FORMULATION AND EVALUATION OF BILAYER TABLETS OF OLMESARTAN MEDOXOMIL AND HYDROCHLOROTHIAZIDE

GOVINDASWAMY.R*, K.UMASANKAR, P.JAYACHANDRA REDDY
Krishna Teja Pharmacy College, Tirupati-517 506, Chittoor (Dist), A.P., India

ABSTRACT

The present investigation relates to the development of Bilayer dosage form containing combination of Olmesartanmedoxomil and Hydrochlorothiazide as a immediate release layer respectively for the treatment of Hypertension. Olmesartanmedoxomil is aangiotensin II receptor antagonist to treat high blood pressure. It has a half life approximately 13 hours.Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle.Hydrochlorothiazide is a first line diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water. This reduces the volume of the blood decreasing lower peripheral vascular resistance.The combination product more effective than monotherapy with the individual components but the combination product allows a low-dose multidrug regimen as an alternative to high-dose monotherapy, thereby, minimizing the dose- related side-effects. Developing a new formula for bilayer tablet containing OlmesartanMedoxomil and Hydrochlorothiazide, by Evaluation of trial products and Drug release profile. Stability testing also should be done as per ICH guidelines.

Keywords: Olmesartanmedoxomil, Hydrochlorothiazide, Bilayer tablets.

Correspondence Author:- P.ThejaswiniEmail Id:- thejareddy43@gmail.com

INTRODUCTION

Dual release is a unit compressed tablet dosage form intended for oral application. It contains two parts, in which one part is having conventional or immediate release part while the other is sustained or controlled released part. In this chemically incompatible materials or those which separate in a mixed granulation present in the same tablet. For sustained action of products each layer may be formulated for different release characteristics. Sometimes different drug formulated in a same tablet to achieve different pharmacological action from a single tablet.

ADVANTAGES OF BILAYER TABLETS:

- ✓ Bilayer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
- ✓ Extension of a conventional technology. Potential use of single entity feed granules.
- ✓ Separation of incompatible components.
- ✓ Patient compliance is enhanced leading to improve drug regimen efficiency.
- ✓ Maintain physical and chemical stability.
- ✓ Retain potency and ensure dose accuracy.

DISADVANTAGES OF BILAYER TABLETS:

- ✓ Insufficient hardness, Layer separation, reduced yield.
- ✓ Inaccurate individual layer weight control.
- ✓ Cross contamination between the layers.

APPLICATIONS:

a) Used in the combination therapy and to deliver the loading dose a sustained dose of the same or different drugs.

b) Used for bilayer floating tablet in which one layer is floating layer and another one is releases layer of the drug and to deliver two different drugs having different releases profiles.

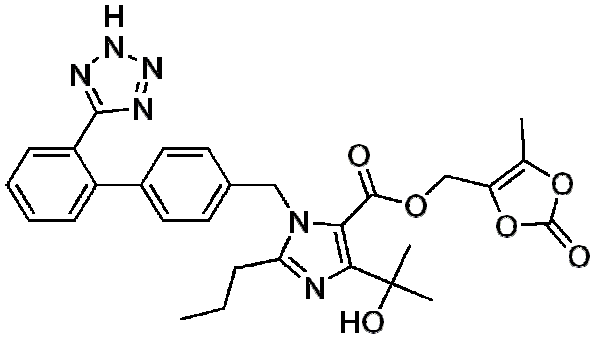
OlmesartanMedoxomil and Hydrochlorothiazide:[23]

OlmesartanMedoxomil and hydrochlorothiazide are used in combination to treat high blood pressure. The OlmesartanMedoxomil acts as a Angiotensin II receptor antagonists, while hydrochlorothiazide component acts as a diuretic.

Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle.

Hydrochlorothiazide helps remove salt and water from the body, providing further action to decrease high blood pressure.

OlmesartanMedoxomil belongs to the class of medicines called angiotensin II receptor antagonist to treat high blood pressure.



FigureNo:1 OlmesartanMedoxomilStructural Formula

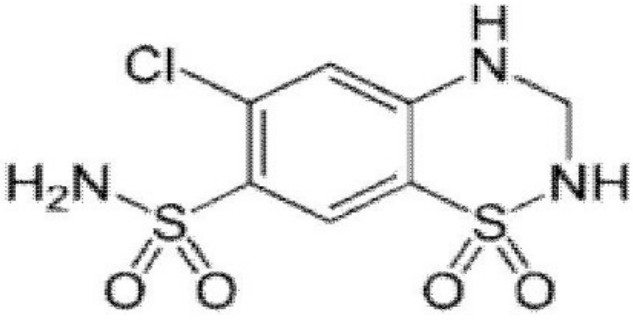


Figure No:2Structural Formula of Hydrochlorothiazide

MATERIALS AND METHODS

Olmesartanmedoxomil and Hydrochlorothiazide was received as gift sample from BafnaPharmaceuticalsLtd. Chennai. Lactose Monohydrate, Low – Substituted Hydroxy Propyl Cellulose (LHPC -11), Hydroxypropyl Cellulose (Klucel LF), Brilliant Blue(ColouringAgent), Magnesium Stearate, Lactose 30 GR, Hypromellose E-15, Hypromellose E-5, Macrogol 6000 was received as gift sample from Bafna pharmaceuticals Ltd. Chennai.

All other chemical and reagent used in this study were of analytical grade.

Method of preparation[4]

Steps involved in formulation of Olmesartanmedoxomil granules

Binder solution:

Take 12.5g of Purified water (temp 65ºC) in 100L stainless steel vessel. Then dissolve 0.80g of HPC (Klucel LF) by stirring with stainless steel paddle. Then take 0.050g of Brilliant blue and dissolved in water separately in small vessel and add to above binder solution slowly.

Dry mixing:

Check weight of OlmesartamMedoxomil and sift through 30# mesh and sift Lactose monohydrate and Low – substituted hydroxy propyl cellulose (LHPC -11) through 40# mesh load in to rapid mixer granulation. Dry mix for 10min at low speed.

Granulation:

Add 70 % of binder to dry mix present in RMG under slow speed for 2 minutes. Rake the mass in RMG, if necessary. Add remaining quantity of binder, continue mixing for 4 - 5 minutes with impeller at SLOW speed and chopper (if required) until desired wet mass obtained. If required add additional quantity of purified water and mix for two more minutes. Discharge the wet mass into Fluid Bed Drier Bowl by opening the discharge port and Operating the impeller and chopper at SLOW speed.

Drying :

Dry the wet milled granules in Fluidized bed dryer for 10min.Rake and check for loss on drying carry on drying for 10min and rake again. Limit: Between 1.0 - 2.0 % W/W (Target 1.5 % w/w) LOD parameter :(105 º C)Dry till loss on drying at 0.6 - 1.2% achieved. Check loss on drying at 105ºC in halogen moisture balance.

Sifting and Dry mixing:

Sift the dried granules through 20 # SS sieve using vibratory sifter. Collect the retention in a poly bag. Pass the retention granules through multimill fitted with 1.5 mm screen Knives forward at slow speed. Collect the milled granules in the IPC bin and transfer to Blender. Pass the milled granules through 20 # SS sieve using vibratory sifter. Collect all the granules passing through 20 # SS sieve and load the granules into the octagonal blender.

Blending and Lubrication:

Load the granules in octagonal blender and blend for 5min at 6rpm. And Prelubrication was done with sifted Low substituted Hydroxy propyl cellulose(L-HPC 11) through #40 mesh to octagonal blender. Add sifted magnesium stearate

through #60 mesh to octagonal blender and blend for 5min at 6rpm.

Steps involved in formulation of Hydrochlorothiazide granules

Dry mixing:

Check weight of Hydrochlorothiazide and sift through 30# mesh and sift Lactose 30GR and Low – substituted hydroxy propyl cellulose (LHPC -11) through 40# mesh load in to rapid mixer granulation. Dry mix for 10min at low speed.

Lubrication:

After dry mixing , Add sifted magnesium stearate through #60 mesh to octagonal blender and blend for 5min at 6rpm.

Formulation Development of OlmesartanMedoxomil& Hydrochlorothiazide Bilayer Tablets.(Table-1)

S. No	Ingredients (mg Per Tablet)	F1	F2	F3	F4	F5
1	**OlmesartanMedoxomil**	20	20	20	20	20
2	Lactose Monohydrate	61.9	68.2	65.9	65.5	66.3
3	Low Substituted Hydroxy Propyl Cellulose(L-HPC 11)	6	-	2.5	3	3
4	HydroxyPropyl Cellulose (KLUCEL LF)	2.6	1.6	3.1	1.7	2.5
5	Brilliant Blue	0.5	0.8	0.4	0.1	0.4
6	Purified Water USP #	30	28	27	25	27
7	Low substituted hydroxy propyl cellulose(L-HPC 11)	4.5	5.3	3.8	5.5	3.5
8	Magnesium stearate	1	0.6	0.8	0.7	0.8
	Total Weight	**96.5**	**96.5**	**96.5**	**96.5**	**96.5**
9	**Hydrochlorothiazide**	12.5	12.5	12.5	12.5	12.5
10	Lactose 30 GR	74.3	72.9	75.3	72	75
11	Low substituted hydroxy propyl cellulose(L-HPC 11)	8.5	9.6	7.5	11	7.6
12	Magnesium stearate	0.7	1	0.7	0.5	0.9
	Total Weight	**96**	**96**	**96**	**96**	**96**
	Core Tablet Weight	**192.5**	**192.5**	**192.5**	**192.5**	**192.5**

COATING						
13	Hypromellose E-15	1.95	1.95	2.2	2.2	2.850
14	Hypromellose E-5	2.9	2.9	2.3	2.3	1.900
15	Macrogol 6000	0.65	0.65	1	1	0.750
16	Purified water #	89	89	89	89	89
17	Isopropyl alcohol BP #	1	1	1	1	1
	Coated Tablet weight	**198**	**198**	**198**	**198**	**198**

(Table No: 2)

S.No	**Ingredients(mg per tablet)**	**F6**	**F7**	**F8**	**F9**
1	**Olmesartanmedoxomil**	20	20	**20**	20
2	Lactose Monohydrate	67.9	69.3	**66.7**	70.4
3	Low substituted hydroxyl propyl cellulose(L-HPC 11)	3	4.8	**4**	-
4	Hydroxyl propyl cellulose (KLUCEL LF)	1.6	1.5	**1.6**	1
5	Brilliant blue	0.2	0.1	**0.1**	0.1
6	Purified Water USP #	27	23	**25**	22
7	Low Substituted Hydroxyl Propyl Cellulose(L-HPC 11)	3.2		**3.5**	4.1
8	Magnesium Stearate	0.6	0.8	**0.6**	0.9
	Total Weight	**96.5**	**96.5**	**96.5**	**96.5**
9	**Hydrochlorothiazide**	12.5	12.5	**12.5**	12.5
10	Lactose 30 GR	80	79.2	**80.5**	78.6
11	Low Substituted Hydroxyl Propyl Cellulose(L-HPC 11)	3	3.5	**2.6**	4.6
12	Magnesium Stearate	0.5	0.8	**0.4**	0.3
	Total Weight	**96**	**96**	**96**	**96**

	Core Tablet Weight	**192.5**	**192.5**	**192.5**	**192.5**
COATING					
13	Hypromellose E-15	2.850	2.850	**2.850**	2.850
14	Hypromellose E-5	1.900	1.900	**1.900**	1.900
15	Macrogol 6000	0.750	0.750	**0.750**	0.750
16	Purified Water #	89	89	**89**	89
17	Isopropyl Alcohol BP #	1	1	**1**	1
	Coated Tablet Weight	**198**	**198**	**198**	**198**

Evaluation of Bilayer tablets

1. General Appearance:

The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odor, taste, surface textures, physical flaws and consistency.

2. Size and shape:

The type of tooling determines the shape and dimensions of compressed tablets during the compression process.

3. Thickness:

The thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within a ± 5% variation of a standard value. Any variation in thickness within a particular lot of tablets or between manufacturer's lots should not be apparent to the unaided eye for consumer acceptance of the product

4. Weight variation:

This test is also known as uniformity of weight. This does not apply to layer or enteric coated tablets. Weights of individual 20 tablets was noted and their mean weight was calculated, and the percentage deviation was calculated by using the formula

$$\text{Percentagedeviation} = \frac{X - X'}{X} \times 100$$

Where,

X = actual weight of the tablet

X^1 = average weight of the tablet

5. Content uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.. For content uniformity test, representative samples of 30tablets are selected and 10 are assayed individually. At least 9 must assay within ±15% of the declared potency and none may exceed ± 25%.

6. Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet

friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up.

$$\text{Friability index} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}}$$

7. Hardness:

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet.

8. Dissolution:

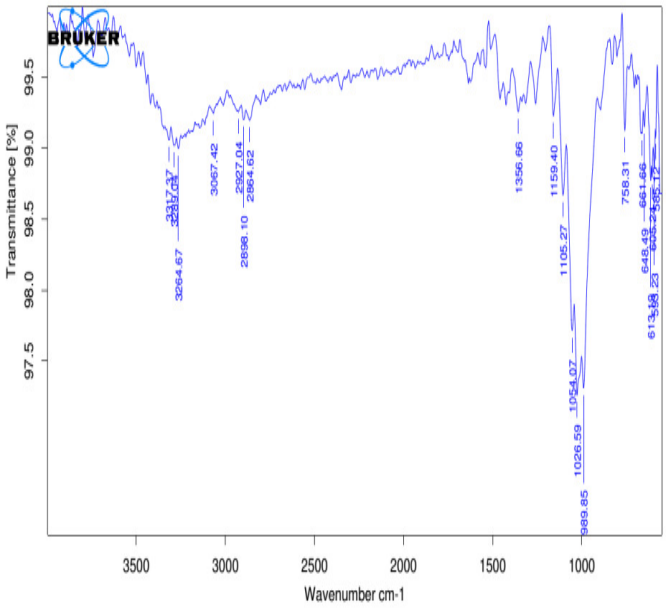
Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

IR studies:

The IR spectra of pure drug OlmesartanMedoxomil& Hydrochlorothiazide and physical mixture with other excipients were compared and are found to be compatable with each other as indicated by no significant change in the drug peaks.

RESULTS AND DISCUSSION

Figure No: 3



IR Spectra of Olmesartanmedoxomil + Excipients.

Inference: The IR spectra of pure drug Olmesartanmedoxomil and physical mixture with other excipients were compared and are found to be compatable with each other as indicated by no significant change in the drug peaks.

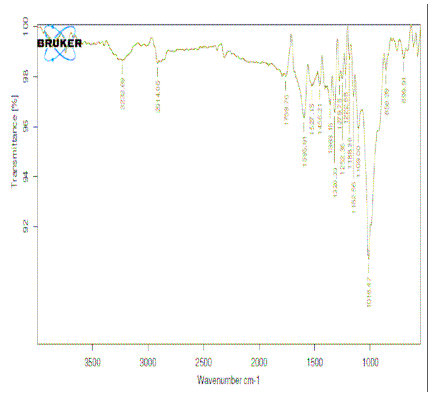


Figure No: 4 IR Spectra of Hydrochlorothiazide + Excipients.

Inference: The IR spectra of pure drug Hydrochlorothiazide and physical mixture with other excipients were compared and are found to be compatable with each other as indicated by no significant change in the drug peaks between pure drug sample and drug excipient physical mixture.

PRE COMPRESSION PARAMETER:

Table No: 3Precompression Parameter of OlmesartanMedoxomilGranules Trials:

Formulations	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	C.I (%)	Angle of repose (^{0})	H.R	Moisture Content
F1	0.44	0.55	27.0	50°.12’	1.44	0.681
F2	0.41	0.51	28.33	47°.32’	1.42	0.630
F3	0.43	0.52	27.3	48°.26’	1.382	0.612
F4	0.41	0.51	29.61	46°.56’	1.255	0.586
F5	0.42	0.54	32.22	42°.21’	1.383	0.323
F6	0.49	0.50	20.0	38°.65’	1.222	0.311
F7	0.48	0.55	18.15	36°.23’	1.25	0.262
F8	0.48	0.51	15.69	28°.13’	1.146	0.216
F9	0.47	0.55	20.0	30°.23’	1.25	0.218

Inference: Formulations F1 to F5 has high angle of repose and Hausners ratio indicating poor flow of granules and the flow property increased in case of F6 and F7 because of inclusion of a dry binder and F8 and F9 has shown good flow as indicated by angle of repose and Hausners ratio because of increase in concentration of lubricant.

Table No: 4Precompression Parameter of Hydrochlorothiazide Granules Trials:

Formulations	Bulk Density (gm/cm^2)	Tapped Density (gm/cm^2)	C.I (%)	Angle of Repose (^{0})	H.R	Moisture Content
F1	0.45	0.56	28.64	46°.66’	1.39	0.621

F2	0.44	0.57	31.8	48º.2’	1.38	0.627
F3	0.41	0.59	30.5	50º.56’	1.40	0.612
F4	0.44	0.57	32.8	46º.99’	1.383	0.531
F5	0.44	0.56	24.42	47º.3’	1.382	0.523
F6	0.43	0.54	20.37	42º.21’	1.255	0.322
F7	0.47	0.59	18.64	34º.56’	1.208	0.292
F8	0.48	0.58	17.24	30º.12’	1.124	0.242
F9	0.45	0.55	18.18	31º.63’	1.125	0.245

Inference: Formulation F1 to F7 has high angle of repose and Hausners ratio and the values reduced by addition of increasing concentration of lubricant that enhanced flow property.

POST COMPRESSION PARAMETER OF OLMESARTAN MEDOXOMIL AND HYDROCHLOROTHIAZIDE TABLETS:

Table No: 5 Post Compression Parameter of Olme sartanmedoxomil and Hydrochlorothiazide Tablets.

Formulations	**Weight Variation (mg)**	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Disintegration time (min)**	**Friability (%)**
F1	195-200	7.1	3.60	4	0.008
F2	197-202	7.8	3.59	5	0.068
F3	194-199	6.8	3.61	6	1.062
F4	196-200	7.0	3.70	6	1.076
F5	193-196	7.5	3.69	5	0.089
F6	198-201	7.8	3.60	4	1.174
F7	197-202	8.0	3.62	5	0.041

F8	195-199	8.3	3.60	6	0.055
F9	198-202	8.5	3.70	5	0.050

DRUG RELEASE:

INNOVATOR DRUG RELEASE PROFILE:

Table No: 6. Innovator Drug Release Profile:

TIME (MIN)	INNOVATOR (OLMESARTAN MEDOXOMIL)	INNOVATOR (HYDROCHLOROTHIAZIDE)
10	72.4%	70.7%
15	84.2%	82.6%
30	93.2%	91.3%
45	96.8%	94.9%
60	98.2%	96.4%

Comparison of Dissolution Profile of Formulations With Innovator

Table No: 7. Comparison of dissolution profile of formulations with innovator

Time (min)	Innovator (O)	Innovator (H)	% Drug Release							
			O	H	O	H	O	H	O	H
			F6	F6	F7	F7	F8	F8	F9	F9
10	72.4	70.7	85.8	59.3	90.2	60.5	**70.4**	**68.7**	70.1	68.2
15	84.2	82.6	90.1	70.6	93.4	73.6	**83.1**	**80.5**	81.9	80.1
30	93.2	91.3	92.5	83.2	95.5	85.6	**91.7**	**89.4**	91.2	89.1
45	96.8	94.9	95.2	86.4	97.3	89.7	**95.2**	**93.2**	94.8	93.0
60	98.2	96.4	96.7	90.2	96.6	91.5	**97.2**	**95.8**	97.0	95.4

Where,O = Olmesartanmedoxomil,H = Hydrochlorothiazide

Comparative Release Profile of Olmesartan Medoxomil in Various Formulations with Innovator

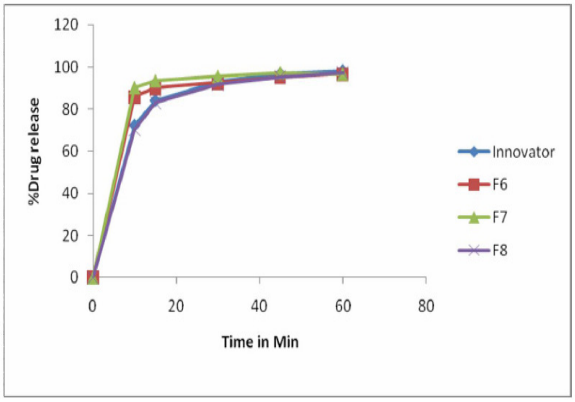


Figure No: 5 Comparative release profile of Olmesartanmedoxomil in various formulation with innovator

Inference: Comparative Release profile of OlmesartanMedoxomilfrom various formulations showing that the release from formulation F8 matching with that of innovator

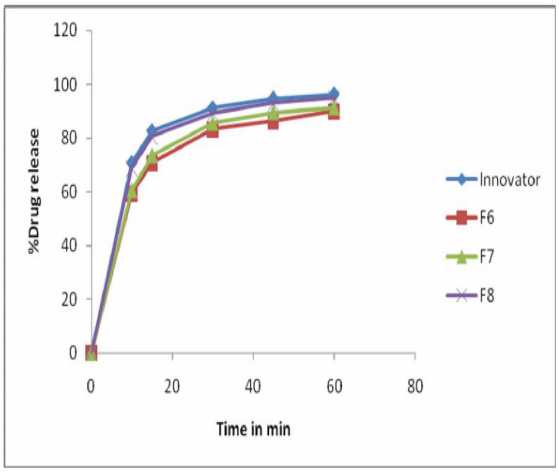


Figure No: 6 Hydrochlorothiazide release from various formulations compared to innovator

Inference: Comparative release profile of Hydrochlorothiazide from various formulations showing that the release from formulation F8 matching with that of innovator.

Comparative Release of Olmesartan Medoxomil From Innovator and F8

Table No: 8. Comparative Release of Olmesartanmedoxomil from innovator and F8

Time(min)	% Release of innovator	% Release from F8
10	72.4	70.4
15	84.2	83.1
30	93.2	91.7
45	96.8	95.2
60	98.2	97.8

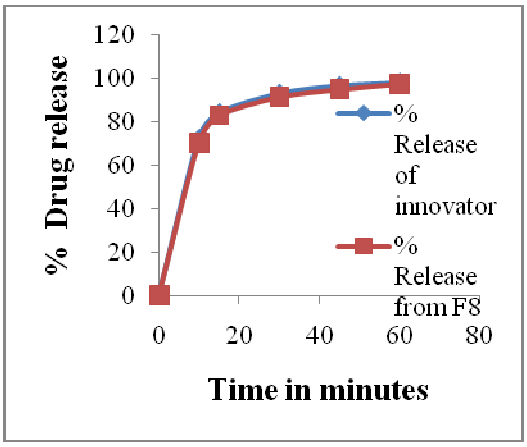


Figure No: 7 Comparative release of Olmesartanmedoxomil from innovator and F8

Inference: The Release profile of Olmesartanmedoxomilfrom F8 was compared to innovator and the release was almost equal and comparable to that of inovator at the end of 45 and 60min.

Table No: 9. Comparative release of Hydrochlorothiazide from innovator and F8

Time(min)	% Release of Innovator	% Release from F8
10	70.7	68.7
15	82.6	80.5
30	91.3	89.4
45	94.9	93.2
60	96.4	95.1

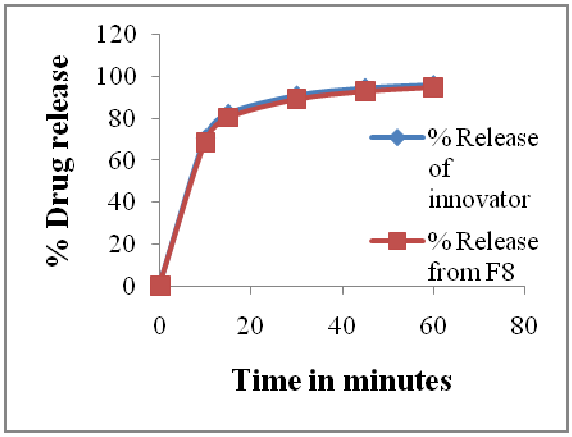


Figure No: 8 Comparative release of Hydrochlorothiazide from innovator and F8

Inference: The Release profile of Hydrochlorothiazide from F8 was compared to innovator and the release was almost equal and comparable to that of inovator at the end of 45 and 60min.

Table No: 10. Drug release of OlmesartanMedoxomiland Hydrochlorothiazide at 25°C & 60%RH

Drug	% Drug release		
	Initial	30 Days	45 Days
OlmesartanMedoxomil	97.2	97.01	97.0
Hydrochlorothiazide	97.2	96.8	96.8

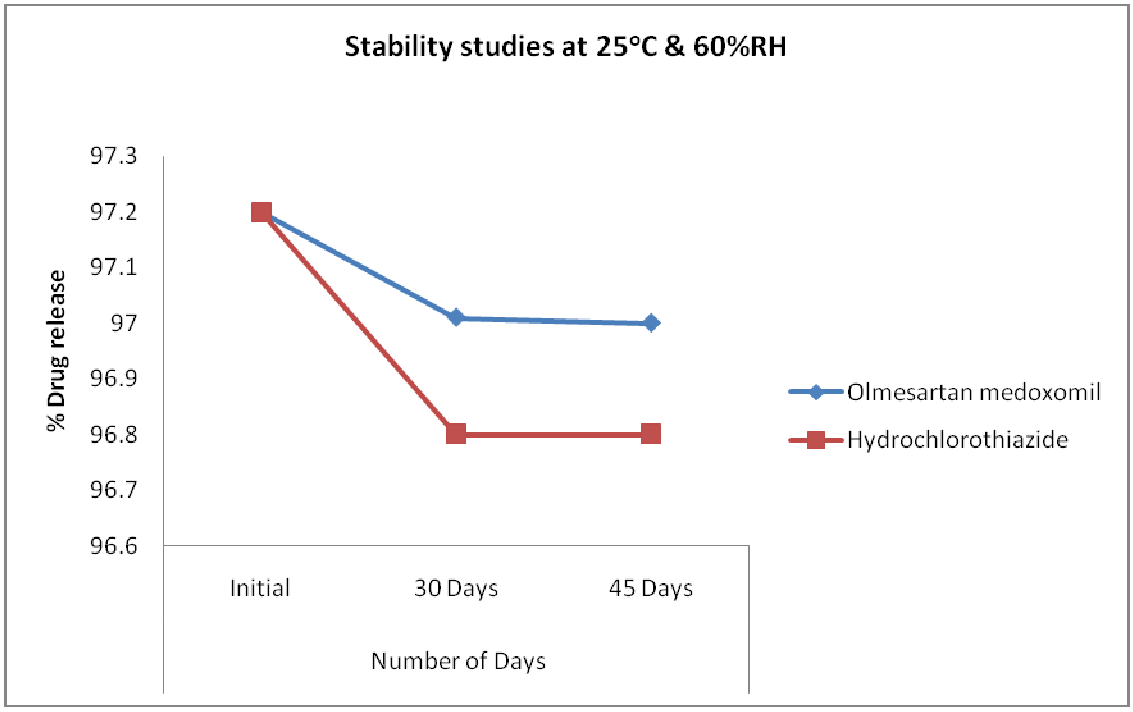


Figure No: 9 Drug Release of Olmesartan Medoxomiland Hydrochloro thiazide at 25°C & 60%RH

Inference: The drug release was not significantly reduced at the end of 30days and 45days storage at 25°C & 60%RH indicating stability of the formulation. All the parameters are with in the limits specified at the end of storage period.

Table No: 11. Drug release of Olmesartanmedoxomil and Hydrochlorothiazide at 40°C & 75%RH

Drug	% Drug Release		
	Initial	30 Days	45 Days
OlmesartanMedoxomil	97.2	97.0	97.0
Hydrochlorothiazide	97.2	96.6	96.6

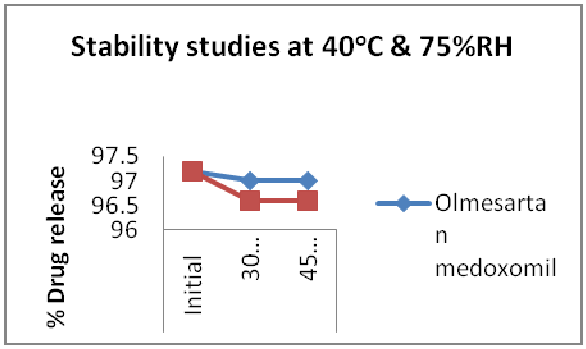


Figure No: 10 Drug release of OlmesartanMedoxomiland Hydrochlorothiazide at 40°C & 75%RH

Inference: The Drug Release was not significantly reduced at the end of 30days and 45days storage at 40°C & 75%RH indicating stability of the formulation. All the parameters are with in the limits specified at the end of storage period.

SUMMARY AND CONCLUSION

The present study was aimed for developing a bilayer tablet of Olmesartanmedoxomil and Hydrochlorothiazide. Nine formulations are prepared with of Olmesartanmedoxomil and Hydrochlorothiazide granules prepared separately in a rapid mixergranules. Pre compression parameters like Bulk density, True density, Angle of repose indicate all the formulations are showing good flow properties.

Tablets are compressed using SEJONG bilayer compression machine and tablets are evaluated for post compression parameters Weight variation, Hardness, Friability, Disintegration and Dissolution parameters.

Formulations F1-F4 does not meet the direct criteria for Hardness and Disintegration time due to improper mixing of binder with the dry mixture.

Formulations F5-F9 has shown post compression parameters within the specified limits of the innovator. The release profile of formulations F5-F9 was compared with innovator and all the formulations has shown a release of 70-95% and formulation F8 has matched the innovator release profile.

The compressed bilayer tablets was packed in blisters and subjected to stability studies at 40°C & 75%RH , 25°Cand 60% RH. Samples were analyzed at regular intervals as mentioned in stability protocol.

From the study, it may be concluded that bilayer tablet of Olmesartanmedoxomil and Hydrochlorothiazide can be prepared as

immediate release formulation compared to conventional formulations.

ACKNOWLEDGEMENTS

Olmesartanmedoxomil and Hydrochlorothiazide was received as gift sample from BafnaPharmaceuticals Ltd. Chennai, India, We also thank Chairman and Principal, Krishna Teja Pharmacy College for providing infrastructure facilities for the work.

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