Formulation and Evaluation of Taste Masking 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 exploration was to build up a non-bitter orally breaking down the tablet of inadequately 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 disintegrants in the formulation. The formulated tablets were assessed for various 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 minutes. From the prepared formulations, formulation using Low substituted hydroxypropyl cellulose with 5% concentration showed 98.89% drug release within 30 minutes. Thus F9 was considered as best among the other formulations With effective dissolution and improves patient intake. Drug release Kinetic analysis ($r^2$) based on best curve fitting method for optimized lercanidipine formulation showed first order kinetics proves that the drug release depends upon its concentration.

INTRODUCTION

The oral route of drug administration has been generally 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 medication, a non-invasive route which makes the solid dosage forms as patient user-friendly. However, the substantial drawbacks of these traditional dosage formulations include dysphagia for pediatric and geriatrics patients. This problem mainly encounters 35% of the general population. These traditional 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 swallowing, suggesting maximum DT of 3 min as calculated in a conventional disintegration test apparatus. Other synonyms of ODT includes quick melts, rapid melts, fast dissolving, fast disintegrating, rapid dissolve or mouth dissolving tablets (Mohanachan-
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 sensation in the throat or mouth. In particular, a bitter taste can reduce patient compliance and thus reduce the efficiency of pharmacotherapy (Suryadevara 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 permeability. Its recommended for relief of seasonal allergic 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 solubility should be targeted by a Bioavailability Improvement 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, Microcrystalline 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.

**Preparation of standard stock solution**

Standard stock solution of Lercanidipine was prepared by dissolving accurately weighed 100mg of Lercanidipine in the little quantity of phosphate buffer pH-6.8 in 100ml volumetric flask. The volume 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 spectrophotometer. 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.

**Drug and Excipient Compatibility by using FTIR**

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

**Standard calibration curve of pureLercanidipine using U.V. spectroscopy**

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, equivalent 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-realized 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 flowability 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 ($\pi r^2$) was determined, radius (r) was calculated and substituted in the formula ($\theta = \tan^{-1} \frac{h}{r}$), to obtain the angle of repose. Repeated the experiment twice more and calculate the average angle of repose (Kaur et al., 2020).

$$\tan (\theta) = \frac{h}{r} \Rightarrow \theta = \tan^{-1} \left( \frac{h}{r} \right)$$

Bulk density
Lubricated blend sieved through #20 was correctly weighed to 25 g and transferred to a graduated cylinder of 100ml. Level the Powder carefully and read the unsettled apparent Volume (V0) without compacting. The apparent bulk density in gm/ml can be depicted as follows,

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

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

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

Carr’s Index
It is an essential parameter to determine the powder compressibility and packing characteristics before the compression process. It can be determined as follows,

$$\text{Carr’s index (\%)} = \frac{[\text{Tapped density} - \text{Bulk density}]}{\text{Tapped density}} \times 100$$

Haussner’s Ratio
Haussner’s Ratio is a number of co-related to a powder’s flowability. The Haussner Ratio formula is as shown in the equation below,

$$\text{Haussner’s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Preparation of tablet
Using the lubricated blend as shown in Table 2, Lercanidipine Orally disintegrating tablets were compressed on 16 stations cadmach rotary compression machine equipped with 9mm biconcave punches and constant hardness is maintained for all the tablets.

Evaluation of tablet

General 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    | Sucrose          | 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 (°) |
|------------------|--------------|----------------|------------------|-----------------|---------------------|
| 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 (%) |
|------|------------------|--------------------------|------------------------------|-----------------------------------|-------------------------------|-----------------|
| 1    | F1               | 42.76 ± 0.12             | 39.30 ± 1.30                 | 51.40 ± 1.06                      | 74.57 ± 1.19                   | 98.0            |
| 2    | F2               | 35.52 ± 1.73             | 37.16 ± 1.51                 | 49.71 ± 1.02                      | 71.71 ± 1.43                   | 99.3            |
| 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 ± 1.32                      | 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

| Time (min.) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | Marketed preparation |
|-------------|----|----|----|----|----|----|----|----|----|----------------------|
| 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 | 71.11 ± 1.12 | 72.98 ± 1.15 | 75.58 ± 1.12 | 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 ± 0.93 | 81.93 ± 0.93 | 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 ± 1.05 | 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 ± 1.01 | 93.57 ± 1.13 | 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 ± 0.58 | 85.13 ± 1.13 | 88.89 ± 1.13 | 95.63 ± 1.14 | 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 ± 1.10 | 85.23 ± 1.10 |

Data represent mean ± SD, n=3

Table 7: Different Dissolution kinetic parameters of optimized formulation F9

| Formulation code | Zero order R² | First order R² | Higuchi model R² | Korsmeyer Peppas R² |
|------------------|---------------|---------------|-----------------|---------------------|
| F9               | 0.595         | 0.94          | 0.851           | 0.710               |

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Table 8: Stability study of tablet properties of optimized formulations (F9)

| S.No | Parameters                              | Controlled F9 | After 15 Days | F9   | After 1 Month |
|------|----------------------------------------|---------------|---------------|------|--------------|
| 1    | Hardness (Kg/cm²)                       | 3.43±0.20     | 3.42±0.28     | 3.91±0.16 |
| 2    | Drug Content (%)                        | 99.8          | 99.8          | 99.7  |
| 3    | In-vitro disintegration time (sec)      | 38.46±0.12    | 39.45±0.94    | 39.46±0.91 |
| 4    | Wetting time (sec)                      | 31.46±1.01    | 33.71±1.25    | 33.72±1.06 |

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

| S.No | Time (Mins) | Controlled F9 | Cumulative %Drug Release |
|------|-------------|---------------|--------------------------|
|      |             |               |                          |
| 1    | After 15 Days | F9             | After 1 Month             |
| 2    | After 1 Month | F9             |                          |

**Figure 3: Dissolution Profile of formulations F1-F9**

**Figure 4: Comparative dissolution profile for F9 and Marketed preparation**

**Hardness 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 forcibly to move the upper plunger until the tablet breaks by applying compressional force. Barrel containing Pointer on the gauge 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 breaking of tablets during compression and handling. It has a plastic chamber spins at 25rpm by lowering the tablets from a distance of six inches for each revolution. 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 taken for the tablet to fully disintegrate into fine particles. Three tablets were randomly chosen from each batch and In- vitro dispersion time was performed using 6.8 phosphate buffer (Lieberman et al., 1987).

**In-Vitro Disintegration Test**
It is one of the most important criteria for the prepared tablets to meet out the needs. It can be performed using disintegration Test apparatus IP. Each tablet is placed into one tube of the glass assembly. 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 30 seconds when subjected to a disintegration test examination.

**Taste evaluation**

Taste assessment using time intensity process conducted in 6 volunteers. A tablet was placed in the oral cavity for 10 seconds and the recorded bitterness levels and continued the test for different time intervals and repeated the test for comparison (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 single 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).

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

**Wetting time**

Tissue papers cut down to a circular shape of 10 cm diameter in size and dipped in 6 ml (w/v) of Methylene 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 quantity of 100 mg drug was transferred to 100 ml volumetric flasks. The powder substance is solubilised with small pH-6.8 phosphate buffer volume and subjected for sonication for half an hour. Later solution was filtered and the desired volume was made using pH-6.8 phosphate buffer. The final concentration was diluted to 10 μg/ml and absorbance was observed at 240 nm (Seager, 1998).

**In-vitro drug release**

Drug release studies carried out using USP type-Ⅱ (paddle) apparatus at a speed of 50 rpm for a specified time period of 30 mins at temperature (37±0.5°C) (Mallet, 1996). The samples were filtered 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 (Figures 3 and 4).

From the above observations, Kinetic analysis (r²) for the optimized formulation of Lercanidipine shows First order kinetics (R²=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 Lercanidipine HCl.

Drug resin complex was prepared in the ratio of 1:1, 1:2, 1:3 among them maximum drug content was observed for 1:2 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 maximum 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 manufacture.

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**Conflict of Interest**

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