FORMULATION AND EVALUATION OF BILAYER TABLETS OF TWO INCOMPATIBLE DRUGS AMLODIPINE BESILATE AND LOSARTAN POTASSIUM

Rama*, Mitesh. R. Bhoot

Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai, India

*Corresponding Author Email: ammujsu@yahoo.co.in

Article Received on: 19/08/13 Revised on: 07/09/13 Approved for publication: 10/09/13

DOI: 10.7897/2230-8407.04929

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

© All rights reserved.

ABSTRACT

The main goal of this study was to develop a stable formulation for two incompatible anti hypertensive drugs Amlodipine besilate and Losartan potassium as an immediate release bi layer tablet and to evaluate its dissolution studies. The formulation development work was initiated with wet granulation for losartan potassium layer and direct compression for amlodipine besilate layer. Super disintegrants like Croscopovidone, Sodium starch glycolate (SSG) were used in all the formulations and its role on disintegration and dissolution properties of the drug were studied. The prepared tablets were evaluated for weight variation, wetting time, hardness, thickness, friability, % drug content, disintegration time, *in vitro* drug release. Formulation F8 showed a highest drug release of 84.02 % for amlodipine besilate and 90.08 % for losartan potassium in 30 minutes which was selected as optimized formulation and considered for further studies. The stability studies, shown that the formulation F8 was stable enough at 40°C / 75 % RH for a period of 6 months. The results suggest the feasibility of developing bi layer tablets consisting of amlodipine besilate and losartan potassium for the convenience of patients with hypertension.

Keywords: Bi layer tablets, Amlodipine besilate, Losartan potassium, croscopovidone, Sodium starch glycolate, *in vitro* drug release.

INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Bi layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose or both the layers can be immediate release. Hypertension is among the most common diseases of adults in industrialized countries and is one of the important modifiable risk factors for cardiovascular and renal disease. The goal of losartan potassium and amlodipine besilate (anti hypertensive drug) is to prevent complications of hypertension. Specially used for the treatment of patients with stage 1 and 2; essential hypertension in comparison with monotherapy regimens of a calcium channel antagonist or an angiotensin II receptor blocker. The two drugs in a functional combination preparation herein have different activities. Composition of amlodipine (dihydropyridine-based calcium channel blocker) and losartan (angiotensin-2 receptor blocker) can achieve improved preventive or therapeutic effects for cardiovascular disorders, such as angina pectoris, hypertension, artery vasospasm, deep vein, cardiac hypertrophy, cerebral infarct, congestive heart failure and myocardial infarction, as compared with conventional single formulations, while minimizing adverse effects of the two drugs and also lower the risk of circulatory complications. The combination drug therapy for the better management of hypertension is recommended. The main objective for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure, to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined, synergistic or additive effects on blood

pressure are achieved. Amlodipine besilate is a long-acting calcium channel blocker (dihydropyridine class) used as an anti-hypertensive and in the treatment of angina. Like other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle. Losartan is an Angiotensin II receptor antagonist drug used mainly to treat high blood pressure. It may also delay progression of diabetic nephropathy, and is also indicated for the reduction of renal disease progression in patients with Type 2 diabetes, hypertension and micro albuminuria¹⁻³.

MATERIALS AND METHODS

Amlodipine besilate, Losartan potassium, Micro crystalline cellulose, sodium starch glycolate, croscopovidone were received from Madras Pharmaceuticals, Chennai, India. Other materials used were purchased from local vendor and were of analytical grade.

Experimental work

Pre formulation Studies

Physicochemical Interaction of drug and polymer

Physicochemical Interaction of drug and excipients for amlodipine was done as per IP by the identification test carried out by the Fourier Transform Infra red spectrophotometer (FTIR) and the report was shown in Figure 1.

Manufacturing process of Losartan potassium immediate release granules

Sift the weighed quantities of Losartan Potassium, Microcrystalline cellulose plain, starch plain and Polyplasdone XL10 through Mesh 30#. Transfer the sifted materials and Binder solution to Granulation area. Load the sifted material into the main bowl of rapid mixer and mix it for 15 minutes. Transfer the sifted materials into FBD main bowl. Dry the granules at 50 degrees Celsius. Sift the Semi-Dried granules through Mesh 20# and pass the retained

granules through Multi-Mill fitted with 1.0 mm screen using knives forward medium speed. Transfer the semidried sifted and milled granules into FBD bowl. Dry the semidried sifted granules at 50 degrees Celsius till the required LOD is achieved. Check the LOD of the granules (Limit: Between 2.0 - 4.0 % w/w at 105°C). Sift the following materials Pre gelatinised Starch, and Polyplasdone XL10 through Mesh 30#. Load the sifted dried granules along with the above sifted materials into blender and blend it for 10 minutes. Finally sift Magnesium Stearate through Mesh 60# and mix for 5 minutes.

Manufacturing process of Amlodipine besilate layer blend

Sift the weighed quantities of Amlodipine Besilate, Dicalcium Phosphate Anhydrous, Micro crystalline cellulose pH 102, starch 1500, sodium starch glycolate, colloidal silicon dioxide and pass through Mesh 30#. Ponceau 4R Lake was passed through Mesh 100# and added to the above blend. Load the sifted materials such as Amlodipine Besilate, Dicalcium Phosphate Anhydrous, Micro crystalline cellulose pH 102, Starch 1500, Sodium Starch glycolate, colloidal silicon dioxide and Ponceau 4R Lake in Hexagonal blender and mix for 15 minutes. Sift Magnesium Stearate through Mesh 60# and add to the above mixture in the blender and mix for another 5 minutes.

Evaluation of Flow Property of Granules

The prepared granules were evaluated for flow property like bulk density, tapped density, carr index, Hausner ratio, angle of repose and results were tabulated in Table 2.

Compression of Bi layer Tablets

The quantity of granules for the immediate-release layer was compressed lightly using 27 stationary double rotary compression machine (Cad mach, India) using 13/32 inch circular standard plain punches. Over this compressed layer, required quantity of the other immediate release layer was placed and compressed to obtain hardness in the range of 8 - 12 kg/cm² to form a bi layer tablet of immediate release of Losartan potassium and Immediate release of Amlodipine besilate. Then the compressed bi layer tablets were evaluated.

Coating of Bi layer Tablets

Film coating solution preparation

Isopropyl alcohol was transferred into a clean stainless steel vessel. Instacoat (IC-S-10) was added to the part of isopropyl alcohol. To another part of isopropyl alcohol, quinoline yellow lake was added and was passed through the colloidal mill and mixed with the above solution. Finally methylene chloride was added to the above solution with continuous stirring. Care was taken that there were no lumps formation in the solution visually. The above solution was filtered through mesh 100# nylon cloth. The above solution was transferred into a SS vessel of pressure vessel fitted with stirrer.

Evaluation of Tablets

All the tablets were evaluated for different parameters like hardness, thickness, friability, drug content, disintegration time, *in-vitro* drug Release⁴.

Thickness

Thickness depends on die filling, physical properties of material to be compressed. There is possibility of small variation in the thickness of individual tablet in a batch. But it

should not be apparent to the unaided eye. The thickness and diameter was measured by vernier calipers. The results were shown in Table 3.

Hardness

Tablet must possess sufficient strength or hardness and can be measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and were evaluated for hardness and can be expressed in Kg/cm². The results were shown in Table 3.

Friability

Friability can be performed in Roche friabilator, Pre weighed ten tablets were introduced in the friabilator. Then the machine was operated for 100 revolutions. Tablets were dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed. Loss of less than 1 % in weight is considered to be within the specifications and acceptable. The results were shown in Table 3.

$$F(\%) = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

Weight variation test

Twenty tablets were selected randomly and weighed individually. The average weight was calculated and compared with the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage of 5 % and none deviate by more than twice the percentage. The results were shown in Table 5.

Disintegration Time

The *in-vitro* disintegration time was determined by using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. The results were shown in Table 3.

Drug content: Assay: (BY HPLC)

For Amlodipine Besilate and Losartan Potassium

Procedure

Chromatographic System

Apparatus: HPLC, PDA detector, Column: Inertsil ODS C8 25 × 4.9 mm, Column temperature: Ambient, Flow rate: 1.0 ml / minute, Injection volume: 20 µl, Detector Wave length: 237 nm, Run time : 25 minutes, Diluent: Buffer: Methanol: ACN (55:18:12), Instrument set up: isocratic.

Standard Preparation

Weigh accurately 40 mg of Amlodipine from amlodipine besilate working standard and transfer into a 100 ml volumetric flask, dissolve and dilute to volume with mobile phase (Solution A). 40 mg of losartan potassium was weighed transferred into standard volumetric flask and 10 ml of solution A was added and the volume was made up with the mobile phase.

Sample Preparation

10 tablets were randomly selected from collected samples of analysis, Powdered and transferred into 250 ml standard flask. 170 ml of mobile phase was added in the flask,

dissolved and sonicated for 30 minutes and diluted to the volume with the mobile phase. 5 ml of the above solution was transferred to 25 ml standard flask and volume was made to 25 ml.

Procedure: Inject 20 μ L portion of diluents as blank, 6 replicate injections of standard preparation and one injection of each test preparation into the HPLC system, record the chromatograms and measure the peaks response.

In vitro Dissolution studies

Procedure of Dissolution of bi layer tablets

Six tablets of Amlodipine Besilate and Losartan Potassium (Bi layer tablets) were introduced in the dissolution apparatus USP Type II (paddle). The medium used was 900 ml of 0.01 M sodium acetate buffer, pH 4.5 maintained with glacial acetic acid and the dissolution mediums were maintained at the temperature of $37.5 \pm 0.5^\circ\text{C}$, the RPM was set at 75. The Dissolution was carried out for 30 minutes and sample withdrawn at pre determined intervals. The estimation was carried out by HPLC method. The optimized formulation was compared with the market product. The readings were shown in Table 4.

Estimation of Amlodipine by HPLC

Chromatographic system

Apparatus: HPLC, PDA Detector, Column: Inertsil ODS C8, 250×4.6 mm, Wave length: 237 nm, Injection volume: 50 μ L, Flow rate: 1.0 ml/min, Column Temperature: Ambient, Diluent: Dissolution medium, Mobile phase: Buffer: Methanol: ACN (55:18:22), Retention time: 15 minutes, Instrument set up: Isocratic.

Standard Preparation

Accurately 75.3 mg of Amlodipine besilate was taken in 100 ml of volumetric flask and 25 ml of diluents were added and sonicated to dissolve and the volume was made up with diluents to 100 ml. From this 10 ml was pipette out in to 100 ml volumetric flask and volume was made with a diluents. From the above solution another 10 ml withdrawn and made up to 100 ml and Filtered through 0.45 micron membrane filter.

Sample Preparation

The dissolution parameters were set and one tablet is placed in each basket and care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, 10 ml of the sample was withdrawn and filter through whatmann filter paper, 10 ml of solution was replaced in to dissolution medium, the same procedure was repeated at other time intervals.

Procedure

50 micro litre of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and responses were measured for major peaks.

Estimation of Losartan by HPLC

Chromatographic system

Apparatus: HPLC, PDA Detector, Column: Inertsil ODS C8, 250×4.6 mm, Wave length: 237 nm, Injection volume: 50 μ L, Flow rate: 1.0 ml/min, Column Temperature: Ambient, Diluent: Acetonitrile and Dissolution medium, Mobile phase: Buffer: Methanol: ACN (55:18:22), Retention time: 15 minutes, Instrument set up: Isocratic.

Standard Preparation

Accurately weighed 56.9 mg of Losartan Potassium was taken in 100 ml volumetric flask and 50 ml of diluents and volume was made up by the diluents to 100 ml. From this 10 ml was pipette out in to 100 ml volumetric flask and volume was made up with dissolution medium.

Sample Preparation

The dissolution parameters were set and one tablet was placed in to each basket care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, 10 ml of the sample was withdrawn and filter through whatmann filter paper, 10 ml of solution was replaced in to dissolution medium, the same procedure was repeated at other time intervals.

Procedure

50 micro litres of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and the responses were measured for the major peaks.

Stability Studies

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F8 formulation was sealed in aluminium packaging laminated with polyethylene. Samples were kept at 40°C and 75 % RH for 1, 2, 3, 6 months. At the end of the study period, the formulation was observed for change in physical appearance, colour and drug content and drug release characteristics⁵.

RESULTS AND DISCUSSION

Drug-excipient interactions were studied using Infrared spectroscopy. The results show that there was no interaction between the drug and excipients.

Pre Compression Studies

The angle of repose for the formulated blend was carried out; it concludes the entire formulations blend for amlodipine besilate was found to be in the range 26.30° to 29.80° and for losartan potassium it was found to be in the range of 26.20° to 32.50° . Hence the entire formulations blend was found to be good, passable flow property. Compressibility index was carried out; it was found between 14.32 % to 21.20 % for Amlodipine besilate blend and 18.19 % to 20.89 % for losartan potassium blend indicating the powder blend has the required flow property for compression. Hausner's ratio was calculated for the blend, it found between 1.16 -1.27 for amlodipine besilate and 1.09 - 1.26 for losartan potassium indicating Powder blend has the required flow property for compression. The results were shown in Table 2.

Evaluation of Bi layer tablets

The hardness, friability, thickness, percentage weight variation, disintegration time, drug content was evaluated for prepared tablets the results were shown in Table 3. The measured hardness of tablets of each batch ranged between 6.4 ± 0.57 to 8.9 ± 0.69 kg/cm². This ensures good handling characteristics of all batches. The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable. The percentage weight variations for all formulations were calculated.

Table 1: Formulation Trials of Bi layer tablets

Ingredients	F-1 (Mg/tab)	F-2 (Mg/tab)	F-3 (Mg/tab)	F-4 (Mg/tab)	F-5 (Mg/tab)	F-6 (Mg/tab)	F-7 (Mg/tab)	F-8 (Mg/tab)
Losartan Layer								
Losartan Potassium	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
MCC Plain	175.50	165.50	148.50	139.00	127.50	110.50	104.00	95.00
Starch Plain	-	10.00	10.00	15.00	15.00	25.00	25.00	30.00
Crospovidone XL 10	-	-	5.00	5.00	7.00	7.00	9.00	11.00
P.Water(For Granulation)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lubrication								
Pregelatinised starch	-	-	7.50	7.50	15.00	20.00	22.50	22.50
Crospovidone XL 10	-	-	4.50	9.00	11.00	13.00	15.00	17.00
Magnesium Stearate	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Amlodipine Layer								
Amlodipine Besylate	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00
DCP	45.00	43.00	43.00	42.00	42.00	40.00	40.00	40.00
MCC pH102	65.0	65.00	62.00	62.00	57.00	58.00	58.00	58.00
Pre gelatinised Starch	-	2.00	4.00	4.00	8.00	8.00	8.00	8.00
SSG	-	-	1.00	2.00	3.00	4.00	4.00	4.00
Aerosil	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ponceau 4R Lake	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total weight	350	350	350	350	350	350	350	350

Table 2: Pre compression parameters for Amlodipine and losartan potassium layer blend

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (°)
A1	0.634 ± 0.002	0.740 ± 0.001	1.16 ± 0.01	14.32 ± 0.65	26.3° ± 0.98
A2	0.623 ± 0.001	0.754 ± 0.003	1.21 ± 0.01	17.37 ± 0.87	29.8° ± 1.17
A3	0.578 ± 0.002	0.722 ± 0.004	1.25 ± 0.03	19.94 ± 1.11	28.8° ± 0.75
A4	0.595 ± 0.004	0.758 ± 0.002	1.27 ± 0.01	21.20 ± 0.87	28.6° ± 0.88
A5	0.589 ± 0.001	0.737 ± 0.002	1.25 ± 0.02	20.08 ± 0.45	28.4° ± 1.24
A6	0.613 ± 0.003	0.766 ± 0.003	1.24 ± 0.02	19.73 ± 0.72	29.4° ± 1.32
L1	0.488 ± 0.002	0.605 ± 0.002	1.17 ± 0.01	19.39 ± 0.89	30.4° ± 1.40
L2	0.479 ± 0.003	0.604 ± 0.006	1.25 ± 0.01	20.60 ± 1.12	31.7° ± 1.23
L3	0.491 ± 0.001	0.617 ± 0.001	1.26 ± 0.03	20.89 ± 1.45	32.5° ± 0.95
L4	0.487 ± 0.002	0.612 ± 0.002	1.25 ± 0.01	20.41 ± 1.23	31.8° ± 0.89
L5	0.490 ± 0.007	0.599 ± 0.002	1.09 ± 0.02	18.19 ± 1.16	26.2° ± 1.15
L6	0.479 ± 0.008	0.605 ± 0.001	1.26 ± 0.01	20.82 ± 1.31	29.9° ± 1.63
L7	0.486 ± 0.009	0.609 ± 0.003	1.25 ± 0.02	20.32 ± 0.93	29.4° ± 1.34
L8	0.477 ± 0.005	0.600 ± 0.004	1.25 ± 0.02	20.51 ± 0.96	30.3° ± 0.90

Table 3: Post compression parameters for bi layer tablets

Batch	Thickness (mm)	Hardness (kg/cm ²)	Friability %	Disintegration Time (Minutes)	Assay %	Weight Variation Test
F-1	4.09 ± 0.011	6.4 ± 0.57	0.22	11m 53s	(A)-92.32 (L)-97.34	362 ± 1.75
F-2	4.21 ± 0.015	7.3 ± 0.73	0.19	9m 14s	(A)-91.66 (L)-98.15	371 ± 2.6
F-3	4.32 ± 0.014	7.8 ± 0.34	0.13	7m 40s	(A)-90.78 (L)-97.56	364 ± 2.23
F-4	4.28 ± 0.012	8.9 ± 0.69	0.09	7m 47s	(A)-94.98 (L)-96.87	369 ± 1.98
F-5	4.24 ± 0.011	8.5 ± 0.76	0.15	6m 18s	(A)-93.71 (L)-97.87	358 ± 1.81
F-6	4.35 ± 0.010	6.4 ± 0.43	0.22	6m 41s	(A)-92.45 (L)-94.79	365 ± 2.55
F-7	4.26 ± 0.011	7.9 ± 0.67	0.18	6m 25s	(A)-94.06 (L)-95.50	370 ± 2.85
F-8	4.19 ± 0.013	8.8 ± 0.82	0.17	5m 30s	(A)-94.70 (L)-96.87	363 ± 2.05

Table 4: In Vitro Dissolution Study of Amlodipine besilate and Losartan Potassium bilayer tablets

Time (minutes)	Formulation Layer	Percentage Drug release							
		F1	F2	F3	F4	F5	F6	F7	F8
5	Amlodipine	24.63 ± 0.08	39.50 ± 0.14	50.60 ± 0.16	55.87 ± 0.09	72.13 ± 0.10	71.87 ± 0.08	70.53 ± 0.05	73.12 ± 0.06
	Losartan	21.12 ± 0.21	26.36 ± 0.11	38.05 ± 0.10	45.67 ± 0.16	61.72 ± 0.08	69.14 ± 0.12	74.12 ± 0.11	77.67 ± 0.08
10	Amlodipine	42.40 ± 0.13	53.76 ± 0.23	57.42 ± 0.21	64.12 ± 0.14	78.97 ± 0.12	77.46 ± 0.10	78.12 ± 0.09	79.54 ± 0.14
	Losartan	36.54 ± 0.43	39.93 ± 0.19	52.38 ± 0.11	61.95 ± 0.11	72.17 ± 0.15	76.87 ± 0.18	78.70 ± 0.15	83.82 ± 0.12
15	Amlodipine	52.13 ± 0.19	59.98 ± 0.12	64.54 ± 0.15	71.26 ± 0.10	82.13 ± 0.11	82.76 ± 0.19	81.23 ± 0.18	82.17 ± 0.11
	Losartan	49.60 ± 0.24	58.12 ± 0.15	66.85 ± 0.19	73.92 ± 0.25	76.32 ± 0.22	81.53 ± 0.17	84.21 ± 0.14	85.05 ± 0.15
20	Amlodipine	61.36 ± 0.24	67.78 ± 0.24	68.91 ± 0.23	77.10 ± 0.56	83.42 ± 0.29	83.15 ± 0.49	82.87 ± 0.31	83.21 ± 0.55
	Losartan	56.65 ± 0.36	64.73 ± 0.33	73.50 ± 0.54	77.65 ± 0.41	81.56 ± 0.12	84.21 ± 0.34	86.78 ± 0.44	88.12 ± 0.48
25	Amlodipine	68.67 ± 0.16	73.31 ± 0.28	74.23 ± 0.87	80.90 ± 0.67	83.91 ± 0.45	84.12 ± 0.70	84.25 ± 0.19	83.64 ± 0.37
	Losartan	62.81 ± 0.87	69.88 ± 0.56	74.81 ± 0.75	80.03 ± 0.78	83.94 ± 0.26	86.92 ± 0.45	88.79 ± 0.54	89.85 ± 0.71
30	Amlodipine	73.62 ± 0.21	76.15 ± 0.75	79.71 ± 0.39	82.23 ± 0.39	84.23 ± 0.47	84.88 ± 0.34	84.32 ± 0.29	84.02 ± 0.68
	Losartan	68.40 ± 0.67	72.25 ± 0.56	77.59 ± 0.81	80.29 ± 0.61	85.56 ± 0.19	87.15 ± 0.38	89.09 ± 0.28	90.08 ± 0.42

Table 5: Stability studies

S. No	Parameters	Conditions				
		Initial	40°C and 75 % RH	40°C and 75 % RH	40°C and 75 % RH	40°C and 75 % RH
		0 Day	1 month	2 month	3 month	6 month
1	Average weight	363 ± 5 mg	363 ± 5 mg	363 ± 5 mg	363 ± 5 mg	363 ± 5 mg
2	Thickness (mm)	4.31 ± 0.014	4.31 ± 0.014	4.31 ± 0.014	4.31 ± 0.014	4.31 ± 0.014
3	Disintegration time	6 minutes 45 sec	7 minutes 17 sec	7 minutes 23 sec	7 minutes 20 sec	7 minutes 55 sec
4	Assay (%)	A-94.70	A-94.66	A-94.49	A-94.45	A-94.21
		L-96.87	L-96.81	L-96.74	L-96.72	L-96.50
		A-84.02	A-83.98	A-83.89	A-83.86	A-83.53
5	Dissolution (30 minutes)	L-90.08	L-89.91	L-89.88	L-89.85	L-89.71

Physicochemical Interaction of Drug and Excipients

Figure 1: IR Spectra of Pure drugs (amlodipine and losartan), tablet (amlodipine layer and losartan layer) and coated tablet

Model Chromatograms

Figure 2: HPLC chromatogram of diluents, sample and standard

Figure 2(a): Assay Diluent sample

Figure 2(b): Assay Sample

Figure 2(c): Assay Standard

Figure 3: *In vitro* Dissolution Profile of Different Formulations
Figure 3 (a): *In vitro* Dissolution Profile for Formulation F1

Figure 3(b): *In vitro* Dissolution Profile for Formulation F2

Figure 3 (c): *In vitro* Dissolution Profile for Formulation F3

Figure 3 (d): *In vitro* Dissolution Profile for Formulation F4

Figure 3 (e): *In vitro* Dissolution Profile for Formulation F5

Figure 3 (f): *In vitro* Dissolution Profile for Formulation F6

Figure 3 (g): *In vitro* Dissolution Profile For Formulation F7

Figure 3 (h): *In vitro* Dissolution Profile For Formulation F8

All the formulated (F1 to F8) tablets passed weight variation test as the Percentage weight variation was within the pharmacopoeia limits of 7.5 % of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The measured thickness of tablets of each batch ranged between 4.09 ± 0.011 to 4.35 ± 0.010 mm for tablets. The disintegration time of all the batches were found between 12 minutes to 5 minutes. The percentage of drug content for F1 to F8 was found to 90.78 % to 94.98 % of Amlodipine besilate and 94.79 % to 98.15 % of Losartan Potassium and it complies with official specifications.

In vitro dissolution for all the formulations was carried out for 30 minutes. The results were shown in Table 4. The maximum drug release was found for the optimized formulation F8 containing 5 % w/w crospovidone for Losartan Potassium layer and 4 % Sodium Starch Glycolate for Amlodipine layer shows least disintegration time and better dissolution properties compared to the other batches (F1- F7). The reason might be at the optimum concentration crospovidone rapidly exhibits high capillary action and pronounced hydration capacity and at optimum concentration of sodium starch glycolate disintegration occurs by rapid uptake of water followed by rapid and enormous swelling and hence F8 was chosen as the optimized formulation for the further stability studies.

Stability Study

According to ICH guidelines, 6 months accelerated stability study at $40 \pm 2^\circ\text{C}$ and 75 % RH optimized formulation (F8) showed negligible change over time for parameters like appearance, drug content, dissolution, etc. No significant difference in the drug content between initial and formulations stored at $40 \pm 2^\circ$ and 75 ± 5 % RH for 6 months.

CONCLUSION

When the combined formulation of amlodipine and losartan is prepared by simply mixing the two drugs, gelation of losartan disadvantageously occurs. Losartan readily dissolves in purified water or is very well released at a relatively high pH (e.g., pH 6.8), but it is very slowly released at a low pH (e.g., pH 2.0 or pH 1.2) because of its gelation⁶. In case of Cozaar (trade mark), a commercially available losartan preparation, the dissolution rate of losartan is below 30 % thereof in 30 minutes at a pH range of 1.2 to 2.0. In the combined formulation of amlodipine and losartan, amlodipine may be locked in the inside of the formulation due to the gelation of losartan. Further, the combined formulation prepared by simply mixing amlodipine and

losartan has very poor storage stability mainly due to an undesired chemical reaction among amlodipine, losartan and excipients. In order to overcome the above-mentioned problems such as losartan gelation and stability lowering, the combined formulation of amlodipine and losartan must be prepared by physically separating amlodipine from losartan. The present research was carried out to develop an Immediate Release Bilayer tablet of Amlodipine Besilate and Losartan Potassium. Combination of Amlodipine Besilate and Losartan Potassium are indicated for the successful treatment and relief of hypertension. Prepared bi layer tablets were film coated in a conventional coating pan. Formulation characteristics such as content uniformity, hardness, friability were found to be satisfactory. *In vitro* dissolution studies of bi layer tablets were conducted for 30 minutes. Samples were analyzed by HPLC. The formulation (F-8) showed acceptable pharmacokinetic properties and complied with the internal specification for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. Reproducibility was checked by intra batch variability study and found no pronounced variation was observed. Accelerated stability profiles of bi layer tablets were found to be satisfactory. No sign of degradation was observed in HPLC analysis. Hence, it is finally concluded that, the Bi layer tablet technology can be successfully applied for Immediate-release of Amlodipine Besilate and Losartan Potassium.

REFERENCES

1. Lachman L, Lieberman HA and Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd ed. Bombay: Varghese Publishing House; 1987. p. 171-198, 293-339, 430-456.
2. YW Chien, YW Marcel. Novel Drug Delivery Systems. Published by: Marcel Dekker, 2nd ed. New York; 2009, 199. p. 1-42.
3. Joel M Neutel. Low dose anti hypertensive combination therapy: its rationale and role in cardiovascular risk management. Am J Hypertens 1999; 12(8): 73-79. [http://dx.doi.org/10.1016/S0895-7061\(99\)00112-0](http://dx.doi.org/10.1016/S0895-7061(99)00112-0)
4. Indian Pharmacopoeia. Government of India, Ministry of health and family welfare, Published by the controller of publications, Delhi; 2007. Volume I and II.
5. Bhardwaj Vineet, BansalMayank, Sharma PK. Formulation and Evaluation of fast Dissolving Tablets of Amlodipine Besilate Using Different Super Disintegrants and Camphor as Sublimating Agent. American-Eurasian J Scien Res 2010; 5(4): 264-269.
6. Singh Abhishek Kumar. Formulation and development of two incompatible anti-hypertensive drugs (losartan potassium and amlodipine besilate) in a single dose. Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka.

Cite this article as:

Rama, Mitesh. R. Bhoot. Formulation and evaluation of bilayer tablets of two incompatible drugs Amlodipine besilate and Losartan potassium. Int. Res. J. Pharm. 2013; 4(9):136-142 <http://dx.doi.org/10.7897/2230-8407.04929>