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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF LERCANIDIPINE CYCLODEXTRIN COMPLEXES

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ABSTRACT

Lercanidipine is very slightly soluble in water and present study attempt has been made to prepare and characterize inclusion complex of Lercanidipine with β-Cyclodextrin. The inclusion complexes prepared by different methods viz. Physical mixture, Kneading and Solvent evaporation methods. The inclusion complex prepared by Kneading method exhibited greatest enhancing in solubility and faster dissolution (93.95% drug release in 60 min) of Lercanidipine. Further, the inclusion complexes containing Lercanidipine: β-Cyclodextrin (1:2) was formulated into immediate release tablets which are stable and enhancing in solubility and faster dissolution. For the development of Lercanidipine tablets, the excipients selected were Starlac as diluents, Croscarmellose sodium and Sodium Starch Glycolate, crosprovidon as super disintegrants. The formulation blend was evaluated for Precompression studies and compressed tablets were evaluated for post compression studies and the results were found to be within the limits.

KEYWORDS: Lercanidipine, β-Cyclodextrin, Crospovidone, Croscarmellose sodium, Sodium starch glycolate.

INTRODUCTION

Oral drug delivery is the simplest and easiest way of drug administration, because of the greater stability, lesser bulk, accurate dosage, cheaper cost of production and easy process, solid oral dosage forms have advantages over other dosage[1] forms. Infact, all the poorly water soluble drugs after oral administrations are not well absorbed. And thus leads to decreased inherent efficiency of drugs. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system.

Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility[2] and dissolution properties of drugs play an important role in the process of formulation development. Problem of solubility is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work. Solid dispersion, solvent deposition, micronization are some vital approaches routinely employed to enhance the solubility[3] of poorly water soluble drugs. Each approach suffers with some limitations and advantages. Among all, complexation technique has been employed more precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs.[4]

Parkinson's disease[5] (PD) is also known as idiopathic or primary parkinsonism, hypo kinetic rigid syndrome/HRS, or paralysis agitans is a progressive, neurodegenerative disorder of the central nervous system. The motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantianigra, a region of the midbrain. Most of the cases the cause of this cell death is unknown. PD cannot yet be cured and sufferers get worse over time as the normal bodily functions, including breathing, balance, movement and heart function worsen, Later thinking and behavioral problems may arise with dementia commonly occurring in the advanced stages of the disease, whereas depression is the most common psychiatric symptom. Other symptoms include sensory, sleep and emotional problems.

Biperiden Hydrochloride is water insoluble compound coming under the chemical class of Pipereden derivative and functions as Anti-cholinergic, mainly used in the management of all kind of Parkinson’s disease. It composed of three primary structures, a hetero bicyclic ring, a phenyl ring and Pipereden ring. In The present work carriedout by enhancement of solubility parameter of Biperiden by inclusion complexes with the β-Cyclo dextrin inclusion complex.

MATERIALS AND METHODS

MATERIALS

Lercanidipine was obtained as a gift sample from S.K health care Pvt. Ltd Hyderabad and remaining excipients[7] β-Cyclodextrin, Sodium starch glycolate, Cross povidone, Sodium starch glycolate, Cross povidone, Croscarmellose sodium, MCCPH101, Starlac, Magnesium Stearate, Aerosil were obtained from Richer Pharmaceuticals Pvt Ltd, Hyderabad. All materials used were of analytical grade.

METHOD

Preparation of Inclusion Complexes With β-Cyclodextrin

1) Physical mixture: Lercanidipine with β-CD in different molar ratios (i.e. 1:1M, 1:2M) were mixed in a mortar for about one hour with constant triturating, passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

2) Kneading method: Lercanidipine with β-CD in different molar ratios (i.e. 1:1M, 1:2M) were taken. First cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and triturating is further continued for one hour. Slurry is then air dried for 24 h, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

C) Solvent evaporation Method: Drug and cyclodextrin in different molar ratio are dissolved in a common solvent to get a clear solution. Mixed the both solutions than the clear solution was kept for stirring on a magnetic stirrer till all the solvent got evaporated. The mass obtained was dried at 50°C and further sieved No. 80 or 100 sieve.

Table 1: Lercanidipine, β-Cyclodextrin Complexes.

Method	Drug to Carrier	Drug to Carrier ratio	Formulation Code
Physical Mixture	Lercanidipine: β-CD	1:1	LP1
	Lercanidipine: β-CD	1:2	LP2
Kneading Method	Lercanidipine: β-CD	1:1	LK1
	Lercanidipine: β-CD	1:2	LK2
Solvent Evaporation method	Lercanidipine: β-CD	1:1	LS1
	Lercanidipine: β-CD	1:2	LS2

Evaluation of Lercanidipine Inclusion Complexes

a) Drug Content Estimation

Inclusion complexes prepared by physical mixture, kneading and solvent evaporation methods were assayed for Lercanidipine content by dissolving a specific amount of the complexes (Drug Equivalent to 2mg) in methanol and analyzing for the Lercanidipine content spectrophotometrically at observed wavelength on a spectrophotometer.

b) Dissolution Characteristics

***In vitro* dissolution studies for Pure drug and its inclusion complexes:-** In vitro drug release studies for the pure Lercanidipine and prepared inclusion complexes were conducted in USP II paddle type dissolution apparatus in 500ml of medium at 37 ± 0.5^0C and at 50 rpm speed. The dissolution studies were carried out in 0.1N HCl. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at observed wavelegth by a UV – visible spectrophotometer. The amount of drug present in the samples was calculated.

Compression of Lercanidipine-B-Cyclodextrin Inclusion Complexes into Immediate Release Tablets by Direct Compression Method

After elucidation of best inclusion complex of drug with β-cyclodextrin which shows the most satisfactory invitro dissolution criteria and better solubility criteria, the particular complex was formulated as **Immediate Release Tablets of Lercanidipine β-cyclodextrin Inclusion Complex** by mixing it with selected excipients. In this present study, the best superdisintegrant among sodium starch glycolate (SSG), Crospovidone (CP) and croscarmellose sodium (CCS) were also screened out. Starlac selected as diluent, MCCPH101 as binder, talc as glidant and Magnesium stearate selected as lubricant. The prepared inclusion complex of drug and excipients were passed through sieve (#60) and mixed thoroughly. The drug and excipients mixture was finally compressed after lubricating with magnesium stearate for 10 min.

Table 2: Formulation of Lercanidipine Inclusion Complexes Tablets.

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Lercanidipine	-	-	-	-	-	-	-	**2**
2	Complexed drug (Lercanidipine: β-CD)	5.89	5.89	5.89	5.89	5.89	5.89	5.89	-
3	Starlac	68.51	66.01	66.01	66.01	63.51	61.01	58.51	67.6
4	MCCPH101	20	20	20	20	20	20	20	20
5	SSG	-	2.5						-
6	Crospovidone	-	-	2.5	-	5	7.5	10	-
7	CCS	-	-	-	2.5				4.8
8	Mag. Stearate	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
9	Talc	2	2	2	2	2	2	2	2
	Total Wt	100	100	100	100	100	100	100	100

*All values are expressed in mg/tablet.

Evaluation of post compression characteristics of tablets

A. Weight variation test

Twenty tablets were selected randomly, weighed individually and average weight was calculated. Not more than two of the individual weights was deviated from the average weight by more than the percentage shown in the table and should deviate by more than twice that percentage.

B. Hardness test

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Monsanto tablet hardness tester. The tablet was held between the edges of the fixed and movable part of the instrument. The scale was adjusted by sliding, so that the zero on the scale coincides with the pointer. The adjustable knob was moved slowly till the tablet breaks. The hardness was measured in kg/cm^2.

C. Thickness

The thickness of prepared tablets was measured, by placing the tablet between the hands of vernier calipers and the thickness of the tablet is read from the vernier scale.

D. Friability

Friability is the measure of tablet strength. About 10 tablets were carefully dedusted and weighed. The tablets were placed in friability test apparatus and rotated 100 times at 25 rpm for 4mins. The tablets were removed, dedusted and weighed. The percent friability was calculated using the formula.

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} X\ 100$$

Drug content uniformity

From each batch 20 randomly selected tablets were weighed accurately and powdered in a clean and dry glass mortar with pestle. Powder equivalent to 2 mg of drug was transferred into 20 mL volumetric flask containing methanol gives 100 µg/ml solution(Stock-1). from the stock-1 4 µg/ml solution was prepared by taking 0.4 ml of stock-1 and make up to 10ml with methanol. The absorbance of 0.4 µg/ml solution was measured at 258 nm, using methanol as a blank.

E. Wetting time

Wetting time of tablet was determined using a simple procedure. A piece of double folded tissue paper was placed in a petri plate containing 6 ml of water and 2 drops of eosin. The tablet was placed on the paper and the time for complete wetting of upper surface of the tablet was measured in seconds.

F. Disintegration Time

The disintegrator as per USP uses 6 glass tubes that are 3 inches long, open at the top and held against a 10-mesh screen at the bottom end of the basket rack assembly. The disintegration time was determined by the tablet is placed in each tube and the basket rack is positioned 0.1N HCl at 37 ± 2^0C, such that the tablets remain 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. A standard motor device is used to move the basket assembly containing the tables up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Then the time was measured, when all the particles passed through the 10-mesh.

G. Dissolution studies

In vitro drug release studies for the prepared Lercanidipinetablets were conducted in USP II paddle type dissolution apparatus in 500ml of medium at 37 ± 0.5^0C and at 50 rpm speed. The dissolution studies were carried out in 0.1N HCl. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 240 nm by a UV–visible spectrophotometer. The amount of drug present in the samples was calculated.

RESULTS AND DISCUSSION

In the present work inclusion complexes of Lercanidipine were prepared with β-cyclodextrin by physical mixture, kneading method and Solvent evaporation method. The complexes were prepared in different molar ratios of drug and cyclodextrin namely 1:1 and 1:2. Prepared complexes were evaluated for *in vitro* drug release studies All the prepared inclusion complexes were white and fine without any stickiness. The drug content of the inclusion complexes was quite uniform as can be observed from the Table 7.4. The percent drug content of the complexes was found to be in the range of 98.35% to 102.493%. with low values of standard deviations.

Table 3: Drug content of complexes.

S.No	Complexation method	Drug: cyclodextrin Ratio	Complex Code	Amount of drug present in 2mg Equivalent powder	%Drug content
1	**Physical Mixture Method**	1:1	LP1	2.02	101
		1:2	LP2	1.967	98.35
2	**Kneading Method**	1:1	LK1	2.044	102.2
		1:2	LK2	1.988	99.4
3	**Solvent Evaporation Method**	1:1	LS1	2.002	101.1
		1:2	LS2	2.04	102

The dissolution rate of Lercanidipine from various inclusion complexes was found to be 79.6106 to 93.9549% in 60 minutes, when compared to pure drug which exhibited only 28.0821% of drug in 60 minutes. The dissolution data of various complexes prepared by various methods were fitted into mathematical models such as zero order and first order models to assess the kinetics. Dissolution data for inclusion complexes obeyed first order kinetic model.

Inclusion complexes of Lercanidipine prepared with β-CD exhibited release of 75.68%, 84.68%, 87.96%, 94.68%, 86.89% and 90.46% from LP1, LP2, LK1, LK2, LS1 and LS2 respectively in 60 minutes, using 0.1N HCL as dissolution media. A marked improvement in dissolution rates of Lercanidipine were observed with LK2 prepared by Kneading method. The higher dissolution rates observed with inclusion complexes prepared by kneading may be due to better interaction of drug and β-cyclodextrin.

Table 4: Comparison of In-vitro dissolution data of all formulations (Pure drug-LS2).

Time (min)	% CDR						
	PURE DRUG	LP1	LP2	LK1	LK2	LS1	LS2
0	0	0	0	0	0	0	0
5	7.81	38.82	39.64	48.68	54.89	39.64	50.36
10	21.63	56.84	59.4	59.67	75.61	56.84	58.42
15	26.32	60.26	64.57	76.84	84.62	72.66	68.96
30	27.58	63.98	79.64	82.54	85.67	78.28	77.84
45	28.84	70.24	81.69	86.94	90.24	84.62	88.64
60	29.02	75.68	84.68	87.96	94.68	86.89	90.46

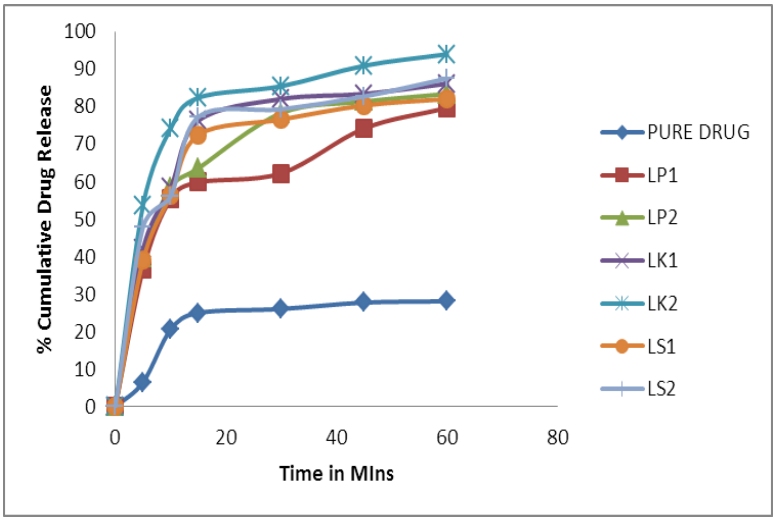

Figure 1: Dissolution Rate Data Profile graph of Lercanidipine and its complexes.

The Lercanidipine Tablets prepared by direct compression method containing LK2 inclusion complexes(drug: β-cyclodextrin ratio is 1:2 and the complex was prepared by Kneading method) were evaluated for their physical characteristics like size, shape, thickness and appearance and from this data all series of Tablets prepared were found to be good.

Table 5: Results of Post-compression parameters.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Hardness (avg ±S.D)	3.46	3.23	3.26	3.3	3.33	3.23	3.23	3.26
Thickness (avg ±S.D)	2.5	2.5	2.51	2.52	2.54	2.51	2.503	2.513
Friability	0.497	0.231	0.264	0.069	0.231	0.296	0.231	0.264
Weight variation	100.55	100.15	99.95	99.8	100.3	99.8	100.15	99.95
Wetting Time (Sec)	38	24	28	29	18	10	22	28
Disintegration time	43	27	32	33	19	16	15	20
% Drug content	101.35	99.78	99.89	101.54	100.62	100.62	99.97	99.8

Values are mean ± SD, n=3.

The hardness of the Lercanidipine tablets is 3.23±0.00577 to 3.46±0.0577 kg/cm^2. The disintegration time of Tablets is in between 16 to 43 sec. the friability percentage and weight variation and wetting time of all the Tablets were found within the standard limits.

Table. No.6: In-vitro Dissolution Studies of all Formulations.

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	**0**	0	0
5	54.86	55.46	54.86	54.33	56.38	56.04	56.72	8.2
10	68.96	69.68	69.18	71.08	74.84	76.19	75.15	24.65
15	76.54	77.42	76.12	83.38	87.46	87.87	88.84	28.64
30	84.62	83.24	82. 73	86.24	94.29	94.59	95.13	39.04
45	89.34	90.12	89.31	89.17	95.66	96.87	96.24	42.12
60	93.56	96.24	95.62	93.61	96.34	98.78	97.25	46.23

The dissolution of Lercanidipine Tablets prepared with LK2 complex and super disintegrants was higher when compared with Lercanidipine Tablets prepared without super disintegrants. Disintegration time and wetting time of Lercanidipine Tablets and it was found that the presence of CCS shown better results when compared with Crospovidone and SSG. The increased concentration of CCS showed improved dissolution criteria along with faster disintegration and wetting time. Formulation F6 containing 4.8% of SSG (when compared with total Tablet weight) showed 98.78% drug release in 60minutes. Further increasing in the SSG concentration (7%) decreased the amount of drug release when compared with the F6 formulation.

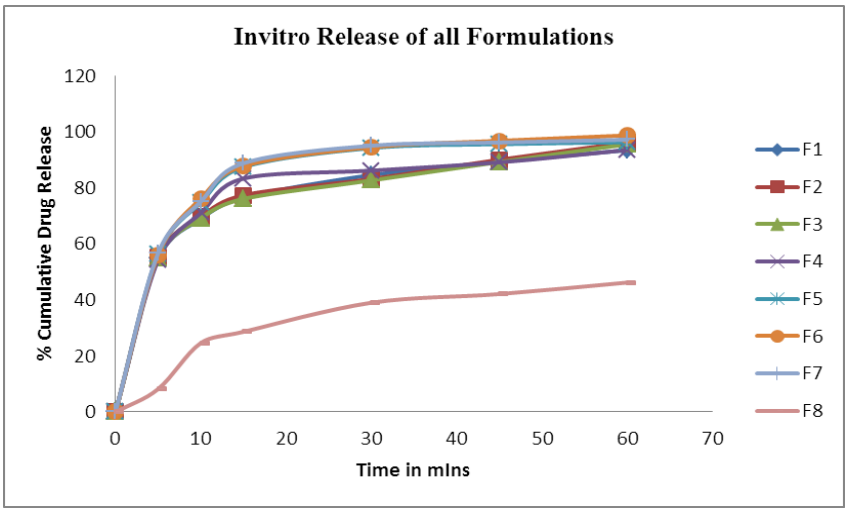

Figure 2: Zero order release Plots for all formulations.

The dissolution data of Lercanidipine Tablets were fitted into mathematical models such as zero order and firs order models to assess the release kinetics. The dissolution data for all 8 formulations (F1 to F8) follows first order release kinetics.

CONCLUSION

The present work has been undertaken with an overall objective of studying the complexation of Lercanidipine with β-cyclodextrin to evaluate the feasibility of enhancing it solubility, dissolution rate, bioavailability and therapeutic efficacy. The feasibility of formulating the cyclodextrin complexes into tablets with enhanced dissolution rate characteristics was also investigated.

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REFERENCES

1. Patil J S, Kadam D V, Marapur S C, et al. Inclusion complex system; A novel technique to improve the solubility and bioavailability of poorly soluble drugs: A Review. Int. J. Pharm. Sci., 2010; 2: 29-34.
2. Loftsson Thorsteinn, Marcus E Brewster. Pharmaceutical applications of cyclodextrins. Journal of Pharmaceutical Sciences, 1996; 85(10): 1017-1026.
3. Marcus E Brewstera, Thorsteinn Loftsson. Cyclodextrin as pharmaceutical solubilizers. Adv. Drug Delivery Reviews. 2007; 59: 645-666.
4. K.P.R. Chowdary and G Kamalakara Reddy. Complexes of Nifedipine with β-and hydroxypropyl β-cyclodextrins in the design of Nifedipine SR tablets. Indian Journal of Pharmaceutical Sciences, Mar-Apr. 2002; 142-146.
5. Sanoferjan AM, Nanjundaswamy NG. Mahesh S and Narasimhamurty S. Formulation and evaluation of β-cyclodextrin complexes of tenoxicam. Ind. J. of Pharm. Sci., March 2000; 62(2): 119-121.
6. Prasanna Kumar Desu, P. Malleswara Rao, A. M. S. Sudhakar Babu, K. Navya Sree, N. S. V. Teja Rameswarapu, K. L. N. Mallikharjuna Rao "Formulation Development And Invitro Evaluation Of Immediate Release Tablets Of Biperiden Hcl Cyclodextrin Complexes", International Journal of Research in Pharmaceutical and Nano Sciences, 2013; (2)(6): 757-767.

7. Chowdary KPR, Vijaya Srinivas. Effect of polyvinyl pyrrolidone on complexation and dissolution rate of β and HPβ-CD complexes of celecoxib. Ind. J. Pharm. Sci. Sept-oct. 2006; 631-634.
8. Muller BW, Albers E. Effect of hydrotropic substances on the complexation of sparingly soluble drugs with cyclodextrin derivatives and the influence of cyclodextrin complexation on the pharmacokinetics of the drugs. J Pharm Sci., 1991; 80: 599Y604.
9. Pasam Venkateswara Rao and Prasanna Kumar Desu, "Formulation Development and Invitro Evaluation of Immediate release tablets of Neverapine Cyclodextrine Complexes" The Pharma Invotation: TPI, 2016; 5(6): 110-114.
10. Tayade NG, Nagarsenker MS. Preparation, characterization and evaluation of HPβ-CD inclusion complexes of antimalarial drug. Scientific abstract 54th IPC Pune, Sept. 2002; 156.
11. Brahmaiah.B, Prasanna Kumar Desu, Sreekanth Nama, S.Satish Babu, Formulation and evaluation of extended release mucoadhesive microspheres of simvastatin, International Journal of Pharmaceutical and biomedical Research, ISSN No. 0976-0350, March 2013; 4(1): 57-64.