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Formulation and Evaluation of Multilayer Matrix Tablet of Captopril for Oral Controlled Delivery

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Abstract

In the present study an effort was made to prepare an oral controlled drug delivery system for a highly water-soluble drug named captopril. Captopril is a highly water-soluble drug if not formulated properly may release the drug immediately and causes toxicity. Half-life of captopril is around 2-3 hours with 60-75% of bioavailability and prescribed thrice a day, due to this reason an attempt was made to prepare multilayer matrix tablet of captopril for its controlled and durable release. Multilayer matrix tablets of captopril were prepared by compressing 100mg of guar gum granules containing either 60%(T1), 70%(T2) and 80%(T3) of guar gum on both sides of matrix powder of captopril containing either 1:2, 1:1 and 2:1 ratio of HPMC and ethyl cellulose, above which an immediate release layer is compressed having the loading dose of captopril forming the fourth layer of the multilayered matrix tablet. The respective formulations were coded as T1M1, T1M2, T1M3, T2M1, T2M2, T2M3, T3M1, T3M2 and T3M3.

Result:

Values for bulk densities, tapped density, compressibility, Hausner ratio and angle of repose for all the prepared powder and granules were found in a range of 0.33 to 0.446, 0.37 to 0.50, 8.002 to 16.27, 1.08 to 1.16 & 25.96 to 27.7 respectively. Whereas, values for thickness, friability, hardness, Weight variation and content uniformity is found to be 7.14±0.27 to 7.29±0.22, 0.15 to 0.33, 5.7±0.28 to 5.9±0.27, 645.4±2.9 to 649.5±4.7 & 97.79±0.52 to 101.12±0.50 respectively. Swelling study indicates the % swelling of the polymers and the study reviles that maximum swelling were obtained with the formulation T3M3. Dissolution profile defines that the concentration of polymer plays an important role in the release of drug. The values of drug release for the formulation T1M1 to T3M3 after 12 hours were found to be in between 68.91 to 96.47 % respectively.

Key Words:

Captopril, Multilayer Matrix Tablet, HPMC, Guar gum, Ethyl cellulose

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1.Introduction

In recent years, the study of controlled release of drugs and other bioactive agents from polymeric devices has attracted many researchers around the world. The development of sustained or controlled drug delivery systems has got momentum over the past decade due to immense focus on the marketing of new drug molecules as the combination of these new drug molecules has increased to counter multiple diseases that require different dosage regimens [1,2]. On other hand formulation of controlled release dosage form for highly water-soluble drug is still a challenge for researcher to deliver the drug in a constant rate so as to maintain steady state concentration as there is a chance of dose dumping with highly water-soluble drugs if they are not formulated properly.[3]

Captopril is indeed a significant medication, particularly in managing essential hypertension and congestive heart failure. Its mechanism as an ACE inhibitor reduces the production of angiotensin II, thereby relaxing blood vessels and lowering blood pressure. Its clinical effectiveness has made it a cornerstone for antihypertensive therapy.

However, the short half-life of about 2 hours necessitates frequent dosing (typically three times a day). This can be inconvenient and affects patient compliance. Controlled-release formulations would be a practical advancement, helping to sustain constant blood levels over a more extended period while reducing dosing frequency.[4]

Captopril's instability poses significant challenges for researchers attempting to create effective oral controlled-release formulations. The drug's susceptibility to degradation in both laboratory and physiological conditions necessitates innovative approaches to maintain its therapeutic efficacy over extended periods. Developing strategies to protect captopril from pH-induced degradation and metabolic breakdown is crucial for achieving successful controlled-release formulations that can provide consistent drug delivery and improved patient outcomes. To address these challenges, researchers have explored various formulation strategies to improve the drug's pharmacokinetic profile. One approach involves developing novel drug delivery systems that can mitigate dose dumping and burst release, such as matrix-based tablets with controlled release properties. Additionally, efforts have been made to enhance the drug's stability and bioavailability in the presence of food.[5]

A multilayered matrix tablet is an advanced drug delivery system designed to optimize the release of active pharmaceutical ingredients (APIs). It consists of multiple layers, each with distinct purposes, such as separating incompatible APIs, achieving immediate release for a loading dose, or providing sustained or controlled release for a maintenance dose. These tablets enable tailored drug release profiles, enhance therapeutic effectiveness, and improve patient compliance, making them especially useful in conditions requiring combination therapy or prolonged drug action, like hypertension. The aim to increase patient compliance with reducing dosage frequency of captopril was the basis of selection of drug for multilayer matrix tablet.

2.Material & Method

Captopril was received from Macleods Pharmaceuticals Ltd., Mumbai, India as a gift sample. Hydroxypropylmethyl cellulose (HPMC), Ethyl cellulose, Guar gum; Dihydrogen orthophosphate, Microcrystalline cellulose, talc, starch was purchased from Loba Chemie (Pvt.) Ltd., Mumbai, India and are of analytical grade.

2.1.Determination of Absorption Maxima (Λ_{max})

To find the maximum absorption, 10 mg of captopril was dissolved in 0.1 N HCl, and the volume has been raised to 100 ml in a volumetric flask. One milliliter of this stock solution was transferred into a ten-milliliter volumetric flask and make up the volume upto 10 ml to produce the required volume of 0.1 N HCl.

The Systronic PC-based double beam spectrophotometer 2202 was used to scan this solution in the 200–400 nm range in order to measure the absorption maxima (λmax) in 0.1 N HCL. The procedure was identical for the phosphate buffer (pH 6.8) medium.

Preparation of Standard Curves

- **Preparation of 0.1N HCl** [6]
  In order to prepare 0.1N HCl, 0.85 ml of hydrochloric acid and 100 ml of distilled water were blended together.
- **Preparation of standard curve in 0.1 N HCl (pH 1.2)**
  10 mg of precisely weighed captopril was dissolved in 0.1 N HCL, and the volume was raised to 100 ml in a volumetric flask.
  The absorbance was measured at 205.6 nm after several dilutions were made from this stock solution in the concentration range of 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 µg/ml in a 10 ml volumetric flask.
- **Preparation of phosphate buffer (pH 6.8)** [6]
- A suitable amount of distilled water was used to dissolve 28.80 g of di-sodium hydrogen phosphate (Na2HPO4) and 11.45 g of potassium dihydrogen phosphate (KH2PO4), resulting in a volume of 1 litre. A pH adjustment to 6.8 was made before quantitative estimation.
- **Preparation of standard curve in phosphate buffer (pH 6.8):**
- Captopril (10 mg) that had been precisely weighed was dissolved in phosphate buffer (pH 6.8) and the volume was increased to 100 ml in a volumetric flask. Absorbance was measured at 206 nm after several dilutions were made from this stock solution in the concentration range of 10, 20, 30, 40, and 50 µg/ml in a 10 ml volumetric flask.

2.2. Preparation of Tablets

100 mg of guar gum granules containing 60% (T1), 70% (T2), and 80% (T3) of guar gum were compressed on both sides of the captopril matrix powder, which contained 1:2, 1:1, and 2:1 ratio of HPMC and ethyl cellulose in their matrix core. On top of this, an immediate release layer containing the loading dose of captopril was compressed, creating the fourth layer of the multilayered matrix tablet. The codes assigned to the corresponding formulations were T1M1, T1M2, T1M3, T2M1, T2M2, T2M3, T3M1, T3M2, and T3M3.

2.2.1.Preparation of Multilayered Matrix Tablet Involved the Following Steps

- Preparation of core matrix powder of captopril containing HPMC and EC.
- Preparation of 60%, 70% & 80% guar gum granules for layering as release retardant layer on both sides of core matrix layer.
- Preparation of immediate release layer of captopril for loading dose.

2.2.2. Formulation of Immediate Release Layer (Loading Dose) [6,7]

The desired drug concentration, or precisely the steady state concentration, is rapidly achieved using the loading dose. In order to achieve a quicker pharmacodynamic response, it increases the plasma drug concentration to therapeutic drug levels.

The immediate release layer of multilayered matrix tablets delivers the loading dose which can be calculated using the formula:

Loading Dose = Css × Vd / F

Where,

Css is the steady state concentration, Vd is the volume of Distribution and F is fraction of drug bioavailability.

2.2.3. Preparation of Immediate Release Layer by Direct Compression Method

Ingredient	Quantity (mg)
Captopril	12
Sodium starch glycolate	5
Microcrystalline cellulose	33

Table: 1. Composition of loading layer

Each element had to pass through mesh 44. To produce a fine powder for direct compression, 12 mg of captopril and additional excipients were combined, and the mixture was thoroughly mixed for 20 minutes.

2.2.4. Formulation of Core Matrix Layer (Maintenance Dose)

For sustained pharmacological effect, a maintenance dose is administered to keep the drug's steady state concentration attained by the loading dose. In this case, the multilayered matrix tablet's core matrix layer delivers the maintenance dose to maintain steady state concentration for an extended period of time.

Maintenance dose can be calculated by using the formula:

Maintenance dose = L. D. / Ke X τ

Where,

L. D. is the loading dose, Ke is the elimination rate and τ is time during which the sustain release is required.

Ingredients	Quantity (mg) present in core matrix tablet powder (400mg)		
	M1(1:2)	M2 (1:1)	M3 (2:1)
Captopril	50	50	50
HPMC	74	110	146
Ethyl cellulose	146	110	74
Microcrystalline cellulose	15	15	15
Disodium edentate	45	45	45
Ascorbic acid	56	56	56
Sodium ascorbate	14	14	14

Table: 2. Composition of core matrix layer for direct compression containing 1:2 (M1), 1:1 (M2) and 2:1 (M3) ratio of HPMC and ethyl cellulose

Each element went through mesh 44. In order to produce a fine powder for direct compression, the necessary amount of captopril and other excipients for the specific formulation were taken, and the mixture was blended evenly for 20 minutes.

2.2.5. Formulation of Release Retardant Layer (Barrier Layer)

The wet granulation technique can be used to produce a release retardant layer that limits the burst release effect and acts as a barrier, preventing the drug from dissolving.

Ingredients	Quantity (mg) present in guar gum release retardant layer formulation (100mg)		
	T1 (60%)	T2 (70%)	T3 (80%)
Guar gum	60	70	80
HPMC	28	18	08
Starch	q.s.	q.s.	q.s.
Talc	2	2	2

Table: 3. composition of barrier layer

Using 10% starch as a paste, the wet granulation process can be used to create the release retardant layer. After thoroughly mixing the guar gum, HPMC, and starch paste, the resulting wet mass was run through a 10# mesh screen, and the wet granules were dried for two hours at 50°C. After being dried, the granules are once more run through mesh 22# and lubricated with talc.

Multilayered matrix tablet can be prepared by adjusting the volume of die cavity equivalent to the weight of the multilayered matrix tablet (650mg). The preweighed amount of barrier layer granules equivalent to the bottom layer (100mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up, and 400mg of the powder of the core matrix formulation were placed over the bottom layer of barrier layer granules in the die cavity and again slightly compressed. Then again, the preweighed amount of barrier layer granules equivalent to (100mg) were placed over the core matrix layer and slightly compressed. The remaining volume of the die cavity was filled with the preweighed amount of immediate release powder equivalent to top layer and compressed with a maximum force of compression on a single station punching machine to obtain multilayered matrix tablet.

3.Evaluation of Directly Compressible Powder and Granules [8-12]

The blend of directly compressible powder and granules prepared as per the formula was subjected to various evaluation parameters including angle of repose, bulk density and tapped density and compressibility index test.

3.1.Bulk Density and Tapped Density

The volume (Vo) was measured after a precisely weighed amount of the powder (W) was cautiously poured into the graduated cylinder. After that, the graduated cylinder was placed into the Electrolab ETD 1020 Tapped Density Tester (USP) Mumbai and covered with a lid. the density apparatus was adjusted to measure the volume (Vf) and kept running until the two subsequent readings were equal, After 500 taps.

The bulk density and tapped density were calculated using the following formulas.

Bulk Density = W/V_o

Tapped density = W/V_f

Where, V_o = initial volume,

V_f = final volume.

3.2.Angle of Repose [8]

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

The angle of repose was determined according to the fixed funnel method reported by Raghuram et al,[13] where by accurately weighed granules (3g) were carefully poured through the funnel with its tip at 2 cm height (H) until the apex of the conical heap so formed just reached the tip of the funnel.

The mean diameter of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation.

$\tan \theta = h/r$

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

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose

Flow Property	Angle of Repose (Degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
poor	46-55
Very poor	56-65
Very very poor	>66

Table: 4. Flow properties and corresponding angle of reposeCompressibility Index [8-12]

The compressibility index and Hausner ratio may be calculated using measured values for

bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows :

$$\text{Compressibility index} = \frac{P_{tapped} - P_{bulk}}{P_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{P_{tapped}}{P_{bulk}}$$

Compressibility Index %	Flow Property	Hausner Ratio
≤10	Excellent	1.00-1.11
Nov-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
32-37	Very Poor	1.46-1.59
>38	Very very Poor	>1.60

Table: 5. Flow properties with corresponding compressibility index and Hausner ratio

4.Evaluation of Controlled Release Multilayer Matrix Tablet [8,9,10,12]

4.1. Thickness

Control of physical dimension of the tablets such as thickness, width and length are essential for consumer acceptance and to maintain tablet to tablet uniformity. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each formulation and their thickness was measured by using vernier caliper. Thickness values were reported in millimeters.

4.2. Hardness

Perfect compactness during packaging, coating, and shipping is sought after in order to achieve an appropriate shape and design.

Using a Pfizer-style hardness tester, a tablet was positioned between anvils, and the force needed to shatter it was measured. Ten tablets of each formulation were tested.

4.3. Drug Content

Ten tablets were taken at random to ascertain the amount of active substance. After precisely weighing the tablets, they were ground into a powder using a mortar and pestle. After dissolving an amount equivalent to 50 mg of captopril in 0.1 N HCl, the mixture was sonicated for 30 minutes. After filtering and appropriately diluting the solution, spectrophotometric analysis was performed at 205.6 nm.

Limit: drug content should be in the range of 90 to 110%.

4.4. Uniformity of Weight

A Denver digital balance was used to weigh each of the twenty tablets that were chosen at random from each formulation. The weight

was stated in milligrams. If no more than two individual tablet weights stray from the average weight by more than the percentage indicated and none do so by more than twice the percentage indicated, the batch passes the weight variation test.

Table: 6. Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test. (USP)	
Average weight of tablet (X mg)	Percentage variation
130 or less	10
130 to324	7.5
more than 324	5

Limit: weight of all individual tablets should be in the limit of average wt ± 5%

4.5. Friability

After ten tablets were weighed and put in the Electrolab, EF-2 Friabilator (USP), the device was rotated for four minutes at 25 rpm. The tablets were weighed once more after being dedusted following revolutions. The percentage friability was measured using the formula,

$$\% F = \{1- (wt/w)\}X\ 100$$

Where, % F = friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after revolution

Limit: All the formulated batches were found under acceptable limit of 0.8 to1% as specified.

4.6. Swelling Study

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by the reported method. [14-16] One tablet of each formulation was weighed and put in a beaker with the typical set of conditions needed to determine the drug's release in vitro. Throughout the investigation, the medium was kept at 37 ± 0.5ºc. Following a predetermined amount of time, the tablet was taken out, blotted to get rid of extra water, and its swollen weight was measured.

The swelling index was calculated using following formula.

Swelling index (S.I) = $[(W_t-W_o)/ W_o) \times 100]$

Where,

S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before placing in beaker Containing specified media.

4.7.Release Study of Multilayered Matrix Tablet

The USP XXIV basket dissolving device (Electrolab-tablet dissolution tester USP-TDT-06P) was used to conduct drug release tests at 100 rpm. The dissolution medium was kept at 37 ºC ± 0.5 ºC and contained 0.1 N hydrochloric acid for the first two hours and phosphate buffer pH 6.8 for the next two to twelve hours (900 ml). The drug concentration was assessed using a UV-visible spectrophotometer set to 205.6 nm for 0.1 N hydrochloric acid medium and 206 nm for phosphate buffer pH 6.8 medium after an aliquot (5 ml) was taken out at predetermined intervals and filtered through Wattman filter paper. It was made clear that none of the chemicals utilised in the matrix formulations

interfered with the assay. The release studies were conducted in duplicate.

4.8. Kinetic Analysis of Dissolution Data

In order to describe the kinetics of the drug release from the controlled release formulation various mathematical equations are used the zero-order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration [17]. The first order Eq. (2) describes the release from systems where release rate is concentration dependent. [18]. Higuchi [19] described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion (Eq. (3)).

$$M_t = k_0 t \quad (1)$$

$$\ln M_t = \ln M_0 - k_1 \cdot t \quad (2)$$

$$M_t = K \cdot S\sqrt{t} = k_H \cdot \sqrt{t} \quad (3)$$

where, M_t is the amount of drug released in time t, M_0 is the initial amount of the drug in tablet, S is the surface area of the tablet and k_0, k_1 and k_H are release rate constants for zero order, first order and Higuchi rate equations, respectively.

In order to define a model which will represent a better fit for the formulations and to predict the possible release mechanism the dissolution data can be further analyzed using Peppas and Korsenmeyer equation (power law). [20-22]

$$Mt / M\infty = kt^n \quad (4)$$

Where, Mt is the amount of drug released at time t and $M\infty$ is the amount released at time $t = \infty$, thus Mt/M∞ is the percentage fractional drug release at time t. The k is a constant related to the property of the drug delivery system and n is the diffusional exponent, which characterizes the drug transport mechanism. A value of n=0.5 indicates Case-I (Fickian) diffusion, 0.5< n < 1.0 indicates anomalous (non-Fickian) diffusion, n = 1.0 indicates Case -II transport and n > 1.0 indicates super Case -II transport. [23,24]

4.9. Stability Study: [25]

The short-term stability study of optimized formulation was performed as per ICH (International Conference on Harmonization) guidelines at 40° C and 75% RH for three months and evaluated for drug content and drug release.

5. Result & Discussion

5.1. Evaluation of Directly Compressible Powder and Granules

Formulation code	Bulk density		Tapped density		Compressibility index (%)		Hausner ratio		Angle of repose (θ)	
	T	M	T	M	T	M	T	M	T	M
T1M1	0.33	0.38	0.37	0.42	9.33	10.29	1.12	1.10	27.11	27.11
T1M2	0.33	0.38	0.37	0.42	9.33	10.29	1.12	1.10	27.11	27.11
T1M3	0.33	0.38	0.37	0.42	9.33	10.29	1.12	1.10	27.11	27.11
T2M1	0.46	0.39	0.50	0.43	8.002	10.0	1.08	1.10	25.96	26.56
T2M2	0.46	0.39	0.50	0.43	8.002	10.0	1.08	1.10	25.96	26.56
T2M3	0.46	0.39	0.50	0.43	8.002	10.0	1.08	1.10	25.96	26.56
T3M1	0.42	0.41	0.49	0.46	16.27	10.6	1.16	1.12	27.7	27.15
T3M2	0.42	0.41	0.49	0.46	16.27	10.6	1.16	1.12	27.7	27.15
T3M3	0.42	0.41	0.49	0.46	16.27	10.6	1.16	1.12	27.7	27.15

Table: 7. Physical properties of directly compressible powder and granule

Angle of repose is used to quantify the flow properties of powders. Frictional forces between the particles cause improper powder flow. The angle of response is used to quantify these frictional forces. The angle of repose values of the various powder mixtures from each formulation ranged from 25.96º to 27.15º, suggesting that the powder had fair to good flow properties.

A powder's tendency to compress is gauged by its compressibility index and Hausner ratio. They are therefore indicators of how significant inter-particulate interactions are. Such interactions are typically less important in a free-flowing powder, because the values of the tapped and bulk densities will be closer. A larger disparity between the bulk and tapped densities will be seen for materials with worse flow because there are often more interparticle interactions. The Hausner Ratio and the compressibility index both show these variations. Each formulation's powder and granule mixtures had Hausner ratios and compressibility indices ranging from 10.0–10.29%, 8.002–16.27 percent, and 1.10–1.22, 1.08–1.16 percent, respectively, indicating medium to good flow ability.

5.2. Determination of absorption maxima (λ_{max})

Table: 8. Absorption maxima (λ-max) of captopril in different media

The drug's absorption maximum (λmax) was ascertained using a Systronic 2202 PC-based UV visible double spectrophotometer. In 0.1N hydrochloric acid and phosphate buffer (pH 6.8), the drug's λmax was 205.6 nm and 206 nm, respectively.

S No.	Medium	Absorbance maxima (λ_{max})
1	0.1 N Hydrochloric acid (pH 1.2)	205.6
2	Phosphate buffer (pH 6.8)	206

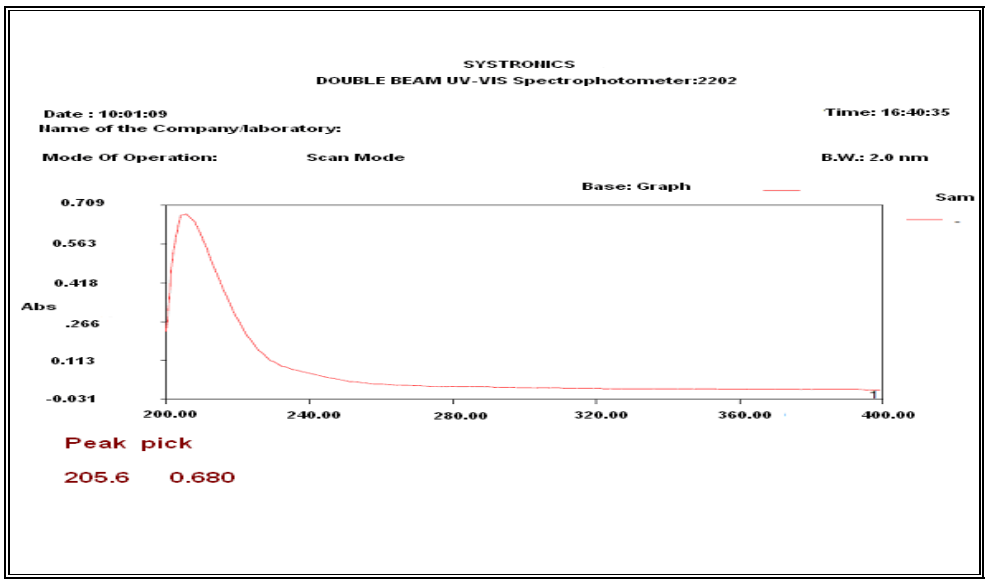

Figure: 1. Absorption maxima (λ_{max}) of captopril in 0.1 N Hydrochloric acid

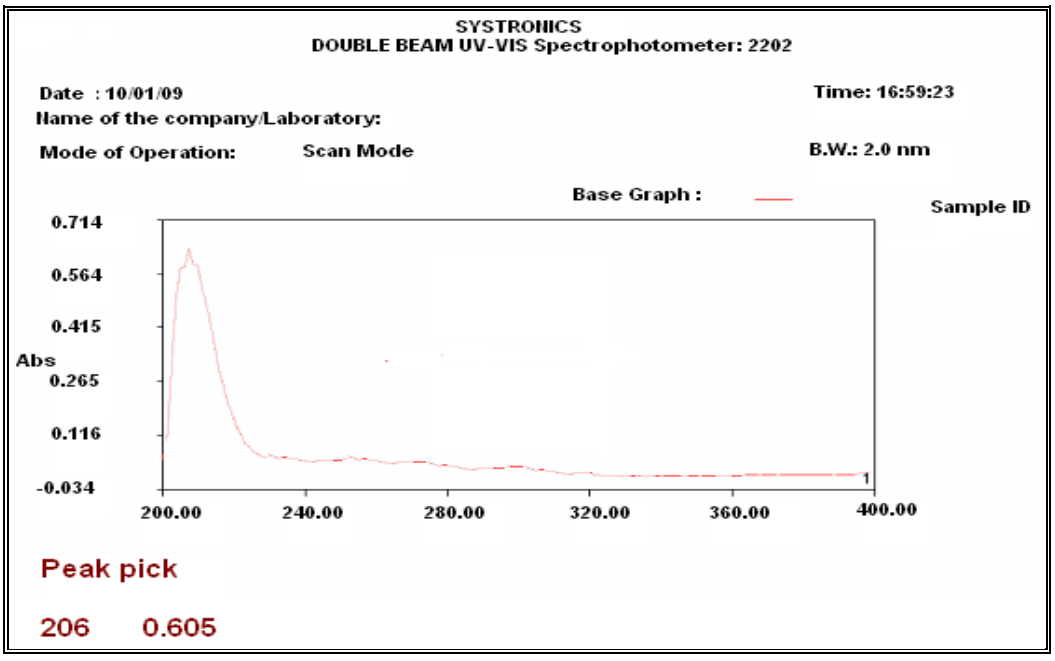

Figure: 2. Absorption maxima (λ_{max}) of captopril in phosphate buffer (6.8pH)

5.3. Preparation of Standard Curve of Captopril

S. no.	Concentration (µg/ml)	Absorbance
0.	0	0
1.	5	0.391
2.	10	0.515
3.	15	0.611
4.	20	0.68
5.	25	0.812
6.	30	0.911
7.	35	1.004
8.	40	1.084
9.	45	1.15
10.	50	1.241

Table: 9. Standard Curve of Captopril in 0.1 N HCl at max 205.6 nm

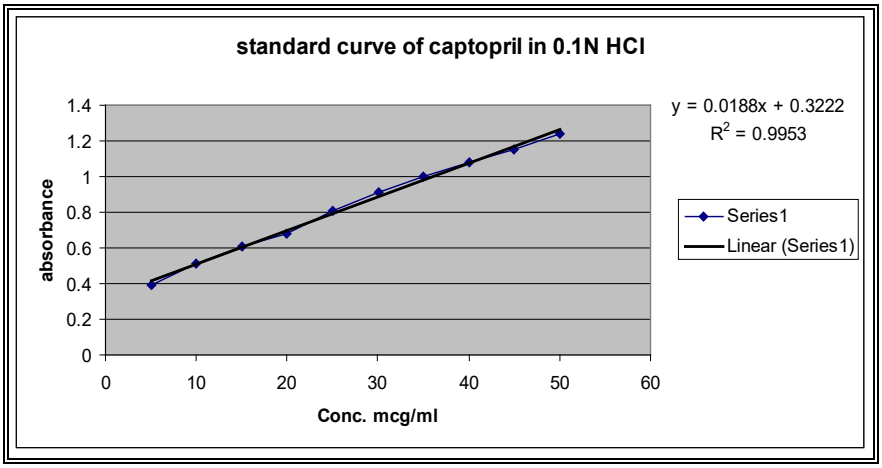

Figure: 3. Standard curve of captopril in 0.1 N HCl at λ-max 205.6nm

S. no.	Concentration (µg/ml)	Absorbance
0.	0	0
1.	10	0.23
2.	20	0.37
3.	30	0.51
4.	40	0.605
5.	50	0.79

Table: 10. Standard curve of captopril in

phosphate buffer (pH 6.8) at λ-max 206nm

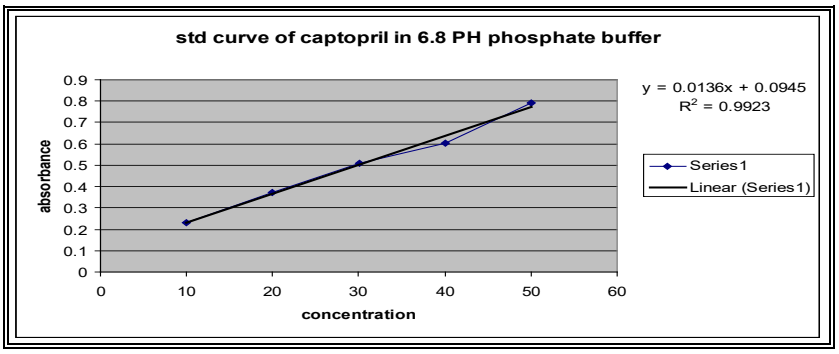

Figure: 4. Standard curve of captopril in phosphate buffer (pH 6.8) at λ-max 206nm

Using 0.1N hydrochloric acid and phosphate buffer pH 6.8, the UV spectra of a solution of 50µg/ml of captopril reveal absorbance maxima (λ-max) at wavelengths of 205.6 nm and 206 nm, respectively. The drug's standard curves were created at concentrations ranging from 5 to 50 µg/ml. The drugs comply with Beer's law, as evidenced by a straight line with regression coefficients (R^2) of 0.9953 and 0.9923 in 0.1N hydrochloric acid and phosphate buffer pH 6.8 media, respectively.

5.4. Evaluation of Controlled Release Multilayer Matrix Tablet

Formulation	Thickness (mm)	Friability (%)	Hardness (Kg)	Weight (mg)	Drug content (%)
T1M1	7.22±025	0.15	5.9 ± 0.27	649.4 ± 4.2	97.79 ± 0.52
T1M2	7.27±0.24	0.21	5.7 ± 0.30	648.5± 3.2	98.3 ± 0.33
T1M3	7.22±0.25	0.26	5.7 ± 0.28	649.5± 4.7	98.69 ± 0.37
T2M1	7.20±0.28	0.19	5.7 ± 0.34	649.1± 3.8	99.67 ± 0.32
T2M2	7.21±0.23	0.22	5.8 ± 0.20	648.5± 2.7	101.12 ± 0.50
T2M3	7.24±0.24	0.26	5.8 ± 0.24	645.4± 2.9	99.21 ± 0.68
T3M1	7.14±0.27	0.29	5.8 ± 0.20	647.8± 3.7	100.45 ± 0.31
T3M2	7.27±0.23	0.32	5.9 ± 0.23	647.4± 3.53	99.11 ± 0.59
T3M3	7.29±0.22	0.33	5.9 ± 0.21	646.8± 4.41	98.03 ± 0.73

Table: 11. Physical properties of Multilayer matrix tablet, in Mean ± S.D

The prepared tablet had a thickness of 7.14±0.27 to 7.29±0.22 mm. It was noted that there was very little variance in thickness. The multilayer matrix tablet's percentage friability fell within an acceptable range, ranging from 0.15 to 0.33 percent. The tablet's hardness varied between 5.72±0.34 and 5.92±0.21, suggesting that an increase in polymer concentration has no effect on the tablet's hardness. All batches of multilayer matrix tablets were determined to have good hardness. The tablet formulations' weight variation (<5%) and drug content (97.8 ± 0.52% to 101.12 ± 0.50%) met specification. Thus, the compressed multilayer tablets' physical characteristics were all essentially under control.

5.5. Swelling Study

Time (hours)	Swelling Index (%)								
	T1M1	T1M2	T1M3	T2M1	T2M2	T2M3	T3M1	T3M2	T3M3
0	0	0	0	0	0	0	0	0	0
1	9.97	10.98	12.44	14.91	16.45	18.52	19.63	20.23	21.36
2	23.11	25.17	26.41	28.94	31.87	33.74	35.65	40.15	48.57
3	48.92	51.55	53.28	56.21	59.49	63.92	65.42	69.32	78.45
4	73.42	75.24	77.83	79.65	81.71	83.47	85.46	89.65	117.48
5	99.02	101.11	106.42	111.44	117.64	121.83	125.64	130.11	143
6	110.09	115.23	121.68	125.19	131.79	135.86	138	140.24	157.88
7	118.74	122.42	125.56	127.94	134.73	138.77	140.23	147.32	168.54
8	120.06	125.11	127.35	130.41	136.47	140.11	141.98	149.89	171.22
9	122.63	127.24	128.56	133.22	138.54	142.95	143.32	151.23	172.12
10	123.34	128.46	129.48	135.26	139.73	143.27	145.72	152.62	173.32
11	122.89	127.21	128.01	134.75	139.03	142.91	145.08	151.26	172.59
12	120.6	126.01	127.33	133.15	137.34	141.24	144.11	150.33	171.34

Table: 12. Swelling Index of Multilayer Matrix Tablets

A study of swelling could be utilized to evaluate how much the polymers (guar gum and HPMC) swelled. The table displayed the proportion of tablet swelling as measured by the swelling index. The formulation's maximum swelling was attained after ten hours. The percentage of swelling rose quite dramatically for the first seven hours, then grew progressively for ten hours, before gradually declining for twelve hours. The swelling index rose as the quantity of polymers increased, as shown in fig. maximal swelling achieved with T3M3 formulation.

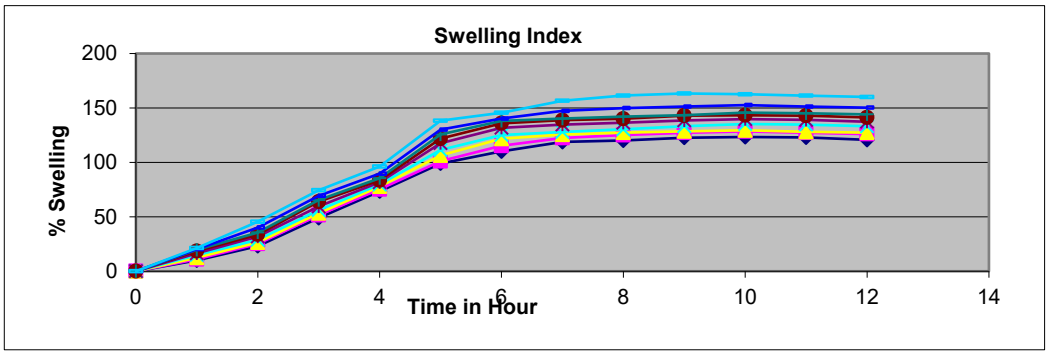

Figure: 5. Figure: 5. Swelling study of multilayer matrix tablets

5.6. Release Study of Multilayered Matrix Tablet

Table: 13. In-vitro release study of controlled release multilayer matrix tablet

Time (hour)	Cumulative % drug release								
	T1M1	T1M2	T1M3	T2M1	T2M2	T2M3	T3M1	T3M2	T3M3
0	0	0	0	0	0	0	0	0	0
1	18.36	18.35	18.07	19.5	18.45	18.57	18.61	18.37	18.11
2	28.03	25.89	23.81	23.04	22.44	21.87	21.31	20.15	19.51
3	35.44	33.61	30.97	29.89	28.99	27.88	30.98	22.17	22.86
4	50.22	54.64	42.38	35.47	39,89	30.39	41.82	30.54	28.69
5	59.81	56.87	45.79	47.89	45.62	39.38	46.35	35.56	33.42
6	61.53	65.84	59.77	58.62	54.92	46.95	51.95	41.68	39.31
7	72.54	68.31	63.41	61.39	56.72	57.36	55.31	43.93	45.95
8	74.43	76.67	65.76	64.31	65.28	59.84	59.86	51.86	48.84
9	84.67	80.31	69.04	72.81	67.97	64.23	63.85	55.84	55.57
10	86.86	87.96	79.96	76.23	73.82	69.19	69.34	62.96	59.84
11	90.17	90.12	86.74	83.76	73.86	75.54	71.89	66.97	63.85
12	96.47	92.55	88.31	86.47	82.94	79.66	77.84	72.93	68.91

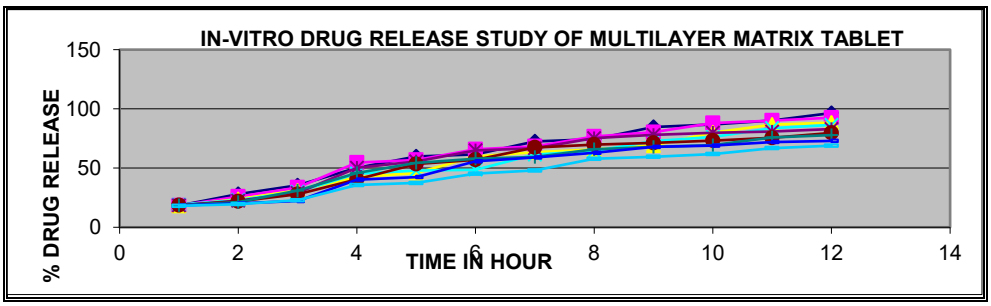

Figure: 6. Drug release study of multilayer matrix tablets

A 12-hour in vitro release study of captopril multilayer matrix tablets was conducted under sink conditions. The dissolution profile of each tablet formulation derived from the dissolution data is displayed in the table and figure. The dissolution profile results demonstrated that the polymer concentration significantly influenced the drug's release. The drug release values for formulations T1M1 through T3M3 were determined to be 96.47, 92.55, 88.31, 86.47, 82.94, 79.66, 77.82, 72.93, and 68.91, respectively, after 12 hours. This suggests that the drug release rate decreases as the concentration of polymers in the barrier layer and matrix core increases.

5.7. Kinetic Analysis of Dissolution Data

Formulations	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	r^2	f2	r^2	f2	r^2	f2	r^2	n
T1M1	0.967	54.67	0.89	28.16	0.991	65.67	0.99	0.684
T1M2	0.951	55.06	0.9	28.2	0.982	61.87	0.98	0.689
T1M3	0.981	50.35	0.942	24.48	0.982	58.67	0.984	0.676
T2M1	0.977	46.91	0.955	23.42	0.982	57.98	0.973	0.652
T2M2	0.907	50.16	0.965	26.91	0.955	61.04	0.951	0.686
T2M3	0.924	47.3	0.958	24.28	0.96	65.29	0.937	0.663
T3M1	0.926	43.42	0.946	24.03	0.968	69.02	0.986	0.639
T3M2	0.932	42.49	0.972	21.35	0.954	63.25	0.978	0.664
T3M3	0.969	64.73	0.958	18.65	0.974	65.67	0.947	0.618

r^2 = correlation coefficient; f2 = similarity factor and n = diffusion release exponent

Table: 14. Kinetic assessments of dissolution data of multilayer matrix tablet

The type of release mechanism was investigated by using the drug release data. All formulations (T1M1 to T3M3) were subjected to release kinetic studies for various kinetic equations (zero order, first order, and Higuchi equation). For all formulations, the Higuchi equation provided the best fit with the highest correlation (r^2 > 0.971), indicating that the release of captopril

from the matrix system was regulated. By entering the release data values into the biopharmaceutic software MB-V6, the release kinetic study was confirmed once more, and it was discovered that all of the controlled release formulations adhere to the Higuchi model. Therefore, we may conclude that the diffusion mechanism was primarily responsible for the release of captopril from the matrix system.

Diffusion swelling and erosion are the three most crucial rate-controlling mechanisms used in formulations for controlled or prolonged release. Fickian diffusion provides the greatest description of the drug release from the polymeric system, which occurs mostly by diffusion. However, when it comes to formulations that incorporate swelling polymers, factors other than diffusion are crucial for examining the drug release mechanism. The solution of Fick's second law of diffusion is complicated by these processes, which include the relaxation of polymer chains, the imbibition of water that causes polymers to swell and change from

Table: 15. stability study of optimized multilayer tablet

Sr. No.	Evaluated Parameter	Results
1.	% drug release up to 12 hr	95.23
2.	% drug content	98.79 ± 0.52

their initial glassy to rubbery state due to swelling, significant volume expansion, and the occurrence of moving diffusion boundaries.[26] Therefore, the Korsmeyer-Peppas model (Eq. 4) was used to further treat the release data. The fact that superimposes two seemingly separate drug transport mechanisms is generalized in this equation. Drug release from a swelling polymer is described by Fickian diffusion and a case II transport. Diffusion-controlled drug release is indicated by n = 0.5, while swelling-controlled drug release is indicated by n = 1. An indicative of both phenomena (anomalous or non-Fickian transport) can be found in values of n between 0.5 and 1.

Model fitting and linear regression analysis revealed that every formulation adhered to the Korsmeyer-Peppas model, which had a higher correlation coefficient (r^2). The table displays the diffusional release exponent (n) value for each formulation together with the regression coefficient (r^2). All formulations (T1M1-T3M3) had release exponent values between 0.618 and 0.689, which suggests anomalous transport or non-Fickian release. Additionally, a slower rate of dissolving was noted for tablets with a higher concentration of polymer in both the barrier layer and matrix core.

5.8.StabilityStudies

According to ICH (International Conference on Harmonisation) requirements, the optimised formulation's short-term stability study was conducted for three months at 40° C and 75% relative humidity. The stability research's findings showed that, throughout the course of a three-month short-term stability trial, neither drug content nor drug release changed.

Results of the stability study indicate that, the optimized formulation is stable at temperature of 40° C and 75% RH.

6. Conclusions

The study successfully demonstrated the potential of multilayer matrix tablets for controlled release of captopril. The powder and granule properties indicated excellent flowability and compressibility, ensuring reliable tablet production. The prepared tablets met all quality standards for thickness, friability, hardness, weight variation, and content uniformity, showcasing their robustness and consistency.

The swelling study highlighted that the T3M3 formulation exhibited the highest swelling, and the dissolution profile confirmed that polymer concentration significantly influenced drug release. The T3M3 formulation, with its optimized polymer content, achieved the highest drug release after 12 hours, making it a promising candidate for achieving controlled and sustained drug delivery while addressing toxicity concerns and improving patient compliance.

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