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EVALUATION OF ANALGESIC ACTIVITY OF METHANOL A NOVEL SUSTAINED RELEASE DELIVERY SYSTEM FOR METHIMAZOLE: ENHANCING THERAPEUTIC EFFICACY AND PATIENT COMPLIANCE

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Abstract:

The present study aimed to develop a novel sustained release delivery system of Methimazole to enhance therapeutic efficacy and improve patient compliance by reducing the frequency of dosing. Methimazole is widely used in the management of Hyperthyroidism, but its conventional dosage forms require frequent administration due to rapid drug release. Therefore, the formulation of sustained release tablets was undertaken using natural and synthetic polymers to achieve controlled drug delivery.

In this study, sustained release tablets of methimazole were prepared using different concentrations and ratios of polymers such as Karaya Gum, Xanthan Gum, and Sodium Stearyl Fumarate. The prepared powder blends were evaluated for various pre-compression parameters including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio to determine their flow properties. The compressed tablets were further evaluated for post-compression parameters such as hardness, thickness, friability, weight variation, and drug content uniformity.

All the evaluated pre-compression and post-compression parameters were found to be within the acceptable limits specified by the Indian Pharmacopoeia, indicating satisfactory flow characteristics, mechanical strength, and uniformity of the tablets. In-vitro dissolution studies were carried out for all formulations to evaluate the drug release pattern over a period of 12 hours. Among the developed formulations, formulation F6 exhibited a maximum cumulative drug release of 99.96% within 12 hours, demonstrating an effective sustained release profile. Hence, formulation F6 was considered the optimized formulation when compared to other formulations.

Keywords: *Methimazole, Karaya Gum, Xanthan Gum, and Sodium Stearyl Fumarate.*

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INTRODUCTION:

A Sustained Release dosage form is engineered to release the active pharmaceutical ingredient (API) slowly and continuously over an extended period of time after a single administration.

This specialized release profile contrasts sharply with conventional dosage forms, which typically release the drug rapidly leading to quick, sharp peaks and troughs in the drug's concentration in the bloodstream.[1]

- The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.
- The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[2]
- The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the pharmaceutical industry for some time.
- The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.
- Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems.[3]
- Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. The goal of an extended release dosage form is to maintain therapeutic drug level in plasma for extended period of time.
- Sustained release systems are particularly beneficial for chronic diseases requiring long-term medication, such as hypertension, diabetes, arthritis, and psychiatric disorders. By reducing the frequency of administration, improving pharmacokinetic predictability, and minimizing adverse effects, these systems significantly enhance the therapeutic index of many drugs.
- The development of polymers, micro/nanocarriers, biodegradable matrices, and osmotic pumps has revolutionized the field, offering more precise control of drug release.[4]
- Sustained Release Drug Delivery Systems (SRDDS) represent an advanced approach in pharmaceutical technology aimed at controlling the release profile of therapeutic agents for extended periods. Conventional immediate-release dosage forms produce rapid drug absorption that often leads to fluctuations in plasma concentration, resulting in peaks (which may cause toxicity) and troughs (sub-therapeutic levels).
- Sustained release formulations are designed specifically to maintain a steady-state concentration within the therapeutic window for prolonged durations, thereby improving treatment efficacy and patient compliance.
- One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix.
- Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue it is considered as controlled release system.
- If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design.[5]
- The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.
- Sustained release dosage forms are made to release medicine at a given rate while keeping the drug level constant for a defined period of time with the minimal adverse effects possible. The fundamental concept behind sustained-release drug delivery systems is to improve the patient's compliance though increasing the bioavailability and effectiveness of the medicines.

- Sustained release with the introduction of extended-release matrix tablet have proved to be an effective tool to control the release of drug without involving the complex production procedures. Through localising the drug to the site of action lowering the dosage needed, and ensuring uniform drug distribution, sustained or controlled delivery systems aim to boost drug effectiveness or decrease the frequency of dosing.
- Numerous sustain release oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed. Intense research has recently focused on the designation of SR systems for poorly water soluble drugs.
- However, designing such a system necessitates a number of factors, among which the half-life and pharmacological effect of the drug play an important role. Therefore, taking into account the shortcomings of the standard drug delivery system, the sustained release.

Concept of Sustained Release.[6]
Sustained release (SR) refers to a dosage form designed to release a drug slowly over an extended period. Unlike controlled release which implies precise, constant or zero-order kinetics sustained release mainly focuses on prolonging the release duration compared with conventional dosage forms.

In sustained release systems:

- The drug does not release immediately.
- A portion may release initially (loading dose), followed by slow release (maintenance dose).
- Release rate may be influenced by drug solubility, polymer characteristics, diffusion, erosion, and osmotic mechanisms.

The primary goal of sustained release tablets is to achieve prolonged therapeutic action while minimizing dose frequency.

The Primary Goals of SR Formulations.[7,8]

The rationale behind developing SR formulations is to improve the overall effectiveness, safety, and convenience of drug therapy. The main objectives are:

1. **Maintain Consistent Drug Levels:** To keep the drug concentration in the plasma (bloodstream) within the therapeutic window for a longer duration. This minimizes the risk of:
    - **Drug Toxicity:** Avoiding high peaks that exceed the Minimum Toxic Concentration (MTC).
    - **Therapeutic Failure:** Preventing low troughs that drop below the Minimum Effective Concentration (MEC).
2. **Reduce Dosing Frequency:** SR formulations often allow for once or twice-daily dosing, as opposed to multiple daily doses required by conventional forms.[9]
3. **Improve Patient Compliance:** Less frequent dosing makes it easier for patients, especially those with chronic conditions, to stick to their medication schedule.
4. **Enhance Safety and Efficacy:** By smoothing out fluctuations in drug levels, the drug works more consistently and may reduce the intensity of local or systemic side effects.[10]

METHODOLOGY:

Analytical method development

a) Determination of absorption maxima:
100 mg of Methimazole pure drug was dissolved in 15 ml of Methanol and make up to 100 ml with 0.1 N HCL (stock solution). 10 ml of above solution was taken and make up to 100 ml by using 0.1 N HCL (stock solution-2 i.e., 100µg.ml). 10 ml of above solution was taken and make up to 100 ml by using 0.1 N HCL (stock solution-3 i.e., 10µg/ml). Scan the 10 µg/ml using double beam UV/VIS spectrophotometer in the range of 200-400 nm.

a) Preparation of calibration curve
100 mg of Methimazole pure drug was dissolved in 15 ml of Methanol and make up the volume up to 100 ml with 0.1 N HCL (stock solution -1). 10 ml of the above solution was taken and make up the volume up to 100 ml by using 0.1 N HCL (stock solution -2 i.e., 100µg/ml). From this take 5,10,15,20 and 25 ml of solution and make up to 100 ml with 0.1 N HCL to obtain 5,10,15,20, and 25µg/ml of Methimazole per ml solution. The absorbance of the above dilutions was measured a 255 nm by using UV-Spectrophotometer taking 0.1 N HCL as blank. Then a graph was plotted by taking concentration on X-axis and Absorbance on Y- axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

7.2. Drug –Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients, In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

7.3 Formulation Development of Sustained Release Tablets

All the formulations were prepared by direct compression method. The compositions of different formulations are given in table. The tablets were prepared as per the procedure given below and aim is to extended release of Methimazole.

Procedure:

1) Methimazole and all other ingredients except sodium stearyl fumarate and talc were individually passed through sieve no #40.
2) Methimazole, MCC, mix thoroughly than add the gum /polymer mix properly up to 15 min.
3) After completion of mixing the mixture is passed through sieve no # 22.
4) The powder mixture was lubricated with sodium stearyl fumarate and talc.
5) Finally go for compression.

Table 7.1: Formulation of sustained release tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Methimazole	20	20	20	20	20	20	20	20	20
Karaya Gum	10	20	30	-	-	-	-	-	-
Xanthan Gum	-	-	-	10	20	30	-	-	-
Sodium Stearyl Fumarate	-	-	-	-	-	-	10	20	30
PVP K 30	8	8	8	8	8	8	8	8	8
Talc	6	6	6	6	6	6	6	6	6
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Lactose	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total weight	120	120	120	120	120	120	120	120	120

7.4 Evaluation parameters

7.4.1 Pre Compression parameters

Bulk density (D_B)

Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of powder/Bulk volume of powder

Bulk density (D_B) = W/V_0

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve no :40) was carefully transferred into 2550 ml measuring cylinder and measure the bulk volume.

Tapped density (D_T)

Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder /tapped volume

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No. 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume)

was obtained (V_f). The tapped density was calculated by using the formula

Tapped density (D_T)= W/V_f

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula,

Hausner's ratio = D_T/D_B

Where, D_T is tapped density

D_B is the bulk density

Compressibility index [75]

Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V_f) after tapping's of sample in a measuring cylinder. It indicates the powder floe properties and expressed in terms of percentage and given in table 14 and calculated by using the formula,

%Compressibility index = V_0-V/V_0x100

Angle of Repose

Angle of repose was measured by fixed funnel method. It determines floe property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane.

The powder was allowed to flow through the funnel fixed to a stand at a definite height (h). By measuring the height and radius of the heap of powder formed (r) , angle of repose was calculated by using formula given below and the calculated values was shown in table no. 7.2.

$$\theta = \tan^{-1}(h/r)$$

Where θ is the angle of repose,

h is the height in cm

r is the radius in cm

Flow property

Table 7.2: The flow property of powder blend

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

7.4.2 Post Compression parameters

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight was calculated as per Indian Pharmacopoeial specification. Tablets with average weight 250 mg, so the % deviation was ±5%.

Table 7.3 IP standards of uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The Friabilator was operated and reweighed the tablets. % loss (F) was calculated by the following formula,

$$F= 100(W_0-W)/W_0$$

Where W_0 = Initial weight, W= Final weight

Hardness test
The hardness of tablets was measured by using Monsanto hardness tester. The results comply with IP specification.

Thickness test
The rule of physical dimension of the tablets such as thickness is necessary for consumer acceptance and maintains tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related hardness can be used as initial control parameter.

Drug content
The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch and weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

***In vitro* drug release studies**
Apparatus : USP-II Paddle method
Dissolution medium : 0.1 N HCL, pH 6.8 Phosphate buffer
RPM : 50
Sampling intervals (hrs) :1,2,3,4,5,6,7,8,9,10,11,12

Temperature : 37˚C±0.5˚C

Procedure:
900 ml of 0.1 N HCL was placed in vessel and the USP apparatus –II(paddle method) was assembled. The media was allowed to equilibrate to temp of 37˚C±0.5˚C. Tablet was placed in the vessel and apparatus was operated for 2 hours. Then 0.1 N HCL was replaced with pH 6.8 phosphate buffer and process was continued up to 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5 ml media was added o maintain the sink condition. Withdrawn samples were analyzed at 255 nm wavelength of drug using UV-spectrophotometer.

7.5 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 kinetics the release rate data are fitted to the following equation.
$F= K_0 t$
Where, F is the drug release at time 't' and 'K_0' 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 increased 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_∞ 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-Fiskian release, the value of n falls between 0.5 and 1.0; while in case of Fiskian diffusion, n= 0.5; foe zero-order release (case I I transport), n=1; and for super case II transport, n>1. In this model, a plot of log (M_t/M_∞) versus log (time) is linear.

RESULTS AND DISCUSSION:

Analytical method
8.1.1Standard graph of Mebeverine in 0.1 N HCL:
The scanning of the 100 µg/ml solution of Mebeverine in the ultraviolet range (200- 400 nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 262 nm. The standard concentrations of Mebeverine (5-25µg/ml) was prepared in 0.1 N HCL showed good linearity with R^2value of 0.997, which suggests that it obeys the Beer – Lamberts law.

Table 8.1: Standard curve of Mebeverine in 0.1 N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.128
10	0.246
15	0.364
20	0.479
25	0.597

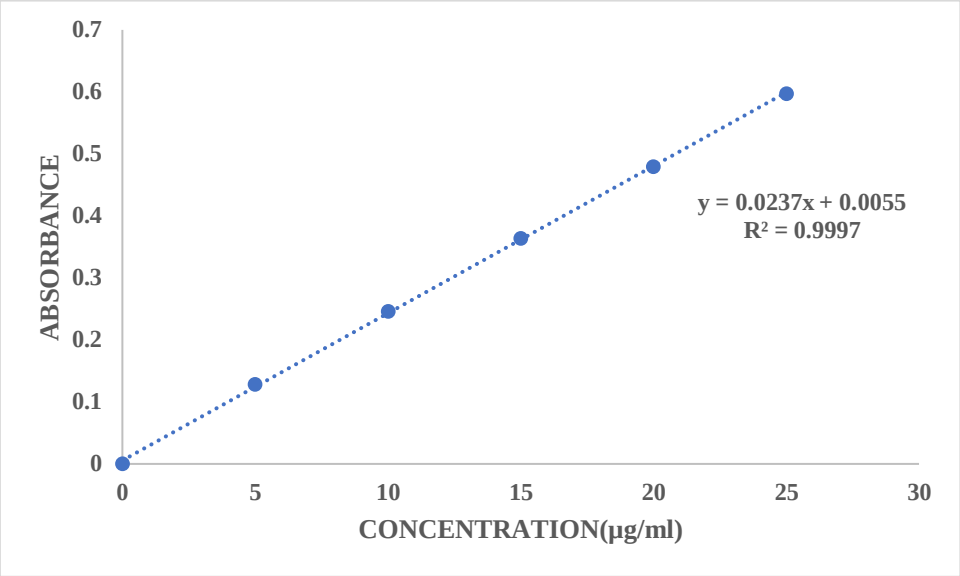


Fig. 8.1: Calibration curve of Mebeverine in 0.1 N HCL at 262 nm

8.1.2 Standard curve of Mebeverine in phosphate buffer pH 6.8

The scanning of 100µg/ml solution of Mebeverine in the ultraviolet range (200-400 nm) against 6.8 pH phosphate the maximum peak observed at the λmax as 262 nm. The standard concentrations of Mebeverine (5-25/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 8.2: Standard curve of Mebeverine in Phosphate buffer pH 6.8

Concentration (µg/ml)	Absorbance
0	0
5	0.154
10	0.301
15	0.442
20	0.588
25	0.735

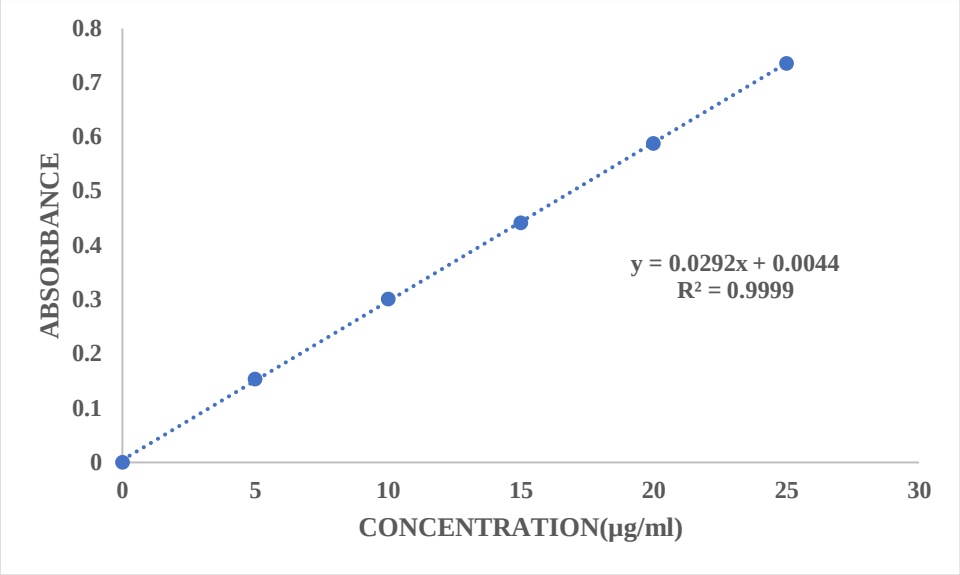


Fig.8.2: Calibration of Mebeverine in phosphate buffer pH 6.8

8.2 Drug and excipient compatibility studies

8.2.1 FTIR study

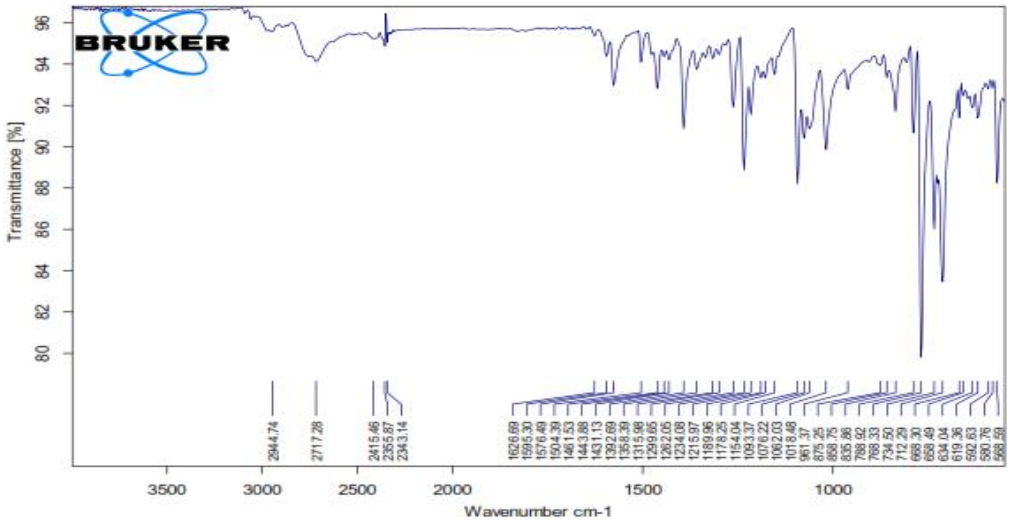


Fig .8.3: FTIR graph of pure drug

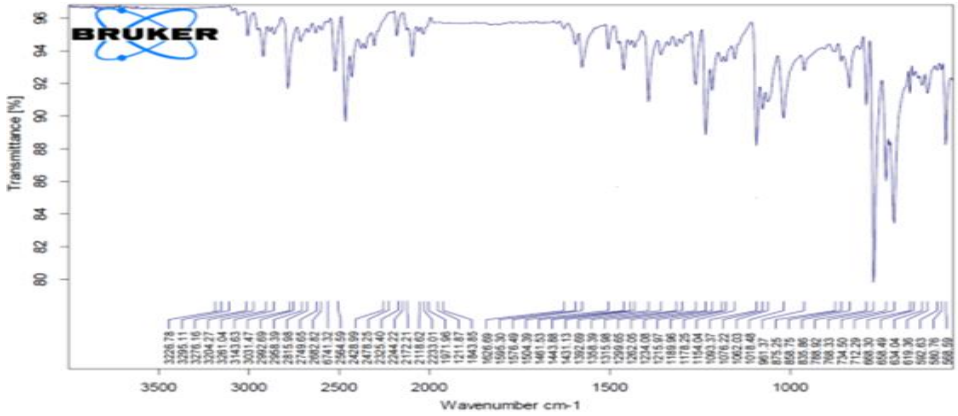


Fig .8.4:' FTIR graph of optimized formulation

From the FTIR data it was evident that the drug and excipients do not have any interactions. Hence, they were compatible.

8.3 EVALUTION PARAMETERS

8.3.1 Pre-compression parameters

Table 8.4: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	29.29	0.4516	0.5109	11.61	1.13
F2	29.01	0.4403	0.5000	11.95	1.14
F3	28.39	0.4605	0.5303	13.16	1.15
F4	27.5	0.4321	0.4930	12.35	1.14
F5	30.03	0.4403	0.5147	14.47	1.17
F6	29.79	0.4545	0.5263	13.64	1.16
F7	30.41	0.4487	0.5109	12.18	1.14
F8	28.39	0.4516	0.5147	12.26	1.14
F9	29.25	0.4545	0.5224	12.99	1.15

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25 to 30, it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.4321 to 0.4605 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in range of 0.4930 to 0.5303 showing the powder has good flow properties. The compressibility index of all formulations was found to be ranging from 11.61 to 14.47 which showed that the powder has good flow properties. All the formulations were showed the Hausner ratio ranging from 0 to 1.15±0.021 indicating the powder has good flow properties.

8.3.2 Post compression parameters for tablets

Table 8.5: Post compression parameters of tablets

Formulation Codes	Average weight (Mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	119.85	2.48	0.26	1.85	97.64
F2	118.62	2.36	0.19	1.93	98.53
F3	121.77	2.51	0.29	1.79	98.49
F4	120.48	2.35	0.22	1.88	99.77
F5	119.32	2.44	0.15	1.87	97.62
F6	120.89	2.39	0.12	1.91	99.31
F7	119.51	2.46	0.37	1.95	99.08
F8	117.44	2.47	0.24	1.82	98.53
F9	121.22	2.39	0.31	1.86	97.45

Weight variation and Thickness:
All the formulations were evaluated for uniformity of weigh using electronic weighing balance and the results are shown in table 8.5. The average tablet weight of all the formulations was found to be between 117.44 to 121.77. The maximum allowed percentage weight variation for tablets

weighing >120 mg is 5% and no formulations are not exceeding this limit. Thus, all formulations were also found to comply with the standards given in I.P. and thickness of all the formulations was also complying with the standards that were found to be between 5.7 ±0.08 to 5.1±0.05.

Hardness and Friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in able 8.5. The average hardness for all the formulations was found to be between (2.35 to 2.51) kg/cm^2 which was found to be acceptable.
Friability was determined to estimate the ability of the tablets to with stand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche Friabilator and the results were shown in table 9.5. The average percentage friability for all the formulations was between 0.12 - 0.37, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 9.5. The drug content values for all formulations were found to be in range of (97.45 to 99.77). According to IP standards the tablets must contain not less than 95% and not more than 105 % of the stated amount of the drug. Thus, all FDT formulations comply with standards given in IP.

***In vitro* drug release studies**

The formulations prepared with different polymers by direct decompression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1 N HCL for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 8.6: Dissolution data of Mebeverine tablets prepared with natural polymer Karaya Gum

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0	0	0	0
0.5	17.58	11.37	19.96
1	22.89	16.93	25.13
2	29.53	21.68	29.64
3	34.34	26.33	36.52
4	38.68	31.76	42.68
5	43.92	34.78	47.88
6	51.72	41.98	51.73
7	54.47	45.64	58.68
8	58.32	52.37	62.22
9	64.98	67.45	69.87
10	68.88	72.08	79.54
11	77.24	85.66	88.15
12	86.65	92.28	97.92

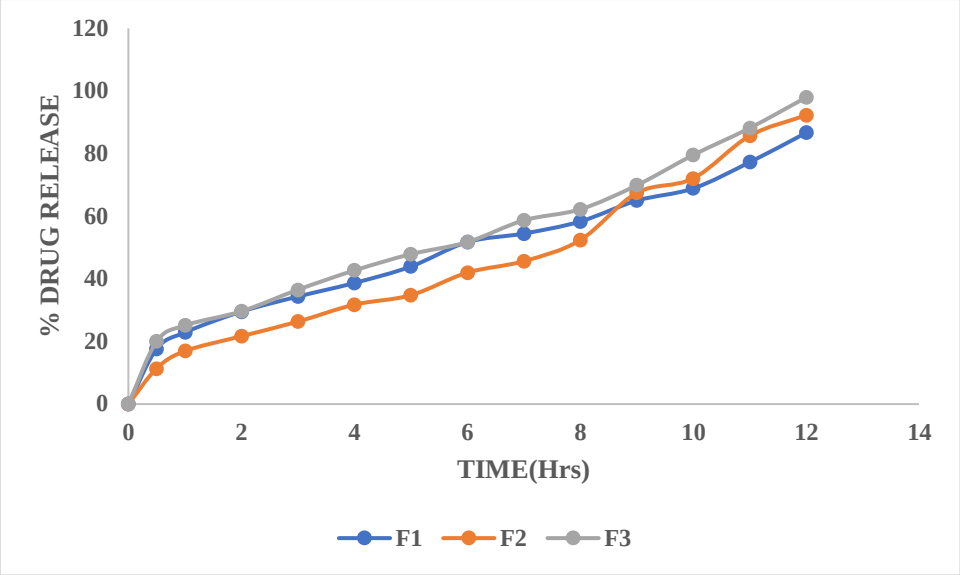


Fig 8.5: Dissolution study of Mebeverine sustained release tablets (F1 to F3)

The % drug release of formulations (F1 o F3) containing Karaya Gum depends on the concentration of polymer. The concentration of Karaya Gum contains F1 and F2 was unable to retard the drug release up to desired time. When the concentration of polymer contain 10,20 mg was able to retard the drug up to 12 hours. In F3 formulation 1:3 ratio (drug: polymer) concentration was used, showed maximum % drug release up to 12 hours i.e.., 97.92%

Table 8.7: Dissolution data of Mebeverine tablets prepared with natural polymer Xanthan Gum

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F4	F5	F6
0	0	0	0
0.5	16.82	21.66	11.85
1	22.32	27.55	17.47
2	37.57	32.43	28.66
3	43.31	41.56	34.23
4	49.66	51.48	42.78
5	55.35	58.75	46.22
6	59.11	63.22	56.93
7	68.76	71.86	62.28
8	74.18	78.16	68.54
9	81.25	85.76	75.87
10	85.28	89.53	82.58
11	89.08	94.38	88.32
12	95.42	99.96	97.62

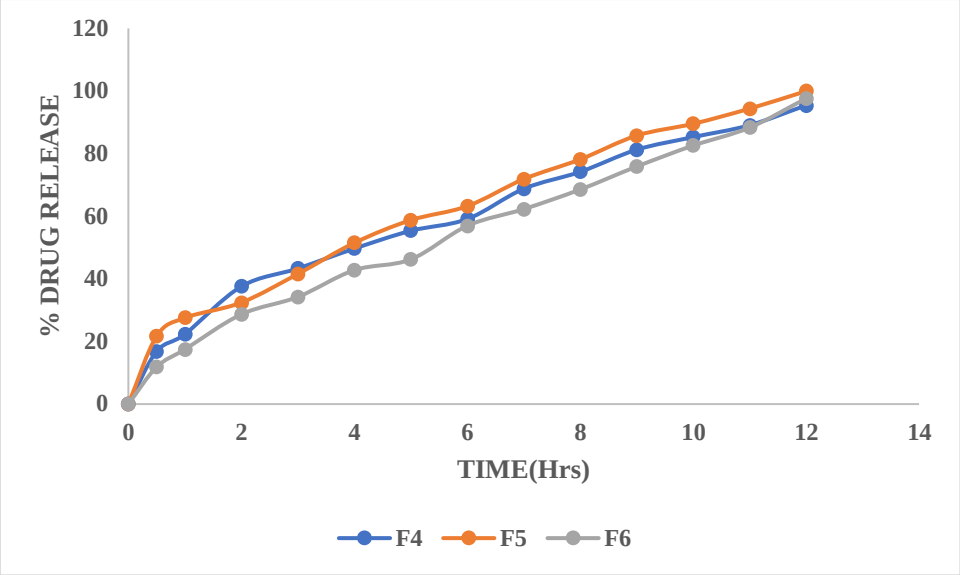


Figure 8.6: Dissolution study of Mebeverine tablets (F4 to F6)

The % drug release of F4 to F6 formulations depends on ratio of polymer in the solution. The concentration of Xanthan Gum was unable to retard the drug release up to desired time. When the concentration of polymer increased in F5 drug polymer ratio is 1:2 showed maximum % drug release i.e.,99.96 % at 12 hours.

Table 8.8: Dissolution Data of Mebeverine by Using Natural Polymer Sodium Stearyl Fumarate

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F
0	0	0	0
0.5	19.47	12.95	17.18
1	22.38	19.47	23.63
2	29.36	28.66	32.22
3	35.24	34.59	39.24
4	42.63	38.84	44.39
5	48.98	46.28	51.85
6	53.83	55.62	58.76
7	62.98	64.89	62.02
8	68.83	71.08	67.48
9	74.57	76.62	73.27
10	76.88	82.53	89.56
11	87.08	89.46	92.47
12	97.57	94.34	98.22

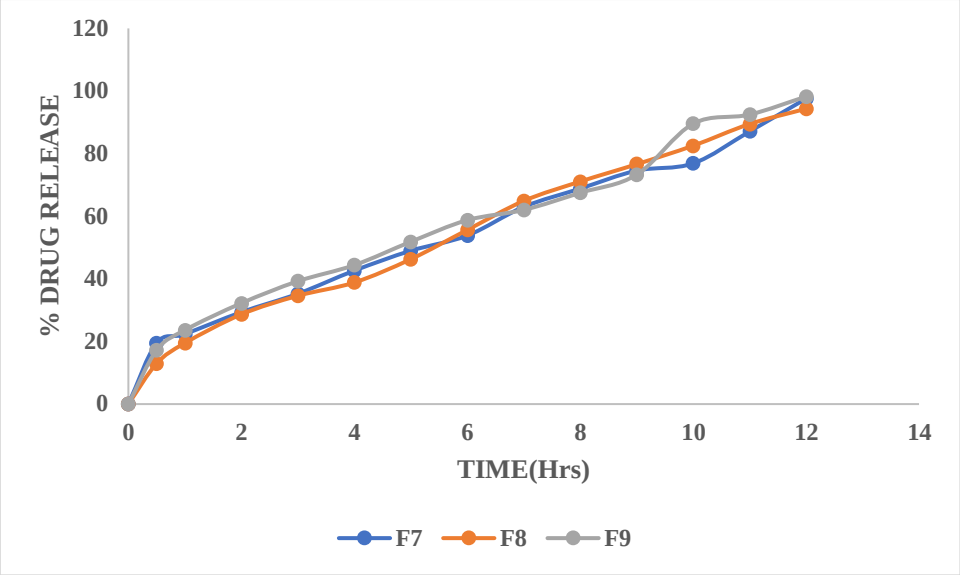


Fig 8.7: Dissolution study of Mebeverine by using Natural polymer Sodium Stearyl Fumarate

The 5-drug release of F6 to F9 formulations depends on polymer ratio Sodium Stearyl Fumarate. The concentration of natural Fenugreek mucilage 1:1 and 1:2 ratio was unable to retard the drug release up to desired time. In F9 formulation showed maximum % drug release i.e., 98.22 % at 12 hours.

Hence based on dissolution data of 9 formulations, F5 formulation contain Xanthan Gum 1:3 ratio of polymer showed better release up to 12 hours. So F5 formulation is optimized formulation.

8.4 Application of Release Rate Kinetics to Dissolution Data

Data of In vitro release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Mebeverine release from sustained tablets . The data was fitted into various kinetic models such as Zero, first order kinetics, Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table.

Table 8.9: Release kinetics data for optimized formulation(F5)

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
21.66	0.5	0.707	0.841	0.917	0.958	0.979	0.989	0.995	0.997	0.999	0.999	-0.001
27.55	1	1.000	1.440	0.000	1.860	27.550	0.0363	-0.560	72.45	4.642	4.169	0.473
32.43	2	1.414	1.511	0.301	1.830	16.215	0.0308	-0.489	67.57	4.642	4.073	0.569
41.56	3	1.732	1.619	0.477	1.767	13.853	0.0241	-0.381	58.44	4.642	3.881	0.761
51.48	4	2.000	1.712	0.602	1.686	12.870	0.0194	-0.288	48.52	4.642	3.647	0.994
58.75	5	2.236	1.769	0.699	1.615	11.750	0.0170	-0.231	41.25	4.642	3.455	1.186
63.22	6	2.449	1.801	0.778	0.389	10.537	0.0158	-0.199	36.78	4.642	3.326	1.316
71.86	7	2.646	1.856	0.845	0.423	10.266	0.0139	-0.144	28.14	4.642	3.042	1.600
78.16	8	2.828	1.893	0.903	0.452	9.770	0.0128	-0.107	21.84	4.642	2.795	1.846
85.76	9	3.000	1.933	0.954	0.477	9.529	0.0117	-0.067	14.24	4.642	2.424	2.218
89.53	10	3.162	1.952	1.000	0.500	8.953	0.0112	-0.048	10.47	4.642	2.188	2.454
94.38	11	3.317	1.975	1.041	0.521	8.580	0.0106	-0.025	5.62	4.642	1.778	2.864
99.96	12	3.464	2.000	1.079	0.540	8.330	0.0100	0.000	0.04	4.642	0.342	4.300

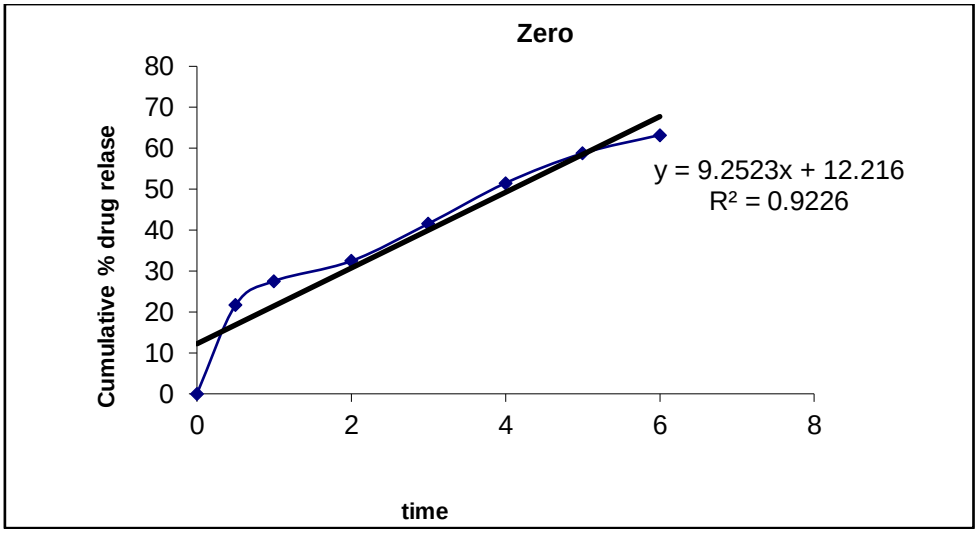


Fig 8.8: Graph of Zero order kinetics

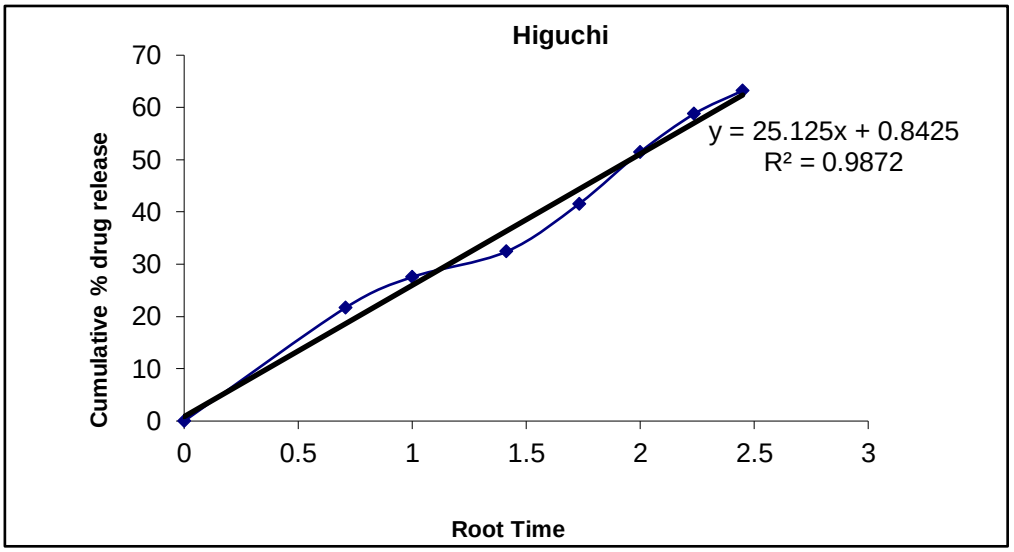


Fig: 8.9: Graph of Higuchi release kinetics

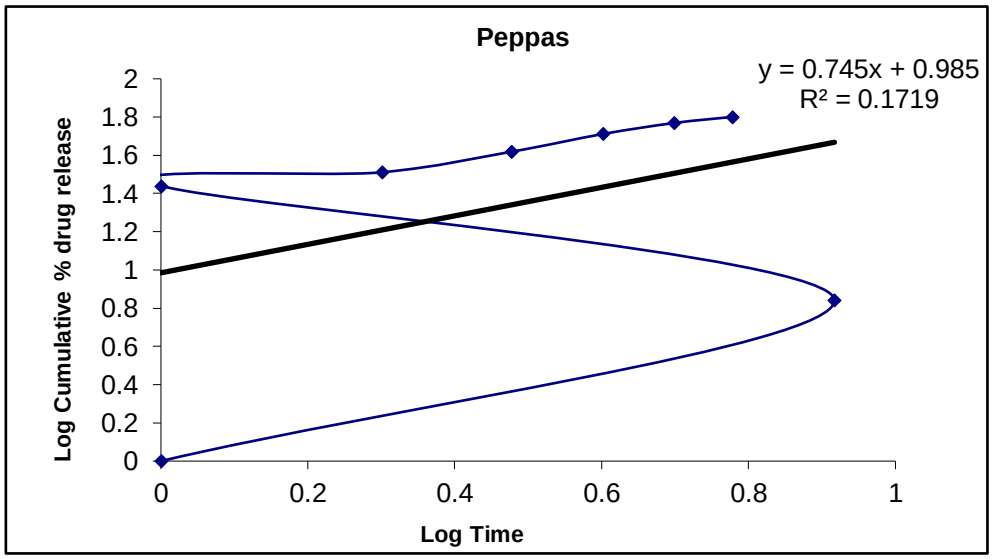


Fig 8.10: Graph of Peppas release kinetics

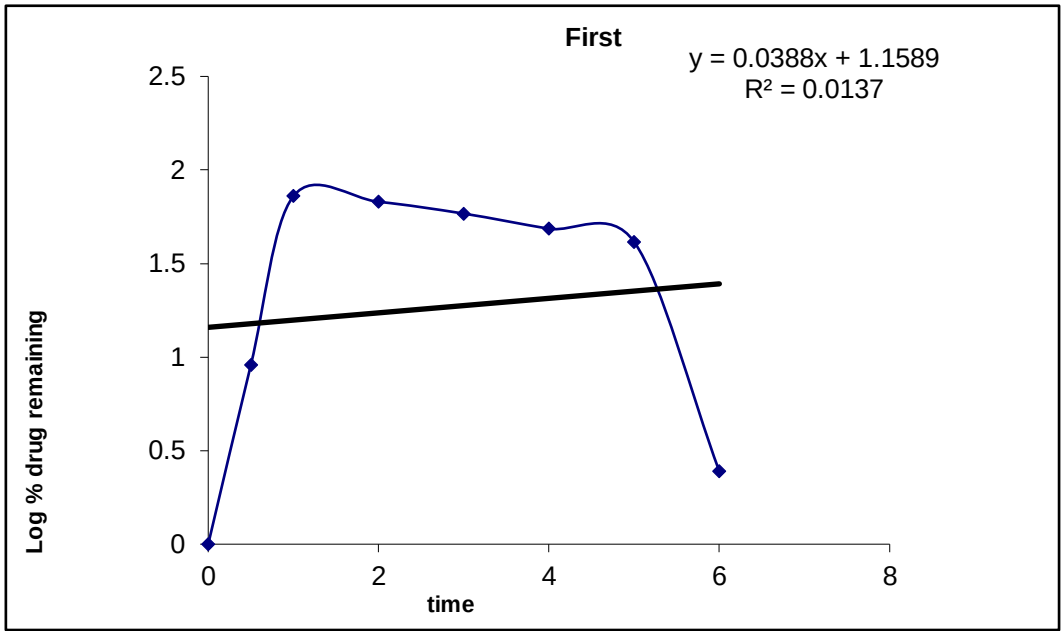


Fig 8.11: Graph of first order release kinetics

Based on the data above results the optimized formulation followed Peppas and zero order kinetics

CONCLUSION:

In the present study, a novel sustained release delivery system of Methimazole was successfully formulated and evaluated with the objective of improving therapeutic efficacy and enhancing patient compliance. The prepared formulations were subjected to comprehensive pre-compression and post-compression evaluations, including flow properties, hardness, friability, weight variation, drug content, and in-vitro drug release studies. All pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio indicated good flow properties of the powder blend, confirming its suitability for compression. The post-compression parameters including hardness, friability, thickness, weight variation, and drug content uniformity were found to be within the acceptable limits specified by the Indian Pharmacopoeia, demonstrating the good mechanical strength and uniformity of the prepared tablets. The optimized formulation exhibited a controlled and sustained drug release profile, which can potentially maintain therapeutic drug levels for an extended period, thereby reducing dosing frequency.

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