ENHANCED SOLUBILITY STUDY OF CANDESARTAN CILEXITIL USING DIFFERENT HYDROTROPIC AGENT

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ABSTRACT

The aim of present work was to perform a comparative study of enhancement of solubility of Candesartan Cilexitil (CC) by using different hydrotropic agent such as sodium salicylate, sodium acetate and 2-Hydroxy N, N-diethyl nicotinamide (HDENA). The enhancement in solubility of CC by different hydrotropic agent was observed in decreasing order as HDENA > sodium salicylate > sodium acetate. It was observed that the solubility increased with the increase in the concentration of each hydrotropic agent. Amongst the various hydrotropic agents used the solubility of CC was enhanced greatest to 106 folds with HDENA at 2M concentration.

Keywords: Hydrotropic agent, Candesartan Cilexitil, HDENA, Solubility enhancement.

INTRODUCTION

The oral route is the most preferred means of drug administration due to the ease, high patient compliance, and low cost of production [1]. Therapeutic effectiveness of a drug depends upon the bioavailability which is mostly dependent on the solubility of drug molecules. Solubility behavior of drugs remains one of the most challenging aspects in formulation development. In the case of poorly soluble drugs, dissolution is the rate limiting step in absorption process. Generally, compounds with aqueous solubility lower than 100 mg/ml show dissolution- limited absorption and erratic and/or incomplete absorption from the gastrointestinal tract of animals and humans. However, 40% of all newly developed drugs are poorly soluble or insoluble in water, leading to ineffective absorption and therapeutic failure [2].

Two critical rate determining steps in the absorption of orally administered drugs are:

1. Rate of dissolution
2. Rate of drug permeation through bio-membrane [3]
Increasing the aqueous solubility of insoluble and slightly soluble drug is of major issue in case of development of formulation of such drugs. Several techniques have been employed to solubilize the poorly water-soluble drugs [4].

Hydrotropic solubilization technique is one answer to such problem. Hydrotropy refers to the ability of a concentrated solution of a chemical compound to increase the aqueous solubility of another compound (usually a sparingly soluble organic compound). Compounds which have this property are called ‘hydrotropes’. Sodium salicylate, sodium acetate, sodium ascorbate, niacinamide, sodium citrate, urea, nicotinamide and their derivatives are the most popular examples of hydrotropic agents which have been used to solubilize a large number of poorly water-soluble compounds [5]. In this research work, Hydrotropic solution of 2-Hydroxy N,N’-diethyl nicotinamide (HDENA), Sodium acetate and sodium salicylate were employed as solubilizing agent to study increase in solubility of slightly water soluble antihypertensive drug CC. HDENA is the derivative of nicotinamide (Vitamin B) used as a hydrotropic agent in solubility enhancement of poorly water soluble drugs [6].

Hydrotropes are amphiphilic in nature i.e. composed of hydrophilic as well as lipophilic portions. These molecules are used to increase solubility of poorly soluble drugs as they are able to form micelles at certain concentration (one of the probable mechanism of solubilization). This method is commonly known as micellar solubilization. In many instances, the aqueous solubility was increased by orders of magnitude simply by mixing with hydrotropic agents in water [7].

Hydrotropic agents self-associate into loose non-covalent assemblies of non-polar microdomains to solubilize hydrophobic solutes. However, the detailed mechanisms of hydrotropy have not been fully understood. Currently, the most widely used method for increasing the aqueous solubility is to add surfactants to the aqueous release media. However, this method is not applicable for polymeric micelle systems because even a small amount of surfactants could destroy their micellar structure and distort their release profiles. A hydrotropic agent could be a good alternative to increasing the aqueous solubility [8].
CC is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. It is administered orally as the prodrug, CC, which is rapidly converted to its active metabolite, Candesartan, during absorption in the gastrointestinal tract. Candesartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); it competes with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II.

As CC

- Is a BCS class II drug
- Is practically insoluble in water (7.71 mg/l) and
- Has low bioavailability (<15%)\(^9\)

So the main objective of this research work was to increase the solubility of CC using different hydrotropes and compare efficiency of each to solubilize CC.

**MATERIALS AND METHODS**

**Materials**

CC was kindly provided as a gift sample from Alembic Pharma (Baroda, Gujarat), 2-hydroxynicotinic acid (HNA) was purchased from Merk Laboratories (Mumbai), Sodium salicylate, Tetra hydro furan (THF), 1,1 Carbonyl diimidazole (CDI) and N,N-diethyl amine (DEA) were purchased from Oxford Chemicals (Vasai, Maharashtra). All chemicals were of laboratory grade.

**Methods**

Three hydrotropic agents were tried in this research work. Among them two i.e. sodium salicylate & sodium acetate were purchased. The third one i.e. HDENA was synthesized in laboratory.

**Synthesis of HDENA**

HNA (5 g) was reacted with CDI (5.8 g) in THF (225 ml) at 70\(^\circ\)C for 24 h. After 24 h, another 100 ml THF was added into the crude solution and DEA (7.5 ml) was slowly dropped and further reaction was performed at 70\(^\circ\)C for 18 h. After 18 h, 70% THF was distilled off and remaining solution was evaporated on water bath at 75\(^\circ\)C. White crystal of 2-hydroxy-DENA (HDENA) was obtained by repeated wash with THF. HDENA was dried at 50\(^\circ\)C & store at room temperature in well closed container until further use\(^{10}\).
Solubility Study

Solubility study was carried out by shake flask method. An excess amount of the CC was placed in contact with water. The samples were shaken for 24 h at 37 0C in a shaker (Remi Pvt Ltd, Mumbai). Then sample was placed undisturbed for 12 h for equilibrium. The supernatant was filtered through 0.45µm filter papers (Milli pore, Bangalore). Concentration of CC in supernatant was measured by UV visible spectrophotometer (Labtronics, Haryana) based on calibration plot prepared at λmax 258 nm.

Comparative solubility analysis with different hydrotropic agents

Solubility studies were performed according to Higuchi and Connors \cite{11}. It was determined in various hydrotropic agents’ solution (Sodium salicylate, sodium acetate and HDENA) of concentration 1M. Excess of CC was added to different 100 ml volumetric flask each containing 50 ml 1M aqueous solution of different hydrotropic substance. Flasks were shaken for 12 h in shaker and kept at 25 0C for 24h for equilibrium. Unsolubilized drug was separated by passing solution through a 0.45 µm filter. Filtrates were analyzed spectrophotometrically at 258 nm using UV-Vis Spectrophotometer. Each hydrotropic agent was analyzed in triplicate.

Solubility analysis in different concentration of HDENA

Solubility was determined in different concentration of HDENA solution (0.5, 1.0, 1.5 and 2.0 M aqueous solution of HDENA). In each solution of different concentration excess of CC was added. Solutions were analyzed as per methods described earlier.

TABLE 1: SOLUBILITY STUDY WITH DIFFERENT HYDROTROPIC AGENT

<table>
<thead>
<tr>
<th>Hydrotropic agent used</th>
<th>Conc. of hydrotropic agent</th>
<th>Solubility of CC (µg/ml)</th>
<th>Avg. Solubility of CC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium acetate</td>
<td>1M</td>
<td>110</td>
<td>111.66 ± 2.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>114</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Sodium salicylate</td>
<td>1M</td>
<td>178</td>
<td>180.33 ± 2.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>180</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>HDENA</td>
<td>1M</td>
<td>270</td>
<td>267.33 ± 2.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>266</td>
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</tbody>
</table>
RESULTS AND DISCUSSION

The aqueous solubility of CC was found to be 5.7µg/ml at 25°C. The solubility of CC at 25°C in 1M solution of Sodium acetate, Sodium salicylate and HDENA is given in table-1. Table-2 represents solubility of CC at different concentration of HDENA.

**TABLE 2: SOLUBILITY STUDY WITH INCREASE IN CONCENTRATION OF HDENA**

<table>
<thead>
<tr>
<th>Concentration of HDENA solution (M)</th>
<th>Solubility of CC (µg/ml)</th>
<th>Avg. Solubility of CC (µg/ml)</th>
<th>Solubility enhancement ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5M</td>
<td>153</td>
<td>152.66 ± 0.57</td>
<td>26.84</td>
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<td></td>
<td>153</td>
<td>153</td>
<td>26.84</td>
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<td></td>
<td>152</td>
<td>152</td>
<td>26.84</td>
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<tr>
<td>1.0M</td>
<td>270</td>
<td>267.33 ± 2.30</td>
<td>46.84</td>
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<tr>
<td></td>
<td>266</td>
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<td>46.84</td>
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<tr>
<td></td>
<td>266</td>
<td>266</td>
<td>46.84</td>
</tr>
<tr>
<td>1.5M</td>
<td>410</td>
<td>412 ± 1.73</td>
<td>72.28</td>
</tr>
<tr>
<td></td>
<td>413</td>
<td>413</td>
<td>72.28</td>
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<tr>
<td></td>
<td>413</td>
<td>413</td>
<td>72.28</td>
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<tr>
<td>2.0M</td>
<td>606</td>
<td>607.66 ± 2.08</td>
<td>106.66</td>
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<tr>
<td></td>
<td>607</td>
<td>610</td>
<td>106.66</td>
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<tr>
<td></td>
<td>610</td>
<td>610</td>
<td>106.66</td>
</tr>
</tbody>
</table>

The solubility enhancement ratios were also calculated.

Solubility enhancement ratio = Solubility in particular hydrotropic solution/
Solubility in Water

Among the three hydrotropic agents studied, HDENA show highest enhancement in solubility, so HDENA was used for extensive study. Fig. 1 shows correlation between concentration of HDENA and solubility of CC. The solubility at 0.5M, 1M, 1.5M and 2.0M HDENA were 153 µg/ml, 267 µg/ml, 412 µg/ml, and 608 µg/ml, respectively. This reveals that solubility increases as concentration of HDENA increase. This may be because of formation of more number of micelles at higher concentration.
CONCLUSION
This study indicates that the hydrotropes can increase solubility of CC. Among the three hydrotropes employed in this study, HDENA showed maximum solubilization at equimolar concentration. Solubilization using HDENA is concentration dependent. This experimental method using a hydrotropic agent provides an alternative tool to increase solubility of poorly soluble drugs in aqueous solution. The proposed method of solubility enhancement is new, simple, cost-effective and environment friendly.

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REFERENCES


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