dx.doi.org/10.14227/DT250118P38

# Dissolution Method Development and Validation for Lercanidipine Hydrochloride Tablets

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## ABSTRACT

Lercanidipine hydrochloride (HCl) is L-type calcium channel blocker widely used in the management of hypertension. According to the BCS classification system, it is classified under BCS class II drugs, showing low solubility and high permeability. The dissolution profile and thus the in vivo performance of this class of drugs widely depend on their solubility and hence their behaviour in dissolution medium. Lercanidipine HCl is not official in any pharmacopeia, so no official dissolution method is available. The present work is mainly focussed on development and validation of a dissolution test that can be used as a quality control test for lercanidipine HCl tablets and formulations. Saturation solubility and sink conditions that can be achieved in different media suggested that 0.1 N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8 can be used as a dissolution medium. Dissolution tests of lercanidipine HCl tablets were carried out in these different media at different rotation speeds using a USP type II (paddle) apparatus. The most suitable dissolution conditions were 0.1 N HCl pH 1.2 (900 mL at 37 ± 0.5 °C) as a dissolution medium and a paddle apparatus at 100 rpm for 60 min. The analysis of released lercanidipine HCl was done by ultraviolet spectrophotometry. The developed method was validated according to ICH guidelines. This method showed linearity with an $r^2$ value of 0.999 within the concentration range of 2–20 µg/mL. The method was found to be accurate with recoveries ranging from 98.50% to 103.72%. The interday and intraday precision was below RSD 2%. The developed method can effectively be used for quality control evaluation of lercanidipine HCl tablets.

**KEYWORDS:** Lercanidipine HCl, dissolution, sink conditions, validation

## INTRODUCTION

Dissolution testing is considered as an important tool to evaluate the performance of oral solid dosage forms, and more stress is given to dissolution testing by pharmaceutical industries and regulatory authorities (*1–6*). Dissolution tests can detect variation in lot-to-lot quality of a drug product during formulation stages and after changes in the manufacturing process (*2, 3)*. It is one of the important quality control tests used to assure product uniformity and batch-to-batch bioequivalence (*7*). It is very challenging to develop an in vitro dissolution test for drugs with limited solubility (*8, 9*). The discriminating power of a dissolution method can be demonstrated by analysing the dissolution profiles under deliberate changes made in the method (*10*). Once the product development stage is over, dissolution is an important test to monitor regular quality of commercial batches of drug formulation, which is the focus of all regulatory agencies worldwide (*11, 12*). Developed dissolution methods are validated in terms of specificity, accuracy, precision, and robustness, to make sure that they are suitable for their intended use (*13, 14*).

Lercanidipine HCl is a new third generation calcium channel blocker belonging to the 1,4-dihydropyridine class. It blocks entry of calcium into L-type calcium channels of smooth muscles resulting in peripheral vasodilatation and reduction in blood pressure (*15*). Chemically it is 2[(3,3-diphenylpropyl) (methyl) amino]-1, 1-dimethylethyl methyl 2,6- dimethyl-4- (3-nitrophenyl)-1, 4-dihydropyridine-3, 5- dicarboxylate hydrochloride (*16*). As per BCS classification, lercanidipine HCl is a BCS class II drug that is freely soluble in methanol and practically insoluble in water, having a pKa value of 6.83 (*17, 18*). Commercially, it is available in tablet dosage forms in strengths of 10 and 20 mg. Lercanidipine HCl is not official in any pharmacopeia and currently no quality control or discriminatory dissolution method is available for raw material and tablets (*19*).

The purpose of this study is to develop and validate a method of dissolution testing that can be used for routine quality control of lercanidipine HCl tablets (and other dosage forms).

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## MATERIALS AND METHODS

### Reagents

Lercanidipine HCl was received as a gift sample from Alembic Research Centre, Vadodara, Gujarat, India. Lotensyl® 10 tablets (Batch No. HSR2259, Sun Pharmaceutical Industries Ltd.) containing 10 mg of lercanidipine were purchased from local market. All chemicals and solvent used were of analytical grade. Potassium dihydrogen phosphate (S D Fine-Chem Limited, India), sodium hydroxide, sodium acetate (Qualigens, India), glacial acetic acid, hydrochloric acid (S D Fine-Chem Limited, India) were used for preparation of different buffer solutions. Double distilled water was used for all the analysis purpose. Phosphate buffer (pH 6.8), acetate buffer (pH 4.5), and 0.1 N HCl were prepared as per *USP* 27.

### Apparatus

The dissolution method was developed using the Tablet Dissolution Tester Model (TDT-08L, Electrolab, Mumbai, India). Ultraviolet (UV) measurements of all samples were done using a UV spectrophotometer (UV-1800 PC, Shimadzu, Japan).

### Solubility determination

Solubility of lercanidipine HCl was determined in three different media: 0.1 M HCl, acetate buffer pH 4.5, and Phosphate buffer pH 6.8. Excess amount of lercanidipine HCl was added into conical flasks containing 25 mL of 0.1 M HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C. The samples were subjected to sonication for 10 min, and closed conical flasks were agitated for 24 h at 37 ± 0.5 °C in an orbital shaker. After achieving equilibrium, samples were filtered through Whatman grade 41 filters (Sigma-Aldrich) and concentration of lercanidipine HCl was measured at 236 nm. All measurements were done in replicates ($n$ = 6).

### Optimization of Dissolution Test

The dissolution test was developed and validated using a multistation ($n$ = 6) USP dissolution apparatus by Electrolab. The effects of different pH of dissolution medium and different rotation speed were evaluated. All tests were performed at 37 ± 0.5 °C with 900 mL of dissolution medium. Sample aliquots were collected at 10, 20, 30, 40, 50, and 60 minutes, a few millilitres of dissolution medium were discarded and filtered, and drug release was assayed using a validated UV spectrophotometric method. The standard solution used for the dissolution tests was prepared with lercanidipine equivalent to 10 mg.

### Validation of Dissolution Test

The developed in vitro dissolution method was validated using recent guidelines (*20–22*). To demonstrate reproducibility and reliability, the method was evaluated for specificity, linearity, accuracy, precision, and robustness.

*Specificity*

Evaluation of specificity was done using placebo samples consisting of all the excipients without active substance. The placebo samples were introduced in dissolution vessels ($n$ = 3) containing 900 mL of dissolution medium maintained at 37 ± 0.5 °C. The vessels were stirred at 75 rpm for 1 hour using a paddle (USP apparatus 2). Aliquots were collected and analysed.

*Linearity*

Aliquots of lercanidipine HCl stock solution (100 µg/mL) were diluted with phosphate buffer pH 6.8, acetate buffer pH 4.5, and 0.1 N HCl to obtain concentration of 2–20 µg/mL. Solutions were prepared in triplicate, and linearity was calculated by least-square linear regression analysis.

*Accuracy and precision*

To evaluate accuracy of the dissolution method, recovery of known amounts of lercanidipine HCl reference standard added to placebo was calculated. Stock solution of 1 mg/mL was prepared in methanol. From the stock solution, aliquots of 4.5, 9, and 13.5 mL were added to make 900 mL of dissolution medium in a dissolution vessel kept at 37 ± 0.5 °C (final concentration of 5, 10, and 15 µg/mL). The dissolution medium was stirred at 150 rpm for 60 minutes. A 10-mL of aliquot was withdrawn, filtered, and analysed at 236 nm. The experiment was repeated on three different days, and recovery of the added drug substance ($n$ = 9) was determined.

The same solutions used in accuracy studies were used to establish intraday and interday precision, which were calculated based on %RSD data of the results.

*Robustness*

To access robustness of the method, parameters like analyst, equipment, and laboratory were changed. The dissolution test of Lotensyl® 10 was carried out in 900 mL of 0.1 N HCl maintained at 37 ± 0.5 °C in a USP type 2 apparatus at 100 rpm with two different instruments, with two different analysts, in two different laboratories. The dissolution data obtained were compared with the initial data.

*Stability studies*

Stability of the solutions was evaluated in comparison with the standard solutions. Sample solutions were kept on a shaker at 37 ± 0.5 °C for 1 hour, then kept at room temperature for 24 hours. Aliquots of sample solutions were evaluated in triplicate at 0, 1, and 24 h using freshly prepared standard solution.

*Evaluation of release kinetics*

Release kinetics of the drug release from tablets were studied using four mathematical models named zero order, first order, Higuchi, and Hixson–Crowell. Details of the mathematical models are as follows.

Zero-order model: $Q_t = Q_0 + K_0 t$;

First-order model: $\log Q_t = \log Q_0 + (K_1 t)/2.303$;

Higuchi model: $f_t = K_H t^{1/2}$;

Hixson–Crowell model: $W_0^{1/3} - W t^{1/3} = K_s t$;

where

$Q_t$ = amount of drug dissolved in time t;

$Q_0$ = initial amount of drug in the solution;

$K_0$ and $K_1$ = zero and first order release constants, respectively;

$ft$ = amount of drug released in time t by surface unity;

$K_H$ = Higuchi dissolution constant;

$W_0$ = initial amount of drug in the pharmaceutical dosage form;

$W_t$ = remaining amount of drug in the pharmaceutical dosage form at time t;

$K_s$ = a constant incorporating the surface–volume relation.

## RESULTS AND DISCUSSION

### Solubility

Lercanidipine HCl showed pH-dependent solubility, with the highest solubility achieved in 0.1 N HCl (Table 1). This can be explained by the pKa value of lercanidipine HCl, which is 6.83, leading to complete ionisation of the drug molecule at a low pH of 0.1 N HCl (pH 1.2). As the pH of the medium is increased, the solubility of lercanidipine HCl markedly decreased from 82.35 µg/mL in 0.1 N HCl to 49.43 µg/mL in acetate buffer pH 4.5 and finally reaching as low as 9.85 µg/mL in phosphate buffer pH 7.0. Above pH 6, solubility remains nearly constant. These solubility data form the basis for selection of dissolution media and sink conditions.

*Table 1. Saturation Solubility of Lercanidipine HCl and Sink Conditions in Different Dissolution Media (n = 3).*

| Medium | Average Absorbance | Solubility (µg/mL), mean ± SD | $C_s$ / $C_d$ |
|---|---|---|---|
| 0.1 N HCl, pH 1.2 | 0.257 | 82.35 ± 1.06 | 7.41 |
| Acetate buffer, pH 4 | 0.157 | 51 ± 0.82 | 4.59 |
| Acetate buffer, pH 4.5 | 0.152 | 49.43 ± 0.51 | 4.44 |
| Acetate buffer, pH 5 | 0.110 | 36.41 ± 0.51 | 3.27 |
| Phosphate buffer, pH 6.2 | 0.037 | 13.56 ± 0.13 | 1.22 |
| Phosphate buffer, pH 6.8 | 0.026 | 10.30 ± 0.06 | 0.927 |
| Phosphate buffer, pH 7.0 | 0.025 | 9.85 ± 0.14 | 0.88 |

*$C_s$, saturation solubility of lercanidipine HCl in 900 mL dissolution medium; $C_d$, dose of lercanidipine HCl in tablet formulation.*

### Dissolution Test Optimization

For development of the dissolution method, the objective was set to achieve a dissolution profile showing < 50% drug release in 15 minutes and > 85% drug release in 30 min for an immediate release dosage form of lercanidipine HCl. Solubility of lercanidipine HCl demonstrated significant change over pH 1.2–6.8, which suggests that dissolution of lercanidipine HCl is dependent on the pH of the medium.

For a formulation not official in monograph, it is recommended that the dissolution profile should be compared in three different compositions of media within the pH range of 1–7.5 (*23*). The effect of pH on the dissolution of lercanidipine HCl tablets was studied in 0.1 N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8 using a USP type 2 apparatus at 50 rpm, as shown in Figure 1A, which covers high, mid, and low solubility regions.

The dissolution process of disintegrating tablets can be best expressed by paddle apparatus, as it has inherent advantages over a rotating basket apparatus (*24*). Hence, all dissolution tests of lercanidipine HCl tablets (disintegrating tablets) were performed with a paddle-type apparatus. To study the effect of rotation speed of paddle, dissolution profiles were generated at 50, 75, and 100 rpm (*3*).

Percent drug release of lercanidipine HCl in different pH dissolution mediums supports the saturation solubility results, wherein the dissolution is incomplete and very slow at pH 6.8. At lower pH 4.5, fast and nearly complete drug release is obtained; however, in 0.1 N HCl, lercanidipine HCl has a gradual ascending and plateau-shaped dissolution curve, which confirms the distinct dissolution profile.

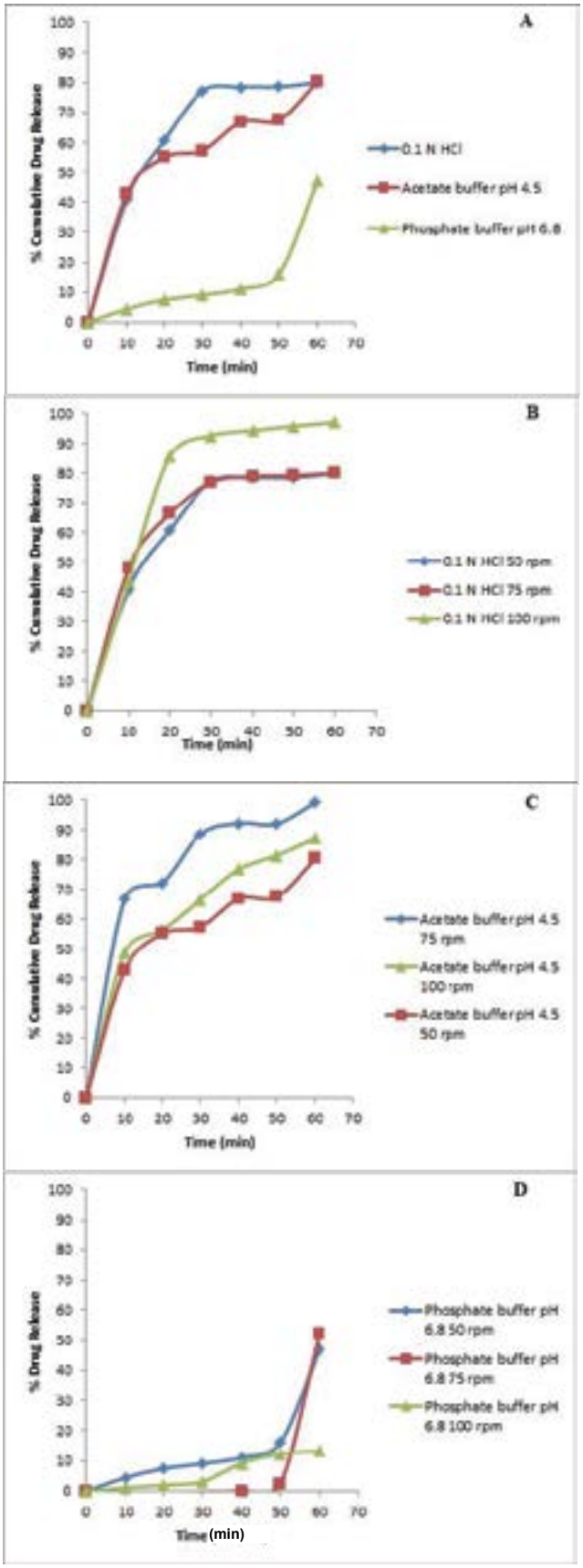


*Figure 1. Dissolution profiles of lercanidipine HCl tablets using paddle apparatus in (A) 900 mL 0.1 N HCl, acetate buffer pH 4.5, and phosphate buffer 6.8 at 50 rpm; (B) 0.1 N HCl at 50, 75, and 100 rpm; (C) acetate buffer pH 4.5 at 50, 75, and 100 rpm; and (D) phosphate buffer pH 6.8 at 50, 75 and 100 rpm.*

Lercanidipine HCl exhibits very low saturation solubility in phosphate buffer pH 6.8 and, in turn, has a low $C_s/C_d$ ratio (where $C_s$ is saturation solubility of lercanidipine HCl in 900 mL dissolution medium; $C_d$ is 10 mg of lercanidipine HCl in tablet formulation) (Table 1). As discussed by Ashokraj et al (*25*), low $C_s/C_d$ ratio results in non-sink conditions, which leads to a slow rate of dissolution due to limited solubility of lercanidipine HCl in phosphate buffer pH 6.8. The non-sink condition of phosphate buffer pH 6.8 is supported by drug release obtained at different rotation speeds in Figure 1D.

The drug release profile of lercanidipine HCl in acetate buffer pH 4.5 at the stirring speeds of 50 and 100 rpm showed less than 85% release in 30 minutes (Figure 1C). These results do not satisfy the minimum criteria for dissolution methods set by the U.S. Food and Drug Administration (*3*). At 75 rpm, the criteria are satisfied, but reproducible dissolution data are not obtained. Therefore, use of acetate buffer pH 4.5 as a dissolution medium is not advisable to develop a dissolution method that can be used for routine quality control testing.

The dissolution profile obtained with 0.1 N HCl at 50, 75, and 100 rpm is shown in Figure 1B. Table 1 depicts that a three-times greater sink condition for the dose level of 20 mg lercanidipine HCl is maintained only with 0.1 N HCl, suggesting that the same media can be used across all dose levels for a given product. From the dissolution profiles, it is evident that, when 0.1 N HCl was employed as dissolution medium, slow and complete release of lercanidipine HCl was observed. At different rotation speeds of the paddle apparatus, lercanidipine HCl had a distinct dissolution profile with gradual increase and then constant plateau, and less than 50% release in 15 min; however, at 50 and 75 rpm, the release obtained at 30 min was 77% and 76%, respectively, which does not meet the objective of more than 85% release at 30 min. Also, release of lercanidipine HCl in 20 min at 75 rpm is lower than that obtained at 50 rpm, which can be explained by various factors such as inconsistent agitation of the dosage form, poor hydrodynamics achieved at this speed, tablet weight, hardness, etc. The dissolution profile obtained with 0.1 N HCl at 100 rpm shows less than 50% drug release in 15 minutes and > 85% drug release in 30 min. The dissolution release pattern of lercanidipine HCl suggests that the extent of release reaches a plateau at about 80% with a 50- and 75-rpm agitation speed, whereas at 100 rpm, nearly complete dissolution of lercanidipine HCl is achieved.

From the experiments conducted and results obtained, a dissolution medium of 900 mL of 0.1 N HCl at 37 °C and a paddle apparatus at 100 rpm was considered the optimum dissolution condition for lercanidipine HCl release.

**Validation of Dissolution Method**

After selecting the optimum dissolution test conditions, the dissolution method was validated (*26, 27*).

*Specificity*

The UV spectrophotometric method is used for the analysis because lercanidipine HCl has a chromophore group (*28*). Specificity of the method was evaluated by scanning the placebo samples with all the excipients without lercanidipine HCl. The UV absorption scan of lercanidipine HCl showed a peak at 236 nm, which was not obtained with placebo samples, and thus, no interference due to excipients used in the formulation was observed (Fig. 2A).

*Linearity*

The analytical method using 236 nm with UV spectrophotometry was found to be linear in the concentration range of 2–20 µg/mL, with a slope of 0.0261 and Y intercept -0.0171. The correlation co-efficient was 0.999. The result of regression analysis confirms that the relationship between concentration and response is linear (Fig. 2B). As recommended, the concentration range evaluated for the dissolution test includes ± 20%, covering both lowest expected and highest expected concentrations.

*Accuracy and precision*

Accuracy of a method was assessed by performing recovery of a known amount of drug reference standard added to the placebo. As recommended, recoveries ranging from 95% to 105% are acceptable for dissolution tests (*4*). The percentage of drug recovered for the dissolution method was found between 98.50% and 103.72%, which lies within the range and shows that the dissolution method is accurate (Table 2). To evaluate intraday precision, three different concentration levels were analysed at different time intervals during a day. For intermediate precision, same solutions were analysed at different days.

The results of precision study are depicted in Table 2, which confirms that the dissolution method shows good precision with RSD lower than 2%.

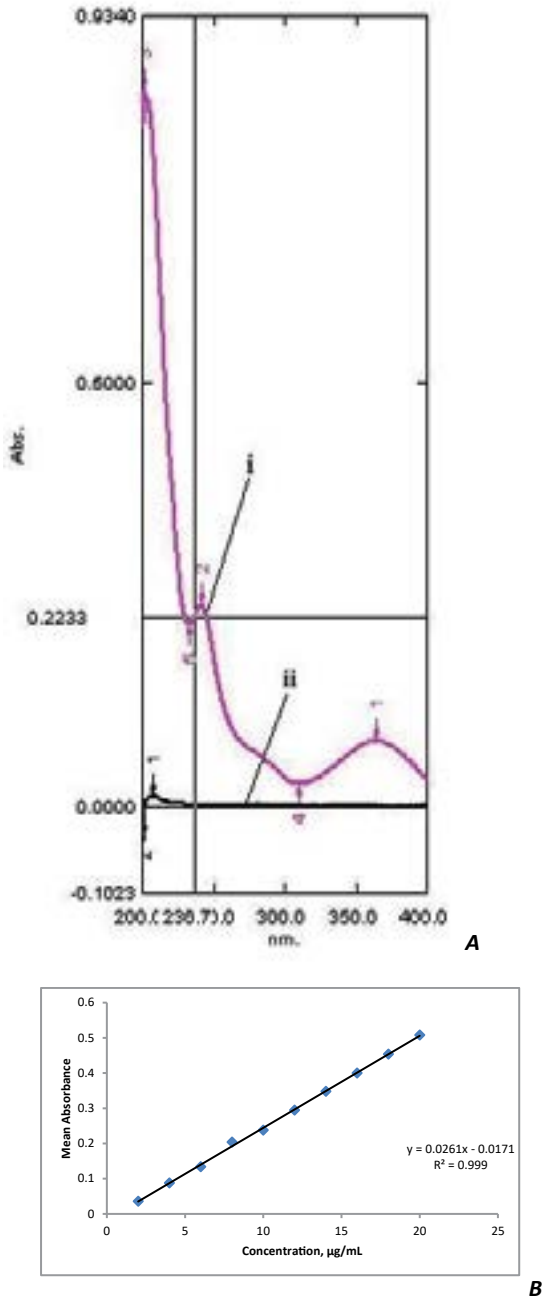


*Figure 2. Ultraviolet spectrophotometry results for lercanidipine HCl in dissolution medium (0.1 N HCl): (A) lercanidipine HCl (i) and placebo (ii); (B) calibration curve of lercanidipine HCl at 236 nm.*

*Table 2. Dissolution Test Accuracy and Precision Results for Lercanidipine HCl (n = 3).*

| Concentration added (µg/mL) | Concentration found (ug/mL), mean ± SD | Recovery (%) |
|---|---|---|
| 5 | 5.07 ± 0.07 | 99.69–103.52 |
| 10 | 9.99 ± 0.17 | 98.50–102.33 |
| 15 | 15.15 ± 0.29 | 99.13–103.72 |
| **Intraday Precision** | | |
| 5 | 5.11 ± 0.09 | 102.20 |
| 10 | 9.88 ± 0.15 | 98.80 |
| 15 | 15.15 ± 0.28 | 101 |
| **Intermediate precision** | | |
| 5 | 4.98 ± 0.03 | 99.60 |
| 10 | 9.92 ± 0.09 | 99.20 |
| 15 | 14.99 ± 0.12 | 99.93 |

*Robustness*

To study the robustness of method, the analytical method was evaluated in different situations such as changing an analyst, changing an instrument, and changing a laboratory. No such change altered the response of the method beyond the permissible limit of RSD 5% (Table 3). These results indicate that the method can withstand small and deliberate changes, illustrating robustness of method employed.

*Stability Studies*

The stability of lercanidipine HCl in different dissolution media was estimated by analysing reference and standard solutions at room temperature for 24 h. The study was performed to demonstrate stability of solutions over the entire period of dissolution profile determination and for an extended time. The result of stability studies demonstrates that the solution of lercanidipine HCl is stable in the pH conditions studied for dissolution method development, with results ranging from 90.96% to 99.04% (Table 4).

## CONCLUSION

Dissolution testing is one of the important analytical tools used to evaluate the effect of any change that takes place in a drug product formulation or process. The dissolution test can also be effectively used to predict the in vivo behaviour of a drug product if proper in vitro/in vivo correlation is established. Using the dissolution profile obtained with different conditions, it was possible to

*Table 3. Robustness of Dissolution Test with Change in Analyst, Equipment, and Laboratory (n = 3).*

| Sample No. | Time (min) | Average % Release ± SD | | | | | |
|---|---|---|---|---|---|---|---|
| | | Analyst I | Analyst II | Instrument I | Instrument II | Laboratory I | Laboratory II |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 10 | 43.04 ± 0.25 | 43.29 ± 0.81 | 42.94 ± 0.39 | 43.39 ± 0.70 | 42.74 ± 0.31 | 43.59 ± 0.54 |
| 3 | 20 | 85.69 ± 0.94 | 86.64 ± 0.74 | 85.91 ± 1.25 | 86.42 ± 0.43 | 86.57 ± 1.19 | 85.75 ± 0.51 |
| 4 | 30 | 94.73 ± 0.86 | 91.96 ± 0.81 | 93.84 ± 0.86 | 92.85 ± 2.00 | 94.05 ± 1.19 | 92.64 ± 1.72 |
| 5 | 40 | 95.61 ± 1.20 | 93.69 ± 0.73 | 95.19 ± 1.21 | 94.11 ± 1.30 | 94.90 ± 0.82 | 94.40 ± 1.73 |
| 6 | 50 | 96.96 ± 0.79 | 95.47 ± 0.85 | 96.84 ± 0.80 | 95.59 ± 1.01 | 96.55 ± 0.44 | 95.88 ± 1.42 |
| 7 | 60 | 98.58 ± 0.63 | 97.00 ± 1.35 | 98.48 ± 0.59 | 97.10 ± 1.48 | 98.45 ± 0.55 | 97.13 ± 1.52 |
| Average at 60 min | | 97.79 ± 0.79 | | 97.79 ± 0.69 | | 97.79 ± 0.66 | |
| %RSD at 60 min | | 0.80 | | 0.69 | | 0.67 | |

*Table 4. Stability Data for Lercanidipine HCl (n = 3).*

| | Concentration (ug/mL) | | | |
|---|---|---|---|---|
| Medium | 0 h | 24 h | w/w (%) | Difference from 0 h (%) |
| 0.1 N HCl, pH 1.2 | 82.35 | 81.56 | 99.04 | 0.96 |
| Acetate buffer, pH 4 | 51.00 | 48.36 | 94.80 | 5.18 |
| Acetate buffer, pH 4.5 | 49.43 | 48.63 | 98.38 | 1.63 |
| Acetate buffer, pH 5 | 36.41 | 34.86 | 95.74 | 4.28 |
| Phosphate buffer, pH 6.2 | 13.56 | 12.65 | 93.28 | 6.73 |
| Phosphate buffer, pH 6.8 | 10.30 | 10.15 | 98.54 | 1.48 |
| Phosphate buffer, pH 7 | 9.85 | 8.96 | 90.96 | 9.07 |

establish dissolution test method for lercanidipine HCl tablets.

Dissolution testing performed with 900 mL of 0.1 N HCl at 37 ± 0.5 °C and 100-rpm speed in USP type II apparatus provides satisfactory results for lercanidipine HCl tablets.

Validation of dissolution method was carried out as per ICH guidelines, and method was found to be specific, linear, accurate, precise, and robust. The validated method can be effectively utilized for the routine assessment of the release profile of lercanidipine HCl from its formulations.

## ACKNOWLEDGEMENT

The authors are thankful to Alembic Pharmaceuticals (Vadodara, Gujarat) for providing Lercanidipine HCl as a gift sample.

## CONFLICT OF INTEREST

No conflict of interest has been declared by authors.

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