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A REVIEW ON RACEMIC MIXTURE AND THEIR MODIFICATION METHODS

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ABSTRACT

Stereochemistry involves the study of the relative spatial arrangement of atoms that form the structure of molecules and their manipulation. An important branch of stereochemistry is the study of chiral molecules. Optical activity is the ability of chiral molecule to rotate the plane of polarized light, measure using a colorimeter. Racemic modification and resolution, both processes are very important in stereochemistry. A mixture of equal parts of enantiomers is called a racemic modification. The process of separating a racemate into pure enantiomers is known as resolution. Recently, various optically active drugs are used for the treatment of various diseases. In these drugs, some are used as mixture of enantiomers and some used as single enantiomers. For preparation of optically active drugs, racemic modification and resolution processes are generally used. Hence, this is very important to know about various steps and types of processes used for the same Racemic modification is advantageous where racemates have more therapeutic advantages than single isomers. Resolution is advantageous where single enantiomer is used for treatment because single enantiomers have less complex and more selective pharmacodynamics profile as compared to racemic mixture so have lesser adverse drug reactions, improved therapeutic profile, less chances of drug interactions than racemic mixtures. Recently used optically active drugs are amlodipine , atenolol , cetirizine , ketamine , metaropolol , omeprazole , pantoprazole , salbutamol , propranolol , clopidogrel , rabeprazole , citalopram , ibuprofen , zopiclone , etodolac and nateglinide.

Keywords: Racemic Mixture, Racemic Modification, Resolution, Enantiomers, Diastereomers, Striochemistry.

I. INTRODUCTION

1) Stereochemistry:-

Stereochemistry involve the study of the relative arrangement of atoms that type the structure of molecules and their Manipulation .A crucial branch of stereochemistry is that the study of chiral molecules.

- Stereochemistry is also known as three dimensionally [3D] chemistry because the prefix “sterio” means 3D.
- Steriomers are the molecules that are identical in atomic constitution and bonding but differ in three.
- An enantiomers is one of two stereoisomer that are mirror image of each other but are non-superimposable (non identical) as ones left and right hands, that are the same effect for opposite orientation.[1,2]

2) CHIRALITY:-

A molecule is referred to as chiral if it not superimposable to its mirror image. The best example of chirality is our two hands cannot be Superimposable identically despite the fact that our fingers of each hand are connected in same way.

The term chiral was derived from Greek word “chiral Meaning hand and was applied as a description of left

And right handedness of crystal structure resulting from

Molecule asymmetry. An atom such as carbon, nitrogen, phosphorous, Sulphur And chemical elements forms to a tetrahedral structure with four completely different term hooked up to them. The individual mirror image forms of a chiral molecules are called optical isomers because they rotate plane polarized light i.e. they are optically active. Today’s optical Isomers are more commonly referred to as enantiomer. [3, 4, 5, 6,]

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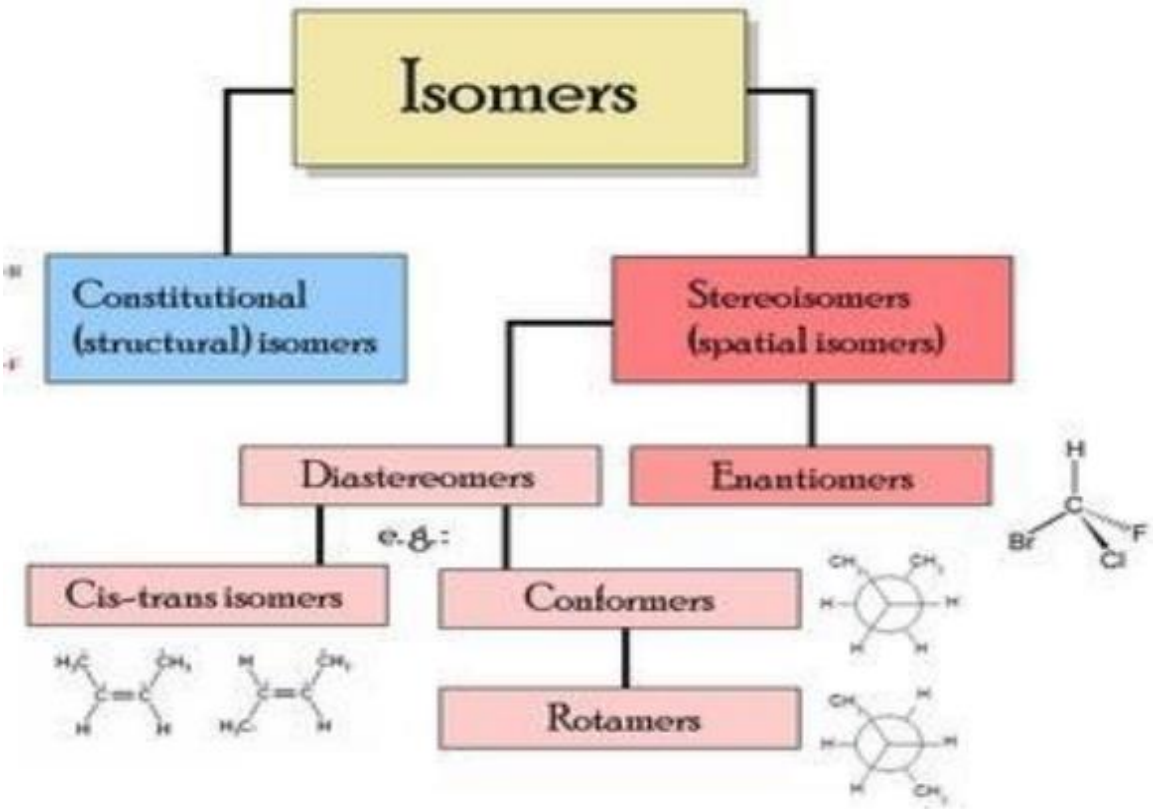
ISOMER:-



An isomer is a molecule with the same chemical formula as another Molecule but with a different chemical structure that is isomers are two or more different substances with the same molecular formula. [7, 8]

Three types of isomerism are possible [9]

- Constitution
- Configuration
- Confirmation

RECEMIC MIXTURE:-

Enantiomers of chiral chemical compound e.g., L and D Alanine. A racemic mixture is a mixture containing equal amounts (50:50) of both By definition of enantiomer excess of racemic mixture is equal to zero. A racemic mixture will induce no rotation of the plane of polarization of light.

RECEMIC MODIFICATION:-

A mixture of equal amount of enantiomers is called a racemic modification.

A racemic modification is optically inactive when enantiomers are mixed together, by rotation caused by an equal and opposite rotation caused by molecules Of its enantiomers.

Racemization is a process where in optically active compounds are converted into an equal mixture of enantiomers with zero optical activity.

E.g.-+_ lactic acid or +_ 2-methyl 1 butane it is useful for to compare a racemic modification with a compound whose molecules are superimposable on their mirror image.

RESOLUTION:-

Resolution is a method of separation of a racemate into pure enantiomers.

Since the first separation of enantiomers by **Louis Pasteur**.

In 1848 who was able to separate tartaric acid manually By various methods.

Separation of racemates into their component enantiomers is a process called resolution of racemic mixture. Enantiomers share the same physical properties such boiling point, solubility melting point conventional

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method cannot separate them. If enantiomers converted into diasteriomers their difference in physical properties can be used to separate diasteriomers.

Pure enantiomers can be regulated by separating them from their respective diasteriomers.[10]

Methods of preparation of Racemic Mixture:-

Mixing- A racemic modification can be achieved when two equal amount of Dextro (+) and Levo (-) isomers are closely mixed together.

Chemical synthesis-Without chiral catalyst a chiral starting material will always produce a chiral racemate as a product of the reaction. A reaction between hydrogen cyanide and acetaldehyde (chiral) leads to $CH_3CHOHCN$ which contains both form of acetonitrile in equal amount.

1) Thermal racemization-Heat can cause Racemization in optically active materials. This leads to a temporary break in one of the four steriocenter bonds. A separating atom or group joins back to the steriocentre to yield another enantiomer.

Eg-when the optically active enantiomer of α-phenethylr chloride is distilled, it is converted into its racemic enantiomers.

2) Walden inversion-This process is called as Walden inversion, in which 2-isooctane is recemized by potassium iodide in refluxing acetone.

3) Epimerization-Specifically, it describes the change in carbon atom configuration at a stereo center in a compound having multiple stereocenters.Diastereo-mers are therefore converted to ane another.

Mutarotation-Biologically, it is a change that occurs when a solution of optically active substance rotates over time unti it achieves equilibrium. The process of autorotation results from epimerization or spontaneous structural changes.Temoerature,solvent and catalyst all play a role in mutarotation.The muta-rotation of glucose is catalyzed by acid-base.[11]

Methods of separation of Racemic mixture:-

1) Mechanical separation-In this process to separate the +tartaric acid and –tartaric acid from ±tartaric acid. The positive and negative form have different crystalline shape. The crystals of opposite shape to be seen under microscope. It is not applicable for solid racemic solutions.

2) Profrational crystallization by Inoculations-It is mainly apply to the racemic mixtures. Here the greater affinity of enantiomers of the molecule of its kind then the other enantiomer explaited.Pure crystal of one enantiomer inculcated in a standard solution of racemic mixture. The molecule of this enantiomers form the solution start depositing on the crystal and growth in size. The crystal of isomorphism substitution may be used for inoculation.

For eg.-phenyl, methyl, carbonyl, hydrogen phthalate is purified 95% by this method using a crystal of its pure enantiomer.

3) Chromatographic separation-Enantiomers react with optically active reagent at a different rates and produce disteriomers of different stabilities. A solution of racemic in a choose solvent is about to pass slowly down on optically active adsorbent like a starch. Enantiomers are adsorb by the active adsorbent at different rates to form disteriomers of different stability. The column is washed with a suitable solvent.

Eg.-(±) Mandalic acid is resolved almost completely using starch as an adsorbent.

1) Biological method-In this method certain micro-organism (bacteria, fungi, enzyme) are allow to grow in racemic mixture. They destroy one of the less important enantiomers at faster ratio compare to other.Hencethe unchane (other) enantiomer retained can be isolate by functional crystallization or chromatography. It is developed by **Pasture** in 1988.

Drawbacks-One enantiomer is sacrifices and if mixture is toxic then they kill the microbs. Eg.-Penecillium can be used to remove the ammonium tartarete from mixture of racemic ammonium Taratrate.

2) Chemical method- In this method racemic modification is converted into mixture of disteriomers of another compound. The separation of enantiomers is difficult because of same physical properties. Enantiomers reacted with optically active compounds to form disteriomers. This disteriomers can be separated due to different in

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their physical properties and after separation they are reconverted into enantiomers by adding mineral acid (H^+) **Eg-**Acid base reaction are obtained use for resolution of racemic alkaloids like quonone,morphine etc.(12)

Examples:

Optically active Drugs	Therapeutic Drugs	Species	Harmful Effect
(-)Ibuprofen	Ant analgesic	Man	Inactive
L-sucrose	Sweetening agent	Man	Non-metabolized
D-Ribose sugar	Sugar	Man	Less-therapeutic
L-penicillumine	Antiarthritic	Man	Toxic

Ibuprofen:-

Racemic Ibuprofen, which contains equal quantities of R (-) Ibuprofen and S (+) Ibuprofen has been used as an anti-inflammatory and analgesic agent for over 30 years. Although the S (+) enantiomer is capable of inhibiting cyclo-oxygenase (cox) at clinically relevant concentration, R (-) ibuprofen is not a cox inhibitor.

Propranolol:-

The optical isomers of propranolol have been compared for their β-blocking and antiarrathmetic activities in blocking the positive inotropic and chronoscopic responses to isoprenaline , (+) propranolol had less than one hundredth the potency of (-) propranolol at dose levels of (+)-propranolol which attenuated the responses to isoprene line there was a significant prolongation of the PR interval of the electrocardiogram.

Salbutamol:-

Salbutamol has been wide use for the treatment of human airway disease and has sometimes been ready because the racemic kind of the drugs .However, recently the R-enantiomer of salbutamol has been introduced into clinical practice in the treatment of asthma in humans and this has been suggested to be an improvement on the racemic from of the drug demonstrated to have adverse effect in the lungs and thus using the R-enantiomer may be improve the therapeutic ratio.

Escitolopram:-

Citalopram a selective serotonin reuptake inhibitor is composed of two enantiomer R-citalopram and S-citalopram two different non superimposable mirror image form of the same molecule separating these two enantiomers has enabled studying their individual properties.

Nateglinide:-

This is used as ant diabetic drug. Two enantiomers D-nateglinide and L-nateglinide are under study of both L-nateglinide is more beneficial than D-nateglinide. According to pharmaceutics studies the L-enantiomer of nateglinide show higher CL and VD compared with nateglinide, especially in the diabetic state. (13)

II. ADVANTAGES AND DISADVANTAGES OF RECEMIC MODIFICATION

Advantages of Racemic Modification:-

- The use of single isomer must be seriously taken .After long clinical assessment between racemate and single enantiomer action because in some cases, racemes have more therapeutic advantages than single isomer.

Disadvantages of Racemic Modification:-

- Single effect of "other "enantiomer must be dangerous.
- Larger or double doses of the drug will have to be taken if drug contains a mixture of enantiomers.

Example-Ethambutol:-

Drug is optically active used to treat tuberculosis .the other enantiomers cause blindness.

Advantages of resolution of racemic modification

1) Reduction in therapeutic dose.

2) Reduction in the intereatient variability in metabolism and in response to treatment.

3) Simplification of relationship between the dose and the response to treatment.

4) Reduce patients dosage by half as pure is more patient.

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Example:-Levorotatory isomers of all βblockers are more potent in blocking β adrenoceptors than their dextro isomers.[13]

III. CONCLUSION

Ever since the chemical synthesis of single enantiomers has been possible and economically sustainable, it has become increasingly frequent to see them being brought out on the market.

This approach is currently required by international regulatory authorities for new drugs.

• The use of the pure enantiomer is not justified when there are on the market racemic mixtures of the same effectiveness and tolerability, shown by trials and prolonged clinical use.

• Of the examples given, levocetirizine, esomeprazole and citalopram have similar effectiveness to the respective racemic compounds, and their marketing seems, above all, linked to economic reasons (expiry of racemic drug patent). On the other hand, compared with ofloxacin, levofloxacin has greater microbiological activity against some bacteria, in particular pneumococcus.

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