DEVELOPMENT AND CHARACTERIZATION OF BILAYERED TABLET CONTAINING HYDROCHLOROTHIAZIDE AS IMMEDIATE RELEASE LAYER AND METOPROLOL AS SUSTAINED RELEASE LAYER

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ABSTRACT

The present study aims to develop and evaluate a bilayered tablet incorporating Hydrochlorothiazide as an immediate release (IR) layer and Metoprolol Succinate as a sustained release (SR) layer, intended for effective and prolonged management of hypertension. Hydrochlorothiazide was formulated using suitable disintegrates to ensure rapid drug release, while Metoprolol Succinate was embedded in a polymer matrix comprising hydrophilic polymers (e.g., HPMC K100M) to sustain the drug release over a 12-hour period. The bilayered tablets were prepared using the direct compression method, ensuring physical and chemical stability of both layers. Preformulation studies including drug-excipient compatibility (FTIR) were performed. The tablets were evaluated for physical parameters (hardness, thickness, friability, weight variation), disintegration time, and in vitro dissolution profile. The sustained release layer released Metoprolol Succinate gradually up to 12 hours, following Higuchi kinetics, indicating a diffusion-controlled release mechanism. The results suggest that the formulated bilayer tablet successfully achieved the dual objective of fast onset and prolonged therapeutic effect,

making it a promising approach for improving patient compliance and efficacy in hypertension management.

Keywords: Hydrochlorothiazide, Metoprolol Succinate, FTIR Studies, Superdisintegrants, Polymers, In vitro drug release studies,

INTRODUCTION

Bilayered tablet technology has emerged as a promising approach for developing FDC formulations, as it allows the incorporation of two drugs with different release profiles within a single dosage form. Typically, one layer provides immediate release for rapid onset of action, while the other provides sustained release for prolonged therapeutic effect. This dual-release system ensures consistent plasma drug concentration and improved patient adherence, particularly in chronic conditions such as hypertension and diabetes.[1] Hydrochlorothiazide (HCTZ) is a thiazide diuretic that acts on the distal convoluted tubule of the nephron to inhibit sodium reabsorption, leading to diuresis and reduction in plasma volume, thereby lowering blood pressure. Owing to its short half-life (6–8 hours), frequent administration is required, which may result in poor compliance.[2] On the other hand, Metoprolol Succinate, a cardioselective β1-adrenergic receptor blocker, is widely used for long-term management of hypertension and angina pectoris. Its controlled-release formulation maintains steady plasma levels and reduces the risk of adverse effects associated with peak concentrations.[3] Developing a bilayered tablet comprising an immediate-release layer of HCTZ and a sustained-release layer of Metoprolol Succinate offers a rational therapeutic combination for effective and prolonged antihypertensive action.[4] The immediate release of HCTZ ensures prompt reduction in blood pressure, while the sustained release of Metoprolol Succinate provides continuous control over an extended period. Furthermore, the combination reduces dosing frequency, enhances patient compliance, and improves overall therapeutic outcomes. Hence, the present study aims to design, develop, and evaluate a bilayered tablet of Hydrochlorothiazide and Metoprolol Succinate by employing suitable polymers and excipients to achieve the desired immediate and sustained release characteristics.[5]

MATERIALS

Hydrochlorothiazide (HCTZ), Metoprolol Succinate were procured from Hetero Labs, HYD. Sodium alginate, Tragacanth, Croscaramellose were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Identification of Hydrochlorothiazide and Metoprolol succinate by FT-IR [6]

IR spectroscopy was used to determine the molecular interaction between polymer and drugs. All physical mixtures and drugs sample were mixed with dried KBR in ratio 1:1. Then small fraction of mixtures was compressed on automatic IR Press at pressure 10 tones to form transparent pellet. Then the IR spectrum of pellets was taken on FTIR spectrophotometer.

FORMULATION DEVELOPMENT:[7]

IR Layer (Hydrochlorothiazide):

1. Dry mix HCTZ, MCC, lactose, disintegrate.
2. Add magnesium stearate and talc.
3. Compress lightly as first layer.

SR Layer (Metoprolol Succinate):

1. Mix Metoprolol Succinate with polymers , lactose, MCC,
2. Granulate with suitable solvent (e.g., isopropyl alcohol).
3. Dry and sieve.
4. Add lubricants (Mg stearate, talc).
5. Compress over IR layer using bilayer tablet press

Table-1: Composition of Hydrochlorothiazide Immediate release layer

S.NO.	INGREDIENTS	F1 (mg)	F 2 (mg)	F 3 (mg)	F 4 (mg)	F 5 (mg)	F 6 (mg)	F 7 (mg)	F 8 (mg)
1	Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5

5	Croscaramellose	5	10	15	20	-	-	-	-
6	Sodium starch glycolate	-	-	-	-	5	10	15	20
7	Lactose								
8	Microcrystalline Cellulose	10	10	10	10	10	10	10	10
9	Talc	2	2	2	2	2	2	2	2
	Magnesium stearate	3	3	3	3	3	3	3	3
10	Total wt	100	100	100	100	100	100	100	100

Table-2: Composition of Metoprolol succinate sustained release layer

S.NO.	**INGREDIENTS**	**F1 (mg)**	**F 2 (mg)**	**F 3 (mg)**	**F 4 (mg)**	**F 5 (mg)**	**F 6 (mg)**	**F 7 (mg)**	**F 8 (mg)**
2	Metoprolol succinate	50	50	50	50	50	50	50	50
3	Sodium alginate	25	50	75	100	-	-	-	-
4	Tragacanth	-	-	-	-	25	50	75	100
7	Lactose	310	285	260	235	310	285	260	235
	MCC	10	10	10	10	10	10	10	10
8	Isopropyl alcohol	q.s	q.s	q. s	q.s	q.s	q.s	q.s	q.s
9	Talc	2	2	2	2	2	2	2	2
	Magnesium stearate	3	3	3	3	3	3	3	3
10	Total wt	400	400	400	400	400	400	400	400

Figure-1: Tablet punching machine

EVALUATION PARAMETERS[8]

Thickness and diameter

Thickness and diameter of tablets were accurately measured by using digital Vernier caliper for desired uniformity in size and shape.

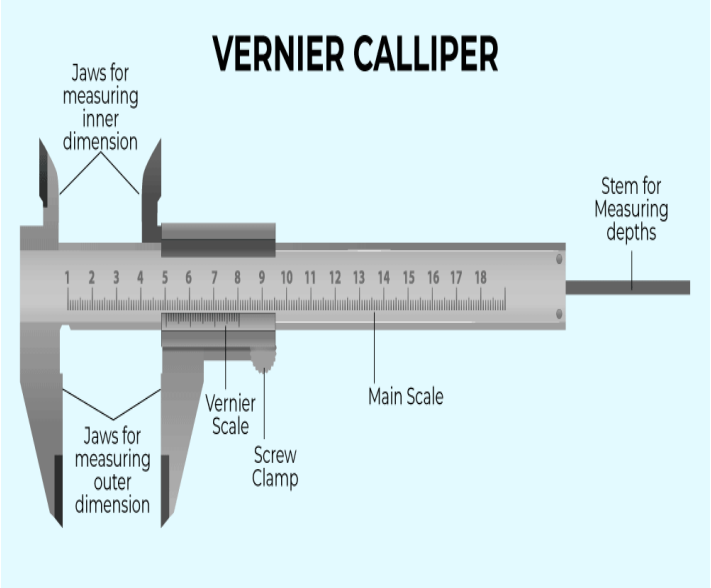

Figure-2: Vernier caliper

Hardness

Tablet requires certain amount of strength or hardness which was measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and was subjected for relative hardness and the value were expressed in Kg/cm 2. [9]

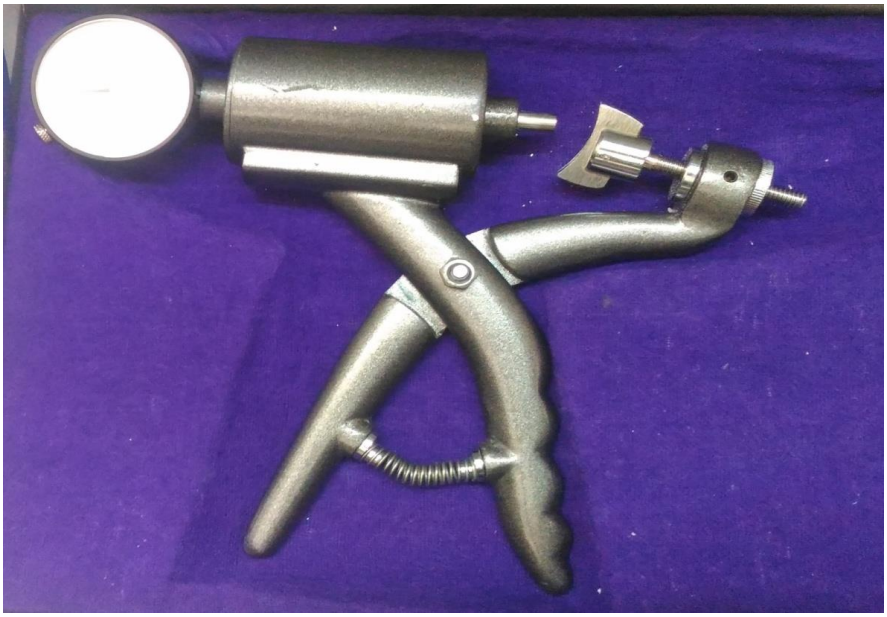

Figure-3: Pfizer hardness tester

Friability

The tablets were subjected to the test of friability with initial weight (Wi) almost equivalent to 6.5g of the tablets. The tablets were allowed to fall on it from a height of 6 inches while the friabilator drum was rotated at 25 rpm for 4 minutes. The final weight (Wf) of the tablets after subjecting to friability was noted and the friability was calculated according to the formula [10]

Friability (%) = (initial weight–final weight)/initial weight*100

Figure-4: Friability apparatus

Disintegration test

Six tablets were selected randomly from each batch for the disintegration test (Electrolab ED-2L). Disintegration test was performed in simulated gastric fluid using Electrolab Disintegration tester (USP). Disintegration time (DT) was measured for immediate release layer tablets and also for bilayer tablets. [11]

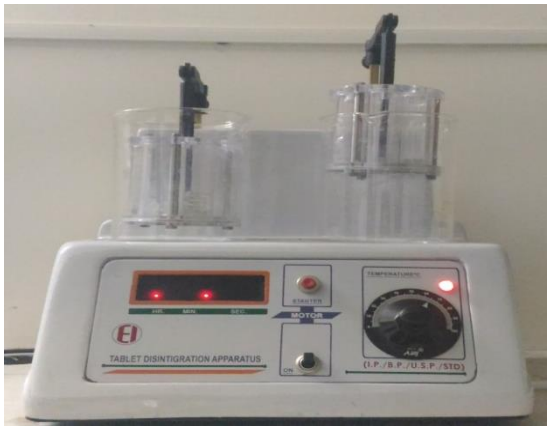

Figure-5: Disintegration apparatus

Drug Content

20 tablets were accurately weighed and powdered. Then powder equivalent to 10 mg of drug was shaken vigorously with 50 ml of 0.1 M hydrochloric acid for 10 min and added sufficient 0.1M hydrochloric acid to produce 100 ml and filtered. Each ml of filtrate was suitably diluted to 10 ml distilled water. The absorbance of resulting solution was measured at maximum 241 nm. From the absorbance the drug content of the tablets was calculated. [12]

Weight Variation

Twenty tablets were selected randomly and weighed individually. Average weight was calculated and compared the individual tablet weight to the average weight.[13]

In-vitro dissolution Study

In vitro drug release study was performed using type II (paddle) apparatus (Electro lab TDT- 08L plus, Dissolution tester USP Mumbai, India) at 50 rpm in 900 ml simulated gastric fluid 1.2 pH for 1hr. and after 6.8 phosphate buffer for 7 hrs. Temperature was maintained at 37 ± 0.5ºC. The 5 ml sample was withdrawn at predetermined time intervals and replaced with same fresh dissolution media to maintain sink condition. The withdrawn samples were filtered through membrane filter 0.45µm, suitably diluted and analyzed by using UV spectrophotometer (UV Lab India 3000+) at λmax 247 nm. [14]

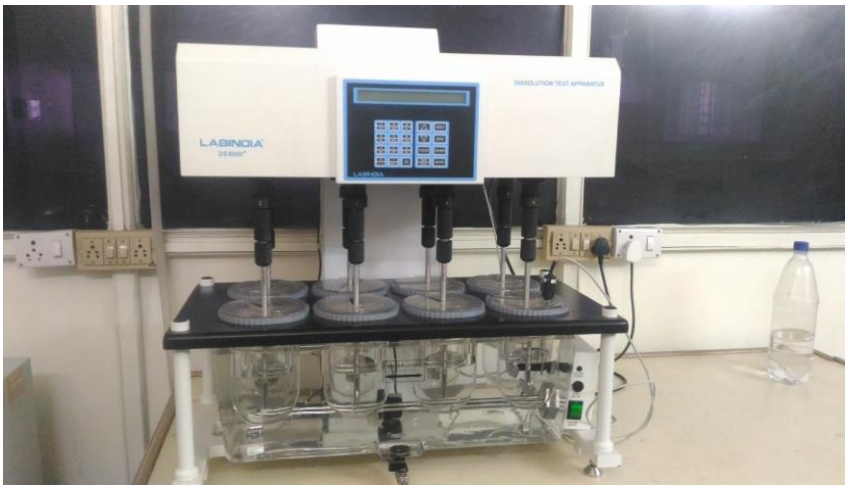

Figure-6: Dissolution apparatus

Kinetics of In-vitro drug release [15]

To study the release kinetics of In-vitro drug release data of above selected batches were applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

Zero order

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

First order Where C0 is the initial concentration of drug, K is the first order constant, and t is the time in hrs.

Higuchi equation

$$\%R=Kt^{0.5}$$

This model is applicable to systems with drug dispersed in uniform swell able polymer matrix as in case of matrix tablets with water soluble drug.

Korsmeyer-Peppas equation :

$$\%R=Kt^{n}$$

This model is widely used, when the release phenomenon could be involved.

Stability Studies and Storage Condition

ICH specifies the guidelines for stability to check the effect of environmental condition or storage conditions on formulation, as a technical requirement for the registration of pharmaceuticals for human use.[16]

RESULTS AND DISCUSSION

Fourier transformation infra-Red (FTIR) analysis :

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan). The instrument was calibrated by using polystyrene film.

Fourier Transformation Infra-Red (FTIR) analysis of Hydrochlorothiazide :

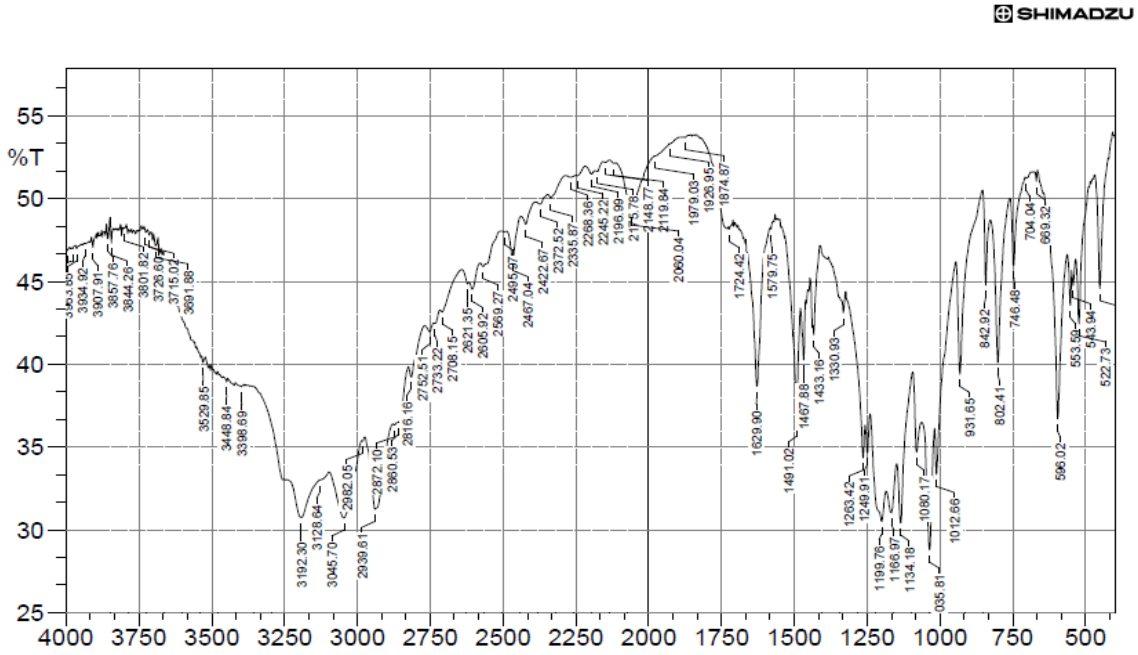

Figure-7: FTIR Studies of Pure drug

Fourier Transformation Infra-red (FTIR) analysis of Metoprolol succinate :

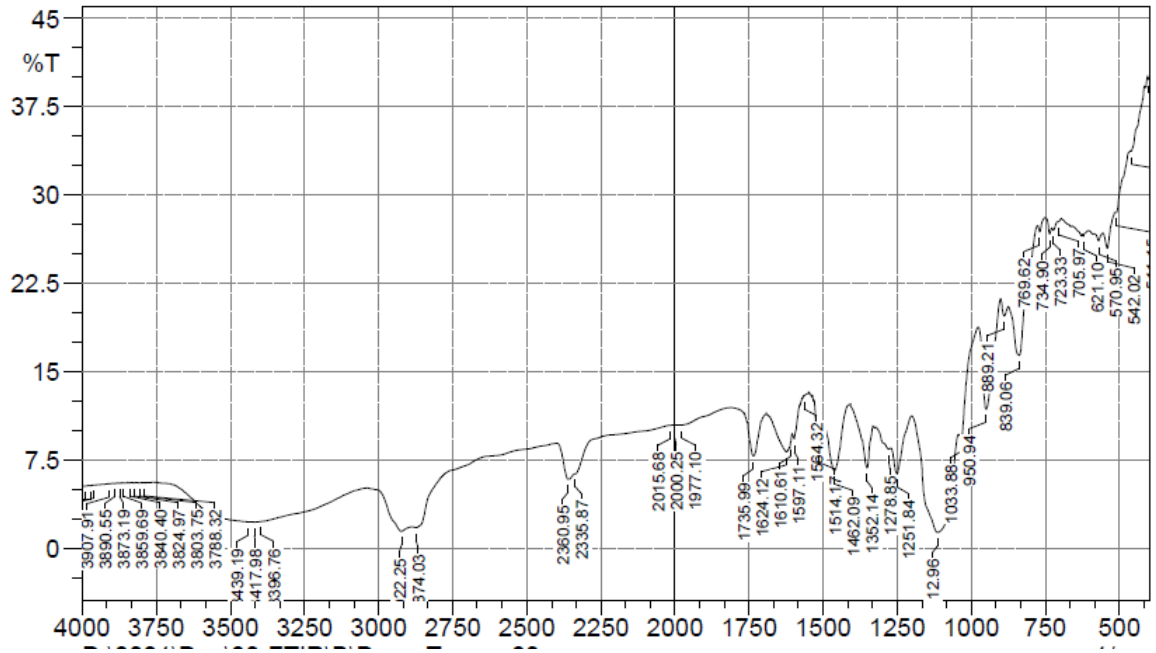

Figure-8: FT-IR graph for Metoprolol succinate

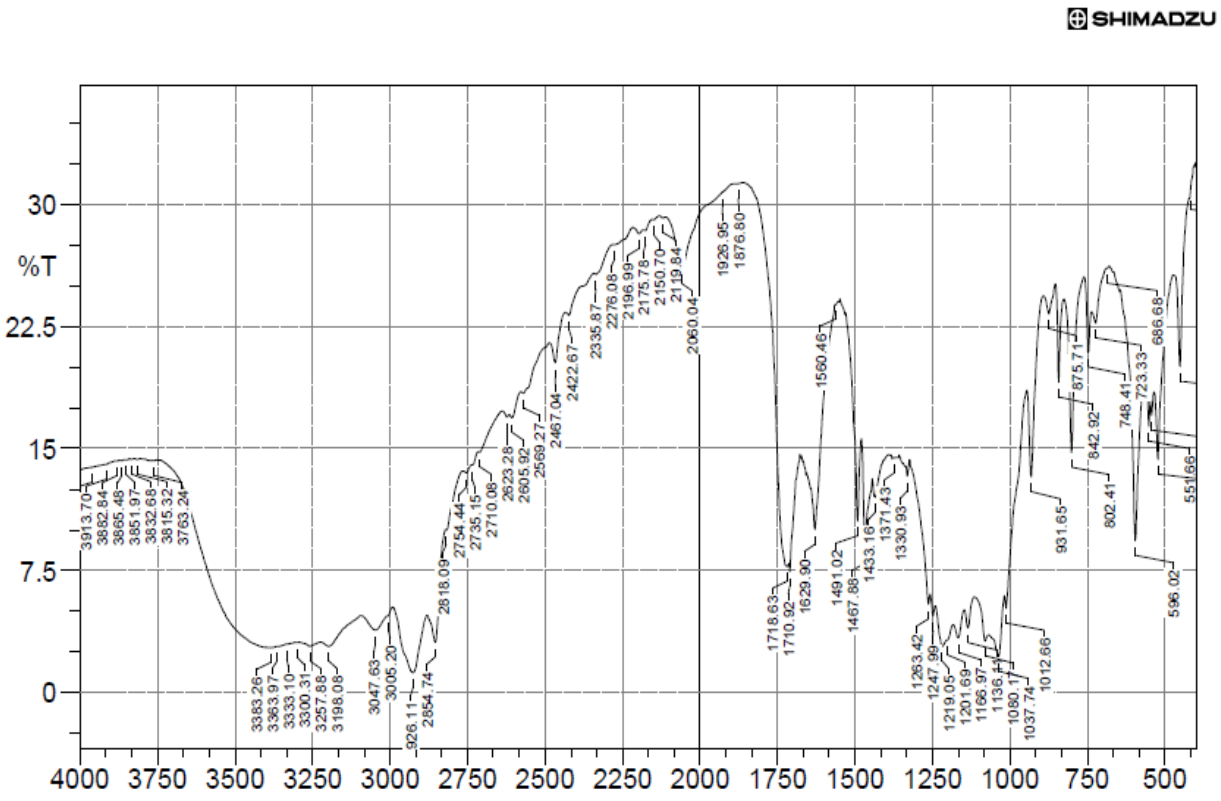

Figure-9: FT-IR graph for Bilayer optimized formulation

In the present study, it has been observed that there is no chemical interaction between Hydrochlorothiazide and Metoprolol succinate and the polymers used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

EVALUATION OF PREPARED BILAYERED TABLETS FOR POST COMPRESSION PARAMETERS:

Table-3: Evaluation of post compression parameters for Bilayered tablets

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Weight variation	500	501	500	499	500	499	500	500
Thickness (mm)	5.1	5.3	5.7	5.4	5.5	5.9	6.1	6.3
Hardness (kg/cm^2)	6.7	6.3	6.8	7.1	7.5	7.2	6.9	6.5
Friability (%)	0.25	0.32	0.29	0.34	0.27	0.22	0.35	0.34
Disintegration time (min)	12.36	15.9	10.14	12.33	11.25	9.68	14.56	13.48
Assay of Hydrochlorothiazide	78.68	80.25	79.68	83.25	82.46	85.49	86.98	84.27
Assay of Metoprolol succinate	85.53	87.19	84.12	86.50	88.72	87.85	90.25	88.38

In vitro Dissolution studies: The dissolution conditions used for studying the drug release from bilayered tablet: Among all formulations, Hydrochlorothiazide and Metoprolol succinate shows better drug release of (96.58 %) at the end of 8 hrs, when compared with all other formulations. So, formulation Hydrochlorothiazide and Metoprolol succinate F7 selected as optimized formula

Table-4: *In-Vitro* dissolution studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	25.89	26.39	22.52	20.28	22.10	24.79	21.24	22.35
2	32.73	35.95	37.76	29.73	32.97	35.98	38.73	40.53
3	40.03	43.09	47.74	38.01	42.16	45.85	47.32	54.86
4	55.67	58.88	59.23	49.96	53.15	56.89	58.67	63.65
6	63.22	65.61	67.58	58.64	63.96	65.58	61.24	62.31
8	71.46	73.49	75.42	71.52	75.91	75.68	79.92	71.66
10	82.48	84.11	86.54	81.96	83.84	86.52	87.78	87.96
12	92.68	94.59	95.68	94.53	96.89	97.82	98.82	92.53

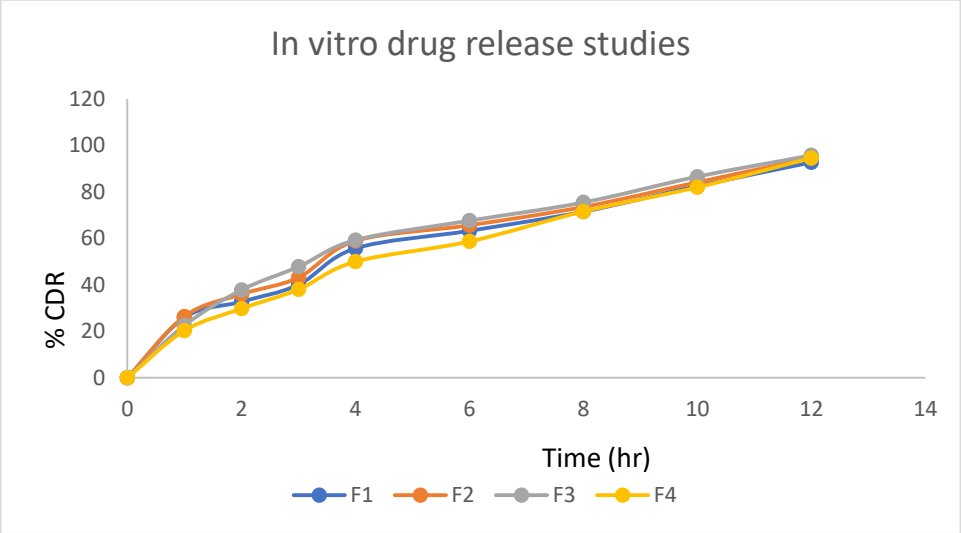

Figure-10: Drug release studies of F1-F4 formulations

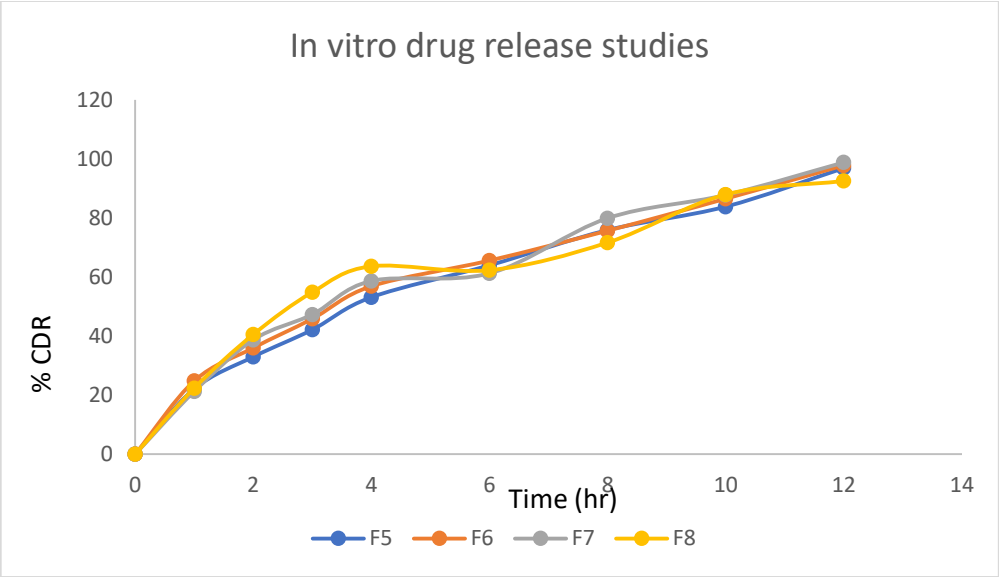

Figure-11: Drug release studies of F5-F8 formulations

Discussion: On comparing all formulated drug release profiles the best/optimized formula i.e., F-7 formulation, it was clearly observed that the drug was fit enough with a release of 98.82 % within 12 hrs.

Drug release kinetic profile

Zero order kinetics

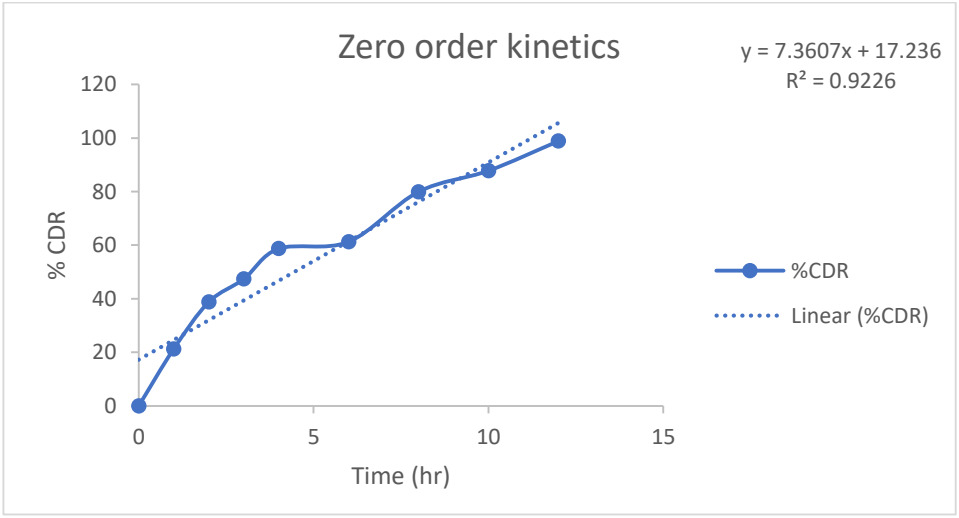

Figure-12: Drug release kinetics of zero order kinetics

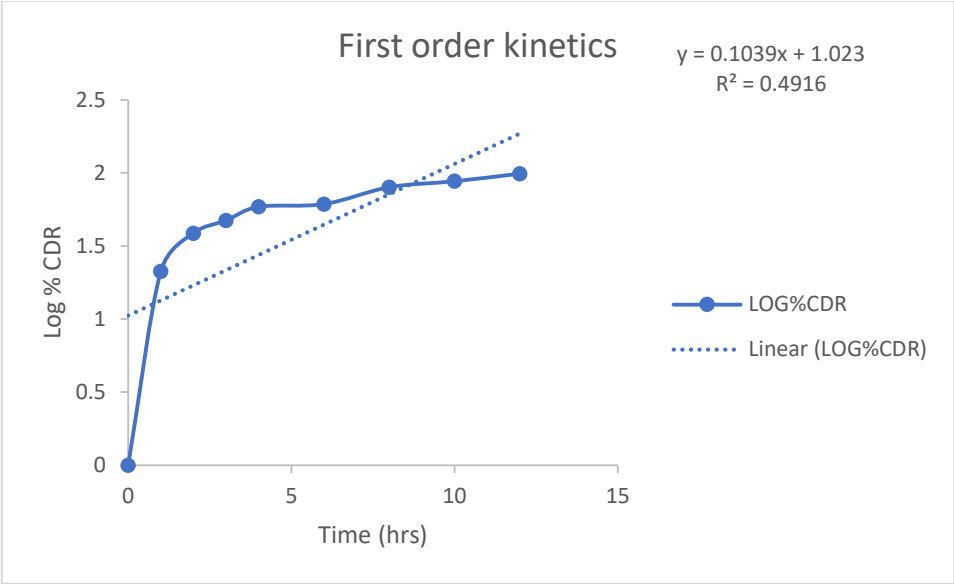

Figure-13: Drug release kinetics of First order kinetics

Higuchi model

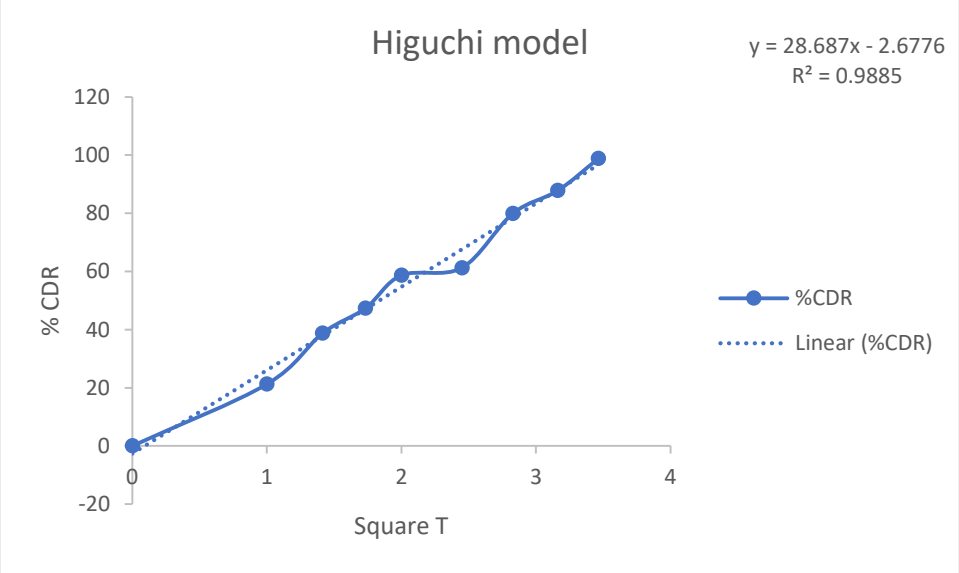

Figure-14: Drug release kinetics of Higuchi model

Korsmeyer peppas

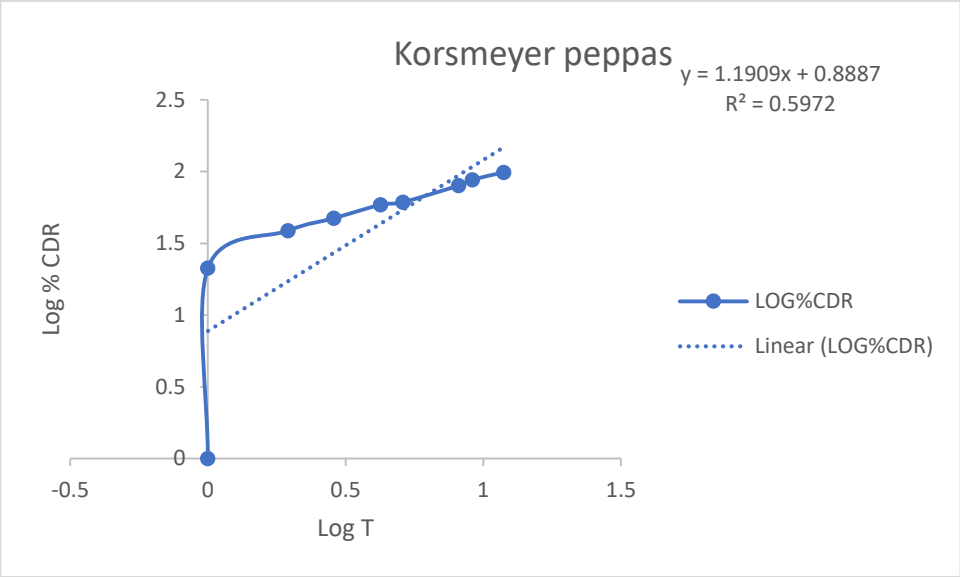

Figure-15: Drug release kinetics of Korsmeyer peppas

The drug release from the bilayered tablets were explained by the using mathematical model equations such as zero order, first order, Higuchi`s Korsmeyer-Peppas equation. Based on the regression values it was concluded that the optimized formulation F7 followed zero order release where the regression value was found to be 0.922. It was also found that the drug was released by diffusion as the regression in Higuchi's plot was 0.988.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-7 after 90 days. Parameters quantified at various time intervals were shown.

Table-5: Stability study for optimized formulation

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-7	**25^{0}C/60%RH**	98.82	97.56	96.35	95.79	**Not less than**
F-7	**30^{0}C/75% RH**	98.82	97.70	96.52	95.25	**Not less than**

CONCLUSION

The present study was aimed at the development and characterization of a bilayered tablet containing Hydrochlorothiazide (HCTZ) as the immediate-release (IR) layer and Metoprolol Succinate as the sustained-release (SR) layer, for effective management of hypertension. The study successfully demonstrated the feasibility of formulating a bilayered tablet that provides immediate release of Hydrochlorothiazide for quick antihypertensive action, along with sustained release of Metoprolol Succinate to maintain long-term blood pressure control. This bilayer approach enhances patient compliance, reduces dosing frequency, and ensures better therapeutic outcomes in the management of chronic hypertension. Preformulation studies were performed to assess the compatibility of the drug with selected excipients using FTIR confirming no major interactions. The IR layer was formulated using superdisintegrants like sodium starch glycolate to ensure rapid release of HCTZ, while the SR layer was prepared using hydrophilic matrix polymers such as HPMC K100M to achieve sustained release of Metoprolol Succinate over 12 hours.

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