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FORMULATION AND CHARACTERIZATION OF METHIMAZOLE-LOADED TRANSDERMAL PATCHES FOR CONTROLLED SYSTEMIC DELIVERY

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Abstract:

Methimazole is an antithyroid agent widely prescribed for the management of hyperthyroidism; however, conventional oral administration is associated with frequent dosing, variable bioavailability, and systemic adverse effects. The present study aimed to formulate and characterize methimazole-loaded transdermal patches for controlled systemic delivery to improve therapeutic efficacy and patient compliance. Prior to formulation, pre-formulation studies were performed to evaluate the physicochemical properties of methimazole, including organoleptic characteristics, solubility profile, melting point, partition coefficient, drug identification, and compatibility with selected polymers using Fourier Transform Infrared (FTIR) spectroscopy. The transdermal patches were prepared by the solvent-casting technique using suitable film-forming polymers, plasticizers, and permeation enhancers.

The formulated patches were characterized for Physio chemical and pharmaceutical properties, including appearance, thickness, weight uniformity, folding endurance, tensile strength, percentage moisture content, moisture uptake, drug content uniformity, surface pH, and flatness. In vitro drug release studies were carried out using a suitable diffusion medium, while ex vivo permeation studies were performed across biological membrane models to assess transdermal drug transport. Release kinetics were analysed using mathematical models to determine the mechanism of drug release. The optimized methimazole transdermal patch demonstrated acceptable physio chemical properties, uniform drug distribution, sustained drug release, satisfactory permeation characteristics, and good stability throughout the study period. The findings suggest that the developed transdermal system has the potential to provide controlled systemic delivery of methimazole, reduce dosing frequency, and enhance patient adherence, making it a promising alternative to conventional oral therapy for the long-term management of hyperthyroidism.

Keywords: *Methimazole, Transdermal Patch*

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INTRODUCTION:

Analytical method development:

A.UV scan:

A 100mg of Methimazole was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10 µg/ml. 10 µg/ml solution was scanned from 200-600nm.

B. Construction of calibration curve:

A 100mg of Methimazole was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 10 to 50 µg /ml. The absorbances of these solutions were determined spectrophotometrically at 254 nm.

7.2. Compatibility study

FTIR study:

The infrared spectrum of the pure Methimazole sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

7.3. Preformulation study

A. Colour, Odour, Taste and Appearance:

The drug sample was evaluated for its Colour, Odour and Appearance.

B. Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

C. Determination of solubility:

The solubility of Methimazole was determined by adding excess amount of drug in the solvent.

The Methimazole has very low aqueous solubility. Its solubility is not reported in any official book, so determination of solubility is important. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Methimazole prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 254 nm and 258 nm for phosphate buffer and distilled water respectively.

7.4. Formulation of transdermal patches [47]

Preparation of blank patches:

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of Drug Incorporated Transdermal Patches:

The matrix-type transdermal patches containing Methimazole were prepared using different concentrations of Hydroxypropyl methyl cellulose, Sodium alginate and Sodium carboxymethyl cellulose. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. DMSO was used as plasticizers. Ethanol was used as the penetration enhancer. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 8 mg. the formulation table is given in table no. 7.3.

Table 7.3: Formulation of Methimazole hydrochloride Patches

Ingredients	M1	M2	M3	M4	M5	M6
Methimazole(mg)	40	40	40	40	40	40
Hydroxypropyl methyl cellulose (mg)	100	200	-	-	-	-
Sodium alginate(mg)	-	-	100	200	-	-
Sodium carboxymethyl cellulose(mg)	-	-	-	-	100	200
Glycerin (ml)	4	4	4	4	4	4
Ethanol (ml)	2	2	2	2	2	2
DMSO(ml)	2	2	2	2	2	2
Water (ml)	3	3	3	3	3	3

7.5. Evaluation Parameters of patches

7.5.1. Physical evaluations

a.

Thickness[47]

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

b. Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

c. Weight variation[47]

The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

d. Drug content Determination

The prepared drug contained patches specified surface area (2 cm^2) were cut and dissolved in (5% of methanol contained) 100ml of pH 7.4 phosphate buffer, and vigorously Shaked for 12hrs, and then sonicated for 15 minutes, centrifuged at 5000 rpm for 30 min. Filter the drug contained polymeric solution through 42 number Whatman filter paper, then 1ml of the filtrate was taken in a test tube and dilute it for five times with same solvent by using double beam Uv-Visible spectrophotometer to determined drug content at λmax 258 nm. Respected Placebo patch was taken as a blank solution.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the center and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = I1 - I2 \text{ X } 100$$

I2 = Final length of each strip

I1 = Initial length of each strip

7.5.2. *In-vitro* Drug Diffussion Study:

The in vitro study of drug permeation through the semi permeable membrane was performed using a Franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5ºC. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 254 nm

7.6. Drug release kinetics:

Diffusion data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released vs time

$$C = K0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

$$Log C = Log C o - k t / 2.258$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi Model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = K t 1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kors meyer Peppas equations:

Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty = Ktn$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that

characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian

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Sodium carboxymethyl cellulose(mg)	-	-	-	-	100	200
Glycerin (ml)	4	4	4	4	4	4
Ethanol (ml)	2	2	2	2	2	2
DMSO(ml)	2	2	2	2	2	2
Water (ml)	3	3	3	3	3	3

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$$Mt/M\infty=Ktn$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian

RESULTS AND DISCUSSION:

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

8.1. Analysis of drug:
A. UV scan:
The lambda max of Methimazole was found to be 254 nm.

B. construction of calibration curve:

Table 8.1: Standard graph of Methimazole

Concentration(µg/ml)	Absorbance (at 254 nm)
0	0
10	0.135
20	0.242
30	0.351
40	0.466
50	0.579

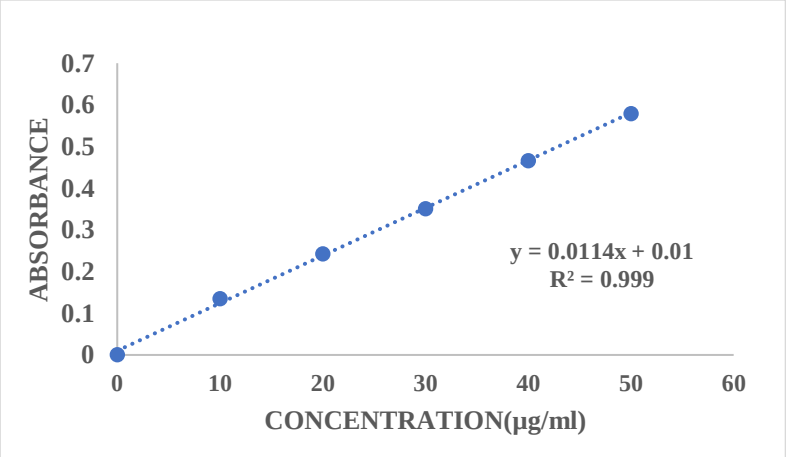


Figure 8.1: Standard calibration curve of Methimazole

8.2. Pre formulation study
Totally, six formulation trials were done with the aim to achieve the successful matrix type Methimazole transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

A. Colour, odour, taste and appearance

Table 8.2: Results of identification tests of drug

Parameter	Methimazole
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 8.3: Results of melting point determination tests of drug

Drug	Reported melting point
Methimazole	171-175 °C.

C. Determination of solubility:

Table 8.4: Solubility Determination

Solvent	Drug solubility(mg/ml)
Distilled water	29
Ph 7.4 phosphate buffer	74.3

8.3 Evaluation of Patch

The formulations M1 to M6 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 146± 5.39 to 186± 5.53mm.

All formulations from M1 to M6 shows weight variation in between 12.33 ± 0.52 to 14.21 ± 0.83mg.

Folding endurance from formulations M1 to M6 was found to be in between 199± 7.38 to 223± 8.08 which can withstand the folding of the skin.

All formulations showed % drug content from 97.95 to 99.78.

Table 8.5: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness (%)	% Drug Content
M1	12.79 ± 0.83	146± 5.39	201± 8.01	99	Transparent	**Flatness (%)**
M2	12.38 ± 0.74	177± 5.81	223± 8.08	98	Transparent	99.32
M3	13.02 ± 0.96	186± 5.53	219± 8.37	101	Transparent	99.19
M4	12.33 ± 0.52	172 ± 5.95	217± 8.26	98	Transparent	97.95
M5	14.21 ± 0.83	169± 5.88	204± 8.71	99	Transparent	98.48
M6	13.19± 10.37	163± 5.60	199± 7.38	97	Transparent	99.78

***In vitro* diffusion study:**

All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 °C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 8.6: *In vitro* drug permeation of Methimazole containing different concentrations of Hydroxypropyl methyl cellulose

Time(hr)	M1	M2
0	0	0
1	12.94	15.43
2	19.45	22.94
3	25.53	26.45
4	29.78	31.27
5	35.44	42.96
6	43.68	48.37
7	57.36	54.75
8	64.17	58.74
9	82.95	72.43
10	87.76	78.54
11	92.14	84.99
12	97.69	98.43

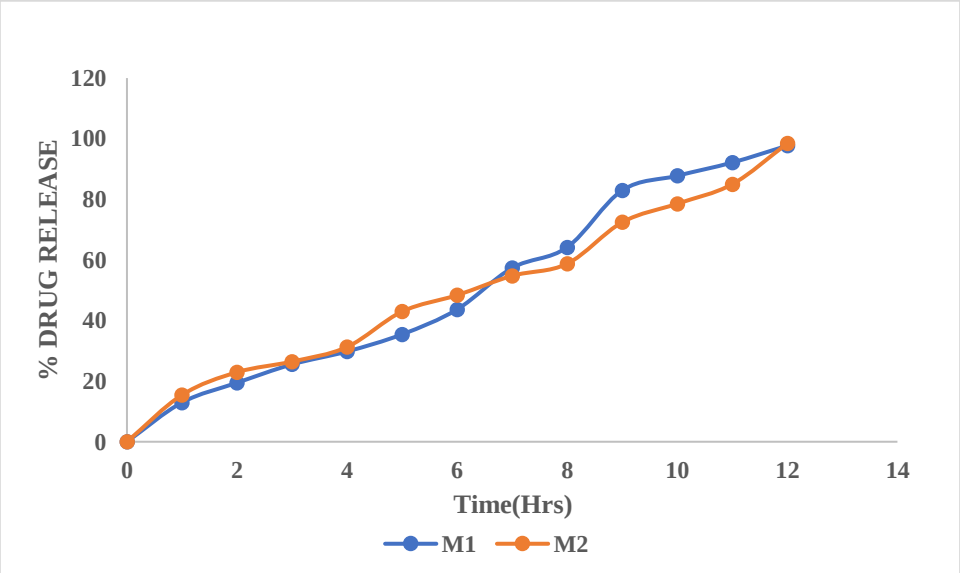


Figure: 8.2 Cumulative % drug permeation of Methimazole patch (M1, M2)

The formulations M1 to M2 were prepared by different concentrations of Hydroxypropyl methyl cellulose (100, 200, mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 12 hours it was total amount of drug was permeated. The 200mg concentration of polymer was showed maximum drug released at 12 hrs. 97.69%. The 400mg concentration of polymer was showed maximum drug release 98.43% at desired time period. Hence in that 2 formulations M2 formulation showed total drug release at desired time period.

Table: 8.7 *In vitro* drug permeation of Methimazole containing different concentrations of Sodium alginate

Time	M3	M4
0	0	0
1	22.62	19.45
2	28.84	24.24
3	36.28	29.66
4	42.34	36.14
5	46.13	47.34
6	62.52	54.37
7	68.68	72.25
8	72.37	79.13
9	75.54	85.62
10	86.82	91.76
11	89.93	95.53
12	98.52	99.64

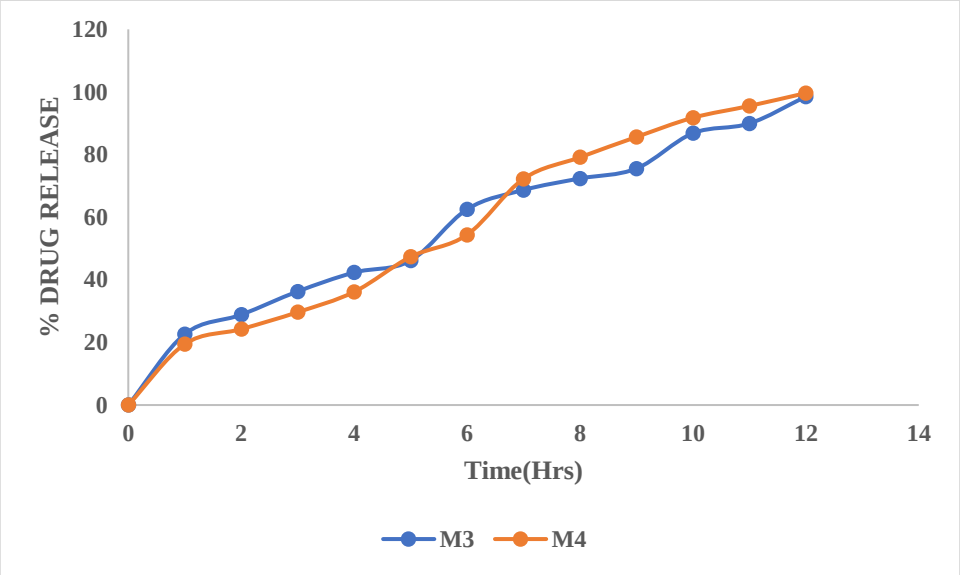


Figure:8.3 Cumulative % drug permeation of Methimazole patch (M3, M4,)

The formulations M3 to M4 were prepared by different concentrations of Sodium carboxymethyl cellulose (100,200mg), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 100mg (M3) concentration of polymer was showed maximum drug release 98.52% within 12 hours. The 200mg (M4) concentration of polymer was showed maximum drug released at 12 hors 98.52%. The 200mg (M4) concentration of polymer was showed less drug release 99.64% at 12 h.

Table 8.8: *In vitro* drug permeation of Methimazole containing different concentrations of Carboxy Methyl Chitosan

Time (hr)	M5	M6
0	0	0
1	17.24	19.63
2	28.13	23.99
3	35.85	27.52
4	48.38	39.54
5	52.54	47.62
6	56.72	52.57
7	59.85	62.28
8	66.23	68.97
9	79.34	74.13
10	88.44	86.35
11	94.82	89.39
12	96.68	98.22

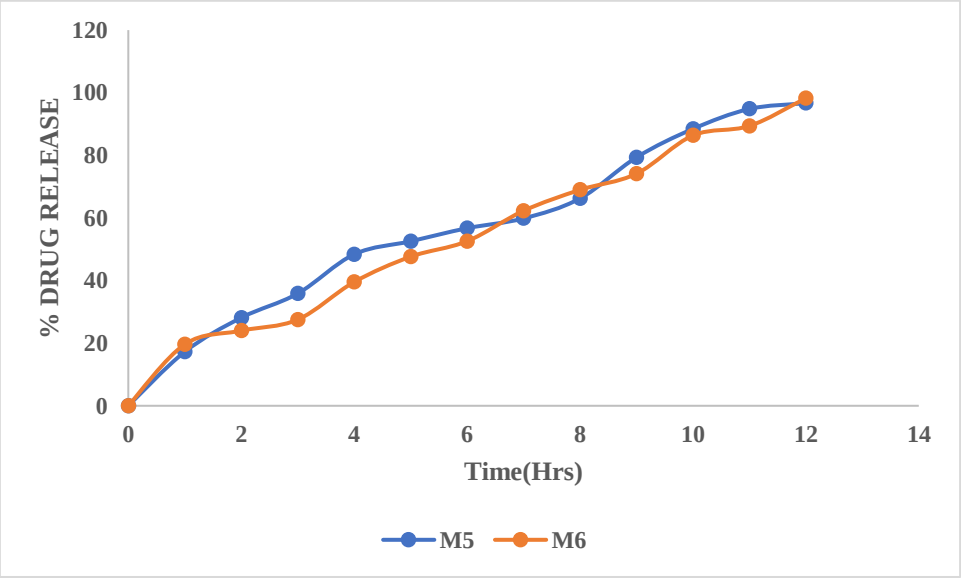


Figure:8.4 Cumulative % drug permeation of Methimazole patch (M5, M6,)

The formulations M5 to M6 were prepared by different concentrations of Sodium carboxymethyl cellulose (100,200 mg), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 100mg (M5) concentration of polymer was showed maximum drug release 96.68 %within 12 hours. The 100mg (M5) concentration of polymer was showed maximum drug released at 12 hors 98.22%. The 200mg (M6) concentration of polymer was showed less drug release 98.22 % at 12 h.

Among all 6 formulations M4 formulation showed good drug permeation from the patch.
Among all *in vitro* evaluation parameters M4 formulation passed all evaluation parameters.

8.4 Kinetic models for Methimazole

Various models were tested for explaining the kinetics of drug release. To analyse 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:8.8 Kinetics data of M4 Methimazole patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	%) REL	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	0	0	0	0	0	0	0	0	0
19.45	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.000
24.24	2	1.414	1.385	0.301	1.879	12.120	0.0413	-0.615	75.76	4.642	4.231	0.410
29.66	3	1.732	1.472	0.477	1.847	9.887	0.0337	-0.528	70.34	4.642	4.128	0.514
36.14	4	2.000	1.558	0.602	1.805	9.035	0.0277	-0.442	63.86	4.642	3.997	0.645
47.34	5	2.236	1.675	0.699	1.721	9.468	0.0211	-0.325	52.66	4.642	3.748	0.893
54.37	6	2.449	1.735	0.778	1.659	9.062	0.0184	-0.265	45.63	4.642	3.573	1.068
72.25	7	2.646	1.859	0.845	0.423	10.321	0.0138	-0.141	27.75	4.642	3.028	1.614
79.13	8	2.828	1.898	0.903	0.452	9.891	0.0126	-0.102	20.87	4.642	2.753	1.888
85.62	9	3.000	1.933	0.954	0.477	9.513	0.0117	-0.067	14.38	4.642	2.432	2.210
91.76	10	3.162	1.963	1.000	0.500	9.176	0.0109	-0.037	8.24	4.642	2.020	2.622
95.53	11	3.317	1.980	1.041	0.521	8.685	0.0105	-0.020	4.47	4.642	1.647	2.994
99.64	12	3.464	1.998	1.079	0.540	8.303	0.0100	-0.002	0.36	4.642	0.711	3.930

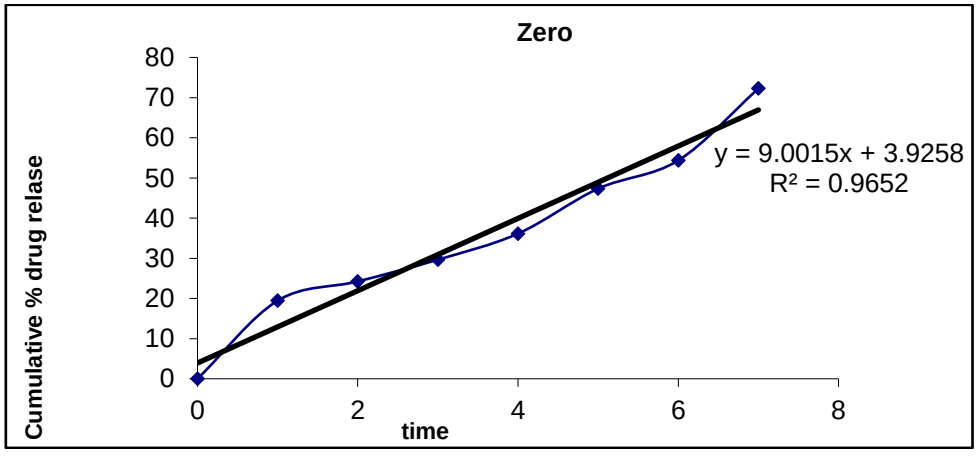


Figure: 8.5 Graph of Zero order kinetics

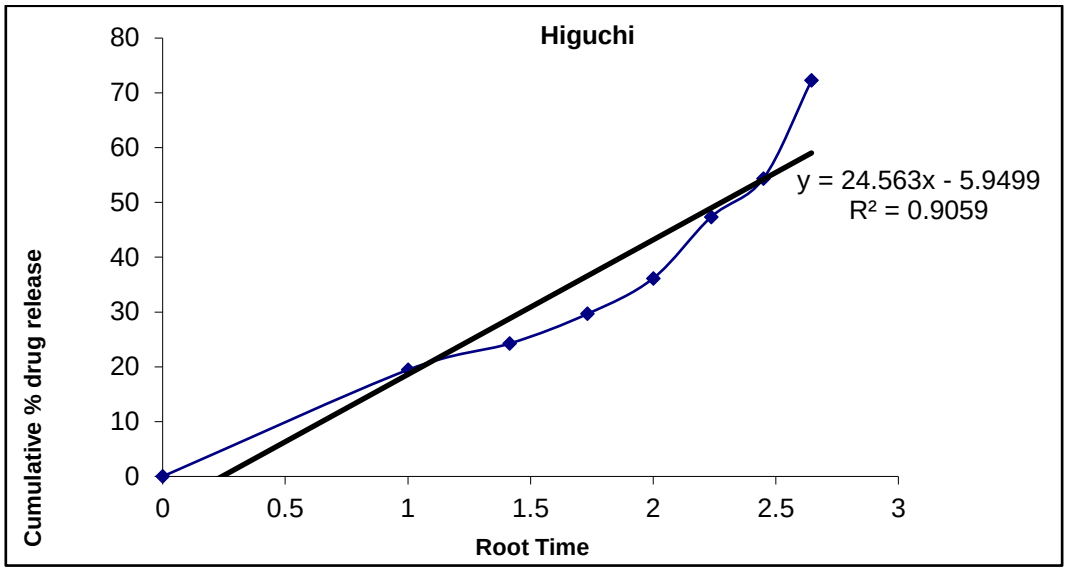


Figure: 8.6 Graph of Higuchi release kinetics

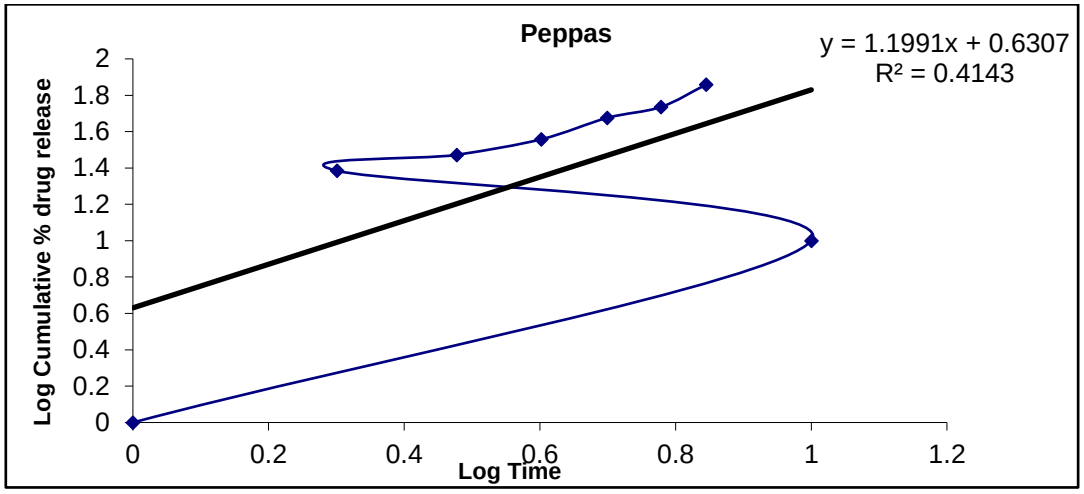


Figure :8.7 Graph of peppas release kinetics

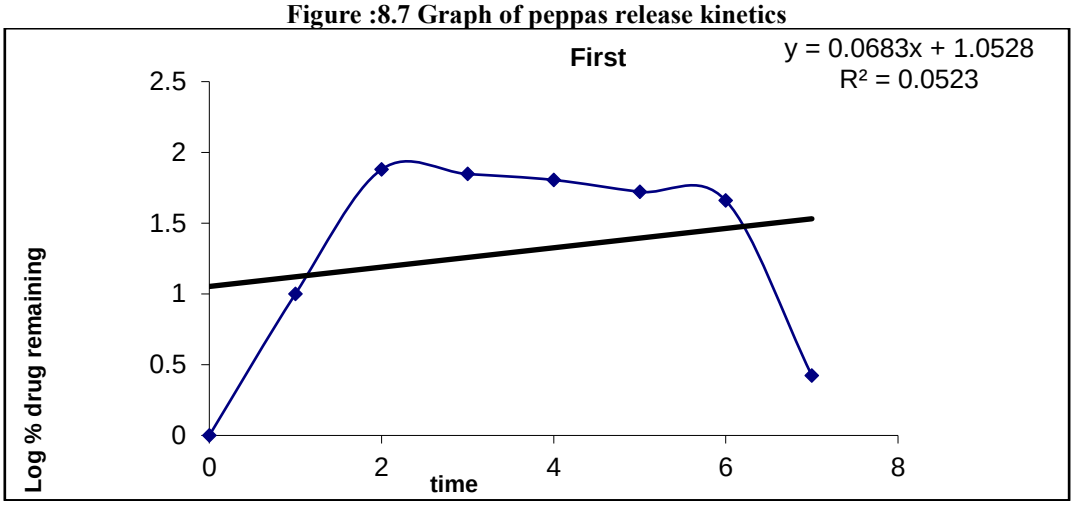


Figure: 8.8 Graph of First order release kinetics

From the above data the optimized formulation followed Zero order kinetics model rule.

7.2. Compatibility studies:
IR SPECTROSCOPY:

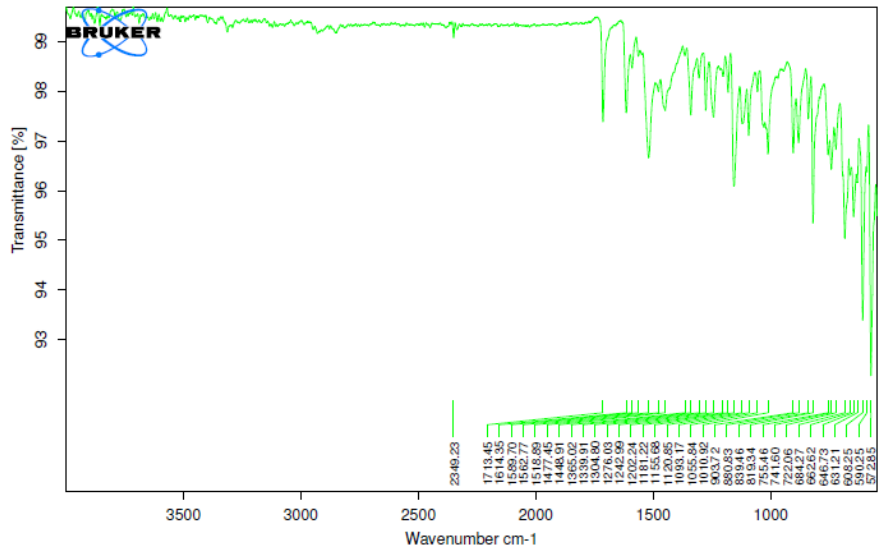


Figure 8.9: FTIR Spectrum of pure Methimazole drug

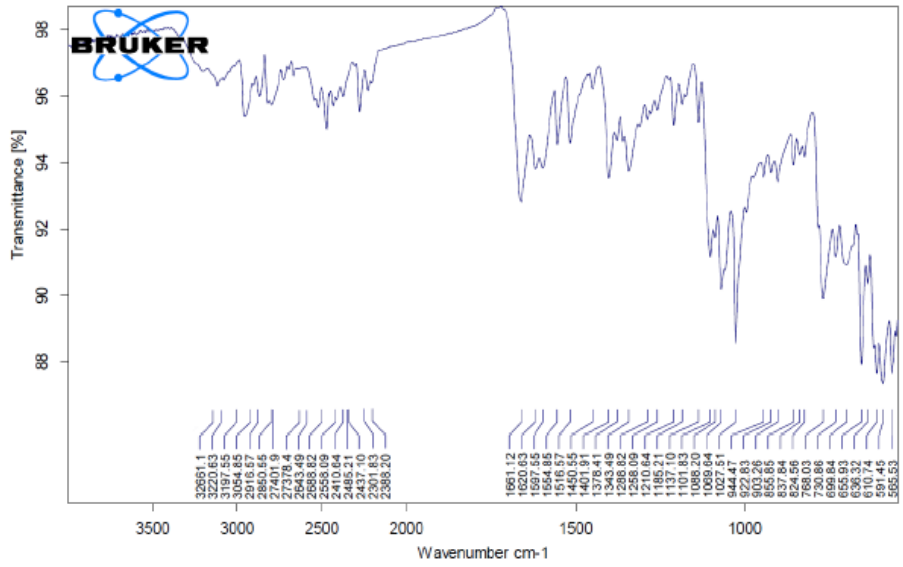


Figure 8.10: FTIR of Optimized formulation

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

CONCLUSION:

The present study successfully achieved the formulation and characterization of methimazole-loaded transdermal patches intended for controlled systemic drug delivery. The prepared patches demonstrated satisfactory physicochemical properties and were found to comply with the acceptable limits prescribed by the Indian Pharmacopoeia (IP) and standard pharmaceutical quality requirements.

The pre-formulation and pre-compression studies confirmed the suitability of methimazole and the selected excipients for transdermal patch development. Drug–excipient compatibility studies revealed no significant chemical interaction, indicating the stability of the formulation components. The formulation blend exhibited good flow characteristics, with bulk density, tapped density, angle of repose, Carr's index, and Hausner ratio all falling within acceptable IP limits, ensuring uniform mixing and reproducible patch preparation.

The prepared transdermal patches were further evaluated for post-formulation (post-compression) parameters. All formulations showed uniform appearance, smooth surface, flexibility, and satisfactory mechanical strength. The thickness, weight variation, folding endurance, tensile strength, moisture content, moisture uptake, and drug content uniformity were found to be within acceptable IP limits, indicating excellent formulation consistency and manufacturing quality. Surface pH remained close to that of the skin, suggesting minimal potential for irritation upon application. The patches also exhibited satisfactory percentage elongation and flatness, confirming their suitability for handling and application.

In vitro drug release studies demonstrated sustained and controlled release of methimazole over the intended period, while permeation studies confirmed efficient drug diffusion across the membrane. Release kinetic analysis indicated that the optimized formulation followed controlled-release behaviour, providing prolonged drug delivery. Stability studies conducted under recommended storage conditions showed no significant changes in physical appearance, drug content, or release characteristics, confirming the stability of the optimized formulation.

Overall, the optimized methimazole-loaded transdermal patch successfully met all the essential pre-compression and post-compression quality evaluation parameters within IP limits and exhibited desirable controlled-release characteristics. These findings suggest that the developed transdermal system has significant potential as an alternative to conventional oral methimazole therapy by improving patient compliance, reducing dosing frequency, minimizing first-pass metabolism, and maintaining sustained therapeutic drug levels.

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