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Formulation and Evaluation of Bilayered Sustained Release Tablet of Candesartan Cilexetil and Captopril for treatment of Kimmelstiel Wilson Syndrome

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ABSTRACT

The main purpose of this study was to design bilayered sustained release tablet of Candesartan Cilexetil and Captopril to provide renoprotection in diabetic nephropathy. The bilayered tablet was prepared by using super disintegrant Cross Carmellose for Candesartan Cilexetil to provide its immediate release and Captopril was made sustained released by using HPMC K4M polymer. The prepared granules were characterized by different parameters like angle of repose, bulk density, tapped density, compressibility index, moisture content .The prepared bilayered tablet was characterized by physical and chemical parameters such as tablet thickness, hardness, diameter, weight variation, drug content, friability and in vitro drug release. The present studies concluded that bilayered tablet of Candesartan Cilexetil and Captopril is novel approach to prevent diabetic nephropathy.

Key words: Bilayered sustained release Tablet, Candesartan Cilexetil, Captopril, Immediate release

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INTRODUCTION

Bilayered tablets are designed to provide different drug release profiles like immediate release with extended release where in one layer of the layered tablet provides the initial dose which has rapidly disintegrating ability while other has extended release. The combination therapy minimizes dose dependent side effects, the presence of one agent can counteract the deleterious effect of other, maintenance of optimum drug level in the body and thus increases the patient compliances[1,2].Diabetic nephropathy (nephropatia diabetica), also known as Kimmelstiel Wilson syndrome, or nodular diabetic glomerulosclerosis [3] or intercapillary glomerulonephritis, is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. The goals of treatment are to slow the progression of kidney damage and control related complications. The main treatment, once proteinuria is established through ACE inhibitor drugs, which usually reduces proteinuria levels and slows the progression of diabetic nephropathy. In hypertensive Type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. Thus combining an ACE inhibitor and an ARB could more effectively oppose the RAS than either agent alone to provide renoprotection[4].

It has been reported that Captopril is dipeptide surrogate of proline which is Angiotensin Converting Enzyme inhibitor abolish the pressor action of A-1 but not that of A-2 .It induces hypotension by decreasing total peripheral resistance. The oral bioavailability is 70%, the plasma half life is 2 hours. ACE inhibitors have been found to prevent or delay end stage renal disease in Type 1 and Type 2 Diabetes. But now in combination with Angiotensin Receptor Blockers are used to provide synergistic effect in Diabetic Nephropathy. Candesaratan Cilexetil is an Angiotensin Receptor Blocker having highest affinity for AT-1 blocker and produces largely unsurmountable antagonism. The plasma half life is 8-12 hours[5]. Thus development of combination therapy has been found to be advantageous in pharmacokinetic point of view as it relies on the fact that the drug release from immediate releasing granules will leads to sudden rise in plasma concentration, while at the same time blood level is maintained at steady state from sustainable formulation.[6] Thus synergistic effect can be obtained from unit dosage form as this combination therapy leads to complete suppression of Renin Angiotensin System and achieve renoprotection in diabetic nephropathy. Candesartan Cilexetil was made as immediate release layer by using Cross Carmellose as superdisintegrant while captopril was made sustainable by using HPMC K4M polymer, the compression of granules of both the drugs leads to the development of bilayered sustained released tablet[7,8].

MATERIALS AND METHODS

Materials

Candesartan Cilexetil was obtained as a gift sample from Dr. Reddy's Laboratories Hyderabad, India, Captopril was obtained as a gift sample from Lupin Pharmaceuticals Ltd India

and HPMC K4M were obtained from the Colourcon India. Talc, Magnesium Stearate, Cross carmellose, Povidone, all other reagents and chemicals used were of analytical reagent grade.

Methods

The bilayered tablet of Candesartan Cilexetil and Captopril was developed stepwise. Separately with different ratios of binder different formulations of sustained released layer of Captopril was prepared by wet granulation technique while immediate release of Candeasartan Cilexetil was prepared by dry granulation. The most optimized formulation of both the granules was used for bilayered tablet formulation.

Preformulation Studies

This is the first step during the rational drug development of a dosage form. It is an investigation step to determine the physical and chemical properties of both the drug with and without the addition of excipients.[9]

FTIR Studies

The identification of two drugs was done by infra red spectroscopy by comparing the spectra of both the drug sample with the standard spectra.

Drug–Excipients Compatibility Studies:

During this study both the drugs Captopril and Candesartan Cilexetil were taken individually in the glass vials, then Candesartan Cilexetil and Captopril with their excipients in the ratio of 1:1 and 1:10 respectively were taken in the glass vial. The above mixtures were then kept under the accelerated conditions at 37±0.5°C (30^{o}C/65%RH) and 40^{o}C/75%RH) for 30 days in stability chamber. The overall processing was carried out for one month in open as well as in closed glass vials. The analysis of sample was carried out by withdrawing the sample at regular predetermined intervals of 10 days to evaluate the physical and chemical properties. Finally the formulation which has shown no sign of changes like color was selected for further processing as per the ICH guidelines.[10]

Preparation of Bilayer Tablet

Preparation of Immediate Release Layer of Candesartan Cilexetil

The immediate release layer of Candesartan Cilexetil was prepared by dry granulation technique, different formulations were prepared as per given in the Table 1.The drug Candesartan Celexetil, lactose and super disintegrant Cross Carmellose was pass through sieve no 40 then Talc and Magnesium Stearate was mixed and passed through sieve no. 60, finally all the ingredients were mixed geometrically in a polybag for uniform mixing Three different

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formulations (CL1, CL2 ,CL3) were prepared as per the procedure and the most optimized formulation was taken for further processing.[11]

Table 1.Preparation of Immediate Release Layer of Candesartan Cilexetil

S.NO	INGREDIENTS	CATEGORY	QTY/TAB (CL1) mg	QTY/TAB (CL2) mg	QTY/TAB (CL3) mg
1.	Candesartan Cilexetil	Active Ingredient	8	8	8
2.	Low substituted hydroxyl propyl cellulose	Binder	100	103	102
3.	Cross Carmellose	Super Disintegrant	12	12	12
4.	Talc	Glidant	4	4	4
5.	Magnesium Stearate	Lubricant	4	4	5
6.	Lactose	Diluent	q s	qs	qs

Preparation of Sustained Release Layer of Captopril

The sustained release layer of Captopril was prepared by wet granulation method. The drug Captopril with the different ratios of binder were taken as per given in Table 2.The drug binder and other excipients were passed through sieve no. 40.Lastly magnesium stearate was added and finally all the ingredients were mixed in the polybag for uniform mixing.Three different formulations (CP1, CP2, CP3) were prepared as per the procedure with different and the most optimized formulation was taken for further processing. [11,12]

Table 2.Preparation of Sustained Release Layer of Captopril

SNO.	INGREDIENTS	CATEGORY	QTY/TAB (CP1) MG	QTY/TAB (CP2) MG	QTY/TAB (CP3) MG
1.	Captopril	Active Ingredient	25	25	25
2.	HPMC K4M	Polymer	20	20	20
3.	Povidone	Binder	52	54	50
4.	Talc	Glidant	4	4	4
5.	Magnesium Stearate	Lubricant	4	4	4
6.	Lactose	Diluent	qs	qs	qs

Precompression Characterization

The granules of both immediate release layer as well as of sustained released layer were evaluated by properties like Tapped density, Bulk Density, Angle of Repose (Funnel Method) and Compressibility index and as per the values given in Table 3 the most optimized formulation of both the granules were taken to formulate bilayerd tablet.[9]

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Preparation of Bilayered Tablets

The bilayered tablet was prepared by using Canderatan Cilexetil immediate release granules and Captopril sustained release granules in oblong shape punch compression machine. During the formulation the sustained released layered granules were introduced first into the die followed by slight precompression for uniform distribution of granules then granules of immediate released layer was added then final compression was made to form bilayered tablet.[13]

Post Compression Characterization [9, 14, 15]

The prepared bilayered tablet was evaluated by the following parameters:

Weight Variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight, standard deviation and relative standard deviation were reported. The tablet compression machine was suitably adjusted to produce tablets of uniform weight.

Tablet thickness:

The thickness in millimetres (mm) was measured individually for 10 preweighted tablets by Vernier Calliper. The average thickness, standard deviation and relative standard deviation were reported.

Tablet hardness:

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilogram and the average hardness, standard deviations, and relative standard deviations were reported. Tablet hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness.

Friability:

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche tablet friabilator. The tablets were dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

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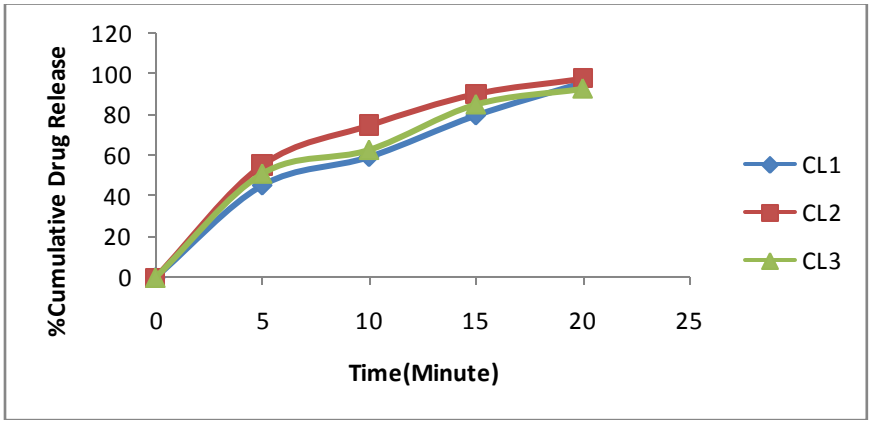
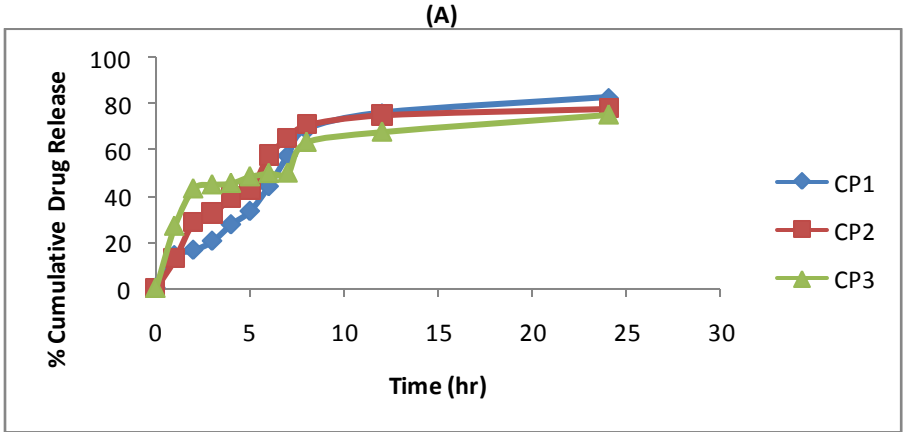
In vitro drug release:

In vitro drug release was performed for the prepared bilayered tablets as per USP Dissolution procedure over a 24 hour period for Captopril sustained release and 1-hour for Candesartan Cilexetil immediate Release. The release rate of Candesartan Cilexetil was determined in USP Paddle 2 Apparatus, 50 rpm speed using 0.35% polysorbate 20 in 0.05M phosphate buffer 6.8 pH as dissolution media and the release profile of Captopril was determined in 0.1 N HCl as dissolution media and the estimation done by UV spectroscopy (Figure 1).



(A)



(B)

Fig.1- Showing the drug release pattern (A)- Immediate release of Candesartan Celexetil (B)-Sustained release of Captopril

RESULT AND DISCUSSION

The FTIR studies identified the two drugs by comparison of peaks with the standard and also state that there was no incompatibility between the active ingredients and excipients. The overall granules of both layers were evaluated by different precompression characterization parameters. The preformulation studies were carried out for both Candesartan Cilexetil and Captopril and were analyzed for their physical and chemical properties. The bulk density and tapped density of optimized immediate release granules of Candesartan Cilexetil was determined as 0.072±0.65g/cm^3 and 0.155±0.08g/cm^{3}and the angle of repose, compressibility

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index, moisture content was found as 14.17 ±0.63^0 , 14.15±1.48% and 0.95% respectively (Table 3).The preformulation studies of optimized sustained released granules were also carried out by determining different physicochemical properties. The bulk density and tapped density was found as 0.157±0.06 g/cm^3 and 0.093±0.28 g/cm^3 respectively. The values of angle of repose, compressibility index and moisture content were determined as 14.78±0.87^0, 14.05±1.78% and 0.94% (Table 3). The different micromeretic properties indicate the good flow property of both granules which confirms the uniformity of contents and reduce the chances of weight variation. The most optimized formulations were found to be CL2 and CP2 which were taken for preparation of bilayerd tablet and the prepared tablet was characterized for different post compression parameters. It was observed that the thickness of prepared bilayered tablet was found to be 5± 0.2 mm. The weight variation, determined by taking 20 tablets, found to be 7.2±2% which is in the acceptable range. The percentage friability and hardness of bilayered tablet was 0.4%±0.2 and 6±0.2kg/cm^2. In vitro study state that Immediate release layer release drug about 97.59% within 15 to 20 minutes and the sustained release layer release drug about 82.66% within 24 hour.

Table 3. Precompression Characterization of Granules of both layers

S.No.	Codes	Bulk density gm/cm^3	Tapped density gm/cm^3	Angle of repose (^{0})	Compressibility index (%)	Moisture content (%)
1.	CL1	0.092±0.63	0.123±0.98	17.12±0.20	13.15±0.12	0.96
2.	CL2	0.072±0.65	0.155±0.08	14.17±0.63	14.95±1.48	0.95
3.	CL3	0.083±0.72	0.113±0.54	15.37±0.32	18.19±0.29	0.97
4.	CP1	0.198±0.11	0.101±0.57	17.21±0.62	15.11±0.28	0.91
5.	CP2	0.157±0.06	0.093±0.28	14.78±0.87	14.05±1.78	0.94
6.	CP3	0.165±0.09	0.165±0.88	16.92±0.81	19.87±0.82	0.92

CONCLUSION

Candesartan cilexetil and captopril loaded bilayered tablet having the potential for the abatement of kimmelstiel wilson syndrome due to its unique release patterns as candesartan cilexitel release very fast on the other hand captopril is release slowly from the bilayered tablet. The prepared bilayer tablet of both the drugs fulfills the entire physical requirement.

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