Bulletin of Pharmaceutical Research 2013;3(1):23-8
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)

RESEARCH ARTICLE

ECO-FRIENDLY QUANTITATIVE ESTIMATION OF LERCANIDIPINE HYDROCHLORIDE: A NOVEL APPROACH USING HYDROTROPIC SOLUBILIZATION TECHNIQUE

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Received: March 21, 2013 / Revised: March 28, 2013 / Accepted: March 29, 2013

Hydrotropic solution may be a proper choice to preclude the use of organic solvents so that, a simple, accurate, novel, safe and precise method could be developed for estimation of poorly water soluble drug, lercanidipine hydrochloride. Solubility of lercanidipine hydrochloride (LER) is increased by using 2M citric acid as hydrotropic agent. There was more than 61 fold solubility enhancement in hydrotropic solution as compared with distilled water. LER showed the maximum absorbance at 363 nm. At this wavelength, hydrotropic agent and other tablet excipients did not show any significant interference in the spectrophotometric assay. The developed method was found to be linear in the range of 50-250 μg/ml with correlation coefficient (r^2) of 0.9997. The mean percent label claims of tablets of LER in formulation-I and formulation-II estimated by the proposed method were found to be 98.63±0.73 to 98.93±0.57 respectively. The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical parameters were found to be in good accordance with the prescribed values. As hydrotropic agent was used in the proposed method, this method is ecofriendly and it can be used in routine quantitative analysis of drug in bulk drug and dosage form in industries.

Key words: Lercanidipine hydrochloride, Citric acid, Hydrotropic solubilization technique.

INTRODUCTION

Lercanidipine hydrochloride (LER) is chemically 2-[(3,3-diphenylpropyl) (methyl) amino]-1,1-dimethylethyl methyl 2,6-dimethyl-4-(3-nitro phenyl) - 1,4-dihydropyridine-3,5-dicarboxylate monohydrochloride (**Figure 1**) and used in the treatment of mild to moderate hypertension, management of angina pectoris and Raynaud's syndrome (Sweetman, 1999; O'Neil *et al* 2001). Lercanidipine hydrochloride is not an official drug in IP, BP and USP. Literature survey revealed that many spectrophotometric methods (Eswar *et al* 2004; Mubeen *et al* 2009; Sastry and Ramakrishna, 2009) and HPLC (Alvarez-Lueje *et al* 2003; Vijaya *et al* 2004), LC-ESI-MS/MS (Fiori *et al* 2006; Salem *et al* 2004) and voltametric method (Ozturk *et al* 2011; Alvarez-Lueje *et al* 2002) has been reported for determination of lercanidipine hydrochloride in bulk drug and in biological fluids. Considering

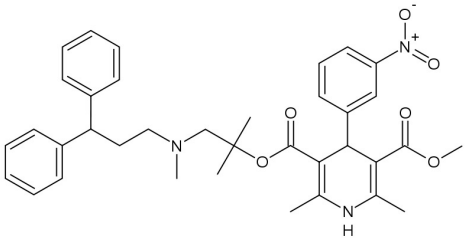

Fig. 1. Chemical structure of LER

the environmental pollution, it is necessary to preclude the use of organic solvents for analysis of drug. Various techniques have been employed to enhance the aqueous solubility; hydrotropy is one of them. Hydrotropic solubilization is the phenomenon by which aqueous solubilities of poorly water soluble drugs and insoluble drugs increase. Many authors have studied and reported use of sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate as the most common examples of hydrotropic agents for increasing the water solubility of drugs (Maheshwari, 2005; 2006; Jain *et al* 2010a; 2010b; 2010c; 2011) and also as eco-friendly solvent system for method development of poorly water soluble drugs (Maheshwari *et al* 2010; 2011a; 2011b; Mehrotra *et al* 2011). Various organic solvents such as methanol, chloroform, dimethyl formamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out spectrophotometric analysis. Drawbacks of organic solvents include their higher cost, toxicity and pollution. Hydrotropic solution may be a proper choice to preclude the use of organic solvents. Therefore, it was thought worthwhile to employ the hydrotropic solution to extract out the drug from fine powder of tablets to carry out spectrophotometric estimation. Present work emphasizes on quantitative estimation of LER in their dosage form by UV spectroscopic methods.

MATERIALS AND METHODS

Instrument

UV-Visible double beam double detector spectrophotometer, Shimadzu model-1700 having spectral bandwidth 3 nm and wavelength accuracy ±1 nm, with 1cm quartz cells was used.

Reagents and chemicals

Analytical pure sample of LER was supplied as gift sample from Glenmark Pharm. Ltd. Nashik. Citric acid was obtained from Merck Chemical Division, Mumbai. Reverse osmosis water was used throughout the study. The marketed formulations, Landip-10 mg (Micro Labs Ltd), Lerka-10 mg (Piramal Healthcare), were purchased from local market of Bhopal.

Preliminary solubility studies of drugs and selection of hydrotropic agent

An excess amount of drug was added to a screw capped 25 ml of volumetric flask containing different aqueous systems viz. distilled water, different combinations of hydrotropic agents. The volumetric flasks were shaken mechanically for 12 h at 25±1°C in a mechanical shaker. These solutions were allowed to equilibrate for next 24 h and then centrifuged for 5 min at 2000 rpm. The supernatant liquid was taken for appropriate dilution after filtering through Whatman filter paper #41 and analyzed spectrophotometrically against corresponding solvent blank. After analysis, it was found that the enhancement in the solubility of LER was more than 61 folds in 2 M citric acid as compared to solubility studies in other solvents. LER was scanned in presence of hydrotropic agent in the spectrum mode over the UV range 200-400 nm.

Establishment of stability profile

Stability of LER was observed by dissolving in 2 M citric acid as hydrotropic agent. Solution of LER was prepared in the concentration of 100 µg/ml and scanned under time scan for 30 min.

Linearity range and calibration graph:

Preparation of standard stock solution (Stock-A)

Accurately weighed 100 mg of the LER was transferred in to 100 ml volumetric flask containing 80 ml of hydrotropic agent and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to the mark with hydrotropic agent to get a concentration of 1000 µg/ml (Stock-A).

Preparation of Working Standard Solution

The standard solution (1000 µg/ml) was further diluted with distilled water to obtain 50, 100, 150, 200 and 250 µg/ml solution and absorbances were noted at 363 nm against distilled water as blank.

Analysis of marketed formulations

Two marketed formulations Landip-10 mg (Micro Labs Ltd), Lerka-10 mg (Piramal Healthcare) were selected for tablet analysis, *i.e.* containing 10 mg LER. Twenty tablets were accurately weighed, average weight determined and ground to fine powder.

An accurately weighed quantity of powder equivalent to 10 mg of LER was transferred into 10 ml volumetric flask containing 8 ml of hydrotropic solution. The flask was sonicated for about 20 min to solublize the drug; volume was adjusted to mark with hydrotropic agent and filtered through whatman filter paper no. 41. The Absorbances of sample solutions were

analyzed on UV spectrophotometer at 363 nm against R.O. water as blank. Drug content of tablet formulations were calculated using calibration curve.

VALIDATION PARAMETERS

The developed method was validated as per ICH guidelines (Linearity, Accuracy, Precision and Robustness) (ICH, 2005).

Linearity

Linearity of LER was established by response ratios of drug. Response ratio of drug was calculated by dividing the absorbance with respective concentrations.

Accuracy

To check the degree of accuracy of the method, recovery studies were performed in triplicate by standard addition method at 80%, 100% and 120%. In preanalyzed tablet solution, a definite amount of drug was added and then its recovery was studied. These studies were performed by adding fixed amount of pure drug solution to the final dilution while varying the concentration of tablet sample solution in the final dilution.

Precision

Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to day and analyst to analyst) and reproducibility. Repeatability was performed by analyzing same 5 concentrations of drug for 5 times. Day to day was performed by analyzing 5 different concentration of the drug for three days in a week. Reproducibility was performed by analyzing same concentration of drugs for five times in different lab.

RESULTS AND DISCUSSION

Based on the solubility, stability and spectral characteristics of the drug, 2 M citric acid was selected as hydrotropic agent. There was more than 61 fold solubility enhanced in hydrotropic solution as compared with distilled water. After solubilizing the Lercanidipine Hydrochloride in selected hydrotropic agent, it was scanned in spectrum mode and the working wavelength for the estimation, considering the reproducibility and variability was found to be 363 nm. The developed method was found to be linear in the range of 50-250 µg/ml with linear equation Y = 0.0077X - 0.0019 and correlation coefficient (r^2) 0.9997. The mean percent label claims of tablets of LER in formulation-I and formulation-II estimated by the proposed method were found to be 98.63±0.73 to 98.93±0.57 respectively. These values are close to 100, indicating the accuracy of the proposed analytical method. A spectrum of LER is shown in **Figure 2**. Calibration curve was plotted between concentrations versus absorbances (**Figure 3**).

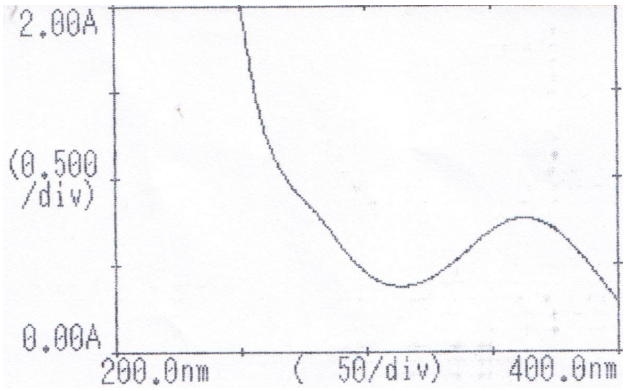

Fig. 2. Spectrum of LER in 2 M citric acid

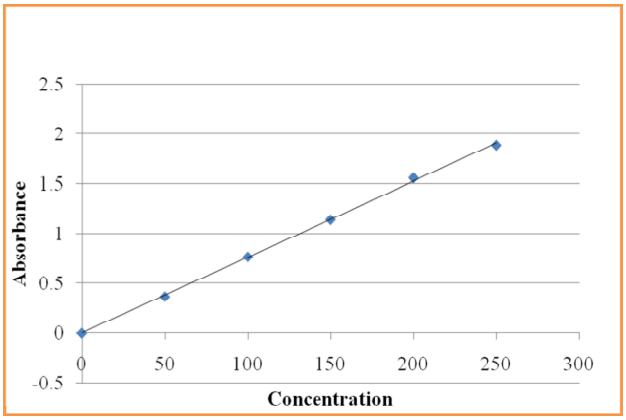

Fig. 3. Calibration curve of LER at 363 nm in 2 M citric acid

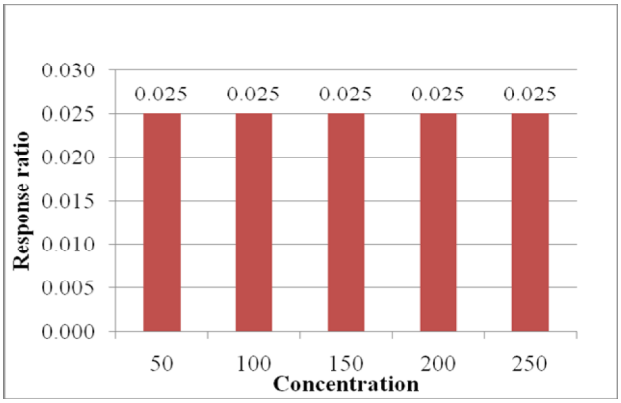

Fig. 4. Response ratio curve of LER in 2 M citric acid

Observation of linearity data and the results of optical characteristics are shown in **Table 1**. The

statistical evaluation of tablet analysis is reported in **Table 2** and **Table 3**. Results have been reported in **Table 4**. Then, a graph was plotted between concentration and response ratio (**Figure 4**). The percentage recovery and percentage relative standard deviation of the recovery were calculated and reported in **Table 5**. The results of precision, reproducibility and repeatability are shown in **Table 6**. The values of mean percent recoveries were also found to show variability ranging from 98.18±1.00 to 98.92±1.10%. All these values were very close to 100. Also the values of standard deviation, percent coefficient of variation and standard error were satisfactorily low. Results of the precision at different levels were found

Table 1. Optical characteristic and linearity data of LER in 2 M citric acid

S. No.	Parameter	2 M Citric Acid
1	Working λ	363 nm
2	Beer's law limit (μg/ml)	50-250
3	Correlation Coefficient (r^2)*	0.9997
4	Slope (m)*	0.0077
5	Intercept (c)*	-0.0019
6	Number of samples (n)	25

*Average of 5 determination of 5 concentrations

Table 2. Results and statistical parameters for Landip – 10 mg tablet analysis using 2 M citric acid

Formulation	Label claim (mg)	Amount found (mg)	% Mean*	S.D.*	%COV*	Standard error*
Landip – 10 mg	10	9.89	98.90	0.96	0.971	0.176
Landip – 10 mg	10	9.83	98.30	0.63	0.641	0.115
Landip – 10 mg	10	9.87	98.70	0.59	0.598	0.108
Mean		9.86	98.63	0.73	0.74	0.13

*Average of five in 3 replicates determination

Table 3. Results and statistical parameters for Lerka – 10 mg tablet analysis using 2 M citric acid

Formulation	Label claim (mg)	Amount found (mg)	% Mean*	S.D.*	%COV*	Standard error*
Lerka – 10 mg	10	9.86	98.60	0.74	0.751	0.135
Lerka – 10 mg	10	9.88	98.80	0.69	0.698	0.126
Lerka – 10 mg	10	9.94	99.40	0.28	0.282	0.051
Mean		9.89	98.93	0.57	0.577	0.104

*Average of five in 3 replicates determination

Table 4. Response ratio of LER in hydrotropic solution

S. No.	2 M Citric acid		
	Conc. (μg/ml)	Absorbance	Response ratio
1.	50	0.375	0.025
2.	100	0.778	0.025
3.	150	1.147	0.025
4.	200	1.529	0.025
5.	250	1.894	0.025

Table 5. Result of recovery studies of tablet formulation with statistic evaluation

Drug	QC conc. (μg/ml)	Recovery level % (Amount drug added)	Amount of drug found (Mean±SD)*	% RSD
LER	100	80	98.42±1.03	1.046
		100	98.18±1.00	1.018
		120	98.47±0.84	0.853
LER	150	80	98.64±0.55	0.557
		100	98.92±1.10	0.111
		120	98.28±0.63	0.641

*Average of five determination

Table 6. Result of precision of LER

	Validation Parameter	Percentage Mean ±SD* (n=6)	Percentage RSD
2 M Citric Acid	Repeatability	98.47±1.11	1.127
	Intermediate precision		
	Day to day	98.89±1.14	1.152
	Analyst to analyst	98.81±1.09	1.103
	Reproducibility	98.75±1.13	1.144

*Mean of fifteen determinations (3 replicates at 5 concentrations level)

within acceptable limits (RSD<2). Presence of hydrotropic agent did not show any significant interference in the spectrophotometric assay, thus further confirming the applicability and reproducibility of the developed method.

CONCLUSION

The proposed methods were new, simple, cost effective, accurate, safe and precise. The advantage of these methods is that the organic solvent is not essential for the analysis and there was no interference of 2 M citric acid in the estimation. There is a good scope for other poorly water-soluble drugs which may be tried to get solubilized in 2 M citric acid solution (as hydrotropic agent) to carry out their spectrophotometric analysis excluding the use of costlier and unsafe organic solvents.

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