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FORMULATION AND EVALUATION OF ANTIHYPERTENSIVE BILAYER TABLET

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ABSTRACT: The present research work was carried out to Formulate and evaluation of bilayer tablet dosage form for the treatment of Hypertension. The objective of this study to compare the specific characteristics of Olmesartan Midoxomil [Angiotensin II receptor antagonist] and Hydrochlorothiazide [Thiazide Diuretics] in order to design stable formulation. It can be concluded that Olmesartan Midoxomil [Angiotensin II receptor antagonist] and Hydrochlorothiazide [Thiazide Diuretics] were successfully formulated in combination as a Bilayer tablet form with Croscarmellose sodium, Lactose monohydrate and microcrystalline cellulose PH101 for immediate release of both drugs. Both drugs were found to be stable in Bilayer tablet formulation and were found to be stable up to 6 months. This bilayer tablet dosage form increases the stability which may reduce loss and cost of formulation. It improves the benefits of producer, retailer, and patients. Recently, greater attention has been focused on development of bilayer tablet formulations. Over the past 30 years, the expenses and complications involved in marketing new drug entities have increased with concomitant recognition of therapeutic advantages of conventional drug delivery system. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, efficient pharmacological effect, better patient compliance, *etc*. Bilayer tablet is becoming new approach for the successful drug delivery system and for better stability in combination. Bilayer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation.

INTRODUCTION: Tablets are solid dosage forms containing a unit dose of one or more medicament. They are intended for oral administration purpose. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersion in water before administration and some are retained in mouth where the active ingredient is liberated completely.

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Preparation intended for administration by other routes of administration, for example, in the form of implants and passerines may also be presented in the form of tablets but because they may require special formulations, methods of manufacture or form of presentation appropriate to the particular use they may not comply with all the requirement of this monograph.

Tables are obtained by compression or confection of uniform volumes of powders or granules by applying high pressure and using punches and dies. The particles to be compressed consist of one or more medicaments, with or without auxiliary substance such as diluents, binders, and disintegration agents, lubricant, glide ants and

substances capable of modifying the behavior of the medicaments in the digestive tracts. Such substances must be innocuous and therapeutically inert in the quantities present. Because of their composition, method of manufacture or intended use, tablets present variety of characteristics and consequently there are several categories of tablets. Useless otherwise stated in the individual monograph, tablets are uncoated. Where coating is permitted the monograph directs coating the statement reads. Unless otherwise directed, tablets may be coated or uncoated tablet administered for oral uses.

Tablets are usually solid, right circulars cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled, they may exist in others shapes like triangular, rectangular, etc. also. They may have lines or break-marks and may bear a symbol or other markings. They are sufficiently hard to withstand handling without crumbling or breaking. Uncoated tablets may be signal-layer tablets resulting from a signal compression of particles or multi-layer tablets costing of parallel layers obtained by successive compression of particles of different compositions, no treatment is applied to such tablets after compression. Any added substances are not ingredients in the digestive fluids. The addition of coloring or flavorings agents to uncoated tablets other than multi-layer tablets is not official unless permitted in the individual monograph. Uncoated tablets have the general characteristics of tablets. When a bracken section of uncoated tablet if the tablets fail to comply the discs the tablets comply the if they all six have disintegrated.

Coated Tablet: Coated tablets are covers with one or more layers mixture of various substances such as resins, gums, inactive, and insoluble fillers, sugars, plasticizes polyhydric alcohols, waxes, *etc*. the coating may also contain medicaments or without medicament in compression-coated tablets the coated is applied by compressing around the tablets granules prepared from tablets the coating is applied as a coating are usually applied as a solution or suspension in condition in which evaporation of the vehicle occurs. When the coating is thin, the tablets are described as a film-coated. Coated tablets may contain flavoring and or one or more coloring agents permitted under the drug and cosmetic rules 1945 coated tablets have a smooth. Usually polished and after colored. Surface: broken sections examined under a lens shows a core surrounded by one or one more continuous layers of a different texture of the tablet.

Coated tablets other than film-coated tablets comply the test for disintegration of tablets and capsules use water a liquids medium add a disc to each tube operate the apparatus for 60 min unless otherwise justified and authorized and examine the state of the tablets if any has not disintegrated repeats the test on a further six tablets replacing water which 0.1 M hydrochloric acid the tablets comply with the test if all six tablets have disintegrated in the acid medium. Film-coated tablets comply with the disintegration test pre cribbed over expect that the apparatus is operated for 30 minutes unless otherwise justified and authorized. If coated tablets or film-coated tablets fail to comply because of adherence to the discs repeat the test on a further six tablets omitting the discs the tablets comply with the test if all six have disintegrated completely.

The Advantages of the Bi-layer Tablet Dosage Form are:

- They are unit dosage form and compromise the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Cost is lower compared to all other oral dosage forms.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallow with least tendency for hang-up.
- Unpleasant odor and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability overall oral dosage form.

Product identification is easy and rapid requiring no additional steps when employing a pressed and/or identified punch face.

Disadvantages of Bi-Layer Tablet Dosage Form are:

- Hard to swallow in case of children and insentient patients.
- Some drugs resist compression into dense compacts, owing to unstructured nature, low-density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide satisfactory or full drug bioavailability.

Bitter testing drugs, drugs with an unpleasant odor or drugs that are sensitive to oxygen may require encapsulation or coating.

General properties of Bi-Layer Tablet Dosage Forms:

- Bi-layer tablet should have elegant product identity while free of defects like chips, cracks, mark, and impurity.
- Should have sufficient strength to withstand mechanical shock during its product packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical characteristics over time.
- The bi-layer tablet must be able to release the medicinal agents in a probable and reproducible manner.
- Must have a chemical stability shelf life, so as not to follow adjustment of the medicinal agents.

Olmesartan Medoxomil:

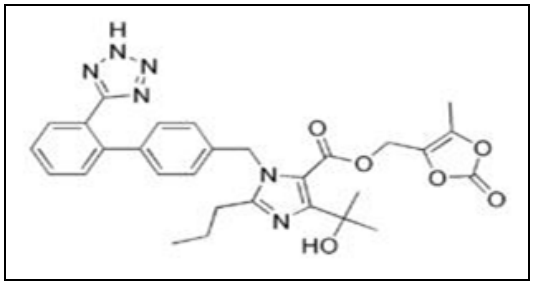


FIG. 1: CHEMICAL STRUCTURE OF OLMESARTAN MEDOXOMIL

IUPAC name: (5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl) methyl 4- (2- hydroxypropan-2-yl)- 2-propyl-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl} methyl)-1*H*-imidazole-5-carboxylate.

Olmesartan medoxomil is an orally active, selective angiotensin II receptor (type AT1) Angiotensin II antagonist is the primary vasoactive hormone of the renin angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT1 receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Hydrohlorothiazide:

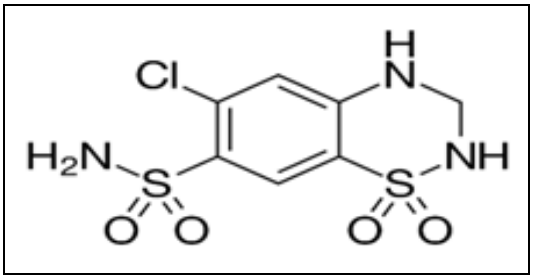


FIG. 2: CHEMICAL STRUCTURE OF HYDROHLOROTHIAZIDE

IUPAC Name: Hydrochlorothiazide is 6-chloro-3, 4- dihydro- 2*H*- 1, 2, 4- benzothiadiazine- 7-sulphonamide 1,1-dioxide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the Antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydro-chlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in

serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, the onset of diuresis occurs at about 2 h and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 h. Epidemiological studies have shown that long-term treatment with hydrochlorothiazide monotherapy reduces the risk of cardiovascular mortality and morbidity.

MATERIALS AND METHODS:

TABLE 1: LIST OF DRUGS AND EXCIPIENTS

S. no.	Ingredients	Category	Mfg./Supplier
1	Olmesartan Medoxomil	API	Aurobindo Pharma Ltd, India
2	Hydrochlorothiazide	API	Alembic Pharmaceuticals Ltd, India
3	Lactose Monohydrate	Diluent, Filler	DFE Pharma, Pune India
4	Mannitol	Diluent	Quingdao bright moon seaweed group co. Ltd, Mumbai, India
5	Maize starch	Diluent, Binder, Disintegrant	DFE Pharma, Pune India
6	Hydroxypropyl cellulose Klucel LF	Release-modifier	Shin-Etsu Chempvt Ltd
7	Low Substituted Hydroxypropyl Cellulose LH-11	Disintegrant	Shangdong head co. Ltd
8	Microcrystalline Cellulose PH-101	Diluent, Disintegrant	Ankit pulps & boards
9	Croscarmellose Sodium	Disintegrant	DFE Pharma, Pune India
10	Colloidal Silicon dioxide	Glidant, Disintegrant	Cabot Sanmer Ltd, Goa, India
11	Crospovidone (Polyplasdone XL 10)	Disintegrant	Quazhou Jianhua Nanhang Industrial co. Ltd.,
12	Sodium starch Glycolate (Primogel)	Disintegrant	Colorcon, 3702 E, 21st street Indianpolis, Indiana - 46218, USA
13	Povidone (PVP K-30)	Binder	BASF Germany
15	Isopropyl Alcohol	Solvent	Deepak fertilizers & petrochemicals Co. Ltd
16	Methylene Chloride	Solvent	Cure medicines(I) Pvt Ltd
17	Purified water	Solvent	-
18	Color lake of Tartrazine	Color	Colorcon, 3702 E, 21st street Indianapolis, Indiana-46218, USA
19	Color Iron red oxide	Color	Standardcon Pvt Ltd, Mumbai, India
20	Color lake of Ponceau 4R	Color	Corel Pharma Chem
21	Magnesium Stearate	Lubricant	Ferro Corporation
22	Talc	Glidant, Lubricant	Luzenac ValChisone SPA Pharmaceutical

Sifting:

- Following material sifted through 40# sieve: Olmesartan medoxomil, micro-crystalline cellulose PH 101 and mixed together in a geometric pattern in polyethylene bag.
- Then following material sifted through 40# sieve: maize starch, sodium starch glycolate (Primogel), Croscarmellose sodium, Colloidal silicon dioxide.
- Color of tartrazine sifted through 100# sieve.

Dry Mixing: Step 2 materials mixed in RMG for 20 min at slow speed.

Methods of Preparation:

Manufacturing Procedure:

For Hydrochlorothiazide Part:

Dispensing: All materials planned in the formula were approximately weighed.

Sifting:

- Following material sifted through 40# sieve: Hydrochlorothiazide, microcrystalline cellulose PH 101 and mixed together in geometric pattern in a polyethylene bag.
- Then following material sifted through 40# sieve: Mannitol, Crospovidone (Poly-plasdone XL10) and Low Substituted Hydroxypropyl cellulose LH-11.

Dry Mixing: Step 2 materials mixed in RMG for 20 min at slow speed *i.e.* mixer speed 150 rpm and mixer current are 1.30 Amp.

Binder: Povidone PVP K-30 added and dissolved in 60 gm isopropyl alcohol and into added 30 gm Methylene chloride under stirring.

Granulation: Step 3 material granulated in RMG in the following manner:

Sizing: Step 5 materials sifted through 10# sieve.

Drying: Step 6 material dried in RFBD as follows:

Sizing: Step 7 materials sifted through 30# sieve.

Pre-lubrication: Colloidal silicon dioxide and croscarmellose sodium sifted through 40# sieve.

Step 8 and 9 mixed in octagonal Blender for 20 min.

Lubrication: Step 10 material mixed with 50# sifted magnesium stearate in Octagonal blender for 5 min.

For OlmesartanMedoxomil Part:

Dispensing: All materials planned in formula were approximately weighed *i.e.* mixer speed 150 rpm and mixer current are 1.30 Amp.

Binder:

- 60 gm of Purified water heated to boil and 30 gm water added separately to maize starch in Polythene bag to form a slurry.
- Slurry added to boiling water under heating condition, continuous agitation has done using spatula and cooked for 2-5 min to form translucent paste.
- This paste kept for cooling at room temperature.

Granulation: Step 3 material granulated in RMG using step 4 paste in the following manner:

Sizing: Step 5 materials sifted through 10# sieve.

Drying: Step 6 material dried in RFBD as follows:

- ✓ Talc
- ✓ Magnesium stearate

Sizing: Step 7 materials sifted through 30# sieve.

Lubrication: Step 8 material mixed with following 60# sifted material in Octagonal blender for 5 min.

TABLE 2: FORMULATION DEVELOPMENT OF OLMESARTAN MEDOXOMIL & HYDROCHLOROTHIAZIDE BILAYER TABLET

S. no.	Ingredients	F1 Prototype	F2	F3	F4	F5	F6	F7	F8, F9, F10 Stability-I, II & III
	Hydrochlorothiazide Part								
	Dry Mix								
1	Hydrochlorothiazide	12.50	12.50	12.50	12.50	12.50	12.50	12.50	12.50
2	Lactose monohydrate	40	40	40	-	-	-	-	-
3	Mannitol	-	-	-	20.69	25.61	23.24	23.24	q.s. to 75.00 [33.24]
4	Microcrystalline cellulose PH 101	18.20	18.35	18.35	30.00	25.00	25.00	25.00	15.00
5	Hydroxypropyl cellulose Klucel LF	3.00	3.00	3.00	-	-	-	-	-
6	Crospovidone (Polyplasdone XL 10)	-	-	-	3.00	3.00	3.00	3.00	3.00
7	Low substituted hydroxypropyl Cellulose LH-11	-	-	-	3.00	3.00	3.00	3.00	3.00
8	Color lake of Ponceau 4R	0.30	0.15	-	-	0.30	-	-	-
9	Color Iron red oxide	-	-	0.150	0.30	-	-	-	-
	Binder								
10	Povidone (PVP K-30)	-	-	-	3.00	3.00	3.00	3.00	3.00
11	Isopropyl alcohol	-	-	-	q.s.	-	q.s.	q.s.	q.s.
12	Methylene chloride	-	-	-	-	q.s.	q.s.	q.s.	q.s.
13	Purified water	q.s.	q.s.	q.s.	-	-	-	-	-
	Pre-lubrication								
14	Croscarmellose sodium	5.00	5.00	5.00	3.00	3.00	3.00	3.00	3.00
15	Colloidal silicon dioxide	-	-	-	1.13	1.13	1.13	1.13	1.13
16	Low substituted hydroxypropyl Cellulose LH-11	-	-	-	2.25	2.25	-	-	-
17	Color lake of Ponceau 4R	-	-	-	-	0.08	-	-	-
	Lubrication								
18	Magnesium stearate	1.00	1.00	1.00	1.13	1.13	1.13	1.13	1.13
	Layer weight (mg)	80.00	80.00	80.00	80.00	75.00	75.00	75.00	75.00

S. no.	Ingredients	F1 Prototype	F2	F3	F4	F5	F6	F7	F8, F9, F10 Stability-I, II & III
Olmesartan Medoxomil Part									
Dry Mix									
1	Olmesartan medoxomil	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
2	Microcrystalline cellulose PH 101	18.00	15.00	15.00	18.70	23.70	23.40	23.40	q.s. to 65mg [23.40]
3	Lactose monohydrate	21.000	24.00	24.00	-	-	-	-	-
4	Maize starch	-	-	-	10.00	10.00	10.00	10.00	10.00
5	Color lake of tartrazine	-	-	-	-	-	0.30	0.30	0.30
6	Sodium starch Glycolate (Primogel)	-	-	-	-	-	3.00	3.00	3.00
7	Croscarmellose sodium	-	-	-	-	-	3.00	3.00	3.00
8	Colloidal silicon dioxide	-	-	-	-	-	1.30	1.30	1.30
Binder									
9	Maize starch	-	-	-	2.60	2.60	2.60	2.60	2.60
10	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Pre-lubrication									
11	Sodium starch glycolate (Primogel)	-	-	-	3.00	3.00	-	-	-
12	Croscarmellose sodium	-	-	-	3.00	3.00	-	-	-
13	Colloidal silicon dioxide	-	-	-	1.30	1.30	-	-	-
Lubrication									
14	Talc	-	-	-	0.70	0.70	0.70	0.70	0.70
15	Magnesium stearate	1.00	1.00	1.00	0.70	0.70	0.70	0.70	0.70
	Layer weight (mg)	60.00	60.00	60.00	60.00	65.00	65.00	65.00	65.00

Evaluation of Bilayer Tablets:

Evaluation of Tablets:

Evaluation of Pre-Compression Parameters: [28]

Total Moisture Content: the Weighed amount of powder (1 g) was placed on the IR balance of LOD apparatus METTLER TOLEDO HG-63 Halogen at 105 ºC and the amount of moisture in the granules was determined.

Acceptance Criteria: the LOD of the granules should be between 2-3%.

Bulk Density: Accurately weighed the quantity of dried granules into graduated 100 ml measuring cylinder, volume was noted and Bulk Density was calculated by given formula.

Bulk Density = Weight of the untapped powder / Volume of the untapped powder

Tapped Density: It was determined by placing a graduated 100 ml measuring cylinder, containing a known mass of dried granules. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at second interval for 100 taps to obtain the constant volume of powder bed. The final volume was noted and Tapped Density was calculated using the following formula.

Tapped Density = Weight of the tapped powder / Volume of the tapped powder

Carr's Compressibility Index: The flow property of the granules was determined by % Carr's Index. It was calculated by the following formula.

(%) Carr's Index = Tapped Density-Bulk Density / Tapped Density × 100

TABLE 3: USP LIMITS FOR CARR's COMPRESSIBILITY INDEX

S. no.	Compressibility Index	Flow Property
1	<10	Excellent
2	11-15	Good
3	16-20	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very poor
7	>38	Very very poor

Hausner's Ratio: Hausner's Ration is an indication of flowability of the granules. It was calculated by following formula.

Hausner's Ratio = Tapped Density / Bulk Density

TABLE 4: USP LIMITS FOR HAUSNER's RATIO

S. no.	Hausner's Ratio	Flow Property
1	1.00-1.11	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very poor
7	>1.60	Very very poor

Sieve Analysis: Sieve Analysis was used to determine the Particle size of granules. The procedure was same as per Particle size determination of API mentioned in Chapter 6.2.1.F.

Evaluation of Post-Compression Parameters: [29]

In-Process Quality Control Test:

Weight Variation: Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. The average weight of tablets was determined and compared with average weight the positive and negative deviation. The tablets meet USP specification if no more than 2 tablets are outside the percentage limit and if no tablets differ by more than 2 than the percentage limit.

Thickness: Thickness of tablet is important for uniformity of tablets size. Thickness was measured using Digital Vernier Caliper. Thickness of the tablet was checked after compression.

Hardness: The resistance of tablets to shipping or breakage, under conditions of storage, transportation, and handling before usage, depends on its hardness. The Hardness of the prepared tablets of each formulation was determined using a PHARMA TEST (PTB-411) hardness tester. Ten tablets were tested for hardness from hardness from each batch and mean and SD was calculated. It was measured in terms of Kp.

Friability: Friability is the measurement of tablet strength. (EF-2) ELECTROLAB friability tester was used for testing the friability. 6.5 g tablets were weighed accurately and placed in the friabilator that revolves at 25 rpm for 4 min dropping the tablets through a distance of six inches with each revolution.

After 100 revolutions the tablets were removed and dedusted, reweighed, and the percentage loss in tablets weight was determined.

Disintegration Time: *In-vitro* disintegration time of the prepared tablets was carried out at (37 ± 2ºC) in 900 ml distilled water using a disintegration test apparatus (Electrolab-ED-2L). 6 tablets were selected randomly and placed in each basket, and the machine was started. The time at which complete tablet get disintegrated was recorded as disintegration time of the tablet.

Assay and Relative substances (By HPLC): [30]

Chromatographic System:

Apparatus: HPLC, PDA detector, column-C_{18}, 250 mm × 4.6 mm, 5 µ Inertsil ODS 3V, column temperature-Ambient, flow rate-1.0ml/min, Injection volume-20 µL, wavelength-237 nm, Run time-15 min, Instrument set up, Isocratic.

Mobile Phase: A mixture of methanol: water in the ratio of 75:25% v/v was used as mobile phase. Mixed solvents were filtered through 0.2 µm cellulose acetate membrane filters (Sartorius Ste-dim Biotech S.A. Aubagne Cedex, France) with a solvent filtration apparatus, degassed and used as mobile phase. Same was used as diluents for the preparation of drug solutions.

Preparation of 0.1M Ammonium Acetate Buffer: Accurately accurate amount of ammonium acetate is dissolved in 1000 ml water, mixed well.

Diluent Blank Preparation: Mobile phase used as diluent blank.

Standard Preparation:

Stock Solution of Olmesartan Medoxomil: Weighed accurate 10 mg amount of Olmesartan Medoxomil sample working standard into 10 ml clean and dry volumetric flask and added about 7 ml of the mobile phase, sonicated to dissolve and diluted to volume with mobile phase.

Stock Solution of Hydrochlorothiazide: Weighed and transferred accurately about 20 mg of Hydrochlorothiazide working standard into 10 ml clean and dry volumetric flask and the volume was made up to with mobile phase. The containers used for storage were screw-capped tubes coated externally by aluminum foil.

Sample Preparation: Weighed and transfer 20 whole tablets (equivalent to about 10 mg of Olmesartan Medoxomil) into a 10 ml volumetric flask, dissolving in the mobile phase, sonicated for about 10 min with intermittent shaking, diluted with mobile phase to volume and mixed well. Filter the solution through 0.45 µ nylon membrane syringe filter. Transfer 5 ml of the filtrate to a 50 ml volumetric flask and to volume with mobile phase. The solution was used for the estimation of Olmesartan Medoxomil and Hydrochlorothiazide (100 µg/ml).

***In-vitro* Drug Release (Dissolution) Study: [31, 13, 23]**

In-vitro drug release studies of all the formulations were carried out using tablets dissolution test

apparatus (USP type-II) at 75 rpm. Phosphate buffer 900 ml, pH 6.8 was used as the dissolution media with the temperature maintained at (37±0.5ºC). Samples (5 ml) were withdrawn at 60min, filtered, diluted suitably and analyzed by HPLC system.

Stability Study: [32]

Introduction: In any rational drug design or evaluation of dosage forms, the stability of the active component must be major criteria in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Objective of the Study: The purpose of the testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, enabling recommended storage conditions, retest periods and shelf-lives.

The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug Products" (QIC) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.

ICH specifies the length of study and storage conditions.

Accelerated Testing: 40±2ºC/75±5% RH for 6 months.

Intermediate Testing: 30±2ºC/65±5% RH for 6 months.

Long-term Testing: 25±2ºC/60±5% RH for 12 months

RESULT AND DISCUSSION:

Preformulation Study: Characterization of API:

TABLE 5: RESULT FOR CHARACTERIZATION OF API

S. no.	Characterization	Olmesartan midoxomil	Hydro-chlorothiazide
1	Color	White to off-white	White
2	Odor	Odorless	Odorless

Solubility Study:

TABLE 6: RESULT FOR SOLUBILITY OF API

S. no.	Characterization	Solubility
1	Olmesartan midoxomil	Soluble in methanol, ethanol, and acetonitrile and insoluble in water
2	Hydrochlorothiazide	Soluble in acetone, methanol sparingly soluble in ethanol (95%); very slightly soluble in water

Melting Point Determination:

TABLE 7: RESULT FOR MELTING POINT DETERMINATION OF API

S. no.	Characterization	Melting point	
		Observed	Reference
1	Olmesartan midoxomil	176-178ºC	178ºC
2	Hydrochlorothiazide	274-276ºC	274ºC

UV Spectrophotometry Study:
λ_{max} Determination:

TABLE 8: RESULT FOR λ_{max} DETERMINATION OF API

S. no.	API	λ_{max}	
		Observed	Reference
1	Olmesartan midoxomil	231.00 nm	231.00 nm
2	Hydrochlorothiazide	283.00 nm	283.00 nm

Preparation of Calibration Curve:
For Olmesartan Midoxomil:

TABLE 9: ABSORBANCE VALUES AT VARIOUS CONCENTRATION OF OLMESARTAN MIOXOMIL IN METHANOL

S. no.	Conc. (µg/ml)	Absorbance
1	0	0
2	4	0.188
3	8	0.312
4	12	0.488
5	16	0.644
6	20	0.799

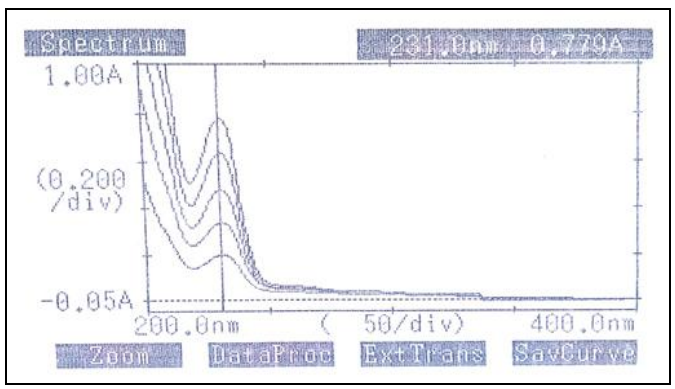


FIG. 3: DETERMINATION OF λ_{max} AND CALIBRATION CURVE OF OLMESARTAN MIDOXOMIL

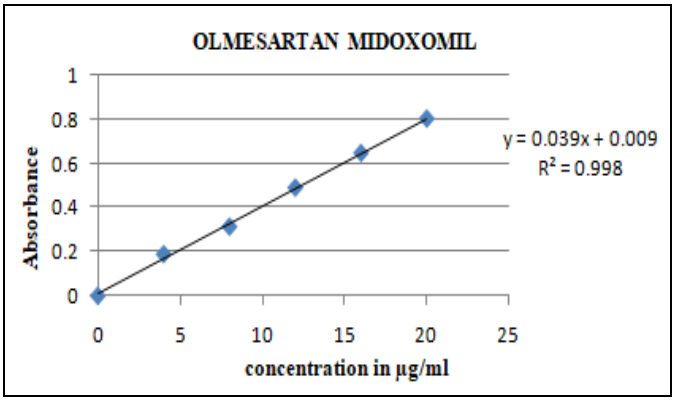


FIG. 4: CALIBRATION CURVE OF OLMESARTAN MIDOXOMIL IN METHANOL

For Hydrochlorothiazide:

TABLE 10: ABSORBANCE VALUES AT VARIOUS CONCENTRATIONS OF HYDROCHLOROTHIAZIDE IN METHANOL

S. no.	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.166
3	8	0.323
4	12	0.483
5	16	0.637
6	20	0.804

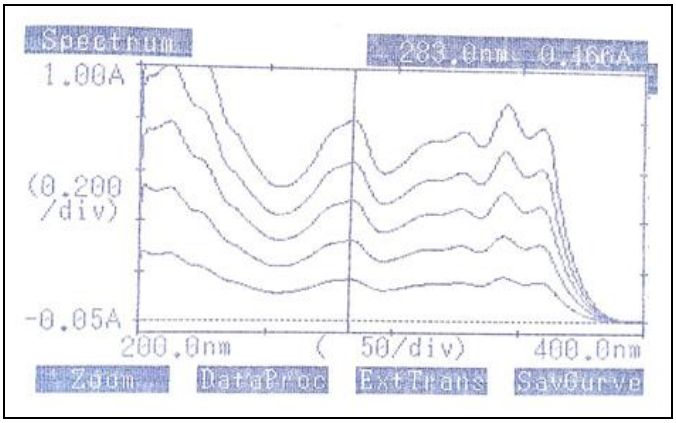


FIG. 5: DETERMINATION OF λ_{max} AND CALIBRATION CURVE OF HYDROCHLOROTHIAZIDE

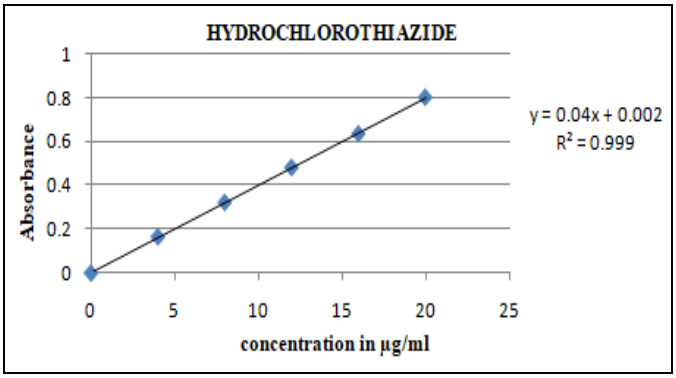


FIG. 6: CALIBRATION CURVE OF HYDROCHLOROTHIAZIDE IN METHANOL

FTIR Study:
Olmesartan Midoxomil:

TABLE 11: INTERPRETATION OF FTIR SPECTRUM OF OLMESARTAN MIDOXOMIL

S. no.	Frequency (cm^{-1})	Description	Mode of Vibration
1	3461	-N-H, O-H	Stretching
2	2981, 2949	Aliphatic –C-H	Stretching
3	2629, 2358	$N\text{-}H^{+}$	Stretching
4	1743	Acid C=O Aromatic –C=C	Stretching
5	1601	Aromatic –C=C	Stretching
6	1496, 1382, 1357	Aliphatic –C-H	Bending
7	1319	-C-N	Stretching
8	1135	Ether C-O	Stretching
9	1092	Aromatic C-Cl	Stretching
10	805, 757, 699	Aromatic C-H	Stretching

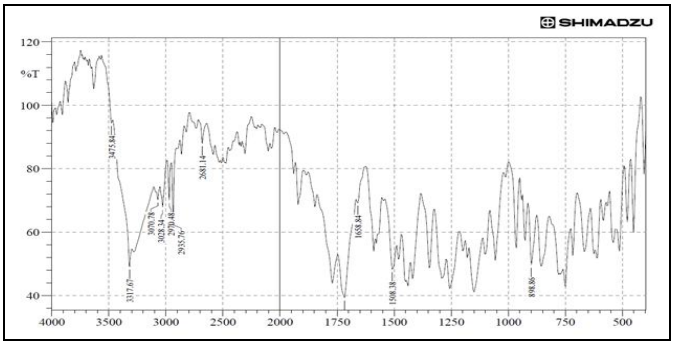


FIG. 7: FTIR CHROMATOGRAM OF OLMESARTAN MIDOXOMIL

Hydrochlorothiazide:

TABLE 12: INTERPRETATION OF FTIR SPECTRUM OF HYDROCHLOROTHIAZIDE

S. no.	Frequency (cm^{-1})	Description	Mode of Vibration
1	3392	O-H	Stretching
2	3058	Aromatic –C-H	Stretching
3	2975, 2928	Aliphatic –C-H	Stretching
4	1637, 1607, 1594, 1497	-C=C	Stretching
5	1563, 1408	-C=O	Stretching
6	1440, 1341	Aliphatic –C-H	Bending
7	1440, 1341	Aliphatic –C-H	Bending
8	1144	-C=O	Stretching
9	1068	-C-Cl	Stretching
10	963, 837, 761	-C-H	Bending

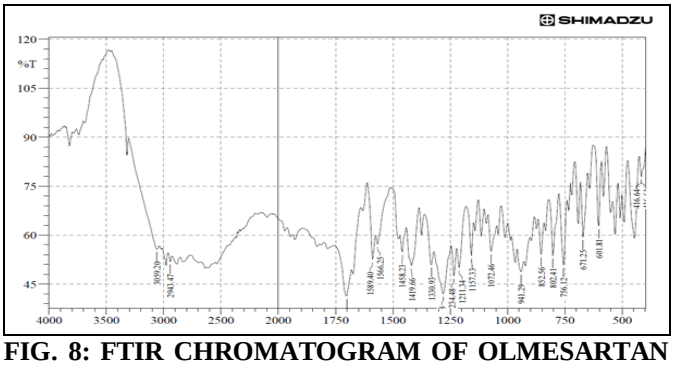


FIG. 8: FTIR CHROMATOGRAM OF OLMESARTAN HYDROCHLOROTHIAZIDE

Particle size Determination of API:

TABLE 13: PARTICLE SIZE ANALYSIS OF API BY SIEVE ANALYSIS

Sieve no.	% Weight retained on the sieve	
	Olmesartan Midoxomil	Hydrochlorothiazide
#20	17.40	14.16
#40	47.56	51.52
#60	04.12	03.89
#80	05.22	04.88
#100	06.02	04.12
Pan	19.68	21.43

Evaluation of Tablets: Evaluation of pre-compression parameters: Dry Mix:

TABLE 14: PRE-COMPRESSION PARAMETER OF DRY MIX OF HYDROCHLOROTHIAZIDE AND OLMESARTAN MIDOXOMIL

Batch	Hydrochlorothiazide				Olmesartan Midoxomil			
	Bulk density (g/ml)	Weight		Loss on Drying (%w/w)	Bulk density (g/ml)	Weight		Loss on Drying (%w/w)
		Theoretical (g)	Actual (g)			Theoretical(g)	Actual(g)	
F1	0.5380	79.00	77.09	2.69	0.3990	59.00	57.81	2.32
F2	0.4785	79.00	76.21	2.46	0.3569	59.00	56.93	2.04
F3	0.5102	118.00	116.21	3.14	0.3837	158.00	157.21	3.02
F4	0.4300	69.49	68.11	2.19	0.4000	48.70	46.94	2.26
F5	0.5236	64.44	63.18	1.65	0.3854	43.46	41.94	1.34
F6	0.4564	66.74	65.19	3.46	0.3800	61.00	59.64	6.47
F7	0.4860	200.22	198.16	2.64	0.3614	183.00	181.48	6.05
F8	0.4500	183.00	181.11	4.47	0.5000	200.22	199.02	2.34
F9	0.4342	200.22	198.31	2.30	0.4838	183.00	181.05	5.26
F10	0.4450	200.22	197.94	1.86	0.4854	183.00	181.39	4.41

Dry Granules:

TABLE 15: PRE-COMPRESSION PARAMETER OF DRY GRANULES OF HYDROCHLOROTHIAZIDE AND OLMESARTAN MIDOXOMIL

Batch	Hydrochlorothiazide			Olmesartan Midoxomil		
	Weight		Loss on Drying	Weight		Loss on Drying
	Theoretical (g)	Actual (g)	(%w/w)	Theoretical(g)	Actual(g)	(%w/w)
F1	79.00	77.48	1.57	59.00	58.12	2.30
F2	79.00	77.68	1.77	59.00	58.11	1.49
F3	118.00	117.44	2.36	158.00	157.69	1.93
F4	72.49	64.81	2.54	51.30	47.69	4.01
F5	67.44	63.02	2.39	56.30	52.42	4.20
F6	69.74	64.83	2.58	63.60	57.26	3.33
F7	209.22	209.91	3.01	190.80	173.81	4.26
F8	190.80	172.62	4.00	209.22	208.14	2.47
F9	209.22	199.54	2.95	190.8	174.85	3.41
F10	209.22	203.05	2.84	190.8	176.45	3.04

Lubricated Granules:

TABLE 16: PRE-COMPRESSION PARAMETERS OF LUBRICATED GRANULES OF HYDROCHLOROTHIAZIDE PART

Batch	Bulk density (g/ml)	Tapped density(g/ml)	Hausner's ratio	Carr's index %	Weight		Loss on Drying (% w/w)
					Theoretical(g)	Actual(g)	
F1	0.5660	0.6530	1.1537	13.3231	80.00	78.19	1.69
F2	0.5379	0.6846	1.2727	21.4286	80.00	78.04	1.83
F3	0.5344	0.6108	1.143	12.5082	120.00	118.13	2.29
F4	0.4500	0.5600	1.2444	19.6429	80.00	72.63	2.93
F5	0.4800	0.6100	1.2708	21.3115	75.00	70.12	3.59
F6	0.3700	0.4700	1.2703	21.2766	75.00	69.48	3.02
F7	0.4600	0.5940	1.2913	22.5589	225.00	213.04	3.15

F8	0.5700	0.7800	1.3684	42.5967	195.00	178.21	4.31
F9	0.5277	0.6303	1.1944	19.4631	225.00	211.23	3.13
F10	0.4926	0.5923	1.2024	21.4286	225.00	215.69	2.75

TABLE 17: PRE-COMPRESSION PARAMETERS OF LUBRICATED GRANULES FOR OLMESARTAN MIDOXOMIL PART

Batch	Bulk density (g/ml)	Tapped density(g/ml)	Hausner's ratio	Carr's index %	Weight		Loss on Drying (% w/w)
					Theoretical(g)	Actual(g)	
F1	0.4280	0.5500	1.2850	22.1818	60	59.02	2.52
F2	0.4711	0.6909	1.4666	31.8136	60	58.96	1.45
F3	0.5000	0.6100	1.2200	18.0328	160	159.14	2.35
F4	0.5600	0.6400	1.1429	12.5000	60	55.14	4.35
F5	0.5200	0.5900	1.1346	11.8644	65	59.48	3.63
F6	0.4700	0.5400	1.1489	12.9630	65	58.28	4.46
F7	0.4800	0.5942	1.2379	19.2191	195	177.81	4.52
F8	0.4200	0.5200	1.2381	14.1412	225	211.96	3.18
F9	0.4375	0.5600	1.2800	19.2982	195	180.02	3.66
F10	0.47	0.5834	1.2413	31.8136	195	180.13	3.90

Sieve Analysis:

TABLE 18: RESULT FOR SIEVE ANALYSIS FOR BLEND OF VARIOUS BATCHES

Batch	Sieve Number	#20	#40	#60	#80	#100	Fines
F1	Hydrochlorothiazide	0.00	57.23	16.83	11.05	4.62	10.27
	Olmesartan Midoxomil	0.00	57.03	14.45	14.93	5.56	8.03
F2	Hydrochlorothiazide	0.00	46.38	20.30	20.54	3.40	9.38
	Olmesartan Midoxomil	0.00	14.27	8.23	9.63	8.64	59.23
F3	Hydrochlorothiazide	0.00	59.35	18.73	10.53	6.50	4.89
	Olmesartan Midoxomil	0.00	43.39	20.06	19.19	3.33	14.03
F4	Hydrochlorothiazide	0.00	48.65	16.23	9.70	3.89	21.53
	Olmesartan Midoxomil	0.00	60.16	18.64	16.8	1.60	2.80
F5	Hydrochlorothiazide	0.00	12.73	8.53	15.24	7.93	55.57
	Olmesartan Midoxomil	0.00	67.23	21.18	9.82	0.85	0.92
F6	Hydrochlorothiazide	0.00	54.82	24.63	15.27	1.53	3.75
	Olmesartan Midoxomil	0.00	27.40	15.15	21.53	7.91	28.01
F7	Hydrochlorothiazide	0.00	21.24	15.94	17.55	20.37	24.90
	Olmesartan Midoxomil	0.00	28.85	19.64	16.81	8.76	25.94
F8	Hydrochlorothiazide	0.00	20.82	16.92	16.05	22.91	23.30
	Olmesartan Midoxomil	0.00	30.09	17.54	14.70	5.66	32.01
F9	Hydrochlorothiazide	0.00	37.63	17.64	12.94	4.53	27.26
	Olmesartan Midoxomil	0.00	16.46	11.56	22.02	10.75	39.21
F10	Hydrochlorothiazide	0.00	36.22	15.99	10.28	6.98	30.53
	Olmesartan Midoxomil	0.00	18.43	13.23	19.63	9.14	39.57

Evaluation of Post-Compression Parameters for Bilayer Tablet:

In-Process Quality Control Test:

TABLE 19: POST-COMPRESSION EVALUATION PARAMETERS FOR BILAYER TABLET

Batch			Target weight	Thickness	Hardness	D.T.
S. no.	Type	Size	(mg)	(mm)	(kp)	(min)
F1	Prototype	1000 Tab	140±5 %	2.6-2.7.	3.91-4.67	8.51
F2	Trial	1000 Tab	140±5 %	2.7-2.8	3.29-4.01	5.12
F3	Trial	2000 Tab	140±5 %	2.6-2.7	3.56-4.15	4.36
F4	Trial	1000 Tab	140±5 %	2.9-3.0	4.81-6.03	6.12
F5	Trial	1000 Tab	140±5 %	2.7-2.8	4.61-4.79	5.23
F6	Trial	1000 Tab	140±5 %	2.6-2.7	4.40-5.49	7.21
F7	Trial	3000 Tab	140±5 %	2.6-2.7	5.12	6.21
F8	Stability	3000 Tab	140±5 %	2.7-2.8	5.12-5.26	4.35
F9	Stability	3000 Tab	140±5 %	2.7-2.8	4.03-5.93	4.26
F10	Stability	3000 Tab	140±5 %	2.7-2.8	3.99-5.93	4.21

Punch Details: 7.4 mm flat-faced beveled edge round plain punches.

Appearance: F1-F5 = Red and white-colored round shaped flat-faced uncoated tablet with beveled edges plain at both sides.

F6-F10 = Yellow and white-colored round shaped flat-faced uncoated tablet with beveled edges plain at both sides.

Assay, % Content Uniformity and *In-vitro* Dissolution Study: Result of an assay, *in-vitro* dissolution study and % content uniformity of trial batches given in **Table 20**. In this F5 Batch showing High Assay, High % CU and Hydrochlorothiazide part gives Low Disso where Olmesartan midoxomil part gives High Disso release.

TABLE 20: RESULT OF ANALYSIS FOR TRIAL BATCHES

			F3		F5		F6		F7	
			Trial							
			HCTZ	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**
Assay (%)	L.G. Blend	Top	93.45	106.27	110.91	105.80	107.16	106.16	108.04	103.52
		Middle	95.26	104.29	109.45	107.56	105.50	104.94	107.26	103.56
		Bottom	103.43	106.24	116.42	112.48	104.14	106.28	109.10	101.98
		Tablet	104.25	108.24	121.51	119.02	108.32	101.68	104.33	102.09
		Reference	(90-110)%		(90-110)%		(90-110)%		(90-110)%	
			HCTZ	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**
Dissolution (NLT Q+5%)			93.24	114.25	73.91	113.79	111.64	105..46	108.24	97.54
			108.37	113.41	43.95	117.78	92.49	96.43	90.8	98.59
			98.26	110.45	70.45	118.77	97.82	106.27	96.96	98.56
			112.35	107.26	60.92	115.38	109.45	91.27	103.05	97.70
			106.27	112.86	55.18	104.73	99.53	92.34	91.37	98.85
			94.26	104.38	80.96	117.12	113.92	91.38	94.6	95.73
		Mean	102.13	110.44	64.23	114.6	104.14	97.19	97.50	97.83
		Reference	85-115	90-110	85-115	90-110	85-115	90-110	85-115	90-110
			HCTZ	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**
% content uniformity (85-115)%			96.53	93.43	119.76	117.69	112.43	114.84	113.95	101.44
			106.25	105.27	114.42	122.40	111.28	112.47	112.71	101.09
			98.34	104.38	118.65	121.74	110.92	94.43	113.25	100.97
			113.28	99.25	118.18	111.76	108.46	112.15	113.85	95.29
			109.34	100.83	123.01	115.30	114.61	109.68	112.48	96.72
		Mean	104.75	100.63	118.80	117.78	111.54	108.72	113.25	99.10
		Reference	(85-115) %		(85-115) %		(85-115) %		(85-115) %	

Assay, % Content Uniformity and *in-vitro* Dissolution Study for Stability Batches: Here at Initial Stage Stability batches F8, F9 and F10 gives the satisfactory values of Assay, % content uniformity and *in-vitro* Dissolution study.

TABLE 21: RESULT OF ANALYSIS FOR STABILITY BATCHES AT INITIAL

			F8		F9		F10	
Assay (%)			**HCTZ**	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**
	L.G. Blend	Top	102.00	104.54	108.06	103.46	108.15	104.34
		Middle	103.68	105.96	109.13	104.91	107.51	106.17
		Bottom	102.46	105.80	108.82	106.48	108.73	104.39
		Tablet	102.23	99.12	106.36	102.58	106.15	98.75
		Reference	(90-110)%		(90-110)%		(90-110)%	
			HCTZ	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**
Dissolution (NLT Q+5%)			103.50	91.02	113.28	98.46	114.65	97.28
			107.47	97.83	103.54	93.58	111.31	94.61
			106.88	98.82	114.48	94.38	110.94	98.34
			111.39	96.67	108.61	96.19	110.47	97.46
			109.56	98.33	109.18	98.56	112.69	99.28
			95.55	98.11	110.64	100.08	111.93	94.99
		Mean	105.73	96.80	109.96	96.88	112.00	97.00

	Reference	85-115	90-110	85-115	90-110	85-115	90-110
		HCTZ	**Olme**	**HCTZ**	**Olme**	**HCTZ**	**Olme**
% content uniformity (85-115)%		111.35	97.00	111.14	96.70	112.32	95.57
		111.85	96.64	103.81	100.05	112.81	96.62
		113.94	97.99	106.53	99.00	113.93	96.07
		112.60	98.42	104.83	106.84	114.31	96.00
		113.79	98.14	99.51	103.78	109.60	91.40
	Mean	112.71	97.64	105.16	101.27	112.59	95.13
	Reference	(85-115) %		(85-115) %		(85-115) %	

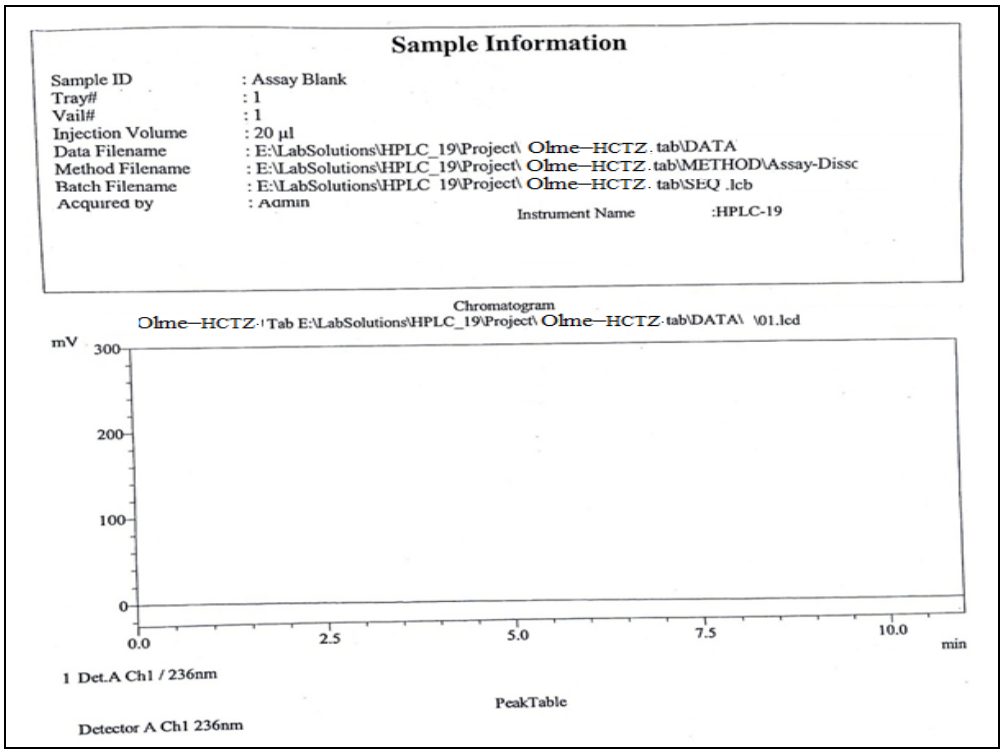
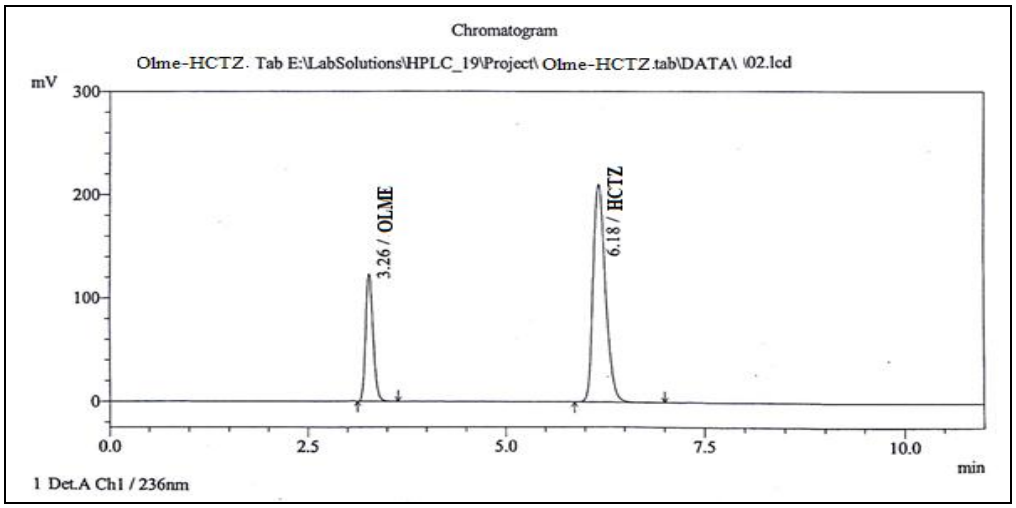


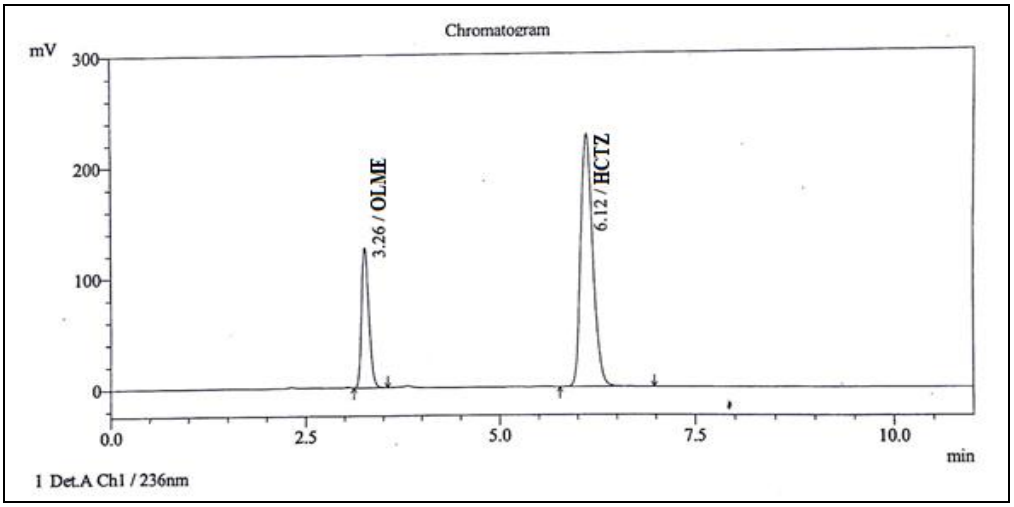
FIG. 9: CHROMATOGRAM OF BLANK FOR ASSAY OF BILAYER TABLET OF OLMESARTAN MIDOXOMIL AND HYDROCHLOROTHIAZIDE



PEAK TABLE

Peak#	Name	RT (min)	Area	Area%	Tailing Factor	Theoretical Plate#
1	OLME	3.264	809178	26.107	1.26	4959
2	HCTZ	6.184	2290316	73.893	1.19	7124
Total			3099495	100.000		

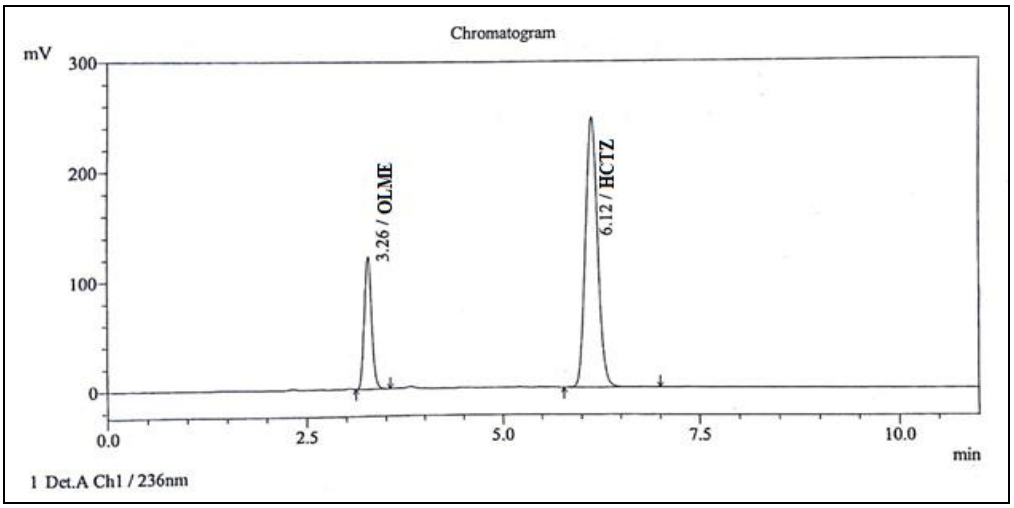
Detector A Ch1 236 nm



PEAK TABLE

Peak#	Name	RT (min)	Area	Area%	Tailing Factor	Theoretical Plate#
1	OLME	3.259	821311	25.137	1.25	5066
2	HCTZ	6.121	2446063	74.863	1.18	7121
Total			3267374	100.000		

Detector A Ch1 236 nm



PEAK TABLE

Peak#	Name	RT (min)	Area	Area%	Tailing Factor	Theoretical Plate#
1	OLME	3.260	790654	22.816	1.25	5081
2	HCTZ	6.118	2674785	77.184	1.19	7122
Total			3465469	100.000		

Detector A Ch1 236 nm

FIG. 10: CHROMATOGRAM OF SAMPLE1 FOR ASSAY AND CONTENT UNIFORMITY

SUMMARY AND CONCLUSION: This bilayer tablet dosage form increases the stability which may reduce loss and cost of formulation. It improves the benefits of producer, retailer, and patients. Allergic rhinitis is a common disorder that affects a large population. The treatment goals for Hypertension are relief of symptoms. Therapeutic options available to achieve this goal include various drugs.

The combination Olmesartan midoxomil with Hydrochlorothiazide gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life is impaired by persistent Hypertension. When tablets of the combination of these are prepared, they tend to become unstable during the shelf life of the formulation. Hence, it is recommended to prepare a bilayer tablet; it improves and increases the

stability by reducing the acid-base interactions of both the drugs in combination thereby increasing the bioavailability. To overcome the shortcoming of single-layer tablet approach in this combination like bilayer can be satisfactorily used. In this study demonstrated the successful formulation and evaluation of an Antihypertensive in a single dosage form as a bilayer.

The parameters like solubility, melting point, λ_{max} were evaluated to identify purity of drug and all parameters were found satisfactory and within prescribed official limits. Preformulation study was carried out. One prototype batch, six trial batches and then three stability batches for formulation and development were prepared using wet granulation and dry granulation. Excipient like Ponceau 4R and water may influence with the Hydrochlorothiazide that changes the color of tablets one part, hence we replace the color with Iron red oxide. Combination of excipient like disintegrants in Olmesartan Midoxomil part. For appropriate immediate release of OlmesartanMidoxomil Lactose were replaced with Starch, Sodium Starch Glycolate and croscarmellose Sodium. Stability study performed as per ICH guidelines and satisfactory results were obtained which concluded that the batches F8, F9, and F10 are supposed to be stable and expected to remain for the period of three years with drugs gives the different release of drug that fixed here in this formulation for the immediate release of both drugs. F1 was planned as a wet granulation with Ponceau 4R in Hydrochlorothiazide part tablet produces color change in that. So, in F6 formulation color is added or more.

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CONFLICT OF INTEREST: Nil

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