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Research Article

NOVEL ANALYTICAL METHOD FOR IMPROVEMENT OF AQUEOUS SOLUBILITY OF CANDESARTAN CILEXETIL USING CO-SOLVENCY APPROACH

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ABSTRACT
The present study was aimed at improving the aqueous solubility of candesartan cilexetil, a poorly water soluble drug, using poly ethylene glycol (PEG) 400 as co-solvent. It was observed that use of 5 % PEG 400 as co-solvent significantly improved the solubility by 50 folds. Beer's law was obeyed in the concentration range of 4-20 µg/mL. Regression value for the calibration curve at wave length 232 nm was close to 1. The analysis of tablets by the proposed method indicated good correlation between estimated and label claim. The results of recovery studies revealed that any small change in the drug concentration could be accurately determined by the proposed method. The low values of limit of detection (LOD) and limit of quantification (LOQ) of candesartan cilexetil in PEG 400 indicated good sensitivity of proposed method. As PEG 400 was cheaper and less toxic when compared to organic solvents, this can be used as a substitute for organic solvents in the analysis. Thus the method developed to improve aqueous solubility of poorly water soluble drugs was found to be economical, eco-friendly, accurate, precise and can be applied in the routine analysis of tablets.
KEY WORDS: Solubilization, Co-solvency, Poly ethylene glycol 400, Candesartan cilexetil

INTRODUCTION

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown[1]. Poor aqueous solubility is a common concern in the pharmaceutical sciences, and several pharmaceutical researchers have established methods for increasing the equilibrium solubility of non–polar drugs in aqueous vehicles[2]. A number of methodologies can be adapted to improve solubilization of poorly water soluble drugs and further to improve its bioavailability. Commonly employed techniques for solubilization include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc[3]. Cosolvency is the addition of water miscible solvents to poorly water soluble to improve its aqueous solubility [2]. Poly ethylene glycol (PEG) has been used to modulate the water solubility of poorly soluble drugs[4,5]. PEG with a molecular weight of 400 (PEG400) has been frequently used as a co-solvent to dissolve poorly water-soluble drugs[6,7] Quantitative analysis of poorly water-soluble drugs involves use of various organic solvents like acetone, chloroform, dimethyl formamide, ethanol, methanol. Drawbacks of organic solvents include their toxicity, higher costs, volatility and pollution[8,9]. The advantage of certain properties such as the solvent character being independent of pH, non-flammability, easy availability of hydrotropes, inexpensive aqueous phase makes this method superior to other solubilization methods[10]. Weak electrolytes and nonpolar molecules have poor water solubility, which can be improved by altering polarity of the solvent system. This can be achieved by addition of another solvent. Co solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute i.e., solvent blending. Most co solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions[11]. This mixed cosolvency technique is based on the principle that instead of using one solubilizer in large concentration for a desired level of solubility, several solubilizers like hydrotropes (sodium ascorbate, urea, sodium benzoate), co-solvents (propylene glycol, PEG 200, 300, 400) and water soluble solids (PEG 4000, 6000, Cyclodextrins) in varying concentrations may be used that may show additive or synergistic enhancement in solubility.[12] Candesartan is a nonpeptide angiotensin II blocker used as an antihypertensive. Candesartan cilexetil, a white crystalline powder with melting point 157-160 ^{0} is insoluble in water, soluble in methanol and is administered orally[13]. In the present study, an attempt was made to increase the aqueous solubility of candesartan cilexetil using 5 % PEG 400 as a co-solvent.

MATERIALS AND METHOD

Candesartan cilexetil bulk drug was a gift sample from Matrix laboratories, Hyderabad. PEG 400 was obtained from E. Merck (India) limited, Mumbai. Tablets of candesartan cilexetil were purchased from local market. Shimadzu UV/Visible recording spectrophotometer (model-UV-1601) with 1cm matched silica cells was employed. All other chemicals and solvents used were of analytical grade.

EXPERIMENTAL METHOD

Saturation solubility studies of Candesartan cilexetil in PEG 400

Solubility of candesartan cilexetil was determined by saturation aqueous solubility method in co -solvent containing 5% PEG 400 in distilled water. An excess amount of drug was added to 50ml beakers containing 50ml of 5 % PEG 400 in distilled water. The beakers were shaken for 12 hours at 28±10^{0}C. The solutions were filtered through Whatman filter paper #41, and the resulting filtrates were suitably diluted and analyzed spectrophotometrically against solvent blank.

Preparation of standard stock and calibration curve

The standard stock solution of candesartan cilexetil was prepared by dissolving 5 mg in 10ml of 5 % PEG 400. From this stock solution, 5ml of solution was diluted to 25 ml with

distilled water to get a solution containing 100µg/ml and scanned in the entire UV range of 400-200 nm to determine the λ max of the drug. The λ max of candesartan cilexetil was found to be 232 nm. Five working standard solutions for the drug having concentration range of 4, 8, 12, 16 and 20 µg/ml was prepared with distilled water from the stock solution. The absorbances of resulting solutions were measured at wavelength of 232 nm and a calibration curve was plotted to get the linearity and regression equation.

Analysis of candesartan cilexetil in marketed tablets using 5% PEG 400

Ten tablets were weighed, powdered and powder equivalent to 4mg of candesartan cilexetil was transferred to 50ml volumetric flask containing 40ml of 5% PEG 400 in distilled water. The flasks were shaken for 20 mins to solubilize the drug completely and volume was made up with distilled water. From this 5ml of solution was pipetted into 25 ml volumetric flask containing distilled water to obtain a concentration of 16 µg/ml. The absorbance of resulting solution was measured at 232 nm against solvent blank and drug content was calculated.

Validation of the proposed method[13]

Recovery studies

Tablet powder equivalent to 4 mg of candesartan cilexetil was transferred to a 100ml volumetric flask containing PEG 400. 2mg of candesartan cilexetil bulk drug was added to the same volumetric flask. The flask was shaken for 20 mins to solubilize the drug. Then solution was filtered through Whatmann filter paper #41. The filtrate was diluted with distilled water appropriately and absorbance was measured at 232 nm against corresponding solvent blank. Drug content was calculated and percent recovery was calculated. Similar procedure was adopted using 4 mg and 6 mg of candesartan cilexetil bulk drugs spiked concentration. The drug contents were determined and percent recoveries were estimated.

Inter- day and Intra- day precision

The intra-day concentration of the drug was calculated by measuring the absorbances of the working standard solutions on the same day at an interval of one hour, whereas the inter day concentration of drug was calculated on three different days within the laboratory conditions.

Linearity

The absorbances of appropriate dilutions of standard stock solutions were measured as per the developed method to confirm the linearity.

Limit of detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of candesartan cilexetil by the proposed method were determined using calibration standards. LOD and LOQ were calculated as 3.3σ /S and 10σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of response.

RESULTS AND DISCUSSION

The results of saturation solubility studies of candesartan cilexetil indicated that there was increase in solubility of candesartan cilexetil in water due to addition of co-solvent PEG 400 by 50 folds. Solubility of candesartan cilexetil in water was found to be 0.012mg/mL, which was significantly improved in the presence of 5% PEG 400 and was found to be 0.6mg/mL. Beer- Lambert's range for candesartan cilexetil in solution employing 5 % PEG 400 as co-solvent was between 4-20µg/mL. Spectrum analysis was done and λ max was found to be 232 nm (Fig. 1). Regression value for the calibration curve at this wave length was 0.9925 that was close to 1, which indicated a good correlation between the amount estimated and the label claim. The estimated label claim was found to be 101.3±0.864 with a standard error of 0.436 (Table 1).

This revealed that use of PEG 400 as co-solvent will effectively determine the drug content in the tablet formulation with out interference by UV analysis. To check drug stability and precipitation of drug in co-solvent, a part of solution was kept in room temperature for 48 hours. The results revealed that estimation of candesartan cilexetil can be done without substantial effect on drug stability as no precipitation was observed. From this study it was obvious that there was no interference of 5% of PEG 400 in estimation of candesartan cilexetil at the wavelength of 232nm. The results of recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. Accuracy, reproducibility and precision of the proposed methods were further confirmed by percent recovery values, which were close to 100, with low values of standard deviation and standard error as shown in Table 2. Repeatability results indicated the precision under the same operating conditions over a short interval time and inter-assay precision. Intermediate precision study expresses within laboratory variation in different days. In both intra and inter-day precision study for the method, co-efficients of variation were not more than 1.0% indicating good intermediate precision. The low values of LOD, 0.1355 µg/ml and LOQ, 0.4108 µg/ml for candesartan cilexetil in 5% PEG 400 indicated good sensitivity of proposed method (Table 3). It was thus concluded that solubilization of candesartan cilexetil using PEG 400 as a co-solvent can be achieved. By this new, simple, accurate, non-toxic, cost- effective and precise developed method, use of costlier, toxic organic solvents in the analysis can be minimized. This method can be successfully employed for estimation of drugs in routine analysis of tablets.

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Table 1: ANALYSIS OF TABLET FORMULATIONS OF CANDESARTAN CILEXETIL

Tablet Formulation	Label Claim (mg)	% Label claim Estimated[a]	Standard error
Commercial tablet with 5% PEG 400 (PEG)	4mg	101.3±0.864	0.436

[a] Mean±S.D (n=6)

Table 2: RESULT OF RECOVERY STUDIES

Formulation	Amount of candesartan cilexetil tablet powder(mg)	Amount of standard drug added (mg)	Percent recovery estimated[a]	Standard error
Commercial tablet with 5 % PEG 400	4	2	102.6 ± 0.638	0.314
	4	4	106.3 ± 0.826	0.418
	4	6	105.5 ± 0.964	0.458

[a] Mean±S.D (n=6)

Table 3: OPTICAL CHARACTERISTICS DATA AND VALIDATION PARAMETERS

Parameters	Values of candesartan cilexetil in 5 % PEG 400
Working λmax (nm)	232
Beer's law limit (µg/ml)	4 – 20
Molar Absorptivity	3.928×10^3
Correlation coefficient[a]	0.9925
Intercept[a]	0.0041
Slope[a]	0.0058
LOD[a] (µg/ml)	0.1355
LOQ[a] (µg/ml)	0.4108
Intra-day[a] (precision) (Co-eff. of variation)	0.425
Inter-day[a] (precision) (Co-eff. of variation)	0.2175
Robustness	Robust

[a] n = 6

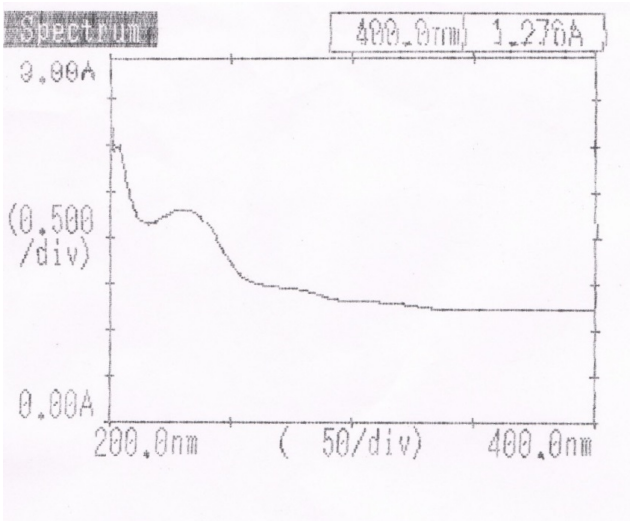

Figure 1 : UV- SPECTRUM OF CANDESARTAN CILEXETIL IN 5 % PEG 400

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