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Formulation and Evaluation of Mouth Dissolving Tablets of Lercanidipine Hydrochloride Oral Disintegrating Tablets

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ABSTRACT

Lercanidipine is an antihypertensive drug. It is a dihydropyridine class of calcium channel blockers. It is extremely bitter. The reason for this explo-ration was to build up a non-bitter orally breaking down the tablet of inade-quately solvent medication viz Lercanidipine. The bitterness of drug, masked through complexing Tulsion 339 in various ratios. Sodium starch glycolate, crospovidone, low substituted hydroxypropyl cellulose selected as super dis-integrants in the formulation. The formulated tablets were assessed for vari-ous properties like Drug content, crushing strength, friability, wetting time, water retention proportion, breaking downtime and in-vitro disintegration time and dissolution studies. The disintegration time obtained in the range between 38.46-51.40 seconds. Release studies observed between 5 to 30 min-utes. From the prepared formulations, formulation using Low substituted hydroxypropyl cellulose with 5% concentration showed 98.89% drug release within 30minutes. Thus F9 was considered as best among the other formu-lations With effective dissolution and improves patient intake. Drug release Kinetic analysis (r^2) based on best curve fitting method for optimized lercan-dipine formulation showed first order kinetics proves that the drug release depends upon its concentration.

INTRODUCTION

The oral route of drug administration has been gen-erally accepted and up to 50-60% of total dosage forms are administered orally. Solid dosage forms viz tablets and capsules are worldwide accepted dosage forms due to its precise dose, self medica-tion, a non-invasive route which makes the soliddosage forms as patient user-friendly. However, the substantial drawbacks of these traditional dosage formulations include dysphagia for pediatric and geriatrics patients. This problem mainly encoun-ters 35% of the general population. These tradi-tional tablets need water for administration. This issue causes difficulty in swallowing when water is not available. Hence Dispersible tablets plays a dominant role for these purposes, which can quickly dissolve or disintegrate in the oral cavity and have drawn a good interest to the patients (Saini and Garg, 2019).

The word “orodispersible tablet” was adapted by European Pharmacopoeia as a tablet to be inserted in the mouth where it easily disappears before swal-lowing, suggesting maximum DT of 3 min as calcu-lated in a conventional disintegration test appara-tus. Other synonyms of ODT includes quick melts, rapid melts, fast dissolving, fast disintegrating, rapid dissolve or mouth dissolving tablets (Mohanachan- dran et al., 2011).

The bitter taste of orally administered medicinal products often results in patient non-compliance with the use of medicinal products, especially for children and the elderly. Sadly, most medicines have a natural, bitter taste that can cause a burning sen- sation in the throat or mouth. In particular, a bit-ter taste can reduce patient compliance and thus reduce the efficiency of pharmacotherapy (Suryade- vara *et al.*, 2017).

The Drug Lercanidipine HCl used in the present study is a type-II biopharmaceutical classification system since it has low solubility and high perme-ability. Its recommended for relief of seasonal aller- gic rhinitis related symptoms in adults and children 2 years of age and is intended for chronic idiopathic urticaria therapy in adults and children 6 months of age and older (Suresh *et al.*, 2007). Lercanidipine HCl shows low bioavailability so its aqueous solubil- ity should be targeted by a Bioavailability Improve- ment strategy.

Chemically Lercanidipine Hydrochloride, a potent antihypertensive and antianginal drug of 2-[(3, 3-diphenylpropyl) methylamine]-1, 1-dimethylethylmethyl 1,4-dihydro-2,6dimethyl- 4-(3-nitrophenyl)-3,5 pyridine carboxylic ester hydrochloride (Saini and Garg, 2019).

It is used in the treatment of Hypertension, due to its selectivity and specificity on the smooth vascular cells.

MATERIALS

Lercanidipine and Polacrallin potassium (Tulsion 339) was obtained from Spectrum pharma research solutions, Mumbai, Sodium starch glycolate, Crosspovidone, Low substituted hydroxypropyl cellulose, Sodium hydroxide and Sucralose were obtained from SD fine chemicals, Mumbai, Micro- crystalline cellulose, Magnesium stearate, Talc were obtained from Central drug house (p) Ltd, New Delhi, potassium dihydrogen phosphate and sodium hydroxide were obtained from Finar chemicals ltd, Ahmedabad.

Drug and Excipient Compatibility by using FTIR

The interaction study between the drug and Tul- sion 339 and other excipients were performed using FTIR. The pellets were prepared on KBR press. The spectra were recorded over the wavenumberrange of 3500 cm^{-1}.The pictorial optimized formulation shown in Figure 2.

Standard calibration curve of pure Lercanidipine using U.V. spectroscopy

Preparation of standard stock solution

Standard stock solution of Lercanidipine was pre- pared by dissolving accurately weighed 100mg of Lercanidipine in the little quantity of phosphate buffer pH-6.8 in 100ml volumetric flask. The Vol- ume was made up to the mark using the same buffer. From this 10ml was pipette out and Volume was made up to 100 ml with phosphate buffer pH- 6.8 to get standard stock solution containing drug 100μg/ml.

Spectrophotometric scanning of Lercanidipine

From the stock solution, the ultraviolet scan was taken between the wavelength 200-400nm. Which gave the highest peak at 240nm and the same was selected for Lercanidipine estimation.

Preparation of standard plot of Lercanidipine

From the standard stock solution series of dilution were made to 5, 10, 15, 20, 25, 30 μg/ml solution using phosphate buffer pH-6.8 and corresponding absorbance was measured at 240 nm in a U.V spec- trophotometer. Results are depicted in Figure 1.

Formulation development

As the drug is highly bitter first attempt was made to mask the bitterness of the drug by using ion exchange resin such as Tulsion 339. Several trails were carried out with different ratios such as 1:1, 1:2, and 1:3, respectively.

Preparation of drug resinate complex

Lercanidipine was complexed with ion exchange resin using polacrillin potassium (Tulsion 339) to masks the taste with the following procedure.

Step-I

Drug resin complex were prepared in the ratios of 1:1, 1:2, 1:3, respectively.

Step-II

Drug resin complexation was prepared by a simple aqueous binding process. The ion-exchange resin particles were uniformly dispersed in a drug ethano- lic solution with a mass ratio under magnetic stir- ring to achieve an equilibrium state.

Step-III

The complexes were subjected to filtration and cured with deionized water to decant the unbound drug and other ions. The complexes further dried in a hot air oven for 4 h at 40 ◦C to get powdered mass and stored in a tight glass vial.

Step-IV

From the above complexes, the best complex is selected based on Drug loading efficiency.

Characterization of the complex for drug content

From the prepared Drug resonated- complex, equiv- alent to 8mg of drug was stirred through magnetic stirrer until the entire drug was leached out from the complex using 100ml of 6.8-phosphate buffer for 60min. The final solution was filtered through Whatman's filter paper after serial dilutions using pH-6.8 phosphate buffer and the drug content was assayed spectrophotometrically at 240 nm.

From the observations Drug & Tulsion 339 complex ratio, as shown in Table 1, 1:2 used for study due to the high percentage of drug content in the complex.

Interpretation of drug- resinated complex palatability

Palatability was determined by time intensity method. Here five human volunteers were selected and sufficient quantity of sample was placed in the mouth for 10 sec. to determine any bitter levels from the given resin complex based on 0-3 scale. A higher value is the sign of strong bitter taste.

Evaluation of the lubricated blend Angle of repose

A glass funnel was selected with a stem of 15-30 mm and fixed to the funnel stand; Below which a graph paper was placed to determine the flowabil- ity of granules. Prepared Granules were assessed to form a heap. Heap circumference was marked and the pile height was measured using two rulers. The height was measured and noted it as (h). The area (πr^2) was determined, radius(r) was calculated and substituted in the formula (θ =$\tan^{-1}$ h/r), to obtain the angle of repose. Repeated the experi- ment twice more and calculate the average angle of repose (Kaur *et al.*, 2020).

$$\tan(\theta) = r/h$$

$$Therefore\ \theta = \tan{-1}\,(\,h/r\,)$$

Bulk density

It is an essential parameter to determine the powder compressibility and packing characterstics before the compression process. It can be deter- mined as follows,

$$Bulk\ density = Weight\ of\ powder\ /\ Bulk\ volume$$

Tapped densit y

It is determined using the standard procedures and calculated as follows,

$$Tapped\ density = \frac{Weight\ of\ powder}{Tapped\ volume}$$

Carr's Index

It is an essential parameter to determine the powder compressibility and packing characterstics before the compression process**.** It can be deter- mined as follows,

$$Carr's\ index\ (\%) = \frac{[(TD - BD)]}{TD} \times 100$$

Hausner's Ratio

Hausner's Ratio is a number of co-related to a pow- der's flowability. The Hausner Ratio formula is as shown in the equation below

$$Hausner's\ Ratio = \frac{TD}{BD}$$

Preparation of tablet

Using the lubricated blend as shown in Table 2, Ler- canidipine Orally disintegrating tablets were com- pressed on 16 stations cadmach rotary compression machine equipped with 9mm biconcave punches and constant hardness is maintained for all the tablets.

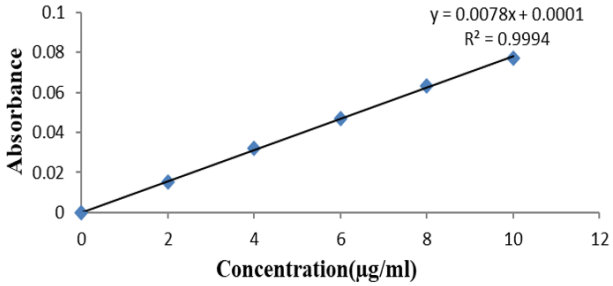

Figure 1: Standard calibration of Lercanidipine Hydrochloride

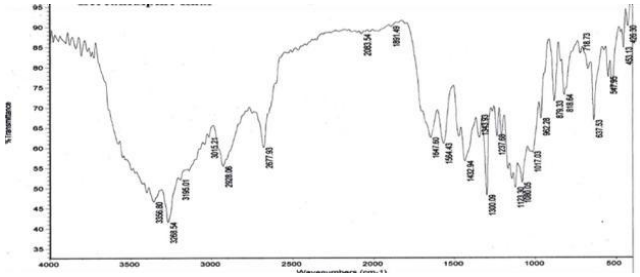

Figure 2: FTIR of Final formulation

Evaluation of tablet

Genera l appearance

Five tablets were randomly selected, checked for color, odor and shape and the data was noted

Thickness

Thickness and diameter was measured for five tablets from all the batches using vernier calipers.

Table 1: Drug Resonated complex formulation

S.No	Drug& Tulsion 339 Ratio	%Drug Content in Complex
1	1:1	84.94
2	1:2	96.88
3	1:3	94.13

Table 2: Formulation of Lercanidipine oral disintegrating tablets prepared by direct compression method

S.No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	DRC(1:2) equivalent to 10 mg drug	30	30	30	30	30	30	30	30	30
2	SSG	6	8	10	-	-	-	-	-	-
3	CP	-	-	-	6	8	10	-	-	-
4	L-HPC	-	-	-	-	-	-	6	8	10
5	MCC	108	104	102	108	104	102	108	104	102
6	Sucralose	2	2	2	2	2	2	2	2	2
7	Mg.Sterate	2	2	2	2	2	2	2	2	2
8	Talc	2	2	2	2	2	2	2	2	2
9	Total Weight	150	150	150	150	150	150	150	150	150

Table 3: Pre-compression parameters

Formulation code	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio	Angle of repose (Θ)
F1	0.535±0.011	0.668±0.014	19.91±0.13	1.24±0.052	23.32±0.23°
F2	0.532±0.010	0.670±0.023	20.59±0.13	1.25±0.043	24.18°±0.13°
F3	0.532±0.004	0.667±0.017	20.23±0.28	1.24±0.023	21.16°±0.21°
F4	0.530±0.018	0.661±0.023	19.81±0.15	1.24±0.058	21.01°±0.31°
F5	0.533±0.014	0.650±0.025	18.50±0.29	1.22±0.045	19.35°±0.11°
F6	0.549±0.013	0.673±0.023	18.42±0.18	1.22±0.021	25.35°±0.15°
F7	0.532±0.018	0.650±0.025	18.15±0.08	1.22±0.073	21.06°±0.23°
F8	0.545±0.004	0.651±0.014	16.28±0.09	1.19±0.058	23.12°±0.21°
F9	0.533±0.013	0.650±0.011	18.50±0.15	1.22±0.035	24.32°±0.23°

Table 4: Post compression parameters

S.No	Formulation code	Weight Variation (mg)	Uniformity of Thickness (mm) (n=3)	Hardness (kg/cm2) (n=3)	Friability %
1	F1	200±0.20	2.73±0.01	3.79±0.15	0.46±0.035
2	F2	198±0.89	2.71±0.04	3.62±0.26	0.47±0.015
3	F3	199±0.75	2.83±0.01	3.53±0.14	0.33±0.025
4	F4	200±0.23	2.76±0.03	3.96±0.25	0.60±0.015
5	F5	200±0.2	2.65±0.04	3.76±0.22	0.53±0.055
6	F6	198±0.25	2.53±0.05	3.84±0.26	0.40±0.065
7.	F7	200±0.20	2.68±0.04	3.36±0.34	0.67±0.053
8.	F8	199±0.75	2.79±0.07	3.71±0.25	0.40±0.065
9.	F9	200±0.23	2.88±0.01	3.43±0.20	0.66±0.035

± S.D, †n=3 average of three Observations, ‡mm-Millimetre

Table 5: Post compression parameters

S.No	Formulation code	Wetting Time (Sec) (n=3)	Water Absorption Ratio(n=3)	In-vitro Disintegration Time (sec)	In-vitro Dispersion Time (sec)	Drug Content (%)
2	F2	42.76±0.72	37.36±1.30	51.40±1.06	74.57±1.49	98.3
3	F3	33.38±1.25	36.92±1.25	48.07±1.20	70.12±1.51	98.6
4	F4	38.66±1.56	27.10±1.41	52.81±1.21	72.74±1.36	99.13
5	F5	34.19±1.02	38.64±1.01	48.13±0.13	71.17±1.23	98.12
6	F6	33.38±1.58	35.31±1.02	41.19± 0.98	65.12±1.20	98.63
7.	F7	33.72±1.85	29.45±1.11	49.12±1.23	67.17±1.24	98.3
8.	F8	32.65±1.72	33.71±1.20	40.81± 1.15	63.18±1.05	98.6
9.	F9	31.46±1.01	38.01±1.23	38.46±0.12	62.00±1.03	99.8

* ± S.D, †n=3average of three Observation

Table 6: Dissolution parameters for prepared Formulations and marketed preparation

Table 6: Dissolution parameters for prepared Formulations and marketed preparation

Time (min.)	Cumulative % Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed prepa-ration
0	0	0	0	0	0	0	0	0	0	0
5	35.53 ±1.25	50.41 ±1.11	50.85 ±1.23	52.63 ±1.65	53.58 ±1.11	70.35 ±1.11	71.1 ±1.11	72.98 ±1.12	75.58 ±1.15	50.57 ±1.12
10	42.34 ±1.10	52.56 ±1.13	55.87 ±1.21	54.38 ±0.87	58.68 ±0.98	77.93 ±0.89	77.65 ±0.93	79.78 ±1.53	81.93 ±0.98	65.35 ±1.15
15	43.38 ± 0.86	60.78 ± 1.17	63.63 ± 0.53	64.63 ± 0.85	64.86 ± 1.53	86.93 ± 1.13	82.53 ± 1.05	84.84 ± 1.55	91.63 ± 0.83	68.43 ± 0.89
20	46.53 ± 0.95	63.48 ± 1.11	68.67 ± 0.79	72.63 ± 1.25	71.57 ± 1.12	89.93 ± 0.89	83.13 ± 1.01	85.58 ± 1.13	93.57 ± 1.51	75.78 ± 1.53
25	49.56 ±1.15	65.89 ±0.98	73.23 ±0.83	75.98 ±1.13	78.13 ±1.13	91.75 ±1.51	85.13 ±1.13	88.89 ±1.11	95.63 ±1.48	85.78 ±1.01
30	54.83 ±1.12	71.35 ±0.91	75.23 ±1.12	80.13 ±0.78	79.23 ±1.11	92.58 ±0.58	93.23 ±1.11	95.73 ±1.10	98.78 ±1.11	85.23 ±1.10

Data represent mean ± SD, n=3

Table 7: Different Dissolution kinetic parameters of optimized formulation F9

Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer Pep-pas R^2
F9	0.595	0.94	0.851	0.710

Table 9: Stability study of in-vitro dissolution for formulations F9 at stored at Room Temperature

S.No	Time (Mins)	Cumulative %Drug Release		
		Controlled F9	F9	
			After 15 Days	After 1 Month
1	0	0	0	0
2	5	75.58±1.14	74.56±1.17	74.48±1.17
3	10	81.93±0.97	81.92±0.98	81.90±0.89
4	15	91.63±0.81	91.62±0.83	91.61±0.15
5	20	93.57±1.51	92.56±1.51	92.55±1.12
6	25	95.63±1.47	95.61±1.50	95.31±1.31
7	30	98.78±1.10	98.11±1.10	98.05±1.11

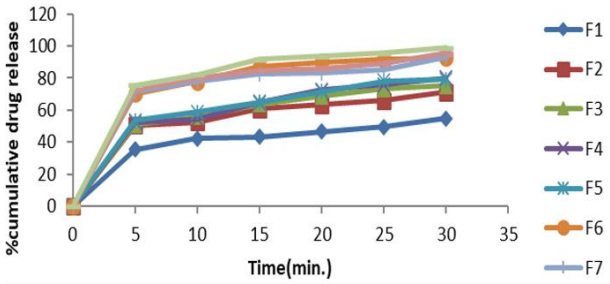

Figure 3: Dissolution Profile of formulations F1-F9

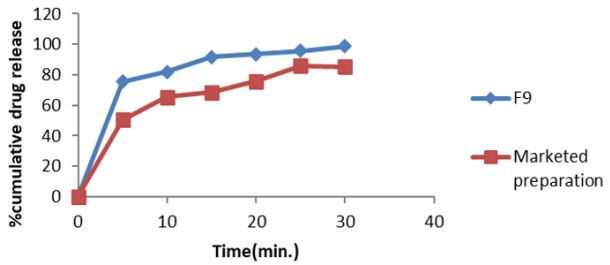

Figure 4: Comparative dissolution profile for F9 and Marketed preparation

Hardnes s test

It was tested using 'Monsanto' Hardness tester. Five tablets were randomly selected and placed between the two plungers using a compressible spring on a stainless steel barrel. The initial reading was noted when the lower plunger was in tablet contact and subjected forcilbly to move the upper plunger until the tablet breaks by appling compressional force. Barell containing Pointer on the guage indicates the force, which is a measure of the hardness of tablet strength.

Weight variation test

20 tablets were randomly selected and determine the individual weights and their average Weight. Calculate the percentage deviation of IP standards.

Friability test

For this test, Roche friabilator was used to assess the friction and shock to overcome chipping and break- ing of tablets during compression and handling. It has a plastic chamber spins at 25rpm y lowering the tablets from a distance of six inches for each revolu- tion. Usually, preweighed tablets are placed in the friabilator subjected to 100 revolutions. The tablets are then de-dusted and reweighed (Panigrahi *et al.*, 2010).

Compressed tablets weigh less than 1.0% of their initial Weight are acceptable for consideration.

***In-Vitro* Dispersion Time**

It is the time takenfor the tablet to fully disintegrate into fine particles. Three tablets were randomly cho- sen from each batch and *In- vitro* dispersion time was performed using 6.8 phosphate buffer (Liber- man *et al.*, 1987).

***In-Vitro D* isintegratio n Test**

It is one of the most important criteria for the pre- pared tablets to meet out the needs. It can be per- formed using disintegration Test apparatus IP. Each tablet is placed into one tube of the glass assem- bly. The entire assembly is suspended in the beaker containing distilled water and subjected for running until the tablet disintegrates, time was noted.

Standard

The tablets must disintegrate within 30seconds when subjected to a disintegration test examination.

Taste evaluation

Taste assessment using time intensity process con- ducted in 6 volunteers. A tablet was placed in the oral cavity for 10 seconds and the recorded bit- terness levels and continued the test for different time intervals and repeated the test for compari- son (Yunxia *et al*., 1996).

Water absorption ratio

A tissue paper of the desired size is taken, folded twice and kept on the surface of a small Petri dish filled with 6 ml of distilled water. The sin- gle tablet was taken and placed on the Petri dish containing paper. Complete wetting time was observed and recorded. The last tablet was then reweighed (Kuchekar *et al*., 2003).

$$\text{Water absorption ratio} = \frac{final\ weight - initial\ weight}{initial\ weight} \times 100$$

Wetting time

Tissue papers cut down to a circular shape of 10cm diameter in size and dipped in 6ml(w/v)of Methy- lene blue dye solution in a Petri dish. A tablet was carefully placed on the surface. The time at which colour development on the upper tablet surface is observed (Yunxia *et al.*, 1999).

Drug content uniformity test

From each formulation**,** 5 tablets were randomly selected weighed and powdered. Equivalent quan- tity of 100mg drug was transferred to 100 ml vol- umetric flasks. The powder substance is solubilised with small pH-6.8 phosphate buffer volume and sub- jected for sonication for half an hour. Later solu- tion was filtered and the desired Volume was made using pH-6.8 phosphate buffer. The final concen- tration was diluted to 10μg/ml and absorbance was observed at 240nm (Seager, 1998).

***Invitro* drug release**

Drug release studies carried out using USP type- (paddle) apparatus at a speed of 50 rpm from a specified time period of 30mins at temperature (37 0.5^{o}c) (Mallet, 1996). The samples were fil- tered and the amount of drug measured at 240 nm using UV Visible Spectrophotometer (Pahwa and Gupta, 2011). All the post compression parameters were tabulated in table Tables 4, 5 and 6 respectively.

Kinetic study

The dissolution data was subjected to various kinetic models such as zero order, first order, Higuchi, Korsmeyer Peppas etc. to know the drug release kinetics of the optimized formulation (Fig- ures 3 and 4). From the above observations, Kinetic analysis (r^2) for the optimized formulation of Lercanidipine shows First order kinetics (R^2=0.94) indicated that the drug release depends upon its concentration (Tables 7, 8 and 9).

CONCLUSIONS

In the present research investigation, an attempt was made to explore by use of cation exchange resins i,e: Tulsion- 339 as a taste masking agent in the formulation of oral disintegrating tablets of Ler- canidipine Hcl.Drug resin complex was prepared in the ratio of 1:1,1:2, 1:3 among them maximum drug content was observed for1:2 ratio i,e.. 96.88% which was further finalized for formulations using super disintegrants sodium starch glycolate, cross povidone and L-HPC. From the above results, F9 with L-HPC showed max- imum drug release 98.89% in 30 min and showed less disintegration of 38.46 seconds. There is no significant change in stability studies. Lercandipine tastes masked ODT are successfully prepared using minimum excipients and a simple method of manu- facture.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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