Design expert assisted mathematical optimization of solubility and study of fast disintegrating tablets of Lercanidipine Hydrochloride

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ABSTRACT

90% of drugs being researched today, posses poor solubility setback which inturn renders the drug with slower rate of absorption from the buccal route; hence dissolution is the rate limiting step for such lipophilic drugs. So, there is a need to keep a check on the dissolution profile of these drugs to ensure maximum therapeutic utilization. The dissolution rate therefore becomes a primary factor which governs the rate and extent of its absorption. Enormous work is being performed in the field of enhancement of solubility and dissolution behaviour of such drugs. Advancements and innovations have developed solid dispersion (SD) technique as the novel method for the solubility enhancement. Precision of dosing and patient’s compliance is a crucial parameter for the management of chronic Antihypertensive treatment, So there arises a need to formulate a system which should resolve the difficulties associated with conventional tablets. This issue can be better tackled with the formulation of orally fast disintegrating tablets. The aim of the present study was to improve the solubility and dissolution rate of Lercanidipine hydrochloride (LRH) by formulating a solid dispersion with Polyvinyl pyrollidine (PVP) and Guar gum. Full Factorial design is exploited to learn and research the effects of different variables on the quality determinant parameters. An appropriate statistical model was selected for the scrutiny of the enhanced dissolution pattern. Finally, these solid dispersions were incorporated into fast disintegrating tablets.

Keywords: Lercanidipine Hydrochloride, Solid dispersion, Statistical design approach, Melt fusion method, Fast disintegrating tablet, In vivo studies

INTRODUCTION

Due to the ongoing technological advancements in the pharmaceutic world of designing various drug delivery systems. Majority drug molecules display poor solubility, which in turn affects the overall bioavailability of the molecule. When dissolution is rate limited, the buccal delivery of such drug candidates is a tedious task. There are number of methodologies which can be targeted for solubility enhancement, such as salt formation, use of cosolvents, particle size reduction, inclusion complexes of cyclodextrins etc. Above all these, fabrication of solid dispersions can serve both the purposes of solubility and dissolution enhancement. These systems have aided in the domain of solubility enhancement, as they surpass the obstacles of the ancient methods. But the real success depends on the carrier selection and its optimization. When such systems come in contact with water, carrier is eroded and drug is set free as a fine colloidal dispersion with exorbitant surface area rendering elevated rates of drug dissolution and biological availability. In relation to all above, a modification from crystallin to amorphous form takes place, which is valuable as dissolution of an amorphous drug is simple and do not need any energy to fragment the crystalline structure.

Lercanidipine hydrochloride chemically is 2\[(3,3-diphenylpropyl) (methyl)amino]-1, 1-imethylcyclic methyl 2,6- dimethyl-4- (3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate hydrochloride. It is reported in 1, 4-dihydropyridine calcium channel blockers pharmacological class. It is a BCS class II drug with low aqueous solubility and bioavailability. So improvement of the drug bioavailability and therapeutic efficacy is a crucial parameter which can only be achieved by increasing the solubility. The main goal is to work on the solubility enhancement by dispersing the drug in the polymer matrix of PVP and Guar Gum in different ratios. Melt fusion method is used for the preparation of solid dispersion and preliminary screening for polymer selection is performed. As oral route being the most suitable route of administration has become a vital
component nowadays, so work has been undertaken to develop a fast dissolving system, which disintegrates and disperses the drug in few seconds and can be conveniently administered. Finally, these solid dispersions were incorporated into fast disintegrating tablets which were further evaluated.

**MATERIALS**

Lercanidipine hydrochloride was received as a free gift sample from Torrent Pharmaceutical Pvt. Limited, Baddi, Himachal Pradesh, India. Polyvinyl pyrollidine (PVP-K30) and Guar Gum was purchased from local vendor. Other materials used were of analytical grade.

**EXPERIMENTAL**

Solubility study

Solubility studies of lercanidipine hydrochloride were checked in water, phosphate buffer pH 6.8, HCl buffer pH 1.2 and phosphate buffer pH 7.2. The saturated solutions were prepared by adding excess drug in the solvent system. The solvent system was shaken for 48 hrs at 25°C. Filtered the solutions through a 0.42 Millipore filter. Samples were analysed by UV spectrophotometer at 236 nm. The solubility data is reported in table 1.

| Solvents                | Solubility (mg/ml) |
|-------------------------|--------------------|
| Water                   | 0.014±0.002        |
| Phosphate buffer pH 6.8 | 0.005±0.001        |
| 0.1 N HCl               | 0.160±0.012        |
| Phosphate buffer pH 7.4 | 0.004±0.015        |

Table 1: Solubility of lercanidipine HCl in various solvent

Infra red Spectral analysis

FT-IR spectrum of pure Lercanidipine hydrochloride and batch LS-5 is shown in Figure 1 and Figure 2 respectively. The IR spectra of Lercanidipine hydrochloride exhibited distinctive peaks at 3443 cm\(^{-1}\) stretching, 1649 cm\(^{-1}\) Amides (RCONH\(_2\)), 1521 cm\(^{-1}\) Aromatics (C-C ring). The FTIR spectra of LS-5 displayed same characteristic peaks which also reveals that the drug and excipients used in the formulation are stable and posses no interaction.

**Evaluation of Solid dispersions**

Solubility studies

The solubility study of various Solid dispersions batches was determined in phosphate buffer pH 6.8. Weighed amount of solid dispersion equivalent to drug dose was added in excess quantity of solvent in screw-capped glass vials. The vials were continuously shaken for 2 hours. Finally the solutions were filtered and analysed spectrophotometrically at 236 nm.

| Formulation Code | Solubility (mg/ml) |
|------------------|--------------------|
| LS-1             | 0.347±0.08         |
| LS-2             | 0.655±0.01         |
| LS-3             | 0.801±0.07         |
| LS-4             | 0.878±0.01         |
| LS-5             | 0.941±0.08         |
| LS-6             | 0.798±0.09         |

Table 2: Solubility data of preliminary solid dispersion batches

Infra red Spectral analysis

FT-IR spectrum of pure Lercanidipine hydrochloride and batch LS-5 is shown in Figure 1 and Figure 2 respectively. The IR spectra of Lercanidipine hydrochloride exhibited distinctive peaks at 3443 cm\(^{-1}\) stretching, 1649 cm\(^{-1}\) Amides (RCONH\(_2\)), 1521 cm\(^{-1}\) Aromatics (C-C ring). The FTIR spectra of LS-5 displayed same characteristic peaks which also reveals that the drug and excipients used in the formulation are stable and posses no interaction.

Figure 1: FTIR Spectra of Lercanidipine Hydrochloride

Figure 2: FTIR Spectra of batch LS-5
Differential scanning calorimetry
The DSC studies were conducted using DSC-60 instrument (Schimadzu corporation Japan). The samples of pure drug and batch LS-5 were sealed and heated at a constant rate at 50ºC/min over a temperature range of 25-175ºC. Inert atmosphere was created by introducing nitrogen gas at 50 ml/min flow rate\textsuperscript{21,22}. DSC thermographs melting endothermic at 179.7ºC (172ºC-183ºC) at 88.97 J/g i.e. melting point and crystalline state of drug. DSC thermograph of LS-5 is shown in Figure 4 which shows no peak i.e. melting point and amorphous state of drug. Disappearance of the drug melting peak confirmed that amorphization had occurred.

Scanning electron microscopy
The drug and batch LS-5 were examined for surface changes using scanning electron microscope as shown in figure 5 and figure 6 respectively. Finally surface topography was studied\textsuperscript{23}.

Figure 3: DSC of Lercanidipine hydrochloride

Figure 4: DSC of batch LS-5

Figure 5: SEM image of the Lercanidipine Hydrochloride
Experimental Design

A three-level, two factor experimental design was chosen for the study as shown in Table 3. The table indicates the ratios of independent variables, Lercanidipine Hydrochloride (A) and screened polymer Guar gum (B). The solubility and drug content, was selected as dependent variables. Response surface methodology computations were performed using Design Expert Software version 11. Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis approach. In addition contour and surface plots were also obtained to represent the effect of independent variables graphically.

Preparation of Lercanidine Hydrochloride Fast disintegrating Tablets containing superdisintegrants

Different batches of fast disintegrating tablets of Lercanidine hydrochloride containing best optimized solid dispersion batch (OLS-1) were prepared according to the proportions given in Table 3. Powdered solid dispersion batch (OLS-1) equivalent to 10 mg of LR, was mixed with other excipients. Finally tablets were compressed on a rotary punch tablet machine (Karnavati, Mumbai, India) keeping final weight of the tablet (100 mg) 24, 25.

Table 3: Optimization parameters of Guar gum loaded solid dispersion

| Run  | Independent variables | Response 1: Solubility (µg/ml) | % drug release in 60 mins (%) |
|------|------------------------|-------------------------------|-------------------------------|
| A:Drug conc. (mg) | B:Polymer conc. (mg) | Factor 1 | Factor 2 | Response 1 | Response 2 |
| OLS-1 | 300 | 400 | 0.941 | 98 |
| OLS-2 | 441.421 | 400 | 0.88 | 98 |
| OLS-3 | 300 | 682.843 | 0.941 | 85 |
| OLS-4 | 200 | 200 | 0.789 | 80 |
| OLS-5 | 158.579 | 400 | 0.699 | 98 |
| OLS-6 | 400 | 200 | 0.87 | 80 |
| OLS-7 | 400 | 600 | 0.87 | 87 |
| OLS-8 | 300 | 117.157 | 0.941 | 63 |
| OLS-9 | 200 | 600 | 0.789 | 87 |

Table 4: ANOVA for Quadratic model Response 1: Solubility

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|--------|----------------|----|-------------|---------|---------|
| Model  | 0.0718         | 5  | 0.0144      | 27.45   | 0.0002 (Significant) |
| A-Drug conc. | 0.0218      | 1  | 0.0218      | 41.77   | 0.0003 |
| B-Polymer conc. | 1.388E-17  | 1  | 1.388E-17 | 2.654E-14 | 1.0000 |
| AB     | 0.0000         | 1  | 0.0000      | 0.0000  | 1.0000  |
| A²     | 0.0499         | 1  | 0.0499      | 95.42   | < 0.0001 |
| B²     | 0.0006         | 1  | 0.0006      | 1.06    | 0.3369  |
| Residual | 0.0037      | 7  | 0.0005      |         |         |
| Lack of Fit | 0.0037   | 3  | 0.0012      |         |         |
| Pure Error | 0.0000   | 4  | 0.0000      |         |         |
| Cor Total | 0.0754    | 12 |             |         |         |
Table 5: ANOVA for Quadratic model Response 2: Drug content

| Source    | Sum of Squares | df | Mean Square | F-value | p-value  |
|-----------|----------------|----|-------------|---------|----------|
| Model     | 1370.59        | 5  | 274.12      | 39.08   | < 0.0001 (Significant) |
| A-Drug conc. | 0.0000        | 1  | 0.0000      | 0.0000  | 1.0000   |
| B-Polymer conc. | 254.39     | 1  | 254.39      | 36.26   | 0.0005   |
| AB        | 0.0000         | 1  | 0.0000      | 0.0000  | 1.0000   |
| A²        | 2.72           | 1  | 2.72        | 0.3874  | 0.5534   |
| B²        | 1108.80        | 1  | 1108.80     | 158.06  | < 0.0001 |
| Residual  | 49.11          | 7  | 7.02        |         |          |
| Lack of Fit | 49.11       | 3  | 16.37      |         |          |
| Pure Error | 0.0000       | 4  | 0.0000     |         |          |
| Cor Total | 1419.69        | 12 |         |         |          |

Pre compression parameters

**Angle of repose:** Accurately weighed quantity of the powder mixture was allowed to freely flow on to a surface from the funnel fixed at an appropriate height. The diameter is noted down. Finally angle of repose was calculated by using the following equation.

\[
\tan \theta = \frac{h}{r}
\]

Where \( \theta \) is angle of repose, \( h \) is height of the cone and \( r \) is radius of the cone base.

**Bulk density:** Accurately weighed quantity of blend was added to a graduated cylinder and the bulk volume was measured using equation 2.

\[
\text{Bulk density} = \frac{\text{weight of the powder}}{\text{bulk volume}}
\]  
(2)

**Tapped density:** Accurately weighed quantity of blend was added to a graduated cylinder and the bulk volume was measured using equation 3.

\[
\text{Tapped density} = \frac{\text{weight of the blend}}{\text{final volume}}
\]  
(3)

Table 6: Composition of Fast Disintegrating Tablet

| Formulation Code | Ingredients in mg |
|------------------|-------------------|
|                  | LT-1 | LT-2 | LT-3 | LT-4 | LT-5 | LT-6 |
| LS equivalent to 10 mg | 50   | 50   | 50   | 50   | 50   | 50   |
| Crosspovidone    | 2    | 4    | 6    | -    | -    | -    |
| Crosscarmellose  | -    | -    | -    | 2    | 4    | 6    |
| Avicel pH 102    | 45   | 43   | 41   | 45   | 43   | 41   |
| Magnesium stearate| 1    | 1    | 1    | 1    | 1    | 1    |
| Talc             | 2    | 2    | 2    | 2    | 2    | 2    |
| Total weight     | 100  | 100  | 100  | 100  | 100  | 100  |
**Compressibility index**: The compressibility index (Carr’s index) indicates the property of a powder to be compressed and can be calculated using equation 4.

\[ \text{Compressibility Index} = \left[ \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \right] \times 100 \quad (4) \]

### Table 7: Data for Precompression parameters

| Formulation Code | Angle of Repose(°) | Bulk Density(g/cc) | Tapped Density (g/cc) | Compressibility Index (%) |
|------------------|-------------------|--------------------|-----------------------|--------------------------|
| LT-1             | 23.7±0.14         | 0.42±0.12          | 0.58±0.17             | 27.38±0.18               |
| LT-2             | 24.7±0.02         | 0.41±0.15          | 0.66±0.05             | 37.87±0.61               |
| LT-3             | 24.8±0.00         | 0.43±0.08          | 0.55±0.09             | 21.81±0.09               |
| LT-4             | 23.2±0.15         | 0.51±0.07          | 0.65±0.19             | 23.95±0.07               |
| LT-5             | 23.1±0.20         | 0.45±0.71          | 0.59±0.23             | 23.72±0.15               |
| LT-6             | 22.8±0.02         | 0.44±0.45          | 0.62±0.05             | 32.25±0.21               |

### Post compression parameters

#### Evaluation of Fast Disintegrating Tablets

The tablet batches were evaluated for weight variation, friability, hardness, thickness, uniformity of weight, disintegration time, wetting time, drug content and *in vitro* dissolution study.

#### Weight variation

Average weight of 20 tablets was determined and then the individual tablet weight was compared with average weight as shown in table 8.

#### Friability

The tablets were weighed (Winitial) and placed in friabilator (Bolinz, India). The apparatus was operated at 25rpm for 4 minutes. Finally the tablets were dedusted and weighed again (Wfinal). The data is reported in table 8.

\[ F = \frac{W\text{initial} - W\text{final} \times 100}{W\text{final}} \quad (5) \]

### Table 8: Data for the post compression parameters

| Batch | Weight variation(mg) | Friability (%) | Hardness (Kg/cm²) | Wetting time(Sec) | Disintegration time(Sec) | Drug content (%) |
|-------|----------------------|----------------|-------------------|-------------------|-------------------------|-----------------|
| LT-1  | 99.1±0.39            | 0.62±0.87      | 2.8±0.21          | 44±0.81           | 55±0.18                 | 98±0.91         |
| LT-2  | 98.4±0.78            | 0.77±0.55      | 2.5±0.76          | 37±0.77           | 45±0.33                 | 99±0.87         |
| LT-3  | 99.8±0.55            | 0.75±0.49      | 2.9±0.86          | 25±0.52           | 37±0.56                 | 99±0.11         |
| LT-4  | 99.3±0.37            | 0.88±0.99      | 3.0±0.12          | 35±0.28           | 47±0.61                 | 98±0.37         |
| LT-5  | 99.3±0.84            | 0.85±0.89      | 2.3±0.11          | 26±0.34           | 40±0.37                 | 99±0.27         |
| LT-6  | 99.4±0.86            | 0.71±0.77      | 2.2±0.85          | 19±0.43           | 30±0.81                 | 99±0.71         |

#### In-vitro dissolution study

Dissolution studies were conducted in a beaker having 30 ml phosphate buffer pH 6.8 which was maintained at 37 ± 0.50 °C. The assembly was placed on a magnetic stirrer and samples were drawn at appropriate time periods with replacement. The aliquots were filtered, diluted and analyzed by spectrophotometrically at 236nm.

#### In vivo study design study

The *in vivo* study procedure (Protocol approval number: RIP/IAEC/2018-19/02) was approved by the Institutional Animal Ethics Committee. Male rabbits (New Zealand) were chosen for the pharmacokinetic data collection. Rabbits (weighing 2.6-3.1 kg) were fasted overnight before the study plan proceeded. Divided the rabbits into two groups. One group received the marketed formulation (Lercanidipine hydrochloride equivalent to 3 mg/kg) whereas the other group received optimized fast disintegrating tablet batch LT-6. Tablet to be tested was kept on the tongue of the rabbit. This has been achieved with the help of body restraint device. Initially the mouth was wetted with water and then tablet was placed on the tongue. Blood samples were withdrawn from the peripheral vein of each rabbit at appropriate interval of 0, 1, 2, 3, 4, 5, 7, 9, 12, 24 hrs.

The samples were centrifuged at 2000 rpm for 20 min. The clear supernatant serum layer was harvested and stored at -40 °C. Frozen samples were thawed at ambient temperature (25±2 °C) for at least 60 min. Serum samples were appropriately diluted with acetonitrile, vortexed and finally centrifuged again. Mixed Lercanidipine HCl with protein free plasma. From this 20μl was injected into an isocratic HPLC system. The column was packed with C18 (250 x 4.6mm, particle size: 5μm, High pressure gradient, Detector : UV Wavelength:240nm). Potassium dihydrogen orthophosphate: ACN pH 4(40:60) was used as mobile phase with a flow rate upto 1.0 ml/min. Various
pharmacokinetic parameters such as peak plasma concentration (Cmax), the time at which peak occurred (tmax) and area under the curve (AUC) were computed from time v/s serum drug concentration values.

![Figure 8: Dissolution release profile of FDT Tablet batches (LT-1 to LT-6)](image)

**Table 9: Pharmacokinetic parameters following after oral administration.**

| Pharmacokinetic parameters | Optimized Formulation LT-6 | Marketed Preparation |
|----------------------------|-----------------------------|----------------------|
| Cmax                       | 20.11                       | 16.31                |
| Tmax                       | 3hr                         | 4hr                  |
| AUC                        | 230                         | 205                  |

![Figure 9: The pharmacokinetic profile of optimized FDT and marketed product.](image)

**Stability Studies**

The best formulation batch was charged for the stability study as per ICH guidelines. They were performed at temperature of 40±2°C / 75% RH for 3 months. LT-6 batch was charged for the study. It was wrapped in a butter paper followed by aluminium foil and sealed in an air-tight plastic pouch. The samples were checked for in vitro disintegration time and drug content for 30 days, 60 days and 90 days after storage.

**Table 10: Stability data of the optimized batch LT-6 batch**

| Evaluation Parameter          | 0 days       | 30 days      | 60 days      | 90 days      |
|------------------------------|--------------|--------------|--------------|--------------|
| Disintegration Time (Sec)     | 30±0.37      | 30±0.27      | 30±0.87      | 30±0.07      |
| Drug Content (%)              | 99.42±0.39   | 99.15±0.45   | 99.12±0.67   | 99.10±0.81   |
DISCUSSION

The solubility and dissolution rate of Lercanidipine hydrochloride has been improved by formulating a solid dispersion with PVP-K30 and Guar gum in the preliminary screening for polymer (Batch LS-1 to LS-6). Various natural and synthetic polymers are used in the preparation as they are economical, readily available, non-toxic, biodegradable and bio compatible. The solubility results are reported in Table 1.

After the preparation of solid dispersions, solubility determination is an important factor which affects the dissolution pattern. The solubility study confirmed that LS-5 exhibited maximum solubility. Also it was revealed that Guar gum showed much enhanced solubility as compared to other carrier. It was observed, that on increasing the polymer concentration, there was a sharp increase in solubility up to a point than further decreased, which can be attributed to the fact that as the polymer concentration increases, polymer gets adsorbs on the surface of drug, which retards the drug dissolution in the long run.

The FTIR spectra of pure drug and solid dispersion batch LS-5 displayed same characteristic peaks and revealed no chemical interaction between the drug and excipients as depicted in figure 1 and figure 2 respectively. Thermograms of drug and batch LS-5 are depicted in figure 3 and figure 4 respectively. DSC reports also reveals that the disappearance of the drug melting peak is a result of amorphization as shown in figure 6. The reduction in drug peak height and its broadening can be considered as a result of the change in the crystalline state to amorphous one. SEM photographs are shown in figure 5 and figure 6.

Optimization of independent variables outlined that solid dispersion prepared with drug: guar gum (1:2 ratio) showed maximum solubility of 0.94±0.08 mg/ml. Based on this result, guar gum polymer was selected for further formulation studies.

Optimization of dependent variables, ANOVA was used for predicting the significance (p < 0.05) of the model and individual response parameters. The various plots were scrutinized to check the impact of independent factors on the measured responses. The quadratic model of F-value 27.65 implies the model is significant p < 0.05. The contour plot and surface response plot in figure 7 showed the effect of different independent variables on solubility. The solubility of solid dispersion increased as the amount of guar gum also increased, but to a certain level then decreased abruptly.

Response 2 (% Drug release at time 60 mins Y2). After ANOVA estimation, the quadratic model of F-value 39.08 implies the model is significant p < 0.0001. The various plots in figure 7 showed the effect of different independent variables on drug release at 60 min. The maximum drug release was obtained upto polymer concentration of 400 mg and further increase decreases the % drug release. This increase in rate of drug dissolution could be because of the dispersion of drug in pores of guar gum and increased wettability. The dissolution rate showed a sharp rise at 1:2 ratio, but then decreased at higher values. This is attributed to the fact that there is firm adsorption of the drug on polymer, which retards the dissolution process of the drug.

Fast disintegrating tablets were prepared by direct compression method using optimized Lercanidipine Solid Dispersion (OSD-1), various super disintegrants crospovidone and croscarmellose are used and evaluated.

Total of six formulations LT-1 – LT-6 with fixed concentration of different super disintegrants were prepared as shown in table 5. Weight variation for all batches was within the range prescribed for uncoated tablets. Friability was reported within 0.62 to 0.88% and hardness within 2.2 to 3.0 kg/cm² range. The wetting times and disintegration time was within 19 to 44 secs and 30 to 55 secs respectively. The accreditation for fast wettability and disintegration could be assigned to the capillary action mechanism of the superdisintegrant which leads to fast puffiness of the dosage form. The drug content was found to be between 98 – 99 % which was within the acceptable limits.

Among all formulations LT-6 showed maximum 97.6 % drug release within 10 min. This may be credited to the brisk dissolution of the tablet, which is due to the usage of super disintegrant and carrier all together in the formulations. The results showed that FDT formulated using croscarmellose sodium with concentration up to 6 % showed better results than FDT formulated with crospovidone.

Finally LT-6 formulation was tested for stability at 25°C/65% and 40°C/75% RH for a period of 3 months. The tablets were once more evaluated for drug content and in vitro disintegration time. At last, no modifications in the disintegration time and drug content of tablets were seen.

CONCLUSION

The above carried research work revealed that the solid dispersion technique could be a lucrative way for solubility enhancement of Lercanidipine hydrochloride, using Poly vinyl pyrollidine (PVP K-30) and guar gum as carriers. From the preliminary screening for polymer, Guar gum was selected for the further formulation studies. Optimized guar gum solid dispersion was finally incorporated into FDT. The FDT were formulated by direct compression method, having crospovidone and croscarmellose as superdisintegrant. Batch LT-6 showed maximum 97.6 % drug release within 10 min. At last, it is summarised that fast disintegrating tablet formulation can be an innovative and promising approach for the delivery of Lercanidipine Hydrochloride with enhanced dissolution and bioavailability, and also as an effective therapy for the treatment of hypertension.

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