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Enantiomeric separation of (*RS*)- Atenolol Using (*S*)- Ibuprofen as Chiral Derivatizing reagent

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Abstracts

(RS)- Atenolol is a beta blocker and is marketed as racemic mixture. Indirect enantioseparation of (RS)- Atenolol was done by using (S)- Ibuprofen as Chiral Derivatizing reagent. Diastereomers of atenolol were prepared. Further Thin layer chromatography was done for enantioseparation. The solvent system MeCN-CH_2Cl_2-MeOH-H_2O, in different ratiowere performed.

Introduction

Enantiomers are chiral (optical isomers) molecules which are mirror images of one another. They have identical physical and chemical properties but differ only in a way of directing a plane polarized light in an opposite direction. In chiral environment they act as two different molecules (known as racemates) with different biological activities. Enantiomers can be classified as [1],*R* and *S* which have different stereochemistry. And racemates are those compounds which contain equimolar mixture of two enantiomers and from the mixture of those enantiomers only one is often safer than other one. Probably drugs are produced in the form of racemic mixture. However, racemate drugs are dangerous for consumption. About more than 50% of drugs currently in use are chiral compounds & approximately 90% are marked as racemates. Only single enantiomer is used for treatment because it has more selective pharmacodynamics and less complex profile moreover, have adverse drug reactions [2].

Instead of racemates pharmaceutical industries prefer production of optically active enantiomer as dosing will become lower. As if the product contains inactive or unwanted enantiomer, then its required dose will become twice as compared to the drug with pure active enantiomer. Sometimes unwanted enantiomer has different biological activities and thus will tend to interfere with the performance of intended enantiomer. Therefore, resolution of enantiomers is very important in field of pharmaceutical industries and in biochemistry.

The synthesis of pharmaceutical drugs is generally simple and less expensive but these are not enantiopure.Separation of enantiomer is very important because some enantiomers show

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completely different biological activities then optical isomers.There are different types of methods for enantiomeric separation for e.g. HPLC (High performance liquid chromatography), GC (Gas chromatography), capillary electrophoresis,TLC (Thin layer chromatography [3]. HPLC is more versatile than all other methods. HPLC is used to separate compounds having high molecular weight and can separate vast range of non-volatile compounds and also provides quick, precise and reliable methods for separation [4].

(*RS*)-Atenolol,(Fig.1), it belongs to the class of beta–blockers and used to treat cardiovascular diseases such as high blood pressure, coronary artery diseases, cardiac arrest, stroke etc.It's IUPAC name is (*RS*)-2-{4-[2-hydroxy-3-(propan-2-ylamino) propoxy] phenyl} acetamide, chemical formula is $C_{14}H_{22}N_2O_3$, molecular weight is 266.341 g/mol and having only single chiral center.It is marketed under the trade name 'Tenormin' and highly soluble in methanol.Most common side effects of atenolol are constipation, dry mouth, depression, confusion, insomnia, impotence, fatigue, low blood pressure, hallucinations, blurred vision, wheezing and noisy breathing, nausea, fever etc.There have been a few reports on enantioresolution of atenolol reported [5-8].

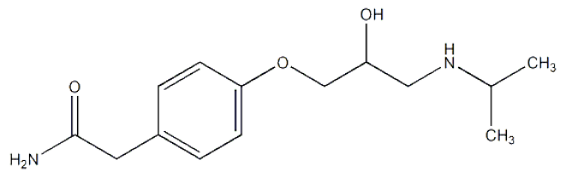


Fig 1. structure of (*RS*)- Atenolol

EXPERIMENTAL –

CHEMICALS AND INSTRUMENTATION

Tablets of Atenolol (Tenormin (obtained from local market). Ibuprofen obtained fromSigma Aldrich (St Louis, MO, USA). Ultraviolet (UV) - visible spectrometer was performed with Hitachi U2001 spectrophotometer (Tokyo, Japan). Silica gel Gwith 17% Ca SO_4 as binder, having Fe, choride and Pb impurities upto 0.002% was purchased from Merk (Mumbai, India). The other chemicals and reagents were purchased from Central Drug House (P) Limited, Daryagang, New Delhi and Merck (Mumbai, India).

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Extraction and purification of atenolol

Take few tablets of uncoated atenolol. Crush them into fine powder using pestle and mortar. Add 15 ml methanol to the atenolol powder and mix it properly. Now sonicate the solution for 30 minutes on sonicator. Then filter the solution and evaporate it on Rota evaporator.

Preparation of Stock solutions-

1.To prepare CDR solution, take 10 mM of ibuprofen in 5 ml DCM.

2.To prepareatenolol solution, take 15 mM extracted atenolol in 5ml DCM.

Synthesis of Diastereomers of atenolol

Take RBF, add atenolol solution and CDR solution to it. Mix both the solution properly and stir it on magnetic stirrer for one hour at room temperature. For quenching add TEA to the mixture. The product formed can be evaporated on water bath. Scheme for the formation of diastereomer of atenolol has been shown in Fig. 2.

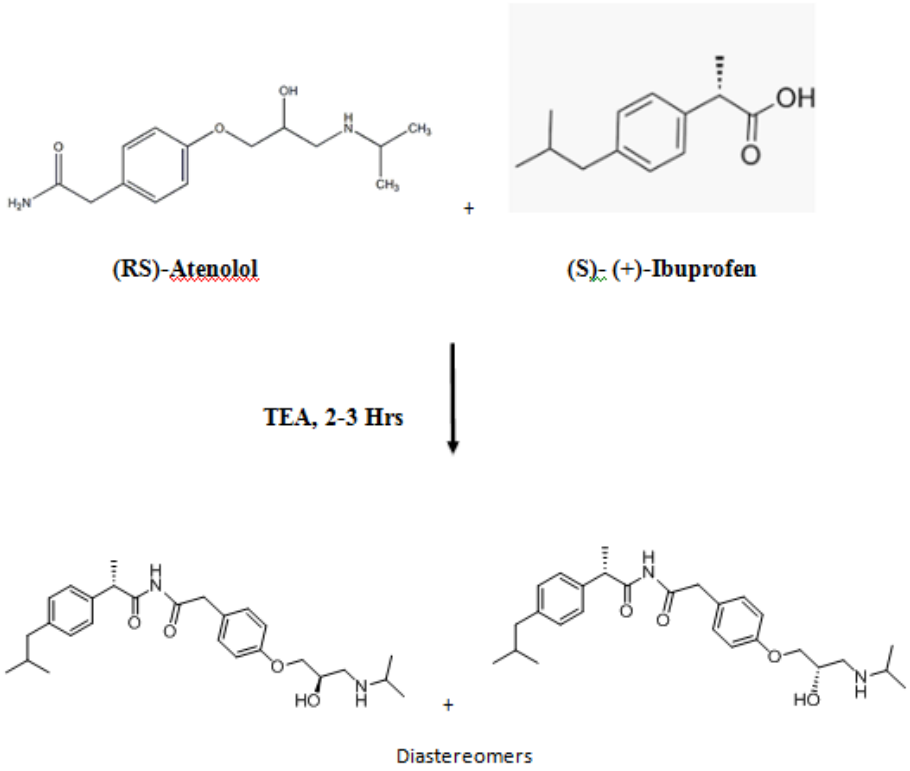


Fig 2. The general scheme for the synthesis of diastereomer of atenolol

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RESULTS AND DISCUSSION-

DISCUSSION ON TLC –Thin layer chromatography is widely used technique for the separation of non-volatile mixtures. It is generally performed on a glass sheet or glass slide, aluminum foil, plastic etc. coated with a layer of material usually silica gel, alumina or cellulose and called as adsorbent. This layer of adsorbent is called as stationary phase. The other phase is mobile phase which can be a solvent or solvent mixture used to carry the sample up via capillary action.

Many TLC's for atenolol using different solvent systems such as MeOH: MeCN: DCM: water, MeOH: MeCN:water (6:2:2);(7,1.5:1.5); MeOH:MeCN:DCM have been done. For atenolol, the best separation was observed in the solvent system acetonitrile: methanol: DCM (0.5:3.5:0.5) (Fig.3). R_f Value calculated was 0.63.



Fig. 3 TLC for enantiomeric separation of atenolol

DISCUSSION ON UV VIS SPECTROSCOPY- UV vis spectroscopy implies to the absorption spectroscopy in the ultraviolet and visible region where wavelength ranges from 190nm to 800nm. It is extensively used in analytical chemistry. UV spectroscopy generally carried out in solutions and used to determine the concentration of absorber in a solution using beer- lambert law. According to this law absorbance of a solution is directly proportional to the concentration of absorbing species.

UV for pure atenolol was taken in methanol. UV for diastereomer of atenolol was taken in DCM. UV for CDR was taken in DCC.it has been shown in Fig. 4 and Fig.5.

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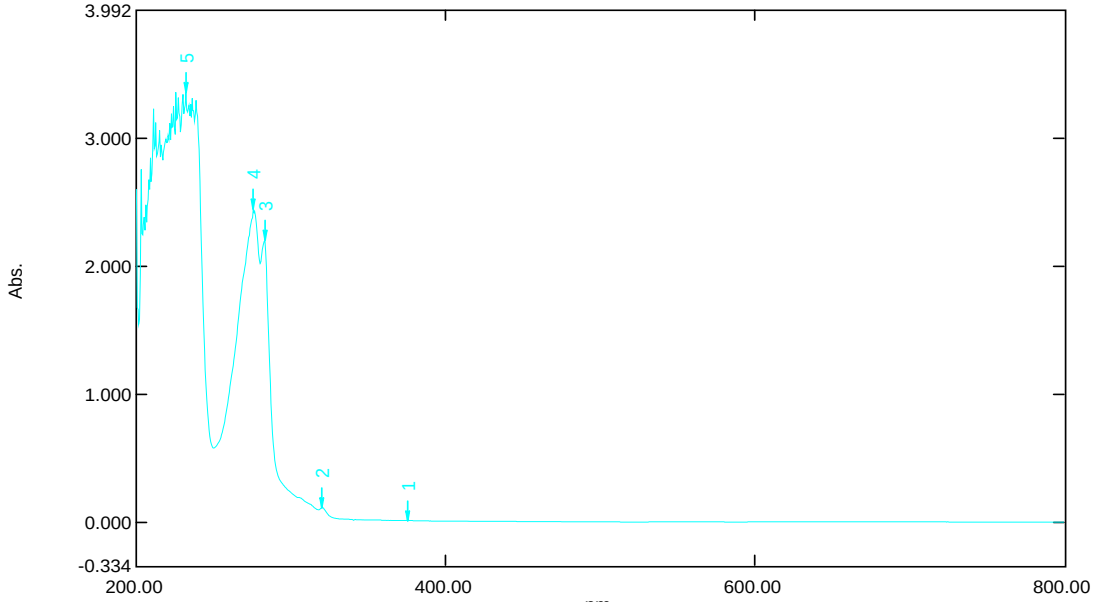


Fig. 4. UV for Pure Atenolol

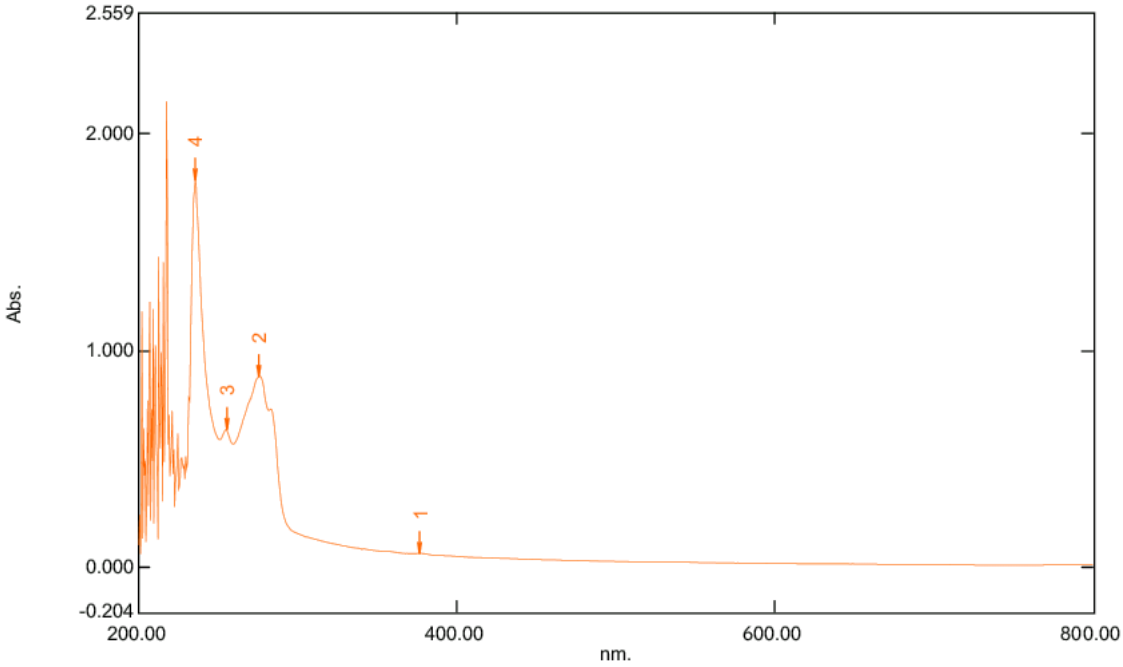


Fig. 5. UV for Diastereomer of Atenolol

CONCLUSION-

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This project resulted into enantiomeric separation of beta- blockers using indirect approach. The method used is highly efficient at laboratory scale. The optimized experimental conditions for synthesis and analytical separation of diastereomers were supported by confirmingthe formation and structures of diastereomers via TLC. This method is very cheap for enantioseparation and can be easily done in industries.

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