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SIGNIFICANCE OF STEREOCHEMISTRY AND EUDESMIC RATIO IN CHIRAL DRUG DEVELOPMENT

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ABSTRACT

Stereochemistry is the study of properties of molecules with respect to spatial arrangement of atoms or groups. A chiral molecule is a molecule which lacks an internal plane of symmetry and has a non superimposable mirror image. The chiral drug has two different stereo isomers with different configurations and complementary binding sites which includes enzymes and receptors. The chiral enantiomer which has desired pharmacological activity or potent enantiomer is called eutomer. The chiral enantiomer which have unwanted activity or inert or toxic is called distomer. The ratio of potency of eutomer to that of the distomer is called eudesmic ratio. It shows the difference in pharmacological activity of eutomer and toxic activity of distomer. Development of a single enantiomer from old racemates is an racemic mixture or chiral switch. Chiral resolution is a procedure of separation of racemic chiral drug into individual isomers. Various analytical techniques are used in development of chiral resolution.

KEYWORDS: Stereochemistry, chiral enantiomer, eutomer, distomer, chiral resolution.

INTRODUCTION

Stereochemistry is the study of properties of molecules with respect to spatial arrangement of atoms or groups. A chiral molecule is a type of molecule that lacks an internal plane of symmetry and has a non superimposable mirror image. The molecules which have same molecular formula but different structural formula are called isomers.[1]

A chemist named Jon battiste biot reported first chiral molecule in 1815. In 1848, the first chiral separation for stereochemistry was reported by Louis Pasteur. In 1858, the two isomers of tartaric acid rotates plane polarized light differently was discovered by Louis Pasteur.[2]

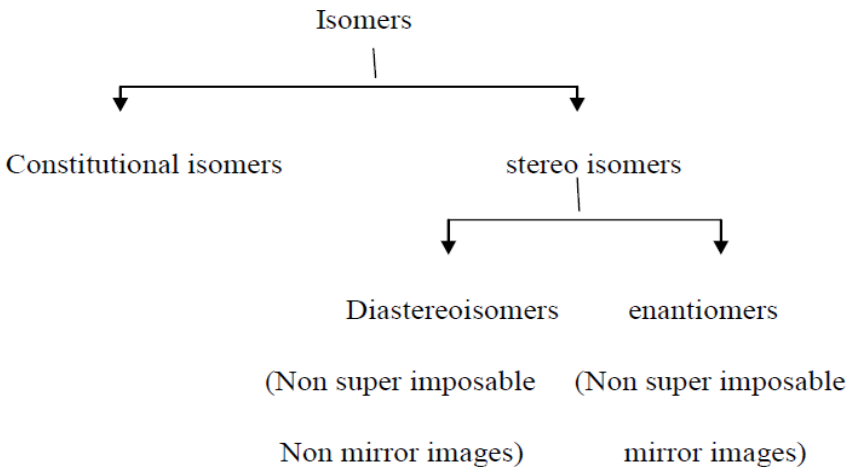
In recent years there has been considerable interest of enantiomers which has different biological activity shown by R-Enantiomer and S-Enantiomer of the racemic drug in biological system. Due to different biological activities of the enantiomers of chiral drugs, importance of single enantiomer utility is more compared to other drugs. Several analytical methods were developed to convert racemic compounds into optically pure compounds.[3]

Single-enantiomer therapeutics shows greater selectivities for their biological target, improved therapeutic indices, and better pharmacokinetics than racemic mixture.[4]

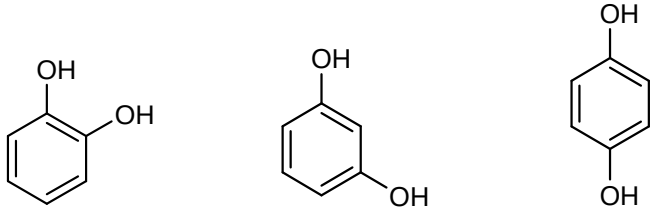
This article reviews, elucidate stereochemistry and enantiomers, emphasizing the potential biological and pharmacologic differences between the two optically active enantiomers of the chiral drug, and illuminate the significance of eudesmic ratio of racemic mixtures in chiral drug discovery and development.

BASIC CONCEPTS

Isomers are the compounds which have same molecular formula but they differ in structural formula. Which are classified into two types 1) Constitutional Isomers 2) Stereo isomers.



1) *Constitutional Isomers*: Isomers which differ in connectivity are called constitutional isomers. Example[5]



Catechol **Resorcinol** **Hydroquinone**

2) *Stereo isomers*: Isomers which different in spatial position of atoms or groups with same bonding order. They are further are of two types[5]

a) Diastereomers

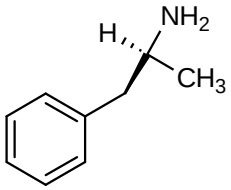
b) Enantiomers

a) *Diastereomers*: They are non superimposable stereo isomers and also non mirror images to each other which have physicochemical properties that differ both in chiral and achiral media.

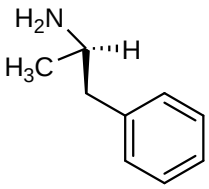
Example: cis-Platin is an anti cancer agent where as trans-platin is an inert agent.[6]

b) *Enantiomers:* They are non superimposable stereo isomers and mirror images to each other. Except in optical activity, they have same physicochemical properties in achiral media. In chiral media they show different activities.[6]

Example;[7]



(+)-Amphetamine



(-)-Amphetamine

CHIRAL SWITCH

A racemic switch or chiral switch is development of single enantiomer from old racemate drugs.[8] Chiral switch has been proposed for obtaining safer alternatives to existing racemates. Switching from existing racemates to one of its isomers has provided safer and efficacious alternatives to drugs ranging from antihistamines like citrizine to anaesthetics like ketamine. Some recent chiral switches have yielded safer or more effective alternatives to the existing racemic drugs. Some of unichiral drugs have more potent than its racemates- Levosalbutamol, S-Ketamine, S-Zopiclone, R-Ondansetron, R-Fluoxetine.

***Advantages of Chiral Switch*[9]**

1) It is used to separate undesired pharmacodynamic side effects and toxic effects in an enantiomer.

2) It helps to reduce the effects related to metabolic, renal and hepatic drug load. It also helps to lower dose of drugs in patients.

3) Easy assessment of pathophysiological activity.

4) Easily assess efficacy and toxicity through pharmacodynamic/pharmacokinetic monitoring of pure enantiomer.

5) Avoids isomer–isomer interactions.

6) Avoids bio inversion.

7) It has less potential for complex drug interactions.

PHARMACOKINETIC IMPLICATIONS OF CHIRALITY

1)Absorption[11,12]	*S Isomer of hexobarbital shows higher plasma levels compared to R-Isomer of hexobarbital. *L Methotrexate shows better absorption than its isomer.
2)Distribution[12,13]	*Levodopa crosses blood brain barrier but its dextro form doesn't. *S-Isomer of warfarin bound to plasma proteins more extensively than R-Isomer. So S-Warfarin has lower volume of distribution. *Levocetrizine has lower volume of distribution than the dextro enantiomer.
3)Metabolism[12,13]	*Warfarin Isomers are metabolized by different paths. S-form metabolized by ring oxidation where as R-form metabolized by side chain reduction. *Methadone isomers metabolized by different routes. R-form metabolized CYP3A4 where as S-form metabolized by CYP2D6.
4)Elimination[14]	*d-amphetamine has more half life than L-amphetamine. *R-fluoxetine half life is more than S-fluoxetine.

PHARMACODYNAMIC IMPLICATIONS OF CHIRALITY[15]

The two stereoisomers of chiral drug have different configurations and their complementary binding sites for receptors, enzymes are also different. So, two enantiomers of same pharmacological agent show different activities. One enantiomer that bind effectively to the target site and show desired therapeutic activity is called eutomer. Another isomer that induce toxic effect or inert that is called distomer.

In racemate, the eutomer may be active while distomer may have:

*No activity

*Quantitatively and qualitatively the same activity

* It qualitatively shows same activity but with lower intensity

*Completely shows separate beneficial and adverse activity

1. Examples where one enantiomer is active while another is inactive.

Racemic drug	Active Enantiomer	Therapeutic Applications
Ofloxacin	(S)-(-)-Levofloxacin	Antibacterial activity
Ketamine	S-(+)-Ketamine	Anesthetic
Methadone	R-(-)-Methadone	Pain reliever and opioid agonist
Fenoldopam	R-(-)-Fenoldopam	Antihypertensive agent
Propranolol	S-(-)-Propranolol	treat hypertension and anxiety
Atenolol	S-(-)-Atenolol	Cardio selective beta adrenergic blocker
Betaxolol	S-(-)-Betaxolol	Reduces elevated intraocular pressure
Cetirizine	R-(-)-Cetirizine Levocetirizine	Antihistaminic agent

2. Examples of more potent enantiomers.

Racemic Drug	More potent enantiomer (Eutomer)	Therapeutic Application
Ondansetron	R-(+)-Ondansetron	Anti emetic
Warfarin	S-Warfarin	Oral anticoagulant Drug
Ibuprofen	S-(+)-Ibuprofen	Used for pain relief and fever
Captopril	S-(-)-Captopril l-isomer	Treats hypertension and congestive heart failure
Tenatoprazole	S-(-)-Tenatoprazole	Used in acid related diseases

3. One enantiomer exhibits beneficial effect while other has adverse effect.

Racemic drug	Beneficial effect of enantiomer	Adverse activity of enantiomer
Ketamine	S-(+)-Ketamine Anesthetic and Analgesic	R-(-)-Distomer hallucination and agitation
Pencillamine	S-Form used for treatment of Arthritis	R-Distomer is toxic
Thalidomide	R-Enantiomer-used in morning sickness	S-Enantiomer is teratogenic

4. Enantiomers that shows entirely different therapeutic activities.

Drug	(+)-Enantiomer	(-)-Enantiomer
Levodopa	Antiparkinsonian agent	Agranuloctosic
Tetramisole	R(+)-Dexamisole Antidepressant	S-(-)-Levamisole nematocidal Immunostimulant
Thalidomide	Mutagenic	Sedative –hypnotic teratogenic
Barbiturates	Excitation	Sedation
Pentazocine	Anxiety	Analgesia, respiratory depression
Methylphenylpropyl Barbituricacid	R-Anaesthetic	S-Convulsant
Albuterol	Pro inflammatory effect	Bronchodilator

5. Presence of beneficial effect in one enantiomer while other enantiomer shows antagonistic activity.

Recemic drug	Agonist(Beneficial activity enantiomer)	Antagonist(Opposite activity enantiomer)
Albuterol (Treatment of asthma)	R-Albuterol	S-Albutarol
Lipoic acid	R-Lipoic acid	S-Lipoic acid
Dobutamine(Acts against alpha adrenoceptors)	(-)-Dobutamine	(+)Dobutamine
Picenadol(Agonist-antagonist analgesic and act at the opiate receptors)	R(+)-Picenadol	S-(-)-Picenadol

EUDESMIC RATIO IN CHIRAL DRUG DEVELOPMENT[16,17]

In any kind of racemic drugs, only one enantiomer is biologically active and other isomer is inactive or toxic.

Eutomer: It is the chiral enantiomer that has required pharmacological activity.

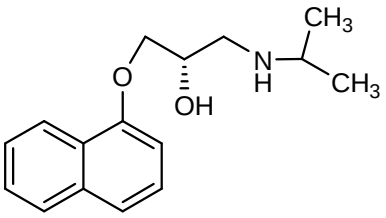
***Distomer*:** It is the chiral enantiomer that has unwanted biological activity or it may be inactive.

Eudesmic ratio*:* Ratio of difference in pharmacologic activity between eutomer and distomer of a drug. Eutomer is more stereo selectively binds to receptors or enzymes compared to the distomer. During the process of preparing single enantiomer having desired pharmacological activity saves material reduces costs and most of the side effects. If eudesmic ratio is higher then, the potency or activity of eutomer is higher. But, in most of the cases only one

enantiomer of the drug contains all the desired bioactivity than the distomer may be less active and has unwanted activity or toxic.

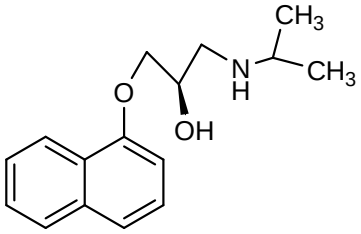
The eudesmic ratio is a mathematical equation that measures quantitatively the difference in activity of eutomer and distomer. If the eudesmic ratio value significantly differs from 1 means that there is a difference in pharmacological activity between the eutomer and distomer.

Propranolol is an anti hypertensive agent. S-enantiomer of the propranolol is 130 fold more potent than R-enantiomer as beta adrenoceptor antagonist. Eudesmic ratio (S/R) value for propranolol is 130. Some drugs shows large eudesmic ratio value like dexetemide that has 10,000 fold greater affinity for the muscarinic acetyl choline receptor than levetimide.



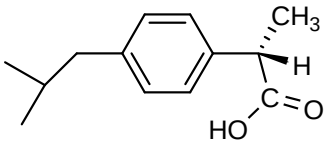
(S)-Propranolol

Eutomer, ER=130



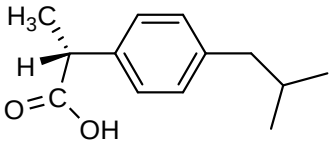
(R)-Propranolol

Distomer



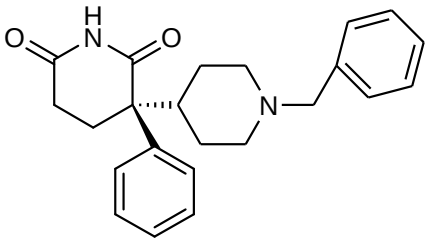
(S)-Ibuprofen

Eutomer, ER=100



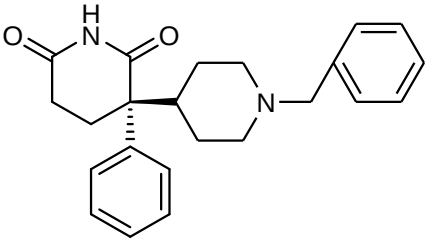
(R)-Ibuprofen

Distomer



(S)- (+)-Dexetimide

Eutomer, ER=10000



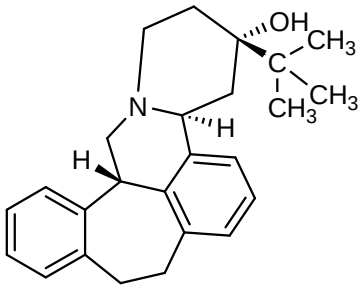
(R)-(-)-Levetimide

Distomer

Drug	Activity	Eudesmic ratio
Propranolol Anti hypertensive agent	Beta blocker	S/R=130
Metoprolol Treats angina, hypertension and heart attack	Cardio selective beta blocker	S/R=33:1
Ibuprofen Anti inflammatory agent	Cox inhibitor	S/R=100
Etodolac Anti inflammatory agent	Cox inhibitor	S/R=100
Citalopram Anti depressant agent	Serotonin reuptake inhibitor	S/R=30
Amlodipine Treat angina, coronary artery disease	Calcium channel blocker	S/R=1000

Eudismic ratio varies with receptors

Example**:** Butaclamol



(+)-Butaclamol

Receptor	Eudismic ratio for (+)-Butaclamol
Alpha 1 receptor	73
D_1 receptor	160
D_2 receptor	1250
r-HT_1 receptor	8
5-HT_2 receptor	73
Muscaranic Ach receptor	0.8

CHIRAL RESOLUTION

Chiral resolution also called as chiral separation is a process of separation of racemic compound into individual isomers.

Preparation of only desired enantiomer (eutomer) having many advantages than racemic drugs. Now a days increase in demand for enantiomerically pure chiral dugs has stimulated development of enantioselective synthetical methodologies which helps to raise the business

of enantiomer pure drugs. This shows increase in demand for stereo selective separation techniques and analytical methods for accurate determination of enantiopure compounds.[18]

***Chiral separation techniques*[19]**

There are several kind of chiral separation techniques. Some of them are.

1. Crystallization.
2. Capillary electrophoresis.
3. Chromatography.
4. Membranes.
5. Liquid-liquid extraction.
6. Enzymatic kinetic resolution.
7. Supercritical fluid extraction.

CONCLUSION

Most of the drugs used clinically are chiral compounds. The rationale for the development of the chiral compounds as single optically pure enantiomer has advantageous as it shows the superior therapy. Each enantiomer interacts with the targets (enzymes/receptors) differently and shows different therapeutic effect. Eudesmic ratio plays an important role in drug discovery and drug designing that higher the eudesmic ratio, better the therapeutic action of the chiral drug. Therefore various chiral separation techniques developed to separate the enantiomer with required biological activity. It is important to give information about chiral drugs to healthcare professionals in order to help them for finding an optimal treatment and a right therapeutic control.

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