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Research Paper

FORMULATION AND EVALUATION OF FILM COATED TABLET CONTAINING AMLODIPINE

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The main objective of this combination therapy is to develop a stable formulation of antihypertensive drugs of telmisartan and amlodipine besylate as an immediate release bilayer tablet and evaluate their pre-compression and post-compression parameters. The FT-IR studies were also conducted and were found to have no interaction between drug and the excipients. The formulation of the developed work was initiated with wet granulation method for both the drugs. Microcrystalline cellulose pH102 and dibasic calcium phosphate were used as diluents. Starch paste was used as the binder. The croscarmellose sodium (CCS) was used as the super disintegrant. Magnesium stearate used as lubricant. The prepared granules were compressed by a double-rotary compression machine. *In vitro* dissolution was carried out using USP dissolution apparatus type 2 (paddle) by using HPLC method. The stability studies for optimized batch were carried out at 30 and 60 days and were found to be stable. The results suggest the feasibility of developing bilayer tablets with drugs amlodipine besylate for the convenience of patients with severe hypertension, especially when monotherapy fails to control the blood pressure.

Key Words: amlodipine besylate,, hypertension, immediate release, *in vitro.*

INTRODUCTION

Hypertension is one of the major public health problems worldwide. Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. If this disease is not controlled on time, it may lead to heart attack, brain stroke or kidney damage. Hence there is a need to develop a proper medication or combination of two or more medications that would control hypertension for longer period of time. In case of initial level of hypertension, single drug therapy is sufficient for the control. But in case of severe hypertension, combination therapy is recommended. Normal blood pressure at rest is within the range of 100-140 mmHg systolic and 60-90 mmHg diastolic. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg. There are many factors causing hypertension, some of them occur due to heredity, gender (more affected in males than females), obesity, age (especially in elder persons which may due to hardening of

arteries or atherosclerosis), sodium salt sensitivity, alcohol use and physical inactivity [1].

Immediate - release dosage forms allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. These dosage forms usually release (dissolve/disperse) the drug in a single action, which means the drug is released initially very quickly and then passes through the mucosal membrane into the body, reaching the highest plasma level in a comparatively short time [2]. Their advantages are releases the drug immediately, more flexibility in adjusting the dose, no dose dumping problem and can be used in initial and final stages of disease [3].

Amlodipine besylate is a long - acting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina and hypertension. It is a prototype second generation dihydropyridine calcium channel blocker. It is sparingly soluble in water and has longer duration of action. It inhibits calcium ion influx across the cell membranes selectively with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine besylate. It has a half-life of 30- 50 hours. It is used in combination with other antihypertensives.

MATERIALS AND METHODS:

Amlodipin Besylate, sodium hydroxide pellets, meglumine, microcrystalline cellulose pH102, polyplasdone XL, dibasic calcium phosphate, maize starch, colour lake of ponceau 4R, croscarmellose sodium, colloidal silicon dioxide, purified talc and magnesium stearate were provided by Cadila Pharmaceuticals Ltd.

Amlodipine Besylate:

Weighted quantity of amlodipine besylate, dicalcium phosphate, maize starch and colour Lake Ponceau 4R were sifted through # 40 sieve and mix well. Starch paste was prepared by adding weighted quantity of maize starch in optimum quantity of hot water and stirred continuously till translucent paste forms. Cool it to below 40ºC. Add prepared paste into above mixed blend and granules were prepared. Prepared granules were dried at 60ºC ± 10ºC. Pass these granules through #20 sieve. Add Croscarmellose Sodium, Colloidal Silicon Dioxide, Purified Talc and Maize Starch to the above dried granules and mix for 7 minutes. Finally add weighted quantity of magnesium stearate to the above granules and mix for 3 minutes in cage blender.

EVALUATION TESTS

PRE-COMPRESSION PARAMETERS [8, 9]:

Bulk Density (BD): Weigh accurately 25 g of granules, which was previously passed

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through #20 sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0).Calculate the apparent bulk density in gm/ml by the following formula

Bulk density = Weight of powder / Bulk volume

MANUFACTURING PROCESS OF GRANULES

Table-1: Composition of amlodipine besylate layer

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Qty(mg/tablet) Blend 2									
	Drug Solution									
1	Amlodipine Besylate	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
2	Dibasic Calcium Phosphate	76.10	75.10	74.10	74.10	72.10	70.10	73.10	71.10	69.10
3	Maize Starch	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
4	Colour Lake of ponceau	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40
	Binder									
5	Maize Starch	2.00	4.00	6.00	2.00	4.00	6.00	2.00	4.00	6.00
6	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Lubrication									
7	Croscarmellose Sodium	1.00	1.00	1.00	2.00	2.00	2.00	3.00	3.00	3.00
8	Purified talc	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
9	Maize starch	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
10	Colloidal Silicon Dioxide	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
11	Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Tapped density (TD):

Weigh accurately 25 g of granules, which was previously passed through #20 sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2). Calculate the tapped density in gm/ml by the following formula.

Tapped density = Weight of powder / Tapped volume

Carr's Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the

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rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index= [(TD-BD)*100]/ TD

Hausner's Ratio: The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = TD/BD

POST-COMPRESSION PARAMETERS [10]:

Friability: Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing,

Table-2 Evaluation of immediate release granules of Amlodipine

S. No.	Formulation Code	Bulk Density (gm/ml)	Tapped ensity(gm/ml)	Carr's Index %	Hausner ratio
1	F1	0.3010	0.4100	26.59	1.360
2	F2	0.3125	0.4166	24.99	1.341
3	F3	0.2779	0.3142	11.56	1.130
4	F4	0.2127	0.2784	23.54	1.308
5	F5	0.1786	0.2217	19.44	1.241
6	F6	0.2274	0.2560	11.17	1.126
7	F7	0.3621	0.3940	8.09	1.089
8	F8	0.3660	0.4050	9.6	1.107
9	F9	0.3710	0.4020	7.73	1.083

Table-3: Evaluation of immediate release granules of Amlodipine

Sr no	Formulation Code	Bulk Density (gm/ml)	Tapped Density(gm/ml)	Carr's Index %	Hausner ratio
1	F1	0.3115	0.3922	20.57	1.250
2	F2	0.3215	0.4200	23.45	1.306
3	F3	0.3572	0.4342	17.73	1.210
4	F4	0.3458	0.4020	13.98	1.160
5	F5	0.3426	0.3944	13.13	1.152
6	F6	0.3544	0.4023	11.90	1.135
7	F7	0.3904	0.4349	10.23	1.113
8	F8	0.3940	0.4420	10.09	1.112
9	F9	0.3940	0.4350	9.400	1.104

transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Acceptable limit was not more than 1.0% of three samples.

$$\%friability = \frac{(initial\ weight - final\ weight)}{Initial\ weight} \times 100$$

Method: accurately weighed 6.5 gm of tablet and transfer into Friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final wt).

Method: accurately weighed 6.5 gm of tablet and transfer into Friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final wt).

***In vitro* disintegration test:** The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

ASSAY BY HPLC METHOD [11]:

Chromatographic condition:

HPLC with PDA detector, column: inertsil ods 3v 150×4.6mm, 5µ, wavelength: 237nm, injection volume: 30µl, flow rate: 1.5ml/min, column temperature: 40ºc ± 0.5ºC, diluent: buffer:acetonitrile:methanol (35: 40 : 10) [buffer preparation: 7ml of triethylamine was diluted in 1000ml of water and adjusted to pH 3.0 with orthophosphoric acid].

Preparation of standard solution:

55mg of amlodipine Besylate WS was accurately weighed and transferred into a 100ml volumetric flask, 30ml of methanol was added to dissolve and volume was made up with the diluent. 32mg of telmisartan WS was accurately weighed and transferred into a 50ml volumetric flask and 30ml of methanol was added and sonicated to dissolve. 5ml of standard stock solution of amlodipine besylate was added and made up the volume with diluent.

Preparation of sample solution:

Two intact tablets equivalent to 160mg of telmisartan was accurately weighed and transferred into a 250ml volumetric flask and 200ml of diluent was added and cooled to room temperature and sonicated for 10 minutes and made up the volume with diluent. Then filtered through whattman filter paper.

Procedure:

30 micro liters of standard and sample solutions was injected into the HPLC system. The chromatograms were recorded and responses were measured for the major peaks.

***In Vitro* Dissolution Studies By HPLCMethod**

Dissolution for Amlodipine :

Six tablets of amlodipine besylate were placed in the apparatus of USP II (paddle). The medium pH 7.5 phosphate buffer 900 ml was used and was maintained at a temperature of

37±0.5ºC and the speed was fixed at 75rpm. The samples were withdrawn at 5, 10, 15, 30 and 45 min. The estimation was carried out using HPLC.

Standard preparation:

Accurately weighed 44mg of Amlodipine was transferred into 100ml volumetric flask. 50ml of methanol was added and made upto volume with methanol. 10ml of above solution was pipetted out into a 50ml volumetric flask and volume made up with pH 7.5 phosphate buffer as dissolution medium.

Sample preparation: The dissolution apparatus was set and tablet was placed into each jar containing 900ml of pH 7.5 phosphate buffer medium, taking care to exclude air bubbles from the surface of the tablet and in medium. The apparatus was started. 10ml of the sample were withdrawn and filtered through whattman filter paper.

HPLC procedure:

30 micro liters of standard and sample solutions were injected into HPLC system. The chromatograms were recorded and responses of major peaks were measured.

Dissolution for Amlodipine Besylate:

Six tablets of telmisartan and amlodipine besylate were placed in the apparatus of USP II(paddle). The medium 0.1N Hcl 500ml was used and was maintained at a temperature of 37±0.5ºC and the speed was fixed at 75rpm. The samples were withdrawn at 5, 10, 15, 30, 45 and 60 min. The estimation was carried out using HPLC.

Standard preparation:

Accurately weighed 69mg of amlodipine Besylate WS was transferred into 100ml volumetric flask and 100ml of dissolution medium (0.01N Hcl) was added to dissolve and made up the volume with dissolution medium. 2ml of above solution was pipetted out into a 100ml volumetric flask and the volume was made up with dissolution medium.

Sample preparation:

The dissolution apparatus was set and tablet was placed into each jar containing 500ml of 0.01N HCl medium,taking care to exclude air bubbles from the surface of the tablet and in medium. The apparatus was started. 10 ml of the sample was withdrawn and filtered through whattman filter paper.

HPLC procedure:

30 micro liters of standard and sample solutions were injected into HPLC system solution. The chromatograms were recorded and responses of major peaks were measured.

Stability Studies [12]:

The tablets were blister packed and stored at 40ºC±2ºC/75%±5% RH for 30 and 60 days in a stability chamber. After 30 and 60 days

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Table-4: Evaluation of Post compression of telmisartan and amlodipine besylate immediate release tablets

Sr no	Tests	Specification	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Description	Round, biconvex,	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes Passes	
		bilayered plain	the test	the test	the test	the	the	the	the	the	the test
		tablets, Amlodipine				test	test	test	test	test	
		besilate layer is									
2	Thickness		4.85	4.61	4.03	4.8	3.89	4.18	4.12	3.92	4.26
3	(mm) Hardness	NLT 5.0 (Kg/cm^2)	6.9	7.6	6.7	7.9	7.5	7.2	7.8	8	8.2
	(Kg/cm^2)										
4	Friability (%	NMT 1 % w/w	1.01	0.81	1.12	0.04	0.93	0.98	0.02	0.87	0.03
	w/w)										
5	Unformity of	Avg wt ± 10 %(Avg	324	332	326	321	330	329	322	325	310
	weight (mg)	wt = 320 mg)									
6	Disintigratio	NMT 15 min	17 Min	16 Min	14 Min	14 Min	6 Min	9 Min	7 Min	15 Min	8 min
	n time		2 Sec	3 Sec	55 Sec	39 Sec	58 Sec	30 Sec	48 Sec	8 Sec	43 Sec

Table-5: *In vitro* dissolution profile of amlodipine besylate

Formulation	Amlodipin later at 45 min (Limit: NLT 70%)
F1	61.26
F2	66.83
F3	71.27
F4	76.17
F5	82.65
F6	83.18
F7	96.38
F8	84.18
F9	81.21

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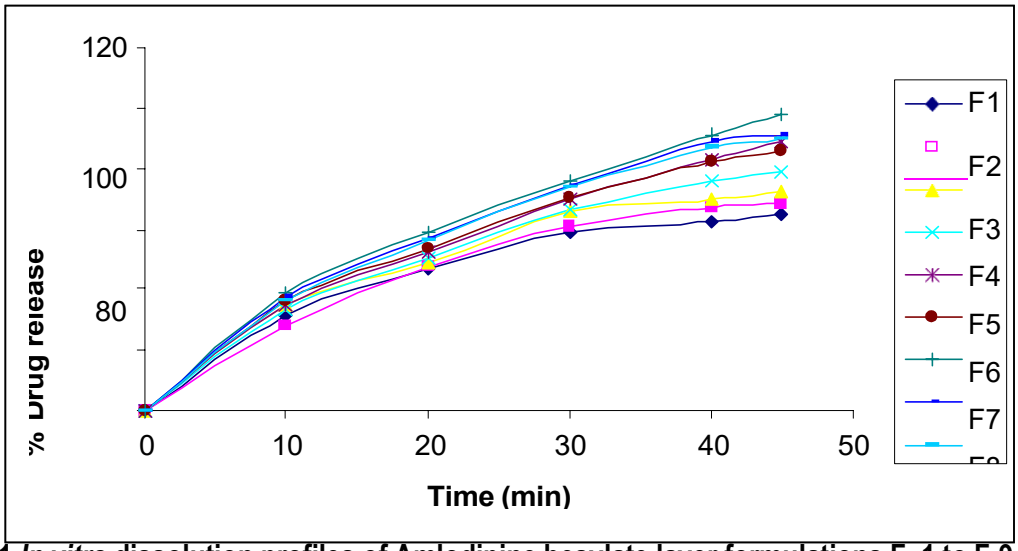

Fig-1 *In vitro* dissolution profiles of Amlodipine besylate layer formulations F- 1 to F-9

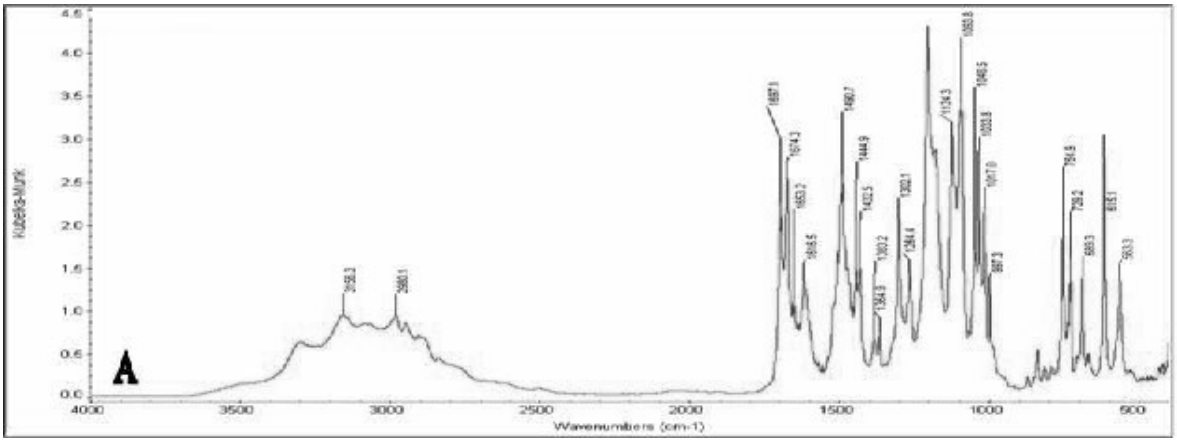

Fig- 2 FT-IR of pure drug Amlodipine Besylate

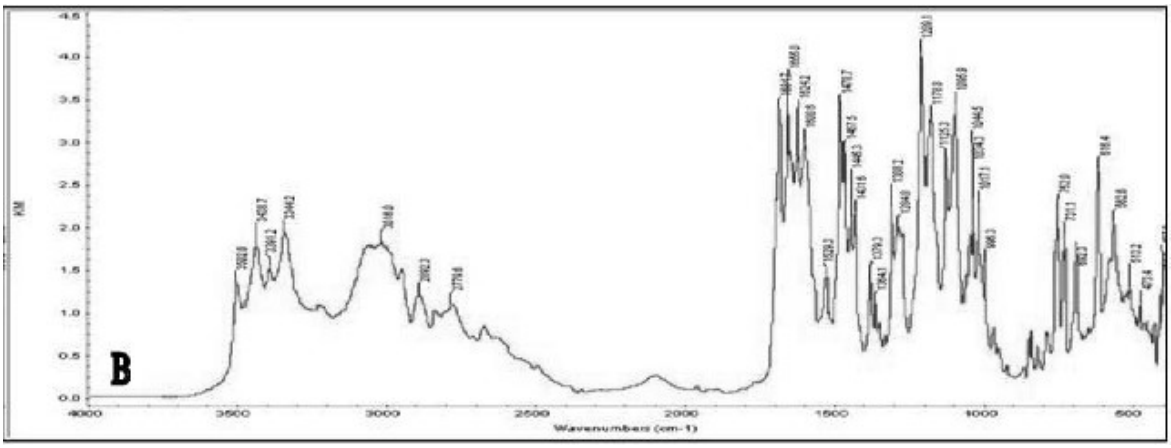

Fig- 3FT-IR of pure drug Amlodipine Besylate with the excipietsn

the tablets were withdrawn and evaluated for its appearance, thickness, hardness, friability, disintegration time, assay and *in vitro* drug release.

RESULTS AND DISCUSSION:

The IR spectrum showed no considerable change in the peaks in bands of telmisartan and amlodipine besilate and hence no interaction between the drug and the excipients found. The immediate release layers of] amlodipine besylate were designed with the dose of 40mg and 5 mg respectively . amlodipin Besylate layers prepared by varying concentration of maize starch (binder) and croscarmellose sodium (superdisintigrant). The pre-compression and post- compression results showed that the values obtained for all formulations except F-1, F-2 and F-8, were within the limits and the drug content was also found to be in the range of 90-110%. Dissolution samples were analyzed by HPLC method. The percentage *In vitro* drug release for F3 to F9 were observed to be within the limits. The drug release of F-7 after 45 min for amlodipine besilate layer was 98.13% and 96.38%. Among the nine trials F-7 was found to be satisfactory. The results are given in Table no: 6 with the corresponding graphs in Fig no: 1 and 2. The stability studies for the optimized batch F-7 after 30 and 60 days were evaluated for its drug release 95.84 % and 95.06 % for amlodipine besylate, which indicated good stability.

CONCLUSION:

This research was carried out to produce a bilayer immediate release tablet of amlodipin Besylate using varying concentration of binders and superdisintegrants. The F-7 formulation showed acceptable results for their pre-compression and post- compression parameters. Drug release was found to increase with increase in super disintegrant croscarmellos sodium concentration, where the disintegrant was used in the concentration of 2%-16% of the average tablet weight. The immediate release bilayer tablets of amlodipine besylate (5mg) was successfullyprepared using the disintegrant croscarmellos sodium. This combination therapy is indicated for the treatment of severe hypertension and coronary heart disease.

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Conflict of Interest

The authors declare that they have no conflict of interest