NOVEL ANALYTICAL METHOD FOR IMPROVEMENT OF AQUEOUS SOLUBILITY OF Candesartan Cilexetil USING CO-SOLVENCY APPROACH

Maddukuri Sravya 1, Deveswaran Rajamanickam 1*, Bharath Srinivasan 2,
Basappa Veerabhadraiah Basavaraj 1, Madhavan Varadharajan 2

1Department of Pharmaceutics, M.S.Ramaiah College of Pharmacy, MSRIT Post, Bangalore-560054 India
2Department of Pharmacognosy, M.S.Ramaiah College of Pharmacy, MSRIT Post, Bengaluru-560054 India

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E-mail: devs_mda@yahoo.com

ABSTRACT

The present study was aimed at improving the aqueous solubility of candesartan, 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. 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. A number of methods 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 1. Cosolvency is the addition of water miscible solvents to poorly water soluble drug to improve its aqueous solubility 2. Poly ethylene glycol (PEG) has been used to modulate the water solubility of poorly soluble drugs 3-5. 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 ºC 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±10ºC. 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...
The intra-

Analysis of candesartan cilexetil in marketed tablets using

The absorbances of appropriate dilutions of standard stock

Limit of detection (LOD) and Limit of Quantitation

Tablet powder equivalent to 4 mg of candesartan cilexetil

Validation of the proposed method

Inter- day and Intra- day precision

The intra-day concentration of the drug was calculated by

Linearity

The absorbances of appropriate dilutions of standard stock

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

The LOD and LOQ of candesartan cilexetil by the proposed

RESULTS AND DISCUSSION

The results of saturation solubility studies of candesartan

close to 1, which indicated a good correlation between

This revealed that use of PEG 400 as co-solvent will

determine the λ max of the drug. The λ max of candesartan cilexetil was

Ten tablets were weighed, powdered and powder equivalent

to 4 mg of candesartan cilexetil was transferred to 50 ml

Recovery studies

Tablet powder equivalent to 4 mg of candesartan cilexetil

Inter- day and Intra- day precision

The intra-day concentration of the drug was calculated by

Linearity

The absorbances of appropriate dilutions of standard stock

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

The LOD and LOQ of candesartan cilexetil by the proposed

RESULTS AND DISCUSSION

The results of saturation solubility studies of candesartan

close to 1, which indicated a good correlation between

This revealed that use of PEG 400 as co-solvent will
effectively determine the drug content in the tablet

Tablet powder equivalent to 4 mg of candesartan cilexetil

Recovery studies

Tablet powder equivalent to 4 mg of candesartan cilexetil

Inter- day and Intra- day precision

The intra-day concentration of the drug was calculated by

Linearity

The absorbances of appropriate dilutions of standard stock

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

The LOD and LOQ of candesartan cilexetil by the proposed

RESULTS AND DISCUSSION

The results of saturation solubility studies of candesartan

close to 1, which indicated a good correlation between

### Table 1: ANALYSIS OF TABLET FORMULATIONS OF CANDESARTAN CILEXETIL

<table>
<thead>
<tr>
<th>Tablet Formulation</th>
<th>Label Claim (mg)</th>
<th>% Label claim Estimated</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial tablet with 5% PEG 400 (PEG)</td>
<td>4mg</td>
<td>101.3±0.864</td>
<td>0.436</td>
</tr>
</tbody>
</table>

* Mean±S.D (n=6)

### Table 2: RESULT OF RECOVERY STUDIES

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Amount of candesartan cilexetil tablet powder(mg)</th>
<th>Amount of standard drug added (mg)</th>
<th>Percent recovery estimated</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial tablet with 5 % PEG 400</td>
<td>4</td>
<td>2</td>
<td>102.6 ± 0.638</td>
<td>0.314</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4</td>
<td>106.3 ± 0.826</td>
<td>0.418</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>105.5 ± 0.964</td>
<td>0.458</td>
</tr>
</tbody>
</table>

* Mean±S.D (n=6)

### Table 3: OPTICAL CHARACTERISTICS DATA AND VALIDATION PARAMETERS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values of candesartan cilexetil in 5 % PEG 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working λ max (nm)</td>
<td>232</td>
</tr>
<tr>
<td>Beer’s law limit (µg/ml)</td>
<td>4 - 20</td>
</tr>
<tr>
<td>Molar Absorptivity</td>
<td>3.928x10^3</td>
</tr>
<tr>
<td>Correlation coefficient*</td>
<td>0.9925</td>
</tr>
<tr>
<td>Intercept*</td>
<td>0.0041</td>
</tr>
<tr>
<td>Slope*</td>
<td>0.0058</td>
</tr>
<tr>
<td>LOD* (µg/ml)</td>
<td>0.1355</td>
</tr>
<tr>
<td>LOQ* (µg/ml)</td>
<td>0.4108</td>
</tr>
<tr>
<td>Intra-day* (precision)</td>
<td>0.425</td>
</tr>
<tr>
<td>(Co-eff. of variation)</td>
<td></td>
</tr>
<tr>
<td>Inter-day* (precision)</td>
<td>0.2175</td>
</tr>
<tr>
<td>(Co-eff. of variation)</td>
<td></td>
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<tr>
<td>Robustness</td>
<td>Robust</td>
</tr>
</tbody>
</table>

* n = 6

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

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