Figure 8: Hixon-Crowell Model for Methimazole Matrix Tables

Table 1: Formulation Methimazole Matrix Tablets:

Formulation code	HPMC (mg)	Na-CMC (mg)	Avicel (mg)	Talc (mg)	Mg-sterate (mg)	Drug (mg)	Total Wt. (mg)
F1	60	60	60	3	2	15	200
F2	50	50	60	3	2	15	180
F3	60	50	60	3	2	15	190
F4	60	50	50	3	2	15	180
F5	50	60	60	3	2	15	190
F6	50	60	50	3	2	15	180
F7	60	60	50	3	2	15	190
F8	50	50	50	3	2	15	170

Table 2: Evaluation of tablets parameters

Formulation code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Average weight (mg)	Friability (%)	Drug content(%)
F1	5.1±0.21	8	6.5±0.65	199±0.95	0.71±0.12	98.12±0.18
F2	5.1±0.18	8	6.8±0.45	178±1.12	0.93±0.16	98.32±0.65
F3	5.2±0.98	8	6.3±0.65	189±0.69	0.88±0.14	99.45±0.64
F4	4.6±0.65	8	6.4±0.63	177±0.96	0.80±0.18	98.35±0.27
F5	4.8±0.85	8	6.7±0.96	189±0.92	0.67±0.11	98.25±0.54
F6	4.9±0.45	8	6.6±0.62	179±0.82	0.79±0.18	98.65±0.32
F7	4.8±0.18	8	6.8±0.85	188±0.78	0.61±0.15	99.45±0.69
F8	4.9±0.96	8	6.7±0.18	168±0.87	0.86±0.12	98.62±0.25

Table 3: Cumulative % Drug Released Profile of Formulation of Methimazole Matrix Tablets.

Time (min)	Cumulative % release (mean ± S.D.) Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
30	23.02±0.71	26.95±2.45	18.90±1.25	19.81±1.23	22.91±0.56	24.28±0.21	20.83±2.12	27.23±3.87
60	41.27±1.02	44.56±1.05	31.40±0.48	33.38±1.56	36.15±0.36	38.07±0.87	36.14± 0.45	41.01±0.85
90	56.36±0.78	55.46±0.11	43.35±0.45	44.95±1.46	48.25±1.65	52.00±1.56	49.52±0.87	57.95±1.56
120	63.73±0.66	65.62±0.78	53.60±0.45	55.82±0.86	61.99±0.85	65.42±0.85	61.90±1.56	64.93±0.87
150	69.80±0.54	75.08±0.45	62.04±1.23	65.98±0.45	71.45±1.85	76.21±0.87	75.05±1.56	70.43±0.85
180	72.24±0.87	77.09±1.02	69.87±0.45	74.57±0.85	81.70±0.45	86.00±0.45	82.40±0.85	74.64±1.56
210	75.86±1.56	81.93±0.25	76.03±0.78	84.51±0.96	87.82±1.36	90.42±0.85	87.22±0.87	77.05±0.45
240	77.45±0.55	85.63±0.78	80.60±0.85	88.21±0.85	90.39±1.64	91.14±0.87	89.80±1.56	80.99±0.87
270	79.86±0.56	90.13±0.45	82.89±0.25	90.48±0.68	90.81±0.85	91.42±1.56	91.11±0.85	84.61±1.56
300	81.82±0.78	94.43±0.74	85.45±1.52	91.54±0.32	92.66±2.98	91.35±0.87	92.30±1.56	88.65±0.85
330	82.58±0.89	97.74±0.87	88.43±1.35	94.60±0.35	93.66±2.36	91.50±0.85	93.86±0.85	90.43±1.56
360	83.64±0.22	97.93±0.25	89.32±2.12	94.89±0.73	95.01±2.56	95.14±2.35	94.96±2.31	90.56±1.56

Table 4: Kinetic treatment of prepared Methimazole floating matrix tablets.

Formulation Code	Coefficient of determination (r^2)					Korsmeyer plot n (release exponent)
	Zero order	First order	Higuchi square root	Hixson Crowell Cube Root	Korsmeyer plot	
F1	0.9120	0.8680	0.9883	0.8236	0.6878	0.5414
F2	0.9602	0.8504	0.9957	0.9590	0.5949	0.5521
F3	0.9866	0.9874	0.9903	0.9723	0.6527	0.6307
F4	0.9945	0.9785	0.9930	0.9703	0.6549	0.5255
F5	0.9860	0.9813	0.9985	0.9648	0.6210	0.5913
F6	0.9894	0.9495	0.9861	0.9131	0.5942	0.5576
F7	0.9634	0.9685	0.9740	0.9160	0.6561	0.6499
F8	0.9729	0.8581	0.9968	0.8086	0.5927	0.5132

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