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FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS OF LOSARTAN POTASSIUM

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ABSTRACT

The aim of present work is the formulation and evaluation of sustained release bilayer tablets of Losartan Potassium. In this formulation loading dosage was incorporated in the immediate release layer so that the minimum effective concentration may be attained within a short period of time after this the maintenance dosage level will be taken over by the drug release from the second layer of bilayer tablets. The tablets were prepared by direct compression method by using superdisintegrants sodium starch glycolate(SSG) for immediate release layer & mucoadhesive materials such as hydroxypropyl methylcellulose(HPMC-K4M) and carbopol 940-P for sustained release layer which could release the drug up to 30 hours in predetermined rate. All the formulations were evaluated for post-compression parameters like hardness, thickness, friability, dug content uniformity, dissolution test and disintegration test. Formulation ME5 was considered to be the optimized formulation which showed the best drug release profile up to 30 hours and fulfilled the many requirements reduced dosing frequency, increase the bioavailability and provide better patient compliance. The results of FTIR and DSC analysis showed that there was no physical and chemical interaction between drug and other excipients. The stability studies of optimized formulation ME5 at 400C/75%RH for 3 months did not show any variation in the tasted parameter and release.

KEYWORDS: Losartan Potassium, Bilayer tablets, Formulation, Evaluation.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The goal of any drug delivery system is to provide a therapeutic amount of the drug at

the site an effective throughout the entire duration of therapy and then maintain the desired drug concentration.

Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues which leads to reduction or loss in Drug effectiveness or increased incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems can decrease the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required and providing uniform drug delivery. Different approaches have been proposed to formulate sustained release tablets for retaining dosage form in stomach. These include bioadhesive or mucoadhesive systems, swelling and expanding systems floating systems and other delayed gastric emptying devices.

In recent years, a growing interest has developed in designing drug delivery systems that include an immediate release (IR) component to extended release (ER) dosages. The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance. Mucoadhesive bilayer tablet is new concept for successful development of sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and an Sustained release (SR) layer. Immediate release layer provide therapeutically effective plasma drug concentration for a short period of time and Sustained release (SR) layer maintain uniform drug levels over a sustained period to reduce dosing intervals and side effects, increase the safety margin for highly-potent drugs and thus offer better patient compliance.

On the basis of these considerations, a new oral delivery device was proposed, in the form of a double-component tablet, one portion is formulated to obtain a prompt release of the drug with the aim of reaching a high serum concentration in a short period of time.

The second portion is a prolonged-release layer which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

Advantages

1. Bi-layer execution with optional single layer conversion kit.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odor and taste can be masked by coating technologies.
5. Flexible concept.
6. Offer greatest precision and the least content uniformity.
7. Easy to swallow with least hang up problems.
8. Fit for large scale production.
9. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
10. Bi-layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release.

Disadvantages

1. Complexity and bi-layer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Imprecise individual layer weight control.
4. Cross contamination between the layers.
5. Difficult to swallow in case of children and unconscious patients.
6. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.
7. Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability.

MATERIALS AND METHODS

Materials

Losartan Potassium was obtained from Aurochem laboratories, Palghar. Carbopol 971 and Hydroxy propyl methyl cellulose were obtained from Noveon Chemicals, Bangalore. Dibasic calcium phosphate was obtained from Enar Chemicals Ltd., Ahmedabad. Sodium starch glycolate was obtained from Sujata Chemicals, Ahmedabad. Polyvinyl pyrollidone and Talc were obtained from Loba Chemie Pvt. Ltd. Mumbai. Magnesium stearate was obtained from Finar Reagents, Mumbai. Hydrochloric acid, Sodium hydroxide and Potassium dihydrogen orthophosphate were obtained from S.D. Fines Chemicals, Mumbai.

Method

The Sustained release bilayer tablets of Losartan Potassium were prepared by direct compression method by using superdisintegrants sodium starch glycolate (SSG) for immediate release layer and mucoadhesive materials such as hydroxyl propyl methyl cellulose(HPMC-K4M) and carbopol 940-P for sustained release layer. Polyvinyl pyrrolidone (PVP) K-30 was used as binder. The drug, polymers and other excipients used for both immediate (IR) and sustained release (SR) layers were passed through sieve # 80 before their use in the formulation. Then prepare the Immediate and Sustained release layer separately.

Formulation of the IR Layer

The IR ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation. The blend was mixed with talc and magnesium stearate for 2 minutes and kept in a desiccators until further used.

Formulation of the SR Layer

The SR ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation and subjected for pre-formulation studies.

Table No. 1: Ingredients for IR Layer.

Sr.No.	Ingredients(mg/tab) For IR Layer	ME1	ME2	ME3	ME4	ME5
1	Losartan Potassium	5	5	5	5	5
2	Sodium Starch Glycolate	12	12	12	12	12
3	PVP- K30	10	10	10	10	10
4	D.C.P.	20.99	20.99	20.99	20.99	20.99
5	Mg. Stearate	1	1	1	1	1
6	Talc	1	1	1	1	1
7	Colour	0.01	0.01	0.01	0.01	0.01
	Total Weight	**50**	**50**	**50**	**50**	**50**

Table No. 2: Ingredients for SR Layer.

Sr.No.	Ingredients(mg/tab) For SR Layer	ME1	ME2	ME3	ME4	ME5
1	Losartan Potassium	45	45	45	45	45
2	HPMC K4M	80	70	60	50	40
3	Carbopol 940-P	-	10	20	30	40
4	D.C.P.	51	51	51	51	51
5	PVP- K30	20	20	20	20	20
6	Mg. Stearate	2	2	2	2	2
7	Talc	2	2	2	2	2
	Total Weight(IR+SR)	**250**	**250**	**250**	**250**	**250**

Compression of Bilayer Tablet

In the present study bilayer tablet was prepared manually using single station punching machine (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat). Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force (2-3 kg/cm^2). After that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 9-mm circular punches (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat). Both the layers were identified on the basis of color since the immediate release layer had pink color and the sustained release layer has white colour.

1) Pre-formulation Evaluation

Fourier transform infrared spectroscopy(FT-IR) study was conducted using shimadzu-8400S to identify purity of the drug and test the compatibility of drug with excipients.

2) Pre-compression Evaluation

The flow properties for Bulk density, Tapped density, Hausner's ratio, compressibility index, Angle of repose were evaluated.

3) Evaluation of Sustained release bilyaer tablets of Losartan Potassium.

A) Hardness test

Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland) was used to determine the crushing strength. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.

B) Thickness uniformity

Three tablets were selected randomly from each batch and thickness were measured by using vernier caliper.

C) Friability test

The friability of tablets was determined using Roche friabilator. Ten tablets were initially weighed (w0 initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w). The % friability was then calculated by,

Percentage of Friability = 100 (1-w/w0)

% friability of tablets less than 1% is considered acceptable.

D) Uniformity of weight

30 tablets are randomly selected for the test. Every tablet in each batch should have a uniform weight. 20 tablets are weighted individually. Average weight is calculated from the total weight of all the tablets. The individual weights are compared with the average weight. The percentage difference in the weight variation should be within the permissible limits. % weight variation = [(individual weight – average weight) / individual weight] x100 Out of 20 tablets, if 2 tablets deviate the limit perform test for other 10 tablets. Out of 30 tablets if not more than 2 tablets, deviate the batch passes test.

E) Drug Content Uniformity: Assay by UV Spectrophotometer[42]

Standard Preparation

Weigh accurately about 8 mg std Losartan Potassium USP working standard in 100ml volumetric flask. Dissolve the drug in the 0.1 N Hcl. Make up volume with the 0.1 N Hcl and shake well.

Sample Preparation

Ten tablets were finely powdered and an amount equivalent to 100 mg of losartan potassium was accurately weighed and transferred to a 100 ml volumetric flask, then 70 ml of buffer pH 1.2 (0.01N HCL) was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for losartan potassium content at 206 nm using a double beam UV/Visible spectrophotometer (Shimadzu 1800, Japan) and 0.01N HCL as blank.

F) Disintegration test

Disintegration test is a method to evaluate the rate of disintegration of tablets. It is also defined as break down of solid dosage form into smaller particles when it is disintegrated. Place 1 tablet in each of the 6 tubes and added a disc to each tube. Maintain the temperature of the disintegration media at 37±2ºC as specified in the monographs.

At the end of time limit specified, left the basket from fluid and observe the tablets. If 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets. Not less than 16 out of 18 tablets tested disintegrate completely.

G) In-Vitro Dissolution Studies[43,44]

The *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II. The tablets were placed in the 0.1N hydrochloric acid for first 2 hours and pH 6.8 phosphate buffers for next 28 hours respectively, then the apparatus was run at 37°C±0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution medium. The 5 ml aliquots were withdrawn at intervals of 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours…..30 hours and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatmann filter paper (No.41). 1 ml of sample was diluted to 9 ml 0.1N HCL for first 2 hours and then with pH 6.8 phosphate buffers for next 28 hours and absorbance was measured at 206 nm using UV spectrophotometer (JASCO V-550). Drug concentrations in the sample were determined from standard calibration curve.

RESULTS AND DISCUSSIONS

1) Pre-formulation Evaluation

Fourier transforms infra-red (FTIR) spectroscopy for Losartan Potassium.

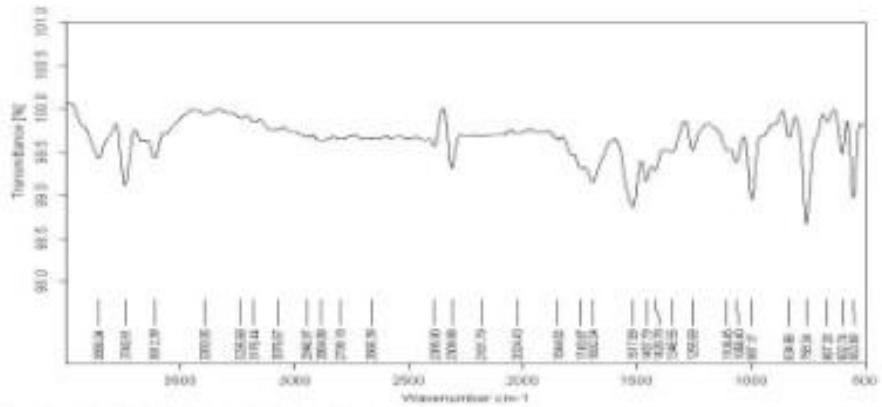

Table No. 3: Table of Functional group and its Frequency.

Functional group	Observed Frequency	Reported Frequency
Free –OH	3750.63	3700
-NH	3590.49	3500
-CH stretching	2290.26	2200
-C=O stretching	1560.55	1500
C-C stretching	1012.25	1100

The major peaks are identical to functional group of Losartan Potassium. Hence, it was confirmed that there was no incompatibility.

2) Pre-compression Evaluation

Table No. 4: Table of Pre-compression evaluation.

Formulation	Bulk Density(g/ml)	Tapped Density(g/ml)	Hausner's ratio	compressibility index(%)	Angle of repose
ME1	0.68	0.81	1.19	16.04	27.34
ME2	0.71	0.86	1.21	17.44	25.80
ME3	0.73	0.90	1.23	15.89	26.59
ME4	0.72	0.93	1.29	15.25	24.88
ME5	0.70	0.89	1.27	17.34	28.24

3) Evaluation of Sustained release bilyaer tablets of Losartan Potassium.

Table No. 5: Table of Post compression evaluation.

Formulation	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Uniformity of weight(gm)	Content Uniformity (%w/w)	Disintegration time (min)
ME1	6.34	3.43	0.22	248	99.80	1 min 25 sec
ME2	7.92	3.45	0.14	250	99.60	1min 39 sec
ME3	7.61	3.47	0.21	249	98.90	1 min 27 sec
ME4	7.11	3.46	0.24	251	99.57	1min 58 sec
ME5	7.10	3.44	0.33	249	99.21	1 min 45 sec

Dissolution Study

Table No. 6: Table for Dissolution Study.

TIME (MIN)	ME1	ME2	ME3	ME4	ME5
5	7.75657	8.17105	10.3263	9.71050	9.39078
10	10.0733	13.1546	13.9244	13.7789	11.6100
15	13.4922	13.8787	15.8370	14.9801	12.2900
20	15.4732	14.5354	19.1453	15.3705	14.5366
25	16.1858	15.9769	20.4938	15.7745	15.9663
30	17.4467	16.9760	22.8440	17.1039	17.1786
60	20.8219	22.3617	24.7567	20.3940	20.3060
120	28.7628	28.3690	27.1174	27.4917	24.7837
180	37.2654	32.8690	30.3029	32.3469	30.1245
240	40.4626	34.8124	33.3877	33.6055	31.5871

300	41.6879	36.3283	36.1556	34.3735	32.2050
360	42.3986	37.1182	37.1908	34.7193	32.9682
420	44.0838	38.7413	38.5015	36.6300	33.5696
480	44.9491	39.8757	39.2743	36.9760	34.1505
540	46.7779	40.7200	40.4538	37.3882	34.9475
600	48.0069	43.2501	42.1021	38.2143	36.3978
660	51.2668	45.2142	43.1657	38.3655	37.1261
720	53.6383	46.5370	44.4721	39.6437	38.3886
780	55.3236	48.6601	45.8564	40.1471	39.6223
840	56.8873	49.6813	46.9163	41.9675	41.8098
900	58.9444	51.1694	48.2420	43.3357	43.4525
960	60.0529	54.2756	50.6758	44.3913	45.3998
1020	61.1548	56.9603	52.1278	47.7379	49.4178
1080	62.3922	58.3920	53.5634	52.0026	52.8300
1140	63.3986	61.0269	55.4800	55.7811	57.0775
1200	65.2623	61.9821	56.3288	58.5142	59.0623
1260	68.1538	63.6876	57.9157	60.6457	60.9260
1320	69.3313	66.8465	58.7172	64.9198	63.5941
1380	70.9878	68.8731	61.0735	68.4351	67.4238
1440	72.5759	69.8913	62.6020	69.8152	70.9400
1500	73.1645	72.0040	64.6340	73.6144	75.0710
1560	74.0200	72.6480	66.4249	78.6942	80.2065
1620	75.9582	74.0509	69.8790	83.4890	85.8286
1680	76.4611	75.9694	71.9607	87.5393	92.3680
1740	77.2971	78.6434	76.3145	91.8828	97.5101
1800	78.1482	81.2598	83.8649	95.4434	100.1559

DISCUSSION

In the present study, an attempt has been made to formulate and evaluate sustained release bilayer tablets of Losartan Potassium by direct compression technique. These tablets were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and for post compression parameters such as hardness, weight variation, drug content uniformity, disintegration time and *in-vitro* dissolution studies.

Pre-compression parameters of blends

The bulk density of pre-compression blends was found to be in the range of 0.68 to 0.73 g/ml, tapped density in the range of 0.81 to 0.93 g/ml, the Carr's index values were in the range of 15.25% to 17.44%, Hausner's ratio in the range of 1.19 to 1.29 and angle of repose between 24.88 to 28.24. All the values were found to be within the prescribed limits according to the I.P, thus ensuring good flow properties to the formulation blends.

Post compression parameters

Hardness and friability

The hardness of the tablet formulations was found to be in the range of 6 to 8 kg/cm^2. The friability and thickness values were found to be in the range of 0.14 to 0.33% and 3.43 to 3.47 mm respectively, which was found to be according to the I.P limits and thus ensuring good mechanical strength to all the formulations.

Uniformity of weight

All the prepared Sustained Release Bilayer tablets of Losartan Potassium were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits.

Uniformity of drug content

The values indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 98.90% to 99.80%.

Disintegration time

It was observed that disintegration time of all tablets ranged between 1 to 2 minutes and it is in the limit according to I.P.

***In vitro* dissolution study**

The formulation ME5 containing 20% of HPMC-K4M and 20%w/w of carbopol 940-P was selected as the optimized batch since it showed the best drug release profile up to 30 hours as compared to the other formulations.

The drug release from the formulation (ME5) was found to 100% after 30 hours. Higuchi's Plot, Peppas's Plot states that release followed the diffusion controlled mechanism. All the other parameters of the batch ME5 were found to be satisfactory.

CONCLUSION

The success of any research work depends on the results obtained there from and conclusion drawn therein, which could bring out the revealed or unrevealed or unexplored scientific explanations. The findings from any research work may further lead to better understanding, explanation, and profound knowledge in any specific area.

The present research was carried out to develop a bilayer tablet of losartan potassium using superdisintegrant sodium starch glycolate for fast release layer and combination of HPMC K4M and carbopol 940-P for sustaining release layer. The tablets showed an initial burst release to provide the loading dose of drug followed by sustained release up to 30 hours. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance.

Finally, bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. It 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers.

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