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FORMULATION AND EVALUATION OF BI-LAYERED TABLET OF ATENOLOL AND HYDROCHLOROTHIAZIDE

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Keywords:

Immediate release bilayer tablet, Atenolol, Hydrochlorothiazide, Hypertension treatment, Preformulation analyses, Flow properties, Drug release mechanisms, Stability

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ABSTRACT: The study focuses on creating and evaluating a specialized bilayer tablet for treating hypertension. It begins with in-depth preformulation analyses of key components like Atenolol, Hydrochlorothiazide, and various excipients. Special emphasis is placed on optimizing the powder blend's flow properties to facilitate tablet compression. A series of tests on resulting tablets (F1 to F8) assess weight variation, thickness, hardness, friability, disintegration time, and drug content, ensuring they meet required specifications with uniform weight and hardness. Dissolution profiles of all formulations are examined, with Formulation 8 (F8) identified as the most suitable for consistent drug release across both layers. The study investigates drug release mechanisms, finding that both layers adhere to the diffusion-controlled release model, particularly the Higuchi model. Stability tests conducted under elevated temperature and humidity (40°C/75% RH) over three months reveal minimal changes in physical attributes, drug content, and drug release profiles, confirming the tablet's stability. In conclusion, the study successfully develops an optimized Immediate Release Bilayer Tablet containing Atenolol and Hydrochlorothiazide. This tablet offers controlled and uniform drug release, vital for managing hypertension. Importantly, the tablet formulation maintains stability over three months. Future research and clinical evaluations are recommended to establish the efficacy and safety of this optimized bilayer tablet for hypertensive patients.

INTRODUCTION: The introduction highlights the significance of the oral route for drug administration, particularly tablets, due to their ease of manufacturing and patient compliance. It emphasizes the advantages of solid oral dosage forms and their popularity.

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The use of excipients is discussed, outlining their role in altering drug release patterns and enhancing various aspects of dosage forms [1].

The manufacturing methods of tablets, including direct compression, dry granulation, wet granulation, and melt granulation, are described. Different types of tablets, such as uncoated, coated, sustained release, immediate release, delayed release, and layered tablets, are explained along with their advantages and disadvantages [2-3]. The focus shifts to immediate release drug delivery systems, explaining their benefits such as improved

compliance, stability, and solubility. Categories of drugs suitable for immediate release are mentioned. Sustained release systems are introduced, highlighting their advantages in maintaining constant drug levels, improving patient compliance, and reducing side effects. The factors influencing the design of sustained release dosage forms, including pharmaceutical, biopharmaceutics/ pharmacokinetics, and pharmacodynamics/clinical pharmacological factors, are outlined. Drug properties affecting sustained release design are discussed, along with the classification of polymers used in sustained release drug delivery systems.

Bilayer Tablets: The bilayer tablet is a model developed in their Geometrix tablet by Skye Pharma PLC, which is self-possessed with various layers. Bilayer tablet distinguishes two incompatible ingredients as well as the maintenance dose for a continuous release dose in which one part released immediately as the early dose and the second layer are delayed released [4-6].

Bilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles improves patient compliance, prolongs the drugs action, avoid saw true kinetics resulting in effective therapy along with better control of plasma drug level.

Bilayer tablet is a solid oral dosage form, usually round, spherical, oval or biconcave in shape and consist of one or more than one medicament designed in two-layer system which can be suitable for combination therapy and biphasic release therapy. Bilayer tablet is the new era for the successful development of controlled release formulation. Bilayer tablet is better than the traditionally used dosage forms. Bi-layer tablets are prepared with one layer of the drug for immediate release while the second layer is designed to release the drug later, either as a second dose or in an extended-release manner. The bi-layered tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and the second layer is maintenance dose. The basic goal of therapy is to achieve a steady-state drug in blood level for an extended period of time.

The mechanism of drug release from matrix and erosion is explained, along with the mathematical models describing drug release kinetics. Challenges in bi-layered tablet manufacturing are presented, along with various approaches and technologies used, including floating drug delivery systems, polymeric bioadhesive systems, and swelling systems.

MATERIALS AND METHODS: Atenolol and Hydrochlorothiazide were gift samples from Modern Labs, Indore, while other excipients were sourced from various suppliers. UV-grade solvents and analytical-grade chemicals were utilized in the project.

Preformulation Studies[7-8]: It involve investigating the physical and chemical properties of a drug substance, both alone and when combined with excipients, in order to establish a rational foundation for dosage form development. This stage informs formulation approaches, minimizes formulation risks, and lays the groundwork for optimizing product quality and performance.

Description: An initial assessment of the substance's color was conducted through a descriptive test.

Solubility: The aqueous solubility of the substances was assessed, considering its implications on absorption and overall efficacy.

Melting Point: Precise determination of the melting point and melting range was performed.

Loss on Drying: The moisture and volatile matter content of the substances were measured using the loss on drying test.

Flow Properties (Angle of Repose): The flow characteristics of the powder and granules were evaluated by measuring the angle of repose, providing insights into their flow behavior.

$$\Theta = \tan -1(h/r)$$

Bulk Density: Bulk density, a powder characteristic, is defined as the mass (M) of the powder filling a known volume (Vo), usually expressed in g/ml. The process involves transferring granules into a 50 ml measuring cylinder using a funnel.

The volume occupied by the granules is measured as the unsettled apparent volume. Bulk density is then calculated using a specific formula.

$$\rho bulk = m/Vo$$

Tapped Density: Measured by tapping a cylinder with powder, recording volume changes after 500 taps using a tester.

$$\rho t = m/V_t$$

Carr's Compressibility Index: Indicates arch formation tendency and failure ease.

$$CI = \rho t - \rho bulk / \rho t \times 100$$

Hausner's Ratio: Hausner's ratio (ρt / ρbulk) predicts flow based on interparticle friction. Lower ratios for free-flowing, higher for cohesive powders.

$$\text{Hausner's Ratio} = \rho t / \rho bulk$$

Particle Size Analysis: Tablet size affects flow, mixing, and stability. Fine particles vulnerable to environmental factors. Sieving method used for particle size distribution. Sieves stacked, weights retained on each determined, percentage calculated with formula.

$$\% \text{ Retained} = W_{Sieve} / W_{Total} \times 100\%$$

IR Spectroscopy: Versatile method for fingerprinting and identifying compounds. Measures energy absorption in infrared range. Analyzes gas, liquid, or solid samples.

Compatibility Studies: Crucial for tablet stability. Drug-excipient interactions impact formulation. Aids in excipient selection. Essential for known drugs.

Physical Compatibility Study [9]: Pre-formulation study assessed drug-excipent interaction.

The Protocol Involved Testing Different Drug: excipient ratios, packing in USP type I glass vials with stopper and seal, storing at 40°C/75% RH (Open and Close), conducting physical observations, filling vials with pure API, excipients, and API with excipients, sealing or leaving them open, placing sets in stability chamber under specified conditions, and analyzed as mentioned in **Table 1** and **2.**

TABLE 1: BINARY MIXTURE FOR RS TEST OF HYDROCHLOROTHIAZIDE

S. no.	Material	Ratio	Initial Observation	Storage condition
1.	API		White crystalline power	40˚C/75%RH
2.	API +Microcrystalline cellulose ph (101)	1:5	White blend	One month
3.	API + Maize starch	1:1	White blend	
4.	API + Sodium starch glycolate	1:0.5	White blend	
5.	API + povidone K 30	1:0.5	White blend	
6.	API + Light magnesium dioxide	1:0.5	White blend	
7.	API + Sodium hydroxide pellets	1:0.5	White blend	
8.	API + Magnesium stearate	1:0.5	White blend	
9.	API + MCC+ Maize Starch	1:5:0.5:0.5:0.5: 0.5:0.5	White blend	

TABLE 2: BINARY MIXTURE FOR RS TEST OF ATENOLOL

S. no.	Material	Ratio	Initial observation	Storage condition
1.	API		White crystalline powder	40˚/75%RH One month
2.	API + Lactose monohydrate	1:10	White blend	
3.	API + HPMC K4M	1:0.5	White blend	
4.	API + Microcrystalline cellulose	1:1	White blend	
5.	API + Talc	1:0.5	White blend	
6.	API + Magnesium stearate	1:0.5	White blend	
7.	API + Lactose monohydrate + HPMC K4M + Microcrystalline cellulose + Talc + Magnesium stearate	1:10:0.5:1:0.5 :0.5	White blend	

Development of Standard Calibration Curves: Standard Calibration Curve Development of Atenolol in Methanol UV Spectroscopy (λ max). The absorption maximum of Atenolol's standard solution was scanned between 200-400 nm on a UV-visible spectrophotometer.

Standard Stock Solution Preparation: About 50 mg of Atenolol was accurately weighed and dissolved in methanol using a bath sonicator. The solution was then diluted to 50 ml to achieve a concentration of 1000 µg/ml. A 5 ml portion was further diluted to 100 µg/ml.

Calibration Curve Preparation: Aliquots of 2, 4, 6, 8, 10, and 12 ml were pipetted from the stock solution into 100 ml volumetric flasks and made up with methanol to obtain concentrations of 2-12 µg/ml. Absorbance at these concentrations was measured at 226 nm using a UV-visible spectrophotometer, with methanol as the blank.

Calibration Curve Development of Hydrochlorothiazide in Phosphate Buffer pH 6.8:

Absorption Maximum Scanning: The absorption maximum of Hydrochlorothiazide's standard solution was scanned within 200-400 nm on a UV-visible spectrophotometer.

Standard Stock Solution Preparation: Approximately 10 mg of Hydrochlorothiazide was accurately weighed and dissolved in phosphate buffer of pH 6.8. The solution was diluted with the same buffer to achieve a concentration of 100 µg/ml.

Calibration Curve Preparation: Aliquots of 2, 4, 6, 8, 10, and 12 ml were pipetted from the stock solution into 100 ml volumetric flasks and made up with phosphate buffer pH 6.8 to obtain concentrations of 2-12 µg/ml. Absorbance at these concentrations was measured at 270 nm using a UV-visible spectrophotometer, with phosphate buffer pH 6.8 as the blank.

Formulation of Immediate Release Bilayer Tablet of Atenolol and Hydrochlorothiazide: The process involves dispensing two distinct blends into separate containers, followed by sifting of API and excipients, wet granulation of each blend separately, drying, pre-lubrication, lubrication, bilayer tablet compression, and final evaluation[10-12].

The formulation of bilayer tablets involves a wet granulation process, encompassing the sequential steps of dispensing two separate blends (layer A and layer B), sifting API and excipients, performing wet granulation for each blend, followed by drying, pre-lubrication, lubrication, bilayer tablet compression, and packaging.

For Layer A, materials are sifted, dry mixed, granulated with binder solution, dried and sifted again, and finally blended. In Layer B, materials are sifted, dry mixed, wet mixed with binder solution, dried and sifted, and then blended, resulting in the production of distinct bilayer tablets detailed in **Table 3** and **4.**

TABLE 3: UNIT COMPOSITION OF "A" LAYER

S. no.	Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8
1	Hydrochlorothiazide	40	40	40	40	40	40	40	40
2	MCC	140	130	120	110	100	90	80	70
3	Maize starch	25	25	25	25	25	25	25	25
4	SSG	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
5	Povidone K- 30	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
6	Light magnesium oxide	34	44	54	64	74	84	94	104
7	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	SSG (pre-lubrication)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Purified water					Qs			
	A layer weight	250	250	250	250	250	250	250	250

TABLE 4: UNIT COMPOSITION OF "B" LAYER

S. no.	Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8
1	Atenolol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
2	Lactose monohydrate	55	50	45	40	35	30	25	20
3	HPMC K4M	22.5	27.5	32.5	37.5	42.5	47.5	52.5	57.5
4	Microcrystalline cellulose	20	20	20	20	20	20	20	20
5	Purified water				Qs				
6	Talc	4	4	4	4	4	4	4	4
7	Magnesium stearate	1	1	1	1	1	1	1	1

B layer weight	115	115	115	115	115	115	115	115
Total weight of the tablet (A and B layer)	365	365	365	365	365	365	365	365

Evaluation of Tablets (Post-compression) [13-15]: Tablet quality assessment included measuring the dimensions (thickness and diameter) of five randomly selected tablets, ensuring they fell within ±5% of standard values.

Weight variation test involved weighing 20 tablets, with no more than two deviating beyond 5% of the average weight and none exceeding double the percentage. Thickness was measured with ±0.5% variation. Hardness, determined by Monsanto tester, met the 4-6 kg/cm^2 range. Friability was assessed using Roche Friabilator, with percent friability calculated using the formula, ensuring it did not exceed 1%.

Assay by UV: UV assay involved weighing and pulverizing ten tablets, taking an equivalent of 100 mg drug powder, dissolving it in pH 6.8 buffer, diluting to 100 mL, filtering, and further diluting by 100 times. Absorbance was measured at 275 nm, with acceptable range set at 95.0% to 105.0% of the label claim.

Disintegration Test: In the Disintegration Test, tablets are placed in glass tubes with mesh screens, immersed in gastric or intestinal fluid at 37±2°C. Tablets move up and down, avoiding floating with plastic disks, and must disintegrate fully, passing through a 10 mesh screen in a specified time. Tablets are placed in the apparatus once the water bath reaches temperature.

Dissolution Studies: A tablet was placed in a mesh-equipped basket attached to a motor. The basket was immersed in a 900 mL pH 6.8 phosphate buffer within a 1000 mL flask, maintained at 37 ± 0.5°C. The motor speed was set to 50 RPM, and samples were withdrawn at regular intervals (5, 10, 15, 20, and 30 minutes) to analyze drug content. Dissolution conditions included pH 6.8 phosphate buffer, USP Type II apparatus, and controlled temperature.

Kinetic Modeling and Mechanism of drug Release of Optimized Formulations: The drug release data of optimized formulations were evaluated for various kinetic models viz. zero order, first order, Higuchi model, Hixson-Crowell model and Korsmeyer-Peppas model. The study was carried out to determine the mode of drug release from the formulation by using DD Solver software.

The Kinetics of *In-vitro* Drug Release:

Zero Order:

$$C = K0\ t$$

Where K0 - is the zero-order rate constant expressed in units of concentration/time and t -is the time in h.

First Order:

$$\text{Log } C = \text{Log } C0 - K1t / 2.303$$

Where C0 - is the initial concentration of drug, K1 - is the first order constant and t – is the time in h

Higuchi:

$$Qt = Kt1/2$$

Where Qt - is the amount of the released drug in time t, K- is the kinetic constant and t- is the time in h.

Korsmeyer-Peppas:

$$Mt / M\infty = Kt\ no$$

Where, Mt - represents amount of the released drug at time t, M∞ - is the overall amount of the drug (whole dose) released after 12 h, K is the diffusional characteristic of drug/polymer system constant, n is a diffusional exponent that characterizes the mechanism of release of a drug.

Stability Studies: The stability of a formulation refers to the duration from its manufacturing date until its chemical or biological activity remains above a predetermined potency level, and its physical attributes remain mostly unchanged. Proper stability analysis is integral to pharmaceutical product development, evaluating the product's safety and stability. This testing provides insights into how a drug substance or product quality changes over time due to environmental factors like temperature, humidity, and light, guiding recommended storage conditions

and shelf life. ICH guidelines prescribe specific storage conditions for stability studies.

RESULTS: The present study was carried out to formulate & evaluate Immediate Release Bilayer Tablet of Atenolol and Hydrochlorothiazide for Treatment of Hypertension. Bilayer Tablet were evaluated for various parameters and the results are presented in appropriate tables and figures.

Preformulation Studies: The following preformulation studies were performed on Atenolol, Hydrochlorothiazide & excipients.

Evaluation of Hydrochlorothiazide (API): The color, solubility, melting point and moisture content of the API were evaluated. It was found to be within the range of the monograph as mentioned in **Table 5.**

TABLE 5: PHYSICAL CHARACTERISTICS OF HYDROCHLOROTHIAZIDE

S. no.	Tests	Specification	Results
1	Physical Description	White or almost white crystalline powder	Conforms
2	Solubility	Soluble in acetone, sparingly soluble in ethanol (96%), very slightly soluble in water, it dissolves in dilute solution of alkali hydroxides.	Positive
3	Melting Point	108º C- 112º C, the range between the beginning and the end of melting point does not exceed 2º C	110.3ºC, range 0.5ºC
4	Moisture content	NMT 0.5 w/w%	0.3%w/w

Evaluation of Atenolol (API): The color, solubility, melting point and moisture content of the API were evaluated. It was found to be within the range of the monographas mentioned in **Table 6.**

TABLE 6: PHYSICAL CHARACTERISTICS OF ATENOLOL

S. no.	Tests	Specification	Results
1	Physical Description	White to off white crystalline powder	Conforms
2	Solubility	Soluble in alcohol and methanol, slightly soluble in water, chloroform and hardly soluble in ethyl ether	Positive
3	Melting Point	158-160º C	155º C
4	Moisture content	NMT 0.5 w/w%	0.3%w/w

Angle of Repose of API's: The angle of repose of API was found to be $28^0.56' \pm 0.69$ for Hydrochlorothiazide, $30^0.10'' \pm 0.66$ for Atenolol and Powder blend $320.12'' \pm 0.33$. Hence the blend belongs to poor flow and requires glidants to improve the flow propertyas mentioned in **Table 7.**

TABLE 7: RESULTS OF ANGLE OF REPOSE

S. no.	Raw material(API)	Angle of repose (Degree)	Average
1	Hydrochlorothiazide	$28^0.14'$	$28^0.56' \pm 0.69$
2		$29^0.36'$	
3		$28^0.12'$	
4	Atenolol	$31^0.10'$	
5		$32^0.16'$	$30^0.10'' \pm 0.66$
6		$29^0.11'$	
7	Blend	$32^0.12'' \pm 0.33$	

Bulk Density and Tapped Density of Atorvastatin calcium: The average bulk density and tapped density was found to be 0.453 ± 0.01 and 0.614± 0.003 g/ml for Hydrochlorothiazide and 0.477 ± 0.33, 0.678± 0.33g/ml for Atenolol and for powder blend is .589 ± 0.22, .609 ± 0.25respectivelyas mentioned in **Table 8.**

TABLE 8: RESULTS OF BULK DENSITY AND TAPPED DENSITY OF DRUGS AND BLEND

S. no.	Raw material (API)	Bulk density (g/ml)	Average bulk density (g/ml)	Tapped density (g/ml)	Average tapped density (g/ml)
1	Hydrochlorothiazide	0.459	0.453 ± 0.01	0.612	0.614± 0.003
2		0.452		0.614	
3		0.448		0.618	
4	Atenolol	0.550	0.477 ± 0.33	0.699	0.678± 0.33

5		0.433	0.678
6		0.449	0.658
7	Blend	.589 ± 0.22	.609 ± 0.25

Powder Compressibility and Hausner's Ratio: Based on Compressibility index and Hausner's ratio, it indicates the Hydrochlorothiazide, Atenolol (API) and blend belongs to poor flow property and need to improveas mentioned in **Table 9.**

TABLE 9: COMPRESSIBILITY INDEX AND HAUSNER'S RATIO

Raw material(API)	Compressibility index (%)	Hausner's ratio
Hydrochlorothiazide	26.22	1.35
Atenolol	28.42	1.29
Bend	31.22	1.55

Particle Size Distribution: From the particle size analysis it was concluded that the particles size of the powder blend was found to be moderately coarse powder as mentioned in **Table 10.**

TABLE 10: PARTICLE SIZE DISTRIBUTION OF POWDER BLEND

Sieve no.	Empty weight of sieve	Quantity retained (gm)	Mass retained (gm)	Cumulative mass retained (gm)	Cumulative % retained	Percentage passing %
#20	367.8	368.55	0.75	0.75	4.34	95.66
#30	417.65	417.85	0.2	0.95	5.5	94.5
#40	358.05	365.65	7.6	8.55	49.56	50.44
#60	343.45	343.65	0.2	8.75	50.72	49.28
#80	340.75	340.9	0.15	8.9	51.59	48.41
#100	332.5	332.85	0.35	9.25	53.62	46.38
Base	540.45	548.45	8	17.25	100	0

Drug - Excipients Compatibility Studies: From the drug excipients compatibility study, it was observed that there was no characteristic change or interaction between drug and excipients brown color appears due to oils. Thus, it was concluded that the excipients selected for the formulation were compatible with Atorvastatin calcium results are shown in **Table 11.**

TABLE 11: DRUG - EXCIPIENTS COMPATIBILITY (INDIVIDUAL AND WHOLE BLEND)

S. no.	Composition	Initial	After 15 days	After 30 days	Conclusion
1	Hydrochlorothiazide	White	NCC	NCC	Complies
2	Atenolol	White	NCC	NCC	Complies
2	Both drugs + All Excipients	Off White	NCC	NCC	Complies

NCC- No Characteristic Change.

Individual: As observed in the above studies (physical observation of related substance) there was no any sign of interaction, therefore drug was compatible with excipientsare shown in **Table 12** and **13.**

TABLE 12: PHYSICAL OBSERVATION STUDIES RESULT OF HYDROCHLOROTHIAZIDE

S. no.	Material	Initial observation	40^0C/75%RH (One month)		40^0C/75%RH (Three month)	
			Open	Close	Open	close
1	API	White crystalline powder	complies	complies	complies	complies
2	API + Microcrystalline cellulose ph (101)	White blend	complies	complies	complies	complies
3	API + Maize Starch	White blend	complies	complies	complies	complies
4	API+ Sodium Starch Glycolate	White blend	complies	complies	complies	complies
5	API+ Povidone K -30	White blend	complies	complies	complies	complies
6	API + Light Magnesium Oxide	White blend	complies	complies	complies	complies
7	API + Magnesium Stearate	White blend	complies	complies	complies	complies
8	API + Microcrystalline cellulose (ph101) + Maize Starch	White blend	complies	complies	complies	complies

As observed in the above studies (physical observation of related substance) there was no any sign of interaction, therefore drug was compatible with excipients.

TABLE 13: PHYSICAL OBSERVATION OF COMPATIBILITY STUDIES OF ATENOLOL

S. no.	Material	Initial observation	40^0C/75%RH (One month)		40^0C/75%RH (Three month)	
			open	Close	open	close
1	API	White crystalline powder	complies	complies	complies	Complies
2	API + Lactose Monohydrate	White blend	complies	complies	complies	Complies
3	API + Microcrystalline cellulose ph (101)	White blend	complies	complies	complies	Complies
4	API + HPMC K4M	White blend	complies	complies	complies	Complies
5	API + Talc	White blend	complies	complies	complies	Complies
6	API + Magnesium Stearate	White blend	complies	complies	complies	Complies

UV-spectroscopic Method Analysis of Atenolol: Linearity and Range of Atenolol Calibration Curve in Methanol: The calibration graph exhibited a straight-line relationship within the concentration range of 2-12 µg/ml of Atenolol in methanol. The linear regression equation was y=0.045x+0.003, with a high correlation coefficient (r2) of 0.999. The linearity of the drug solution's analyzed concentration was confirmed based on the calibration curve's linear regression data (r2 value) are shown in **Table 14** and **Fig. 1.**

TABLE 14: CALIBRATION DATA FOR ATENOLOL IN METHANOL

S. no.	Concentration (µg/ml)	Absorbance
1.	2	0.0913
2.	4	0.1908
3.	6	0.2836
4.	8	0.3774
5.	10	0.4625
6.	12	0.5465

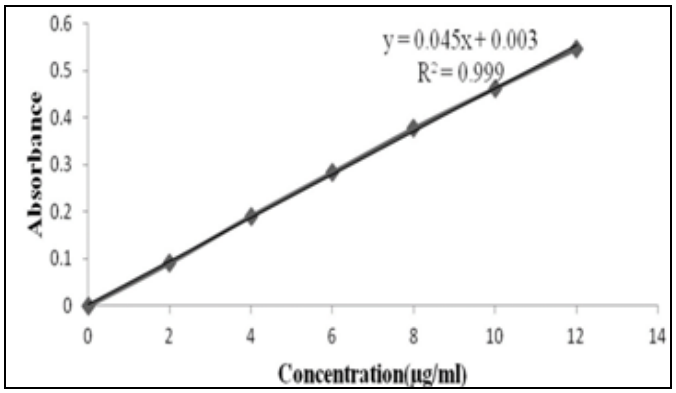

FIG. 1: CALIBRATION CURVE OF ATENOLOL IN METHANOL

Calibration Curve Linearity and Range for Hydrochlorothiazide in pH 6.8 Phosphate Buffer: A linear calibration graph was established within the 2-12 µg/ml concentration range of Hydrochlorothiazide in pH 6.8 phosphate buffer. The linear regression equation for Hydrochlorothiazide in this buffer was y=0.012x+0.001, showing a high correlation coefficient of 0.999. The calibration curve's linear regression data (r2 value) confirms the conformity of the analyzed drug solution concentration to linearity are shown in **Table 15** and **Fig. 2.**

TABLE 15: CALIBRATION DATA FOR HYDROCHLOROTHIAZIDE IN PHOSPHATE BUFFER PH 6.8

S. no.	Concentration(µg/ml)	Absorbance
1.	2	0.0265
2.	4	0.0529
3.	6	0.0795
4.	8	0.1046
5.	10	0.1279
6.	12	0.1535

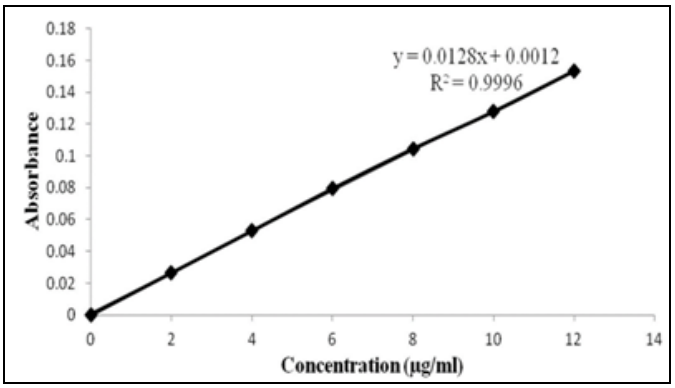

FIG. 2: CALIBRATION CURVE OF HYDROCHLOROTHIAZIDE IN PHOSPHATE BUFFER PH 6.8

IR Spectroscopyo f Hydrochlorothiazide and Atenolol: In **Fig. 3** and **4**, the IR spectroscopy results for Hydrochlorothiazide and Atenolol are presented. The spectra were obtained under and show distinct peaks characteristic of the compound.

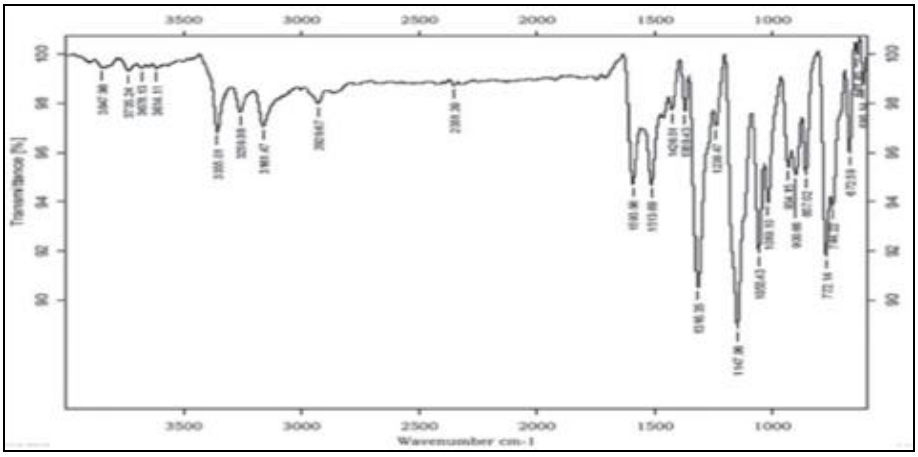

FIG. 3: IR SPECTROSCOPY OF HYDROCHLOROTHIAZIDE

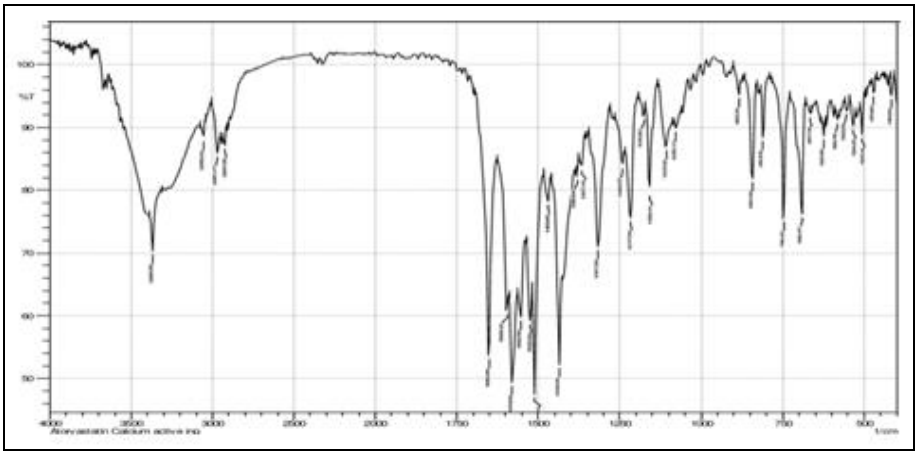

FIG. 4: IR SPECTROSCOPY OF ATENOLOL

Pre-compression Parameters: Parameters such as tapped density, bulk density, Carr's index, and Hausner's ratio were evaluated, all indicating favorable flow properties of the powder. The results fell within acceptable limits for the powder blend (F1-F8) and were deemed satisfactory results are mentioned in **Table 16** and **17.**

TABLE 16: PRE COMPRESSION PARAMETER OF BLEND OF DRUG A

Parameter/Batch No.	F1	F2	F3	F4	F5	F6	F7	F8
Bulk Density (g/ml)	0.55	0.35	0.53	0.52	0.64	0.44	0.47	0.47
Tapped Density (g/ml)	0.69	0.88	0.71	0.66	0.81	0.55	0.56	0.56
Hausner's ratio	1.32	1.54	1.33	1.26	1.26	1.25	1.19	1.19
Compressibility Index (%)	25	35	25	21	22	20	16	16

TABLE 17: PRE COMPRESSION PARAMETER OF BLEND OF DRUG-B

Parameter/Batch No.	F1	F2	F3	F4	F5	F6	F7	F8
Bulk Density (g/ml)	0.51	0.52	0.55	0.56	0.56	0.55	0.55	0.55
Tapped Density (g/ml)	0.68	0.67	0.56	0.57	0.57	0.57	0.57	0.56
Hausner's ratio	1.33	1.32	1.19	1.2	1.2	1.21	1.21	1.19
Compressibility Index (%)	25	25	16	18	18	17	17	16

Post compression studies: Individual tablet weight variation was performed and found to be within acceptable limits. Tablet thickness was measured using Vernier calipers, showing uniform values ranging from 4.92 to 4.96 mm across formulations, indicating proper compression. The hardness test conducted with a Monsanto hardness tester yielded results within specified limits. Disintegration times for all formulations, determined as per USP, are presented in the table, suggesting an effective internal structure promoting water penetration and swelling for disintegration results are mentioned in **Table 18.**

TABLE 18: POST COMPRESSION PARAMETERS OF TABLET

Parameters/Batch number		F1	F2	F3	F4	F5	F6	F7	F8
Individual weight variation of tablet (mg)	Max	345	346	367	366	367	367	368	370
	Avg	342	342	364.8	362	360	361	365	365
Thickness (mm)	Min	4.76	4.74	4.71	5.07	4.72	4.89	4.86	4.92
	Max	4.81	4.81	4.9	5.17	4.78	4.97	4.94	4.96
	Avg	4.78	4.77	4.8	5.11	4.76	4.93	4.90	4.94
Hardness	Avg	83	82	84	54	41	58	74	74
	Min	79	76	80	45	33	59	69	71
	Max	86	85	85	61	48	64	81	80
Disintegration Time (sec)	Min	10.24	16.44	7.40	13.24	13.24	17.40	7.31	4.36
	Max	12.45	17.53	9.20	15.56	14.51	20.51	9.05	7.03
Friability (%w/w)		0.06	0.1	0.26	0.16	0.18	0.13	0.24	0.13

Assay: Assay values were found to be within limit (95-105 %).

TABLE 19: ASSAY VALUES OF THE FORMULATION

Batch no.	F1	F2	F3	F4	F5	F6	F7	F8
Assay	96	97	95	98	96	99	99	101

Dissolution Profile of Eight Formulations: Dissolution profile were found best with Formulation 8 (F8). Therefore, F8 was found to be optimized formulation.

TABLE 20: DISSOLUTION RESULTS FOR PREPARED FORMULATION (F1-F8) LAYER –A

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
	%CDR							
5	84	85	85	86	83	81	81	79
10	85	90	90	87	86	83	87	81
15	86	91	91	88	88	85	88	87
20	87	91	91	89	90	86	88	91
30	89	91	91	89	90	87	88	91
45	89	91	91	89	91	87	88	91
60	90	91	91	90	91	88	89	93

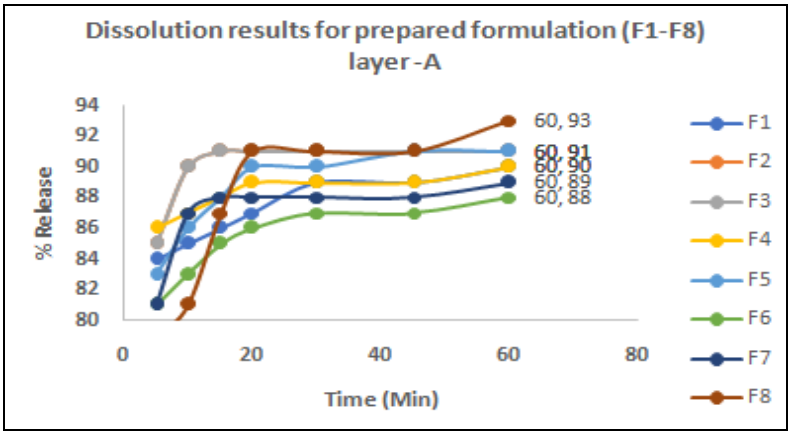

FIG. 5: DRUG RELEASE FROM LAYER A

TABLE 21: DISSOLUTION RESULTS FOR PREPARED FORMULATION (F1-F8) LAYER –B

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8
	%CDR							
30 (min)	13	13	17	11	14	9	18	30
1	27	25	36	22	29	19	34	48
2	40	38	58	40	42	27	43	55
3	55	50	79	71	73	34	55	65
4	75	70	85	86	82	62	65	72
5	85	86	95	92	88	75	72	86
6	99	100	97	93	91	84	100	99

Observation: Dissolution profile of were found to be similar with Formulation 8 (F8). Therefore, F8 was found to be optimized formulation.

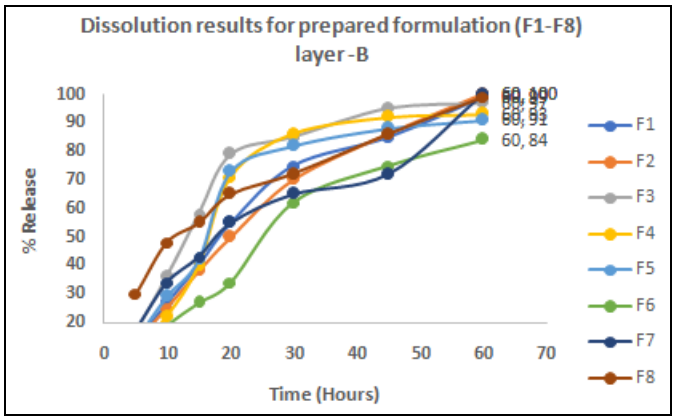

FIG. 6: DRUG RELEASE FROM LAYER B

Kinetic Release

For Layer A:

TABLE 22: KINETIC RELEASE FOR LAYER A

Formulation code	Kinetic Models				
	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer n R^2	
F1	0.8362	0.9816	0.9689	0.8915	0.6657
F2	0.8228	0.9844	0.9677	0.8694	0.6263
F3	0.8231	0.9819	0.9643	0.8711	0.6336
F4	0.7068	0.9850	0.9059	0.8424	0.5642
F5	0.7101	0.9606	0.9055	0.804	0.5134
F6	0.6835	0.9792	0.8945	0.8034	0.5129
F7	0.8030	0.9019	0.8603	0.8735	0.6536
F8	0.7018	0.8850	0.9151	0.7424	0.6642

For Layer B:

TABLE 23: KINETIC RELEASE FOR LAYER B

Formulation Code	Kinetic Models				
	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer n R^2	
F1	0.9821	0.8296	0.9653	0.6549	0.9975
F2	0.9838	0.7303	0.9074	0.6426	0.9794
F3	0.9838	0.8986	0.9297	0.6296	0.9699
F4	0.9736	0.7718	0.9794	0.6510	0.9983
F5	0.9918	0.8975	0.9404	0.6571	0.9736
F6	0.9847	0.8975	0.9518	0.6064	0.9692
F7	0.9827	0.7693	0.9685	0.6528	0.9987
F8	0.9873	0.7926	0.9427	0.6634	0.9602

Stability Studies: The bi-layered tablets were subjected to short term stability study, storing the formulation at 40°C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and *in-vitro* drug release rate were observed mentioned in **Table 24.**

TABLE 24: STABILITY DATA

Stability period	40°C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release Layer A	Layer B
Initial	7.05±0.67	0.36±0.01	99.23±0.532	99.413	95.823

1 month	7.08±0.49	0.43±0.03	99.35±0.751	99.581	95.421
2 month	6.41±0.49	0.56±0.06	98.96±0.792	99.142	94.736
3 month	5.33±0.60	0.73±0.03	96.94±0.921	98.728	94.381

DISCUSSION: This study aimed to create an effective Bilayer tablet for hypertension treatment. The researchers formulated and optimized the tablet's immediate-release layer using wet granulation with excipients like Sodium starch glycolate and microcrystalline cellulose. Pre-compression parameters were within Pharmacopeia limits, ensuring suitable tablet compression. The optimized formulation achieved a drug release profile similar to the innovators over 30 minutes, indicating controlled release for effective hypertension management. Relative error calculation validated the match. Overall, this innovative Bilayer tablet holds promise for controlled drug release and improved patient compliance in hypertension treatment.

CONCLUSION: The study successfully developed an optimized Immediate Release Bilayer Tablet containing Atenolol and Hydrochlorothiazide, demonstrating controlled and uniform drug release crucial for effective hypertension management. The formulation also exhibited satisfactory stability over the study period. Further investigations and clinical assessments are recommended to confirm the therapeutic efficacy and safety of the optimized bilayer tablet for hypertensive patients.

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