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FORMULATION OF BILAYERED TABLET OF LOSARTAN POTASSIUM AND AMLODIPINE

V.P.Pandey, R.Sathish Kumar and A.Sathish Babu*

Department of Pharmacy, Annamalai University, Annamalainagar – 608002, Tamilnadu, India.
*The Madras Pharmaceuticals, Karapakkam. Chennai – 600096, Tamilnadu, India.

ABSTRACT

In the combined formulation of amlodipine and losartan, amlodipine may be locked in inside of the formulation due to gelation of losartan and formulation with simple mixing of two have very poor storage stability. To avoid such problem, bilayer tablet of losartan and amlodipine is tried in present study. Five formulations (F1, F2, F3, F4 and F5) of bilayer tablet were prepared and evaluated for physical parameters and *in vitro* study. One bilayer tablet formulation (F5) was found suitable in evaluation. It was subject to stability study for 45 days at 25^{o} C/ 60 % RH as per ICH guidelines and found stable.

Keywords: Losartan potassium, Amlodipine, Bilayered tablet, Antihypertensive.

INTRODUCTION

In the recent times, multi-layer matrix tablets are gaining importance in the design of oral drug delivery systems. Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit. They are preferred for the following reasons: to co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for stagged drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing [1].

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 also while the second layer is also designed to release the drug immediately. Bilayer tablet is suitable for sequential release of two drugs in combination and separate two incompatible substances [2].
Hypertension and angina pectoris the most common cardiovascular diseases that require constant monitoring. High blood pressure is one of the most important modifiable disease factors for cardiovascular disease. Hypertension is designated as either primary hypertension or secondary hypertension or secondary hypertension [3].
Amlodipine is a prototype second generation dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has a longer duration of action (ie) half life of 40 hours and the initial effects are cumulative over many days and more over for patient compliance in case of anti-angina patients, a rapid onset of action is necessary for immediate pain relief. Hence Amlodipine can be given as a single immediate release dose.

Losartan potassium is an angiotensin II receptor antagonist [4]. The half life of losartan potassium is 1.5- 2 hours. It suppresses the effects of angiotensin II at its receptors, thereby blocking the rennin- angiotensin system. The rennin-angiotensin system plays a crucial role in the control of blood pressure, and in particular it is felt to play crucial role in hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectively, and tolerability [5]. Generally, losartan potassium is employed in the management of essential hypertension with lower incidence of side-effects like cough [6]. It is readily absorbed and undergoes rapid hepatic metabolism to an active metabolite, EXP-3174, via cytochrome P-450 system.

The aim of this investigation is to design and develop bilayered tablet of Losartan potassium and

Corresponding Author:- **A.Sathish Babu** Email:- vppnp@rediffmail.com

Amlodipine besylate the two drugs in a combination preparation herein have different activities 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.

MATERIALS AND METHODS

Materials

Losartan potassium and amlodipine besylate were obtained from Arthi Drugs and Chemicals, Chennai Pvt. Ltd. Starch plain, starch 1500, Di-calcium phosphate, sodium starch glycolate were purchased from Samsung Fine Chemicals, Mumbai. Microcrystalline cellulose plain and microcrystalline cellulose – PH 102 were purchased from Ranq Remedies, Mumbai. Cross Povidone XL 10, Colloidal silicon dioxide and methylene chloride were purchased from Fischer Ltd, Chennai. Magnesium stearate, Instacoat (IC-S-010) and Quinoline Yellow Lake were purchased from Allandhu Biotech. Ponceau 4 R lake were purchased from Kanphu labs, Chennai. Other materials and excipients used in the preparation of bilayer tablets of I.P Grade. All materials used throughout the study were of analytical grade and from commercial sources.

Methods

Preformulation Studies

Preformulation studies were carried out inorder to find out the drug excipients interactions and its flow property during the formulation process. The objective of the preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer. The characteristic peaks were recorded. Compatibility studies of Losartan potassium with its excipients and Amlodipine besylate with its additives were done for one month.

Preparation of Bilayer Tablets

Preparation of Losartan Potassium granules

The drug Losartan potassium and the excipients microcrystalline cellulose plain, starch plain and polyplasdone XL 10 were passed through sieve no 30#. Then the materials were transferred to the rapid mixer and mixed for 15 minutes. The binder as starch paste was added and the granulation was continued at high speed till a coherent mass was obtained. The wet granules were transferred into fluidized bed dryer and they were dried at 50^{o} C and then passed through 20# mesh till the required Loss on drying achieved. Pregelatinised starch and polyplasdone XL 10 were passed through 30# mesh. The sifted materials and dried granules were blended for 10 minutes. The granules were prepared by wet granulation technique. Finally magnesium stearates were sifted through 60# and mix it with granules for 5 minutes (Table 1).

Preparation of Amlodipine besylate granules

The drug amlodipine besylate and dicalcium phosphate, anhydrous (DC Grade), microcrystalline cellulose PH 102, starch 1500, sodium starch glycolate, colloidal silicon dioxide were passed through sieve 30# and ponceau 4R lake through sieve 100# and it is sifted to hexagonal blender and mix it for15 minutes. The granules were prepared by dry granulation method. Then Magnesium stearate is added to the mixed material then compressed by using Rotary compression machine using 13/32 inch punch of standard concave plain (Table No: 2).

Compression

Finally bilayer tablets were compressed as one layer only for Losartan Potassium (F1, F2, F3, F4 & F5) and second layer for Amlodipine besylate (F1, F2, F3, F4 & F5) using 10.3 mm standard concave punch in 12 station double hopper bilayered press (Cadmech-Ahmedabad). The tablets were compressed as a bilayer tablet using both Losartan Potassium and Amlodipine besylate granules. In this, Losartan Potassium granules were introduced first into the die cavity and slight pre-compression was made so that layer was uniformly distributed and after that Amlodipine besylate granules were added and final compression was made.

Precompression Parameters

The flow properties of powders are critical for an efficient tabletting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets [7]. Prior to compression, granules were evaluated for their characteristic parameter such as tapped density and Carr's Index. Carr's compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus.

Coating of Losartan Potassium and Amlodipine besylate bilayer tablets

One part of Isopropyl alcohol was taken and to that instacoat added and to another part quinoline yellow lake were added and passed through colloidal mill. Finally methylene chloride were added and stirred without lumps formation and filtered through 100# nylon cloth. The above solutions were used for coating of the compressed bilayer tablets (F1, F2, F3, F4 & F5).

EVALAUTION OF BILAYER TABLETS

Weight Variation

Twenty tablets were weighed collectively and individually for finding out weight variation[7]. Procedure was followed as prescribed by Indian Pharmacopoeia 1996. These results were reported in Table No: 3.

Hardness

Hardness of the tablet was tested by placing the tablet longitudinally in between the two plungers of the Monsanto tablet hardness tester and the obtained hardness was mentioned in terms of kg/sq.cm in Table No: 3.

Friability and disintegration

The friability of the tablets was determined by Roche Friabilator in which the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets were placed in the friabilator and allowed to rotate for 100 revolutions. Later the tablets were dedusted and the tablets were reweighed. Percent friability was found out [8].

The disintegration time (D.T) of a tablet was determined using disintegration test apparatus per I.P specifications and given in Table No: 3.

Estimation of Drug Content

The tablets were finely powdered and amount equivalents were transferred to a volumetric flask and dissolve in mobile phase and disperse completely. Finally the volume was made up to mark with mobile phase and analyzed by HPLC (Shimadzu) at 237nm respectively. The assay results are depicted in Table No: 4.

***In vitro* Dissolution Studies**

An *in vitro* drug release study of the prepared bilayered tablets was determined using the USP eight station Dissolution Test Apparatus employing a paddle stirrer. 900 ml of water was used as dissolution media and maintained at 37±0.5^{o}C at a rotational speed of 50 rpm respectively [9]. Then the dissolution samples were analyzed by using HPLC (Shimadzu), at 237nm. From the datas obtained from the chromatogram the dissolution was found to be within the limits for losartan potassium and amlodipine besylate. These results were reported in Figure No: 2.

Stability studies

Stability study was conducted for F5 tablet formulation with primary package in an oven at 25^{o} C/ 60 % RH for 45 days [10] and results are shown in Table No: 5.

RESULTS AND DISCUSSION

The prepared bilayer tablets were evaluated for various physical properties. FT- IR spectrum of losartan potassium and Amlodipine besylate bilayer sustained release tablets revealed there is no major interaction between drug and polymers used in the study. The bulk density for the granules of various formulations ranged between 0.42 -.0.54 gm/ml as determined by the tap method. This value of bulk density indicates of good packing character. The compressibility Index (CI) for formulation was found to be below 30% indicating desirable flow properties.The flow properties of granules were further analyzed by determining Hausner's ratio for all granules which ranged between 1.35 - 1.41.Carr's index for losartan granules were found in range of 26.02-32.34 and for amlodipine granules was found in range of 33.33 – 41.66 for all five formulations. Then the granule are lubricated with magnesium stearate to prevent the adhesion of the tablet materials to the surface of surface of dies and punches, reduce interparticle friction and may improve the rate of flow of the tablet granules. It produced round biconvex tablet after punching. Film coating was done with instacoat IC-S-010 with quinoline yellow lake. Weight Variation, Friability, hardness, thickness and Disintegration of tablets were 348.3 – 350.5 g, Friability was 0.187-3.03%, hardness was 7.44 – 8.52 kg/cm^{2}, thickness was 3.296 – 3.238 mm and the disintegration were within the limit of 12.02 – 5.325. Increase in the concentration of cross povidone decreases the disintegration time and thereby increasing quality attribute of the tablet. Bilayer tablets passed the weight variation and friability test. Hardness was also within desired limits. Assay and dissolution studies (invitro study) were done by using Shimadzu HPLC. The obtained chromatograms revealed that the formulations (F1 – F5) were releasing the drug in a regular manner. Calculation is done by using the following formula

$$\% \text{ of drugs} = \frac{\text{Sampl. area}}{\text{Std area}} \times \frac{\text{std dil.}}{\text{sampl. dil.}} \times \frac{\text{Av. weight}}{\text{abel claim}} \times \text{conversion factor} \times 100$$

$$\text{Conversion factor} = \frac{\text{Mol. Wt. of amlodipine Besylate}}{\text{Mol. Wt. of losartan potassium}}$$

Retention time for dissolution study of losartan potassium and amlodipine besylate was around 12.5 minutes and 19.5 minutes where as for assay it was around 13 minutes and 17 minutes respectively. In the present study 70% of both drugs were released in 15 minutes in dissolution study for F5 which is suitable for present bilayer tablet formulation. In vitro study results are depicted in Figure: 2. Stability study was carried out using package at 25^{o} C / 60 % RH for 45 days and results are shown in Table No: 7. Stability study results showed that F5 is stable in all parameters and suitable to be taken as successful bilayer tablet of losartan potassium and amlodipine besylate.

Figure 1. Disintegration time of Losartan potassium and Amlodipine besylate bilayer tablets

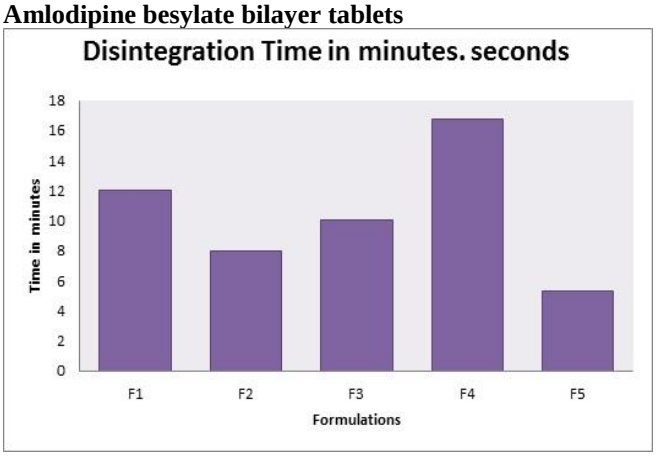

Figure 2. Invitro Drug release profile of Losartan potassium and Amlodipine besylate

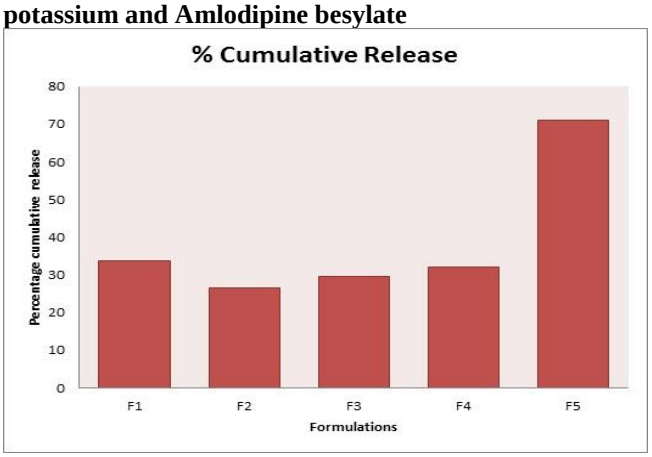

Table 1. Composition for Losartan potassium layer

S.No	Ingredients in mg	F1	F2	F3	F4	F5
1	Losartan potassium	50.0	50.0	50.0	50.0	50.0
2	Microcrystalline cellulose plain	95.0	95.0	95.0	95.0	95.0
3	Starch plain	30.0	30.0	30.0	30.0	30.0
4	Cross povidone XL 10	6.0	9.0	8.0	4.0	11.0
5	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
6	Starch 1500	22.5	22.5	22.5	22.5	22.5
7	Cross povidone XL 10	17.0	17.0	17.0	17.0	17.0
8	Magnesium Stearate	4.5	4.5	4.5	4.5	4.5

Table 2. Composition for Amlodipine besylate layer

S.No	Ingredients in mg	F1	F2	F3	F4	F5
1	Amlodipine besylate	5.0	5.0	5.0	5.0	5.0
2	Dicalcium phosphate	40.0	40.0	40.0	40.0	40.0
3	Microcrystalline cellulose	58.0	58 .0	58.0	58.0	58.0
4	Starch 1500	2.0	4.0	3.0	1.0	8.0
5	Sodium starch glycolate	1.0	2.0	1.5	0.5	4.0
6	Colloidal silicon dioxide	1.0	1.0	1.0	1.0	1.0
7	Ponceau 4 R lake	1.0	1.0	1.0	1.0	1.0
8	Magnesium Stearate	1.0	1.0	1.0	1.0	1.0

Table 3. Physical parameters of Losartan potassium and Amlodipine besylate Bilayered tablet

S.No	Batch No	Weight Variation in mg	Friability in %	Hardness in kg/cm^2	Thickness in mm
1	F1	348.3	1.26	7.44	3.296
2	F2	351.9	3.03	7.56	3.294
3	F3	349.1	1.33	7.42	3.282
4	F4	351	1.23	7.54	3.316
5	F5	350.5	0.187	8.52	3.238

Table 4. *In vitro* Drug release profile of Losartan potassium and Amlodipine besylate

S.No	Formulation	% Cumulative Release
1	F1	33.61
2	F2	26.62
3	F3	29.68
4	F4	31.94
5	F5	70.98

Table 5. Stability study sheet

S.No	Storage Condition	Description	Content of Losartan Potassium	Identification
1	After 15 days storage	Yellow, round biconvex tablet	101.01 %	Complies
2	After 30 days storage	Yellow, round biconvex tablet	100.46 %	Complies
3	After 45 days storage	Yellow, round biconvex tablet	99.98 %	Complies

CONCLUSION

Losartan potassium & Amlodipine besylate are Anti hypertensive drugs. But when they were combined by simple mixing and made a formulation, Losartan was showing the gelation property which reduced the dissolution capacity of a drug. So to overcome this problem, the formulation was made into bilayered tablet which maintain the dissolution constantly in the stomach at any pH value, which leads to constant release of the drug. Five trials (F1-F5) has been taken for the formulation. In that F5 batch only passes all the evaluation tests like weight variation, thickness, hardness, disintegration, dissolution studies and assay. The optimized formulation was kept for various evaluation studies and stability studies. In the evaluation results, the formulation showed the results which were found to be within the limits of Pharmacopoeia. The stability studies of the formulation were stable at the given condition for the prolonged time and hence suitable to formulate Bilayered tablets.

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