RESEARCH PAPER

QbD-Guided Development, Optimization, and In-Vitro Characterization of a Dual-Release Bilayer Tablet System of Metoprolol Succinate Extended Release and Chlorthalidone Immediate Release for Improved Hypertension Therapy

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Abstract
Hypertension remains one of the most prevalent cardiovascular disorders worldwide and is a major risk factor for stroke, myocardial infarction, heart failure, and chronic kidney disease. Combination therapy employing antihypertensive agents with complementary mechanisms of action has demonstrated superior blood pressure control compared with monotherapy. The present study aimed to develop and optimize a dual-release bilayer tablet comprising Metoprolol Succinate as an extended-release (ER) layer and Chlorthalidone as an immediate-release (IR) layer using the Quality by Design (QbD) approach. The immediate-release layer was formulated using superdisintegrants to achieve rapid drug release, while the extended-release layer employed hydrophilic polymers to provide sustained drug delivery over 24 hours. A Design of Experiments based optimization strategy was applied to establish the design space and optimize formulation variables. The developed bilayer tablets were evaluated for physicochemical properties, drug content uniformity, hardness, friability, disintegration time, dissolution behavior, and drug release kinetics. The optimized formulation demonstrated satisfactory tablet characteristics, rapid release of Chlorthalidone within the initial period, and controlled release of Metoprolol Succinate extending up to 24 hours. Drug release profiles were comparable to marketed formulations and complied with Pharmacopoeial specifications. The study confirmed that the QbD-based bilayer tablet system provides a robust platform for sequential drug delivery and may improve patient compliance, therapeutic efficacy, and hypertension management.
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Introduction

Hypertension is a chronic cardiovascular disorder characterized by persistently elevated arterial blood pressure and is considered a major public health concern worldwide. Combination therapy involving agents with different mechanisms of action has become a preferred treatment strategy for achieving optimal blood pressure control while minimizing adverse effects.

Metoprolol Succinate is a selective β1-adrenergic receptor blocker widely prescribed for the management of hypertension, angina pectoris, and heart failure. Due to its relatively short elimination half-life, extended-release formulations are often employed to maintain therapeutic plasma concentrations and provide sustained blood pressure control over a 24-hour period. Chlorthalidone, a thiazide-like diuretic, is considered one of the most effective first-line antihypertensive agents because of its prolonged duration of action and superior cardiovascular outcomes. Rapid onset of action is desirable for Chlorthalidone to achieve immediate diuretic and antihypertensive effects.

Bilayer tablet technology offers a versatile platform for incorporating two drugs with distinct release profiles within a single dosage form. This approach enables the simultaneous administration of immediate-release and extended-release medications, thereby improving patient convenience, reducing pill burden, and enhancing therapeutic effectiveness. The combination of Metoprolol Succinate extended release and Chlorthalidone immediate release in a bilayer tablet can provide rapid initiation of antihypertensive action followed by sustained blood pressure control throughout the dosing interval.

The pharmaceutical industry increasingly adopts Quality by Design (QbD) as a systematic development approach recommended by the International Council for Harmonisation (ICH Q8, Q9, and Q10 guidelines). QbD emphasizes predefined objectives, scientific understanding, risk assessment, and process control to ensure consistent product quality.

Materials and Method

The material Metoprolol Succinate and Chlorthalidone was a gift sample from Pharmaceutical companies. Avicel 101, Methocel K15, Carbopol 934P, Sodium Starch Glycolate and coloring agent from Color corn. The batches formulated using 2^2 factorial design taking binder and polymer variables.

EXPERIMENTAL WORK

PREFORMULATION

Preformulation is the first step in rational development of dosage forms. It is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Preformulation study can be divided into two subclasses:

1. API characterization

2. Drug excipients compatibility study

API characterization

Physical characterization

To check whether it is crystalline or amorphous.

Organoleptic properties

Color, Taste and odor were evaluated by human volunteers.

Solubility

Solubility was studied in different solvents. Parts of solvents required to dissolve one part of the drug is evaluated and reported.

LOD

LOD was determined by heating at temperature 105ºC in analytical moisture balance and percent loss was determined.

Melting point

The melting point of pure drug was determined by melting point apparatus PMPD, Veego. Bulk density

Bulk density of drug Metoprolol Succinate and Chlorthalidone was determined by pouring gently 15 gm of sample through a glass funnel into 100 ml graduated cylinder.

The volume occupied by the sample was recorded, Bulk density was calculated as:

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of the sample}}{\text{Vo}}$$

Where, V_o= Volume occupied by the powder

The volume was noted and taped density is calculated using following formula:

$$\text{Tapped density (g/ml)} = \frac{\text{Weight of the sample(gm)}}{\text{Vo}}$$

Where, V_o= Volume occupied by the powder

Tapped density

Tapped density was determined by using Electrolab density tester. A sufficient number of taps should be employed to assure reproducibility for the material in question.

Compressibility Index and Hausner's ratio

The compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

Assay (I.P.)

The assay of drug perform as per the I.P. procedure.

1. Metoprolol Succinate

2. Chlorthalidone

Drug Excipients Compatibility Studies

The selection of excipients for the compatibility study is performed on the basis of literature search.. Procedure:-Drug was mixed with excipients in a defined ratio. These mixtures were kept in 5ml transparent glass vials and were kept in both closed and open conditions. These vials are exposed to 25ºC/60% RH, 40ºC/75% RH (accelerated study),55ºC

The samples were evaluated initially and after a period of 1 month and following parameters were analyzed.

Physical compatibility

Related substance

FORMULATION

The calculated amount of drug along with other excipients was dispenses corresponding to a batch size 100 tablets. Then the tablets were evaluated for dissolution. The dissolution profile of drug Metoprolol Succinate extended release layer was set as per I.P. specifications.

A] Extended Release Layer drug

Key Processing Factors:

Granulation: The granulation should be optimum to ensure uniform wetting.

Drying: LOD should not be more than the specified limit as it may cause hardness and dissolution problem.

Compression: The hardness should be adjusted to keep thickness and friability within limits.

SIFTING

Weigh the selected materials for extended release layer and sift through mess number 40#, 100#.

BINDER PREPARATION

Weigh PVP K-15 and dissolve in isopropyl alcohol in a stainless steel container with continuous stirring till clear solution formed.

GRANULATION

The sifted materials are mixed in a rapid mixer granulator (RMG) for 10 minutes (Dry mixing).

DRYING

Load the wet mass in Alliance Fluidized Bed Dryer (FBD).

SIZING OF DRIED GRANULES

Sift the dried granules through 1mm Multi mill screen.

B] Immediate Release Layer Drug

SIFTING

Weigh the selected materials for immediate release layer and sift through mess number 40#, 100#.

MIXING

Load the sifted Chlorthalidone, Avicel pH-101, SSG, Aerosil-200 and Brilliant blue in a rapid mixer granulator and start the mixer at slow speed of impeller with chopper off for 10 min.

BINDER PREPARATION

Take purified water and dissolved sifted coloring agent in it add Pregelatinized starch and maintain temperature about 80^0c- 90^0c.Cool down the temperature add it in dry blend.

GRANULATION

The sifted materials are mixed in a rapid mixer granulator (RMG) for 10 minutes (Dry mixing).

DRYING

Load the wet mass in Alliance Fluidized Bed Dryer (FBD).

Dry the wet mass till LOD between 2.5%- 3.5% w/w is achieved when checked at 105^0c on Halogen/IR moisture balance (Sartorius M150).

SIZING OF DRIED GRANULES

The dried granules sifted through #20.

COMPRESSION OF BILAYER TABLETS:- Compression done using 9mm punch for low dose tablet by maintaining in process parameters like avg. weight 400mg ± 5%, thickness 5.56 ± 0.2mm, hardness150-200N, friability NMT 1% w/w, disintegration time NMT 3 min for IR layer.

Formulation Development Strategy

Drug Metoprolol Succinate belongs to BCS-Class I having high solubility and high permeability, which is used in the extended release layer and Drug Chlorthalidone from BCS-Class IV having low solubility and low permeability which is used in immediate release layer. A number of small trial batches of extended release tablets were carried out using matrix tablet approach, in which the levels of the different excipients were varied until a formulation was established which gave a dissolution profile comparable to Pharmacopoeia and also demonstrated acceptable physical properties. Various small scale trials were taken to decide on the matrix tablets having compatible excipients with varying quantities of diluents, binder, glidant and release controlling polymer. Excipients were selected from Preformulation studies.

A] LOW DOSE TABLETS

a]Drug Metoprolol Succinate in ER layer

Sr. No.	**Composition (mg/tab)**	**A1 ER 19mm**	**A2 ER 210mm**	**A3 ER 39mm**	**A4 ER 49mm**
Drug Metoprolol Succinate					
Intragranular					
1	Metoprolol Succinate	47.5	47.5	47.5	47.5
2	Microcrystalline cellulose	22	22	22	-
3	Avicel pH 101	-	-	-	11.90
4	HPMC K 15	61	61	61	61
5	Carbopol 934P	22	22	22	32
6	PVK 15	30	30	30	30
7	IPA	q.s.	q.s.	q.s.	q.s.
Extragranular					
8	HPMC K 15	60	60	60	60
9	Mg. stearate	2	2	2	2
Wt of Drug in layer		245	245	245	245

Table No: Formula for Drug Metoprolol Succinate layer of Lower Strength

b]Drug Chlorthalidone in IR layer

Sr. No.	**Composition (mg/tab)**	**A1 IR 1**	**A2 IR 2**	**A3 IR 3**	**A4 IR 4**
Drug Chlorthalidone					
Intragranular					
1	Chlorthalidone	12.5	12.5	12.5 size reduced	12.5size reduced

2	Avicel pH 101	-	-	-	84.45
3	Lactose monohydrate	83.45	83.45	83.4	-
4	SSG (Primojel)	3.25	3.25	3.25	3.25
5	SLS	1.00	1.00	1.00	1.00
6	Aerosil-200	1.00	1.00	1.00	1.00
7	Brilliant Blue	0.20	0.20	0.20	0.20
8	Tartrazine	0.20	0.20	0.20	0.20
9	Pregelatinized Starch	1.83	1.83	1.83	1.83
10	Purified Water	q.s.	q.s.	q.s.	q.s.
Extragranular					
11	SSG	3.24	3.24	3.24	3.24
12	Aerosil-200	1.00	1.00	1.00	1.00
13	Purified talc	0.83	0.83	0.83	0.83
14	Mg. stearate	1.50	1.50	1.50	1.50
15	Avicel pH 101	-	-	-	40.00
Wt. of Drug in layer		110.0	110	110	150.0
Wt. of Core Tablet		355	355	355	395

Table No: Formulas for Drug Chlorthalidone IR layer

Compression of the two granulations into bilayer tablet:

Through the development strategies are reported separately for each layer, the blends of the corresponding batches were compressed together using ELIZA PRESS bilayer tablet machine, the total weight of bilayer tablet of lower strength was 390 and then evaluated.

EVALUATION TESTS:

EVALUATION OF LUBRICATED GRANULES:

FLOW PROPERTIES:

Granules were evaluated for the following parameters as per the procedure given to check the flow properties like bulk, tapped density, Compressibility index (Carr's index), Hausner's Ratio.

LOSS ON DRYING:

LOD was done as per the procedure described in section of preformulation.

PARTICLE SIZE DISTRIBUTION:

PSD of the granules was measured by sieve analysis. 20g of powder blend was loaded on to sieve placed in order of #20, #40, #60, #80 and #100 starting from the top. The sieve shaker was switched ON which vibrates at a power 10 for 3 min. The amount of blend retained on each sieve was weighed and the cumulative % retained is calculated.

EVALUATION OF FINISHED PRODUCT OF BILAYER TABLETS

Evaluation of prepared tablets

Hardness

Hardness of tablet was measured using Monsanto hardness tester. which was expressed in kg/cm^2.

Weight variation

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average USP weight variation test.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose.

Content Uniformity

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually; the tablet should be within 85% to 115% of the labeled claim.

Thickness

The thickness of the tablet was measured using Vernier caliper. Thickness of five tablets from

each batch was measured and mean was calculated.

Disintegration Time (IP 2022)

The disintegration apparatus, described in I.P. was used for the study.

Dissolution:

Dissolution parameters were set as per USP limits.

ASSAY: Metoprolol Succinate and Chlorthalidone (in bilayer tablet): It is performed using HPLC study as per I.P. standard.

MARKET PRODUCT EVALUATION

The same combination of drug used in Extended Release layer and Immediate Release layer for both the strengths of tablets is not available in market. Therefore comparative study with marketed formulations was not possible in bilayer tablet but the lower strength tablet dose available in market in matrix tablet so the comparative study get performed.

STABILITY STUDIES

The primary aim of stability testing is to derive data which assists in determining shelf life of the pharmaceutical product and storage specifications for the product.

Formulation of stability batch:

Batch F4 of lower strength and F7 of higher strength was formulated and selected as the optimized batch and to check the reproducibility three batches were taken with the same formula and were subjected to stability testing.

Batch condition	**Packing material**	**Testing frequency(months)**
40^0C/75% RH (accelerated stability batch condition)	PVC-PVDC blister and Alu-Alu – Blister.	1M, 3M

Table No: Stability Batch Conditions

Evaluation:

The sample were observed periodically (initially, at intervals (1 and 3 months) for any change in the following physicochemical parameters a) Physical Evaluation:-Appearance, weight variation, hardness, thickness, disintegration time for IR layer.In- vitro Dissolution, Drug Content (Assay).

RESULTS AND DISCUSSION

Preformulation Results: API Characterization

Sr. No.	Characters	Drug Metoprolol Succinate	Drug Chlorthalidone
1	Organoleptic evaluation	White to off-white powder.	White to yellowish white, crystalline powder.
2	Solubility	Freely soluble in water; soluble in methanol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol.	Partially insoluble in water, in ether and in chloroform; soluble in methanol; slightly soluble in alcohol.
3	Loss on Drying	NMT0.2% w/w	NMT 0.4% w/w
4	Bulk density	0.62%w/w	0.36%w/w
5	Tapped density	0.83g/ml	0.64g/ml
6	Hauser's Ratio	1.34	1.31
7	Compressibility Index	24.09%	23%
8	Sieve analysis	100% (#40)	100% (#40)
9	Melting point	138^0C	240^0C
10	Assay	100%	100%

Table No: API Characterizations

Discussion: Drug Metoprolol Succinate was freely soluble in water whereas Drug Chlorthalidone is poorly water soluble. From the compressibility index and Hausner's ratio, it can be concluded that Metoprolol Succinate and Chlorthalidone have poor flow properties. From the observed melting points, it can be concluded that both drugs were authentic and pure.

HPLC Studies

The chromatogram of Drug Metoprolol Succinate and Drug Chlorthalidone are shown in figures respectively which were compared with standard chromatogram of drugs as shown respectively.

Drug Metoprolol Succinate

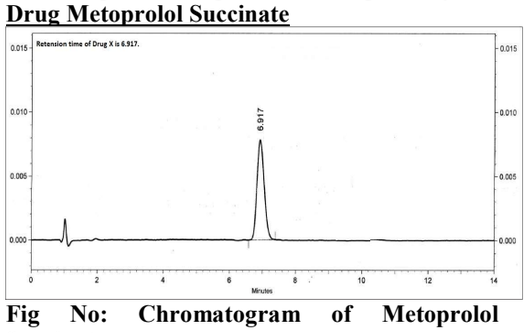


Fig No: Chromatogram of Metoprolol Succinate

Drug Chlorthalidone

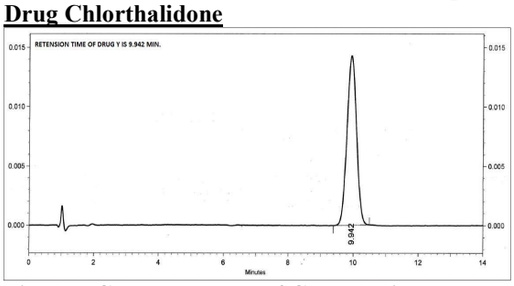


Fig No: Chromatogram of Chlorthalidone

DRUG EXCIPIENTS COMPATIBILITY STUDIES

Physical compatibility

The physical compatibility of drug substances with various excipients was carried out with an aim to select suitable excipients for a stable and robust formulation. The samples were evaluated at initial and 1 month for drug interaction study and impurity profile at both open and closed conditions.

Sr. No	**Excipients**	**Physical Description Initial**	**25 ^{O}C/ 60 % RH**		**40 ^{O}C/ 75 % RH**		**55^{O} C**	
			Open	**Closed**	**Open**	**Closed**	**Open**	**Closed**
			1 M	**1 M**	**1 M**	**1 M**	**1 M**	**1 M**
1	Metoprolol Succinate	white to off white powder	NC	NC	NC	NC	NC	NC
2	Chlorthalidone	White to yellowish white, crystalline powder	NC	NC	NC	NC	NC	NC
3	Avicel pH 101	-	NC	NC	NC	NC	NC	NC
4	Methocel K 15	-	NC	NC	NC	NC	NC	NC
5	Carbopol 934P	-	NC	NC	NC	NC	NC	NC
6	PVP K-15	-	NC	NC	NC	NC	NC	NC
7	SSG	-	NC	NC	NC	NC	NC	NC
8	Aerosil 200	-	NC	NC	NC	NC	NC	NC
9	Tartrazine	-	NC	NC	NC	NC	NC	NC
10	Brilliant Blue	-	NC	NC	NC	NC	NC	NC
11	Pregelatinized Starch	-	NC	NC	NC	NC	NC	NC
12	Purified Talc	-	NC	NC	NC	NC	NC	NC
13	Mg. Sterate	-	NC	NC	NC	NC	NC	NC
14	Opadry Clear	-	NC	NC	NC	NC	NC	NC
15	Prototype blend Active Meto.Succi(X)	-	NC	NC	NC	NC	NC	NC
16	Prototype blend Active Chlorthalidone (Y)	-	NC	NC	NC	NC	NC	NC
17	Prototype blend Active (X)+(Y)	-	NC	NC	NC	NC	NC	NC
18	Prototype blend Placebo of X	-	NC	NC	NC	NC	NC	NC
19	Prototype blend Placebo of Y	-	NC	NC	NC	NC	NC	NC
20	Prototype blend Active(X)+ Inactive (Y)	-	NC	NC	NC	NC	NC	NC
21	Prototype blend Inactive	-	NC	NC	NC	NC	NC	NC

	(X)+ Active (Y)							
21	Active Prototype blend Inactive (X)+ Inactive (Y)	-	NC	NC	NC	NC	NC	NC

Table no: Drug –Excipients Compatibility for 1 month at 25ºC/60% RH, 40ºC/75% RH and at 55ºC
NC: No change observed in physical appearance.

Discussion: As seen in the above table no major physical incompatibilities were seen in the interaction studies and thus all the excipients were then studied for chemical incompatibility [Related substances] by HPLC.

RESULTS OF FORMULATION DEVELOPMENT

In process blend result before compression: Properties of lubricated blend before compression: **ER layer of Drug Metoprolol Succinate**

Batch No	LOD (w/w) of Lubricated Blend	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner Ratio	Type of Flow
F1	2.6	0.42	0.53	20.75	1.25	Fair
F2	2.6	0.42	0.53	20.74	1.25	Fair
F3	2.59	0.41	0.53	22.03	1.28	Passable
F4	2.59	0.42	0.53	20.75	1.25	Fair

Table No: In- process Blend Result of Development Batches of ER Layer

IR layer of Drug Chlorthalidone

Batch No	LOD (w/w) Of Lubricated Blend	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner Ratio	Type Of Flow
F1	2.60	0.64	0.80	20	1.25	Fair
F2	2.61	0.54	0.72	25	1.33	Passable
F3	2.59	0.52	0.67	22.39	1.29	Passable
F4	2.56	0.59	0.68	13.24	1.15	Good

Table No: In- process Blend Result of Development Batches of IR Layer
:-LOD- Loss on Drying
Sieve Analysis of Lubricated Blend: ER layer of Drug Metoprolol Succinate

Batch No	Sieve Number						
	20# 850 µ	30# 600 µ	40# 425 µ	60# 250 µ	80# 180µ	100# 150 µ	Fines
F1	1.147	4.499	1.908	8.569	1.03	0.781	1.718
F2	0.616	1.36	2.169	6.912	4.278	1.453	4.431
F3	0.233	1.54	3.67	5.091	2.212	1.654	7.062
F4	0.15	1.661	5.992	8.068	3.22	1.032	1.846

Table No: Sieve analysis of blends as compression of all batches of ER layer

Sieve Analysis of IR layer: Drug Chlorthalidone

Batch No	Sieve Number						
	20# 850 µ	30# 600 µ	40# 425 µ	60# 250 µ	80# 180 µ	100# 150 µ	Fines
F1	3.52	8.625	2.403	4.62	0.763	0.941	3.824
F2	1.32	2.54	1.23	6.891	2.87	1.798	6.213
F3	0.832	1.76	2.78	8.49	2.93	1.097	4.863
F4	0.342	3.12	1.72	7.543	2.761	1.897	3.652

Table No: Sieve Analysis of Blends as compression of all Batches of IR layer

RESULT OF FORMULATION DEVELOPMENT

Critical observation of formulation development of Lower Strength Tablets

Batch No.	Plan of Batch	Observation
A1	In the Immediate release layer: superdisintegrants were used for faster release. Initially SSG, SLS used as superdisintegrants. In the Extended release layer: MCC used as a diluents initially. HPMC K-15 M CR used as a release retardant. 9 mm Punch used initially.	% Drug release was not satisfactory. In Immediate release layer Drug solubility problem was found.
A2	This batch was took just for a punch selection using same formula like batch A1, either 9mm or 10 mm; so in this batch 10 mm punch was used. Dissolution not performed.	10mm gives Bulk size tablets than 9mm; so 9mm punch was final selection
A3	Micronized form of drug used in Immediate release layer, to improve drug solubility.	Drug solubility problem was solved and hardness issue was obtained. This batch then selected as first batch for Higher strength tab as this batch was satisfactory.
A4	In this batch A7 batch blend used for Higher strength tablets	Problems related to drug solubility, tablet hardness get solved also tablet parameters and % drug release was in limit.

Table No: Critical observation of formulation development of lower strength tablets

Discussion: The A4 batch of Lower Strength Tablets was found to be optimized and hence, it gets finalized. Further, three batches were manufactured using same formula and incubated for stability study. The tablets of this batch were evaluated.

Physical Parameters of Tablets: Lower strength

In Process Core Tablet Evaluation of Development Batches F1-F4:

Batch No	Weight (Mg)	Thickness (mm)	Hardness In Newton (N)	Disintegration Time(Min) For Ir Layer (Min)	Friability (%)
A1	Core-355 Coated-362	Core4.63-4.80 Coated 4.76-4.91	Core 65- 76 Coated 72-84	Core-2 Coated 3min	0.4
A2	Core-355 Coated 362	Core 4.69-4.80	Core 61-70	Core-2	0.5
A3	Core-355 Coated 362	Core 5.54-5.92	Core 200-250	Core 5	0.2
A4	Core-395 Coated 404.8	Core 5.56-5.66 Coated 5.59-5.80	Core 156-182 Coated 190-250	Core 1.5 Coated 2 min	0.4

Table No: In-process Core Tablet Evaluation of Development Batches F1-F4

LOWER STRENGTH TABLET

Dissolution profile of development batches F1-F4

EXTENDED RELEASE TABLET (Layer 1): Release of DRUG

Time (Hr)	USP Limit Amount Dissolved (%)	A1	A2	A3	A4
		ER1	ER2	ER3	ER4
1	USP-NMT 20 INH-NMT 30	22	ND	19	15
2		28		28	23
4	20-40	46		42	35
6		53		53	45
8	USP-NMT 40-60 INH-	63		63	53

	35-65				
12		78		78	67
20	USP-NLT 80 INH-NLT80	95		95	87
24		99		99	93

Table No: Drug release profile of development batches F1-F4

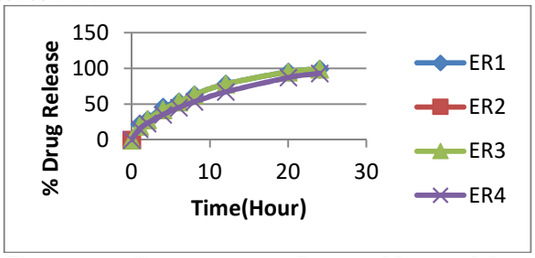
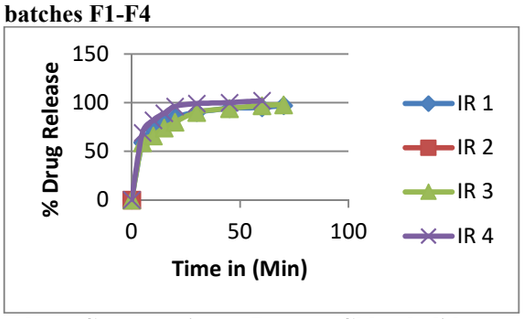


Fig no: Comparative Drug Metoprolol Succinate Release Profile of Formulation batches A1-A4

IMMEDIATE RELEASE TABLET (Layer 2): Drug Chlorthalidone

Time (M) And Limit Amount Dissolved (%)	A1 IR 1	A2 IR 2	A3 IR 3	A4 IR 4
5	59	ND	59	69
10	73		66	82
15	80		74	89
20	85		80	96
30	90		90	99
45 Min (EP NLT 80%)	94		94	100
60 Min (USP NLT 70%)	95		97	102
10 Min More	97		98	

Table No: Release of Chlorthalidone of batches F1-F4



Graph: Comparative Drug Chlorthalidone Release Profile of Formulation batches A1-A4

Assay of Bilayer Tablet of Lower Strength:

Assay results of all batches are shown in the following table:

Batch No	Assay	
	Metoprolol Succinate (mg)	Chlorthalidone (mg)
A1	99.9	100
A2	100.1	100
A3	101	100
A4	101.1	100.1

Table No: Results of Drug Content (Assay) of Lower Strength

Discussion: F4 was taken as the final batch as it passed flow properties, tablet parameters, dissolution and assay.

STABILITY STUDIES: LOWER STRENGTH TABLETS

RELATED SUBSTANCES

Rela Subs	Batch	CPS %	CCA %	Unknown Maxi. Impurity %	Total Impurity %
	F4a	0.12	0.00	0.01	0.35
	F4b	0.13	0.00	0.01	0.35
	F4c	0.13	0.00	0.01	0.38

Table No: Detection of Related Substances of Stability batch A4a, A4b and A4c by HPLC at 40ºC/75% RH

: CPSC- [2-chloro-5 (-3-oxy-2, 3-dihydro-1H-isoindol-1yl) benzene sulphonamide]

CCA-[4-chloro-3-sulfamoyl-2 benzophenone carboxylic acid]

LOWER STRENGTH BILAYER TABLETS OF BATCHE A4a

Physical Parameters: 40ºC/75% RH

Sr. No.	Test	Limits	ial	1St Month	2St Month
1	Appearance	IR layer –white ER layer-slight green	NC (No change)	NC	NC
2	DT for IR layer	NMT 3 min	2 min 5 sec	2 min 30 sec	2 min 25 sec
3	Average weight	±2% from targeted weight	400-414	400-414	400-414

		(mg)			
4	**Hardness**	191 - 256 (N)	180-200	180-200	180-200

Table No: Physical evaluation of stability batch A4a at 40ºC/75% RH

Dissolution

Drug	**Dissolution**			
		Initial	**1 Month**	**2 Month**
Metoprolol Succinate	**1 Hour 4Hour 20 Hour**	14% - 17%; Mean 15% 34% - 41%; Mean 34% 85% - 95%; Mean 88%	14% - 18%; Mean 15% 33% - 37%; Mean 34% 82% - 87%; Mean 85%	14% - 18%; Mean 16% 33% - 37%; Mean 34% 82% - 87%; Mean 86%
Chlorthalidone	**NLT 70% IN 60 Min**	100%-104%; Mean 102%	97% - 102%; Mean 99%	97% - 102%; Mean 99%

Table No: Dissolution of stability batch A4a at 40ºC/75% RH

Dissolution: 40ºC/75% RH

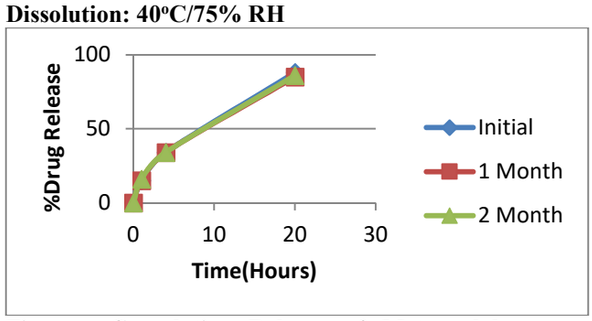


Fig no: Cumulative Release of Metoprolol Succinate in stability batch F4a at 40ºC/75% RH

Dissolution: 40ºC/75% RH

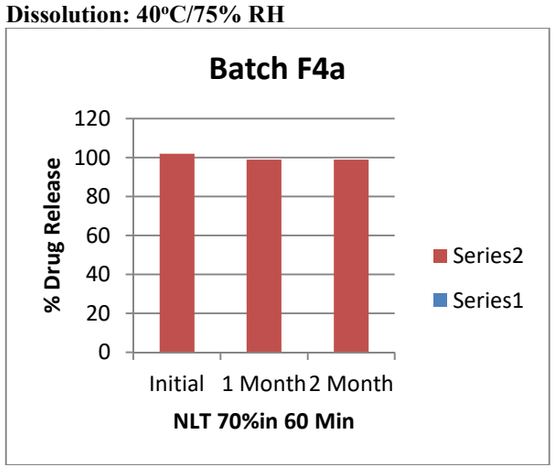


Fig no: Cumulative Drug Release of Drug Chlorthalidone in stability batch F4a at 40ºC/75% RH

Assay

Drug	**Assay**	**F4a**	
		1 Month	**2 Month**
Metoprolol Succinate	**98.0% - 102%**	99.9	99.9
Chlorthalidone	**98.0% - 102%**	99	99

Table No: Assay of stability batch F4a at 40ºC/75% RH

STABILITY STUDIES OF LOWER STRENGTH BILAYER TABLETS OF BATCHE F4b and F4c

Physical Parameters: 40ºC/75% RH

S. No	**Test**	**Limits**	**F4b**			**F4c**		
			Initial	**1 Month**	**2 Month**	**Initial**	**1 Month**	**2 Month**

	Appearance	IR layer – white ER layer - slight green	NC	NC	NC	NC	NC	NC
	DT for IR layer	NMT 3 min	1min 30 sec	1 min 35 sec	1 min 37 sec	1min 25 sec	1 min 25 sec	1 min 40 sec
	Average weight	±2% from targeted weight (mg)	400-414	400-414	400-414	400-414	400-414	400-414
	Hardness	150-200 (N)	180-190	180-190	180-190	180-190	180-190	180-190

Table No: Physical evaluation of Stability batch F4b and F4c at 40ºC/75% RH
NC- No Change.

Dissolution:

Drug	**Dissolution**	**F4b**			**F4c**		
		Initial (%)	**1Month (%)**	**2 Month (%)**	**Initial (%)**	**1Month (%)**	**2 Month (%)**
Metopro. Succinate	**1 Hour 4Hour 20 Hour**	14-16; Mean-14 34-38; Mean-35	14 -15; Mean-15 30-37; Mean-35 % 84 -91; Mean-89	14-15; Mean-15 30-38; Mean-35 84-91; Mean -89	14-17; Mean-16 34-39; Mean-36 85-	14-17; Mean-15 34 -38; Mean-35 85 -92; Mean-88	14-17; Mean-15 34-38; Mean-35 85-92; Mean-88
					91; Mean-87		93; Mean-88
Chlorthalidone	**NLT 70% IN 60 Min**	100-103; Mean-102	100-103; Mean-101	100-103; Mean-101	100-104; Mean-102	98 -102; Mean-99	98-102; Mean-99

Table No: Dissolution of stability batch F4b and F4c at 40ºC/75% RH
Dissolution: 40ºC/75% RH

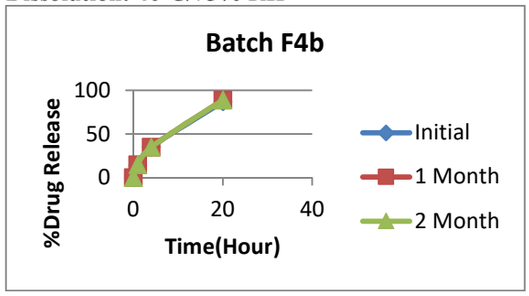


Fig no: Cumulative Drug Release of Drug Metoprolol Succinate in stability batch F4b at 40ºC/75% RH

Dissolution: 40ºC/75% RH

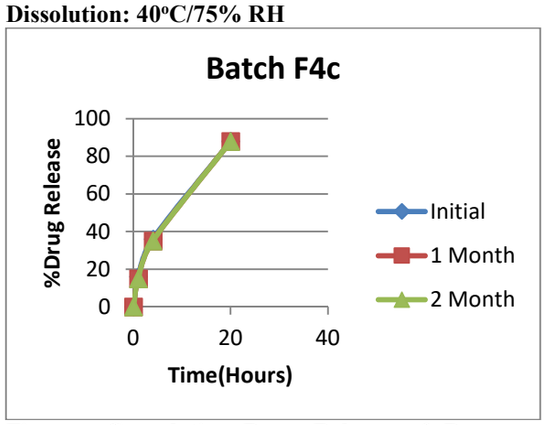


Fig no: Cumulative Drug Release of Drug Metoprolol Succinate in stability batch F4c at 40ºC/75% RH

Dissolution: 40ºC/75% RH

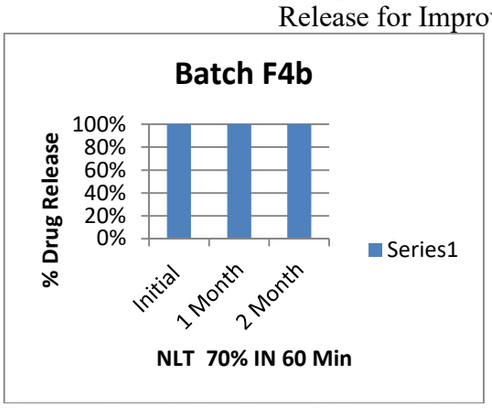


Fig no: Cumulative Drug Release of Drug Chlorthalidone in stability batch F4b at 40ºC/75% RH
Dissolution: 40ºC/75% RH

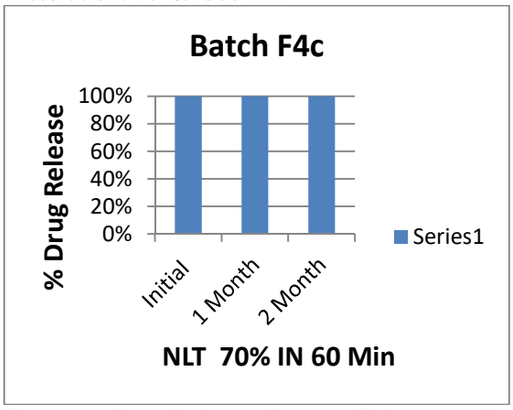


Fig no:Cumulative Drug Release of Drug Chlorthalidone in stability batch F4c at 40ºC/75% RH
Assay: [By HPLC]

Drug	Assay	F4b		F4c	
		1 Month	2 Month	1 Month	2 Month
Meto.Succi.	98.0%-102%	Complies	Complies	Complies	Complies
Chlorthalidone	98.0% - 102%	Complies	Complies	Complies	Complies

Table No: Assay of stability batch F4b and F4c at 40ºC/75% RH

Comparative study of bilayer tablet of Metoprolol Succinate extended release and Chlorthalidone immediate release tablet with the marketed same combination product

The optimized batch was taken for comparison:- As same product not available in market in bilayer form but available in matrix tablet so the research bilayer tablet is compared with marketed matrix tablet.

Physical parameters

Sr. No	Parameters	Marketed Product	Research Product
1	**Structure**	Single matrix tablet	Two separate layer bilayer tablet
2	**Drug separation**	Drug dispersed in same polymer matrix	Physically both the drug dispersed in two separate layer
3	**Metoprolol Dose**	50mg	50mg
4	**Metoprolol Release**	Polymer matrix controlled so, good release	Dedicated extended release and predetermined release controlled
5	**Chlorthalidone Dose**	12.5mg	12.5mg
6	**Chlorthalidone Release**	Embedded in matrix and release moderate controlled	Rapid release of immediate release layer, so release is excellence
7	**Manufacturing process**	By industrial process	Bilayer compression
8	**Appearance**	Single intact tablet	Two distinct layer in single tablet
9	**Polymer hydration**	Uniform swelling	Layer specific swelling
10	**Release mechanism**	Diffusion+ erosion	Independent IR+SR release
11	**Release control**	Combined matrix diffusion	Independent layer control
12	**Burst release**	Higher	Lower
13	**Biphasic release**	Difficult	Excellent
14	**Polymer swelling**	Uniform	Layer specific
15	**Drug diffusion Path**	Complex	Controlled

14	**Release Pattern**	Not predetermined	Drug release is predetermined
15	**Zero order kinetic/ tendency**	Less/poor	More/Good

Table: Comparative study of marketed formulation and research formulation

DISSOLUTION/RELEASE PROFILE OF IMMEDIATE RELEASE DRUG

A.	**Chlorthalidone Release in %**					
Sr. no.	**Time** (min)	**Research Bilayer Tablet**	**Marketed Matrix Tablet**	MT 2	MT 3	MT 4
1	**5**	**69**	**15**			
2	**10**	**82**	**25**	**20**	**16**	**25**
3	**15**	**89**	**40**	**35**	**30**	**38**
4	**20**	**96**	**55**	**45**	**55**	**42**
5	**30**	**99**	**70**	**50**	**65**	**52**
6	**45**	**100**	**85**	**60**	**75**	**68**
7	**60**		**96**	**80**	**85**	**76**

Table: Comparative study of marketed formulation and research formulation

B. Metoprolol Succinate % Drug Release					
Time (hrs.)	**Research Bilayer Tablet**	**Marketed Matrix Tablet**	**MT 2**	**MT 3**	**MT 4**
1	**15**	**11**	**12**	**13**	**14**
2	**23**	**18**	**22**	**18**	**20**
4	**35**	**23**	**30**	**32**	**34**
6	**45**	**38**	**42**	**40**	**43**
8	**53**	**47**	**55**	**56**	**54**
12	**67**	**60**	**67**	**65**	**68**
20	**87**	**75**	**72**	**78**	**80**
24	**93**	**83**	**88**	**87**	**91**

Table: Comparative study of marketed formulation and research formulation

Observations:-

In Marketed matrix tablet the Chlorthalidone and Metoprolol Succinate were dispersed within the hydrophilic polymer matrix in the matrix tablet when the tablet came in contact with dissolution medium, both the drug release simultaneously through the tablet as Metoprolol Succinate drug is highly water soluble, some amount diffuses rapidly before complete gel stabilization. Whereas in Research bilayer tablet the Chlorthalidone immediate release layer disintegrates rapidly where Metoprolol layer remain intact as extended release action get controlled by release retardant polymer here it was found that the drug release becomes biphasic and controlled. Hence, rapid antihypertensive action from Chlorthalidone and maintaining controlled therapy by Metoprolol occurs.

Conclusion:-

The aim of this research work was to formulate and develop a fixed Dose Combination product as a bilayer tablet formulation was achieved. Extended Release layer consist of Antihypertensive Drug belonging to class β-selective adrenergic blocking agent without partial agonist or membrane stabilizing properties. Extended release preparation provides sustained release and reduces the chances of tough related side effects. In selected cases of extended release preparation this drug used in treatment of hypertension and congestive heart failure. The clinical studies have shown beneficial role of this drug as a extended release preparation.The Immediate Release layer of bilayer tablet consists of Antihypertensive Drug belonging to class Diuretic; it affects the distal renal tubular mechanism of electrolyte absorption. The objective is to meet the target as per required specifications. The combination of Drug Metoprolol Succinate with Chlorthalidone will provide a synergistic response because of its different mechanism of action making it be best suited for the treatment of hypertension and also for the treatment of heart failure with improved compliance.

Future scope

Further detailed investigation and elaborative study need to be carried out for bioavailability, clinical

studies for providing platform for further development and optimization of this drug delivery system in the form extended release tablets.

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