Using L-Phenyl alanine as chiral impregnating reagent for enantioseparation of (RS)-Zopiclone

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Abstract

Resolution of (RS)-Zopiclone enantiomers were achieved by using direct thin layer chromatography by using optically pure (L-Phenyl alanine) impregnated silica gel plates as chiral selector. By using the solvent system like binary and ternary system of methanol, dichloromethane, chloroform, acetonitrile etc of different ratio were used for resolution of (RS)-Zopiclone. Iodine chamber were used for detection of the spot.

Introduction

A large number of pharmaceutical drugs are enantiomers, and only one of the two enantiomers offers the desired biological activity. The unnecessary enantiomer results in side effects caused by the multiple medical and pharmacological activities of one enantiomer. Concerning the concern to preserve and improve environmental health, a general understanding has been generated within the scientific community of the U.S. Food and Drug Administration along with other regulatory bodies. Accordingly, racemic drug trafficking has led regulatory bodies in several countries participating in the registration process of all new active ingredients to pay a possible priority on the registration of a single drug enantiomer along with the stereo selectivity and stereo drug specificity.

Because chiral environment is undoubtedly a primary prerequisite for chiral separation, L-amino acids will provide the chiral environment for chromatographic resolution. L- Enantiomerically pure amino acids can be used as chiral selectors, mobile phase additives and other chiral auxiliaries in the preparation of chiral derivatives [1-4]. In Figure 1 structure of L-Phenyl alanine has been shown. Zopiclone (Figure 1) 6-(5-chloro-2-pyridyl)-7-(4-methyl-lpiperazinyl) carbonyloxy-6,7-dihydro [5-pyrro-o [3,4-b]pyrazin-5-on], is an anti-depressant, used for the treatment of insomnia. It is a non-benzodiazepine hypnotic drug belonging cyclopyrrolone class is commercialized as a racemate[5-6]. Its both the enantiomers have a different rate of metabolism like (+)-Zopiclone has 50-60 times greater receptor binding potency towards the benzodiazepine than (-)-zopiclone [7]. Europe and Japan commercialized this drug as a racemate. FDA has approved the enantiomer (+)-zopiclone having higher pharmacological activity compared to the other enantiomer [8]. For the enantioseparation of (RS)-Zopiclone few reports have been reported [9-10].
Experimental:-

Chemicals and instrumentation:-
Silica gel was purchased from LOBA CHEMIE pvt ltd. (Mumbai, India). Pharmaceutical drug marketed as zopiclone (10 mg) by ALKEM Laboratories Ltd. (Mumbai, India) was purchased from a local drug store. UV visible spectrometry was performed by spectrophotometer SHIMADZU-UV-1800. IR analysis was performed using FTIR by SHIMDZU. Amino acid (L-Phenyl alanine) marketed by Lobachemie Pvt Ltd. (Mumbai, India) and other solvents are marketed by Qualikems Fine chem. Pvt Ltd. and ALPHA CHEMIKA (Mumbai India).

Isolation and purification of \((RS)\)- Zopiclone
Tablets of \((RS)\)- Zopiclone were taken. Coating was removed by using knife and then grinding it to fine powder using pistil. As \((RS)\)- Zopiclone is maximum soluble in methanol so the powder obtained was dissolved into it. The solution was sonicated about 5 to 6 times. The filtration was done using 190µm thick Whatman filter paper having pore size 8µm. The filtrate obtained was evaporated in air and crystals of pure sample were achieved at room temperature. UV and IR the sample was done for confirmation of the purification of the sample. In Figure 2 and 3 UV and IR has been shown.
Thin Layer Chromatography

Separation was carried out through direct method using amino acid L-Phenylalanine as chiral impregnating reagents.

Impregnation of the TLC plate was done using L-Phenylalanine in silica gel. Slurry was prepared and then TLC plates were made. It was activated for nearly 6-8 hours at the temperature of 60 °C. After that spot of the drug was applied on the TLC plate and further left in the mobile phase. Resolution of the drug was carried out using different binary and ternary solvent systems.
Results and Discussion

TLC plates were impregnated with L-Phenylalanine. Different binary and ternary solvent systems using acetonitrile, methanol and water were used. It was observed that resolution was not achieved using the binary solvent systems. Only in the case of ternary solvent system of acetonitrile, dichloromethane and methanol the separation was achieved. The different ratios tried for resolution were 6:3:1, 3:4:3, 5:4:1 etc. The successful ratio of resolution of (RS)- Zopiclone using L- Phenyl alanine as impregnating agent are given in the Table 1. Spots were located in an iodine chamber. Chromatograms achieved showing resolutions through this method are given below in Figure 4.

Figure 4: Pictures of chromatograms showing resolution of (RS)- Zopiclone using L- Phenyl alanine as impregnating agent, successful solvent system: acetonitrile, dichloromethane and methanol
Table 1: For enantioseparation of (RS)-Zopiclone using L- Phenyl alanine the Rs and hRf (Rf x100) values are shown below:

<table>
<thead>
<tr>
<th>Approach</th>
<th>Solvent system</th>
<th>hRf</th>
<th>Rs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acetonitrile-methanol-water(4.3:3 v/v)</td>
<td>42</td>
<td>95</td>
</tr>
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References