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EFFECT OF HYDROXYLPROPYLATED-β-CYCLODEXTRIN AND pH ON SOLUBILITY OF TELMISARTAN

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ABSTRACT

The present study was undertaken to examine the effect of pH and concentration of hydroxypropylated-β-cyclodextrin (HP-β-CD) on the solubility of telmisartan as it shows the pH dependent solubility. The equilibrium solubility of telmisartan in a series of solutions of varying pH (from 1.2 to 11) was determined and compared with the equilibrium solubility of telmisartan in the presence of 20% HP-β-CD at same pH values. It was observed that solubility of protonated form is more than the neutral molecule. HP-β-CD resulted in increased solubility at all the pH. But inclusion in the cavity of HP-β-CD might depend upon charge state of the molecule. So it can be concluded that solubility of telmisartan can be increased either by the addition of HP-β-CD or by adding pH lowering agents. If both these methods are to be used together, pH should be selected carefully.

Key words: Telmisartan, Hydroxypropylated-β-cyclodextrin, Solubility, Bioavailability, pH.

INTRODUCTION

Telmisartan is chemically 4'-[(1,4'-dimethyl- 2'-propyl [2, 6-bi-1H benzimidazole-1'yl] methyl) [1, 1'-biphenyl] carboxylic acid[1]. It is pharmacologically angiotensin II receptor antagonist and acts as antihypertensive agent[2]. It is also used in other cardiovascular disorders such as angina pectoris, cardiac arrhythmias and myocardial infarction [3].

Because of these therapeutic effects, it has emerged as one of the important and promising drug substance for cardiovascular diseases, especially due to the noticeable improvement of survival rates in patients with chronic cardiac insufficiency. But the major problem with telmisartan is its limited solubility in water. This limits not only its bioavailability to 25-35% but also formulation into desired dosage forms.

Hydroxypropyl-β-cyclodextrin (HP-β-CD) has been used in improving the aqueous

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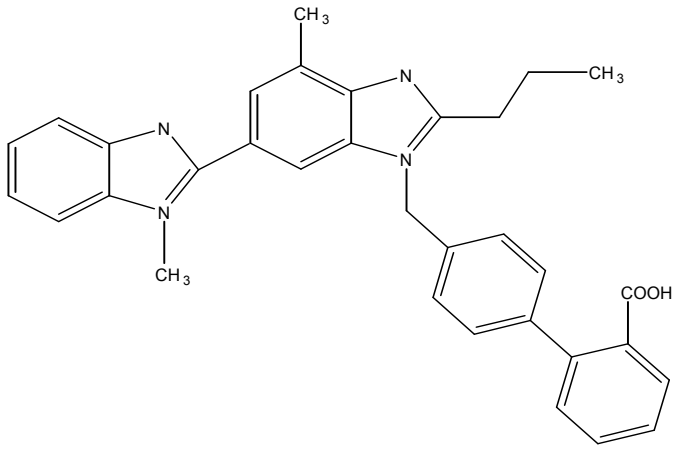
solubility of a variety of compounds[4]. It is a cyclic oligosaccharide containing seven D-(+)-glucopyranose units, with an average of one hydroxypropyl group per unit. The circular arrangement of the glucose units produces a torus-shaped molecule with methylene groups and ether linkages facing the hollow interior of the configuration results in a nonpolar cavity and a polar exterior. When a compound with appropriate geometry and HP-β-CD are in the same solution, the non-polar aromatic portions of the compound tend to enter the nonpolar interior of the HP-β-CD molecule. This complexation isolates the aromatic portion of the molecule from the water; thereby; increasing its aqueous solubility.



Structure of Talmisartan

EXPERIMENTAL

HP-β-CD was obtained as a gift sample from ZIM Laboratories Ltd., India. Telmisartan was purchased from Ultratech, India. All other chemicals were of analytical grade and used without further purification.

All pH measurements were performed using Elico pH meter (Model -140) calibrated using pH 4, 7, and 10 standard buffers. Telmisartan concentrations were determined using SHIMADZU UVPC-2401 spectrophotometer at 297 nm.

Initially, the solubility of telmisartan as a function of pH was studied. A series of buffer solutions from pH range 1.2 to 11 were prepared and telmisartan was added in sufficient quantity to saturate each solution. To avoid change in concentration due to evaporation, solution vials were sealed with teflon lined screw caps and wrapped with paraffin. All solutions were then placed on a test tube rotator and checked daily for the saturation and if necessary, pH was adjusted. To ensure the attainment of equilibrium, all

solutions were rotated for 1 week. Then the solutions were diluted suitably and determined spectrophotometrically at 297 nm. Similar studies were repeated after the addition of 20% HP-β-CD to the series of buffer solutions.

To explore the effect of cyclodextrin concentration on the solubility of telmisartan, phase solubility studies were performed[5]. A series of solutions containing varying concentrations of HP-β-CD (1% to 40%) in pH 7.4 buffer were prepared. Telmisartan was added to each solution in sufficient quantity to ensure saturation, and previously described procedure was used for determining effect of HP-β-CD concentration on the solubility of telmisartan.

RESULTS AND DISCUSSION

Telmisartan exhibits pH dependent solubility. The pH dependence of the complexation of drug with HP-β-CD was investigated on the basis of solubility/pH profiles. Fig. 1 shows the solubility profile of telmisartan in the presence and absence of HP-β-CD, as a function of pH.

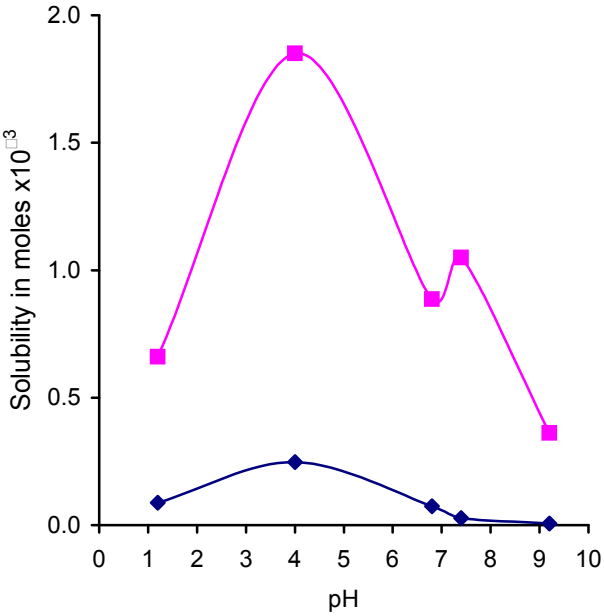


Fig. 1: Solubility of telmisartan as a function of pH. Without HP-β-CD (♦) and in the presence of 20% HP-β-CD(■).

From Fig. 1, it can be seen that telmisartan exhibited pH dependent solubility in both; in the presence and absence of HP-β-CD. Its solubility increases with decreasing pH and then starts decreasing after pH 4. At lower pH values, protonated form of telmisartan and its salt generated *in-situ* will determine its solubility. At basic pH, as the pH increases from 9.2 to 11, its solubility remains more or less constant (2.5 µg/mL ± 0.5).

The addition of HP-β-CD results in a solubility profile as a function of pH similar in shape to that obtained in the absence of complexing agent. However, it shows a significant rise in the solubility of telmisartan at all pH values tested. Addition of 20% HP-β-CD increased the solubility to about 8 times at pH 1.2 and 4; 13 times at pH 6.8; 38 times at pH 7.4; 56 times at pH 9.2 and 65 times at pH 11.

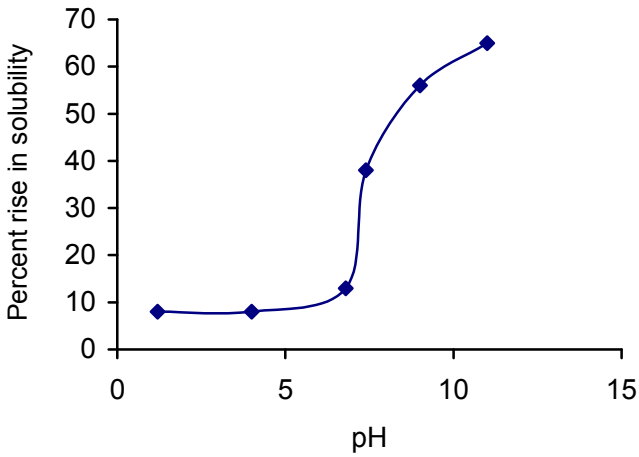


Fig. 2: Effect of HP-β-CD on the percent rise solubility of Telmisartan.

Fig. 2 shows the percent rise in the solubility of telmisartan by HP-β-CD. This pattern indicates that degree of ionization has a decisive influence on the complexibility, and hence, on the solubility of telmisartan at different pH. Both protonated and neutral molecules are not included in the HP-β-CD cavity with same ease. At acidic pH, molecule exists in protonated form, which might be not getting complexed with HP-β-CD. This justifies the limited rise in solubility at acidic pH by HP-β-CD. While at basic pH, the major fraction of the molecules exists in unionized form, which is hydrophobic. The interior environment of a cyclodextrin cavity is hydrophobic; hence, it can entrap unionized form of the molecule which is too hydrophobic[6]. This can be well explained by Handerson-Hesselbach equation[7]

For weak acid,

$$pH = pKa + \log \frac{\text{Ionized drug concentration}}{\text{Unionized drug concentration}}$$

For weak bases,

$$pH = pKa + \log \frac{\text{Unionized drug concentration}}{\text{Ionized drug concentration}}$$

At the acidic pH, telmisartan not only shows appreciable solubility due to its ionization but also does not form the complex with β-CD. At the basic pH, drug does not get solubilise and remain in its unionized form and get enclosed in the hydrophobic cavity of β-CD and forms the complexation results in enhancing the solubility.

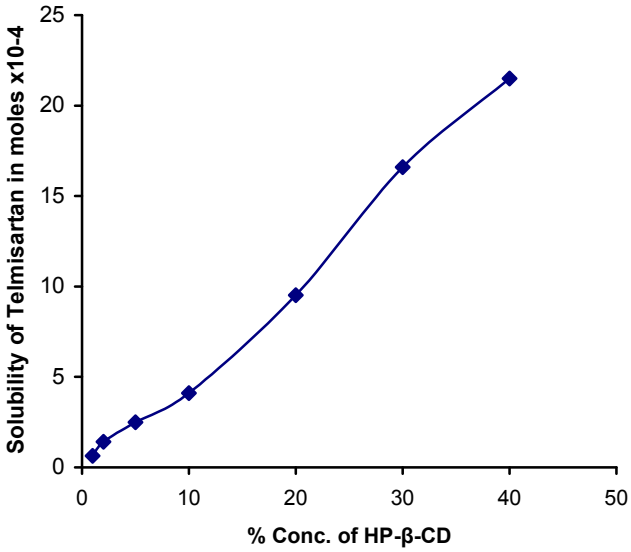


Fig. 3: At pH 7.4, solubility of telmisartan versus concentration of HP-β-CD.

Phase solubility studies of telmisartan were performed at pH 7.4. Fig. 3 shows the changes in the solubility of telmisartan with the increasing concentration of HP-β-CD. It shows a linear rise in solubility. The apparent stability constant was calculated with the assumption of 1 : 1 stoichiometry and was found to be 4.19×10^4 at pH 7.4. The value of stability constant indicates that complex is adequately stable and HP-β-CD can be used to

improve the aqueous solubility of telmisartan. But since improvement in solubility is not constant at all the pH values, due attention should be paid while preparing formulation and carrying out its bioavailability studies. A suitable acidifying agent must be incorporated to get a steady enhancement in solubility.

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