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# Chiral Recognition of Enantiomers of Chiral Drugs with Novel Carbohydrate Based Gemini Surfactants by Micellization – A New Approach

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## ABSTRACT

Chirality in drug action is getting greater attention in medical practice these days, as two enantiomers of a chiral drug may differ in their bioavailability, rate of metabolism, excretion, potency and selectively for a particular receptor in the body. The drug in the form recemates, consisting of an equimolar mixture of two enantiomers, generally causes side effects in the body, because one of the isomer is active while other is not. About more than half of the drugs currently in use are chiral compounds and nearly 90% are marketed as recemates. Chiral separation is one of the methods to separate two isomers of racemic compound. In an new approach, we synthesized a novel carbohydrate derived gemini surfactants and explore them for encapsulation of some poorly water soluble drugs and chiral recognition of some aromatic α-amino acids, these gemini surfactants can be used to chiral recognition of isomers of chiral drugs.

**Keywords**: Micellization, chiral recognition, chiral drugs, Gemini surfactants, carbohydrate.

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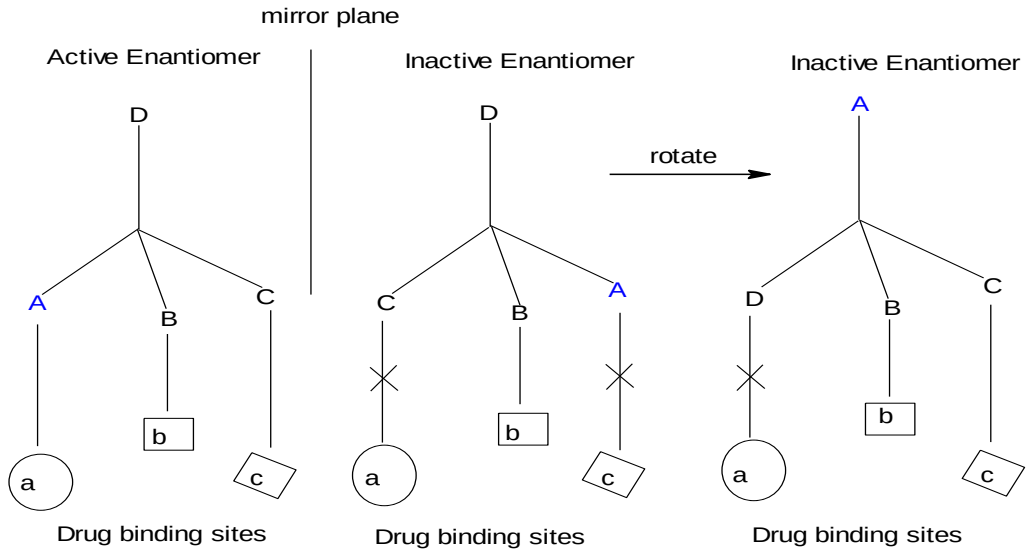
# INTRODUCTION

## Chirality and Enantiomers

Chirality is generally defined as the geometric property of a rigid object that is non-superimposable with its mirror image. A molecule is said to be chiral, if the carbon atom present in that molecule directly linked with four different atoms or group of atoms. Chirality is the property of substance found throughout biological systems. The two non-superimposable mirror images of the chiral molecule are called enantiomers. These enantiomers are identical with respect to physical and chemical properties but can be identified on the basis of their absolute configuration or their optical rotation. The terms d, or dextro, and *l*, or levo, are considered obsolete and should be avoided. Instead, the R/S system for absolute configuration and +/- system for optical rotation should be used. R is from the Latin rectus and means the isomer which rotates the plane polarized light to the right or clockwise and S is from the Latin sinister that means the isomer which rotates the plane polarized light to the left or anticlockwise. There are some rules based on atomic number and mass number for determining whether a particular chiral centre has R or S configuration.

## Interaction of Biological systems with Chiral Drugs

As all living systems are themselves chiral, each of the enantiomers of a chiral drug behaves very differently in vivo. The enantiomers show different pharmacological properties. In other words, R-enantiomer of a drug will not necessarily behave the same way as the S-enantiomer of the same drug when taken by a patient. Recognition of chiral drugs by specific drug receptors is explained by a three-point interaction of the drug with the receptor site, as proposed by *Easson and Stedman.* The interactions behavior of the two enantiomers of a chiral drug with its receptor is illustrated below.



**The active enantiomer has a 3-dimensional structure that allows domain A to interact with binding site domain a, B to interact with b, and C to interact with c. In contrast, the inactive enantiomer cannot be aligned to bind the same 3 sites simultaneously. The difference in 3-dimensional structure allows active enantiomer to bind and have a biological effect, whereas the inactive enantiomer cannot.**

This is a hypothetical interaction given by Easson-Stedman between the two enantiomers of a racemic drug with a receptor at the drug binding sites: The three substituents A, B, C of the active enantiomer (left) can interact with three binding sites a, b, c of a receptor by forming three contacts Aa, Bb and Cc, whereas the inactive enantiomer (right) cannot because the contact is insufficient. More the interaction of the drug with the receptor in the living system more will be its therapeutic effect.

In this case, one enantiomer is biologically active while the other enantiomer is not. Their must be proper interaction between the substituent of the active enantiomer drug labeled A, B, and C must with the corresponding binding site of the receptor, labeled a, b, and c. In this case, this fitting interaction produces an active pharmacological effect. The inactive enantiomer cannot bind in a proper way with its receptor; thus, there is no active response. This attachment of an enantiomer to the chiral receptor is analogous to a hand fitting into a glove. Indeed, a right hand can only fit into a right hand glove. Similarly, only a particular enantiomer that has a complementary shape to the receptor site can fit into a receptor site. The other enantiomer will not fit, like a right hand will never fit into a left glove.

**Importance of chirality in drugs**

Most of the drugs are available as racemic mixtures or equimolar mixture of two enantiomers that are non-superimposable mirror image of each other. They are named as dextrorotatory and levorotatory enantiomer, or R/S- isomers. Approximately 50% of marketed drugs are chiral and of these approximately 50% are racemic mixture of enantiomer rather than a single enantiomer[1].

Our body recognizes Chirality; there can be tremendous difference between enantiomers in their pharmacological profile[2]. For example the enantiomers of chiral drugs such as omeprazole, ibuprofen and DOPA show different pharmacological and pharmacokinetic activities because they interact differently with enzymes and receptors consisting of amino acids and other chiral biomolecules[3]. The first drug sold as a single enantiomer was the antiturberculosis drug ethambutol which was sold as a single enantiomer shortly after it discovery in 1961. In fact, the name “ethambutol” refers specifically to the dextrorotatory (+) isomer of 2,2’-(ethylenediimino)-di-1-butanol.

**Different biological activities of Enantiomers of chiral drugs**

Single-enantiomer drugs will become increasingly more available to the practicing physician, and both the single-enantiomer form and racemic form of the given drug may be available at the same time. The single enantiomer would provide better medication and may be preferred over the racemic form of the same drug. There are many drugs, whose one enantiomer is active, while the other is totally inactive or one enantiomer is more effective than the other and a racemic mixture. The racemic mixture drugs generally causes side effects, because out of the two enantiomers present in the racemic mixture, only one is effective against the particular disease, so the other enantiomer is like a foreign substance for the body, so that enantiomer may cause any sort of side effects. If the drug is taken as a single enantiomer, it will be more effective without causing any side effect.

Albuterol; D-isomer may aggravate airway constriction; L-isomer avoids side effects. Ethambutol; (S,S)-form of ethambutol is a tuberculostatic agent; (R,R)-form causes optical neuritis that can lead to blindness. Levodopa: levodopa (L-dopa) is a Parkinson's disease agent; D-dopa causes serious side effects, such as granulocytopenia. Penicillamine: (S)-enantiomer has antiarthritic activity; (R)-form is very toxic. Propoxyphene ; L-isomer is antitussive (cough); D-isomer is analgesic (pain). Thalidomide: (S)-isomer has the desired ant nausea effects; (R)-form is teratogenic and causes fetal abnormalities, such as severely underdeveloped limbs. Single-enantiomer formulations of (S)-albuterol, a $\beta_2$-aderenergic receptor agonist for treatment of asthma, and (S)-omeprazole, a proton pump inhibitor for treatment of gastro esophageal reflux, have been shown to be superior to their racemic formulations in clinical trails[4]. In other cases however, both enantiomers of a chiral drugs may contribute to the therapeutic effects, and the use of a single enantiomer may be less effective or even less safe than the racemic form. For example, the (-)-enantiomer of sotalol has β-blocker and antiarrhythic activity, whereas the (+)-enantiomer has antiarrhythmic activity only but lacks other activity[5-6].

In the case of citalopram, the S-enantiomer is primarily responsible for antagonism of serotonin reuptake while the R-enantiomer is 30-fold less potent[7]. Single–enantiomer formulation of fluoxetine for the treatment of depression was unsuccessful. While (R)-fluoxetine and (S)-fluoxetineare similarly effective at blocking serotonin reuptake[8].

Ofloxacin is a fluoroquinolone, which is a racemic mixture was marketed since 1987. Only levorotatory enantiomer of the racemic drugs ofloxacin exhibit antibacterial activity (levofloxacin)[9-10]. From the microbiological point of view, levofloxacin is up to 128 times more

potent than the dextrorotatory enantiomer and upto twice as effective as the racemic mixture according to the Gram positive and Gram negative bacterial stocked assayed[10].

Both (S)-omeprazole and (R)-omeprazole enantiomers are partially inactivated: S-omeprazole is inactivated to a lesser extent than R-omeprazole, thus reaching greater blood concentration. At gastric cell level there occurs the transformation of both isomers in omeprazole-sulfenamide, the active metabolite on the proton pump.[10-12]

As a result of different inactivation of the two enantiomers, administration of 20 mg of esomeprazole makes it possible to obtain blood concentration of the drug 70-90% higher than those obtained by administrating 20 mg of the racemic drug.[12-13] .Due to the higher serum level obtained, 20 mg of esomeprazole administered for 5 days cause 90% suppression of gastric acidity, higher than the 79% obtained with 20 mg of omeprazole[14].

**Different potency of enantiomers of chiral drugs: Classification**

**I: One enantiomer is active while other is almost inactive**

e.g. the drugs in which *l*-isomer is active whereas d-isomer is inactive are: Abuterol and Salmeterol (bronchodilators used in the treatment of asthma)[15-16], Hexobarbital and Secobarbital (hypnotics used in psychiatric treatment)[17-18].The drugs in which d-isomer is active whereas *l*-isomer is inactive are Ketamine and isoflurane (anesthetic)[19-20]

**II: One enantiomer is therapeutically active while other is less active**

**e.g. drugs in which** *l*-isomer is 10-20 times more active than d-isomer are : Verapamil and Nicardipine (calcium channel antagonists used for cardiovascular therapy)[21-22] . Drugs in which *l*-isomer is more potent than d-isomer are : Captopril and Benazepril[23]. Drugs in which *l*-isomer is 25-5- times more active than d-isomer are: Methadone[24-25]

III: **Both enantiomers having almost equal therapeutic potency**

e.g. Cyclophosphamide, Flecainide and Fluoxetine[26]

**IV: Both enantiomers having different pharmacological activities:**

e.g. Propanolol: d-isomer reduces plasma concentration of T3 cells and used to treat hyperthyroidism while l-isomer is β-blocking drug used as an antihypertensive[27-28]. Propoxyphene: d-isomer is painkiller, whereas the l-isomer is a cough suppressant[29].

## MATERIALS AND METHOD

**Techniques used for separation of enantiomers of chiral drugs**

For the study of interaction of drug enantiomers in the body, it is necessary to determine them side by side in the same sample. Separation of enantiomers has been considered one of the most

difficult problems in separation science because in a symmetric environment enantiomers have identical physical and chemical properties, with the exception of the rotation of plane-polarized light. Therefore, separation generally requires an asymmetric medium[30].

There are many techniques for the separation of enantiomers of chiral drugs viz. chiral inclusion complexes and crystallization, biological methods, preparative liquid and gas chromatographic methods has been reported. However, the conventional method of separating the optical isomers of racemic compounds is difficult and expensive. Chiral separation can be used to simultaneously produce both enantiomers (dualisomer recovery) or it can be used in a way that generates only one enantiomer (single-isomer recovery).

Enantiomer separation for about 59 chiral drugs by capillary zone electrophoresis was studied with α-cyclodextrin as a chiral solvating agent, six enantiomeric paris should be resolved. Baseline separation was achieved for clidinium bromide, oxomemazine and tetryzoline, whereas ketamine, orphenadrine, tropicamide and others require further optimization[31].

The separation of enantiomers by preparing diasteromeric intermediate which then be separated from each other by differential crystallization was reported[32], hydrolysis and purification. Inclusion complexation is one of the methods in which racemic compound form complex with chiral host compound from which the chiral guest can be obtained. When this separation is combined with distillation technique, for example, enantiomer separation can be accomplished by fractional distillation in the presence of a chiral host compound. This represents a modern and "green" procedure of enantiomer separation[33].

Capillary electrophoresis (CE) is a special case of using an electrical field to separate the components of a mixture. Electrophoresis in a capillary is differentiated from other forms of electrophoresis in that it is carried out within the confines of a narrow tube.

For a wide range of applications in the chemical process industries (CPI), liquid-liquid extraction technology was used. Extraction separates components based on their relative solubility in two immiscible liquids, it is not based on boiling point like distillation. So, extraction is typically chosen over distillation for separation applications that would not be cost-effective, or even possible, with distillation.

The separation of enantiomeric acid mixtures by applying SFE was reported. (±)-*cis*- and (±)-*trans*-permetric acids were resolved with *R*-(+)-α-phenylethylamine and *S*-(+)-2-benzylaminobutan-1-ol, respectively[34]. Chiral separation of d- and l- enantiomers of doxylamine succinate in rat plasma was reported[35]. Bio-analytical chiral chromatography method for the enantioselective separation of carbinoxamine maleate in human plasma was reported[36].

Separation of (R, S)-enantiomers of valsartan with resolution was achieved[37] by capillary zone electrophoresis method. Separation of enantiomers of drug by capillary electrophoresis using ovoglycoprotein as chiral selector was reported[38].

**Use of Gemini Surfactants as chiral recognition of enantiomer of poorly water soluble chiral drugs:**

Gemini Surfactants are the amphiphiles consisting of two hydrophobic tails and two hydrophilic heads connected via a spacer; spacer may be flexible or rigid. The Gemini Surfactants are more effective than conventional surfactants, having one tail and one head. Gemini surfactants or dimeric surfactants are novel class of amphiphiles molecules, first reported in 1971[39]. Gemini amphiphile molecule consists of two conventional surfactants connected by a flexible[40] or rigid[41] spacer, which can be hydrophilic or hydrophobic[42].

## CONCLUSION

It is concluded that the separation of enantiomers of chiral drugs is essential, as racemic mixture causes side effects. This is because, one enantiomer of drug is generally active and show proper therapeutic effect in the body, while the other is inactive or less active against the particular disease, and that inactive enantiomer causes side effect in the body. So, in order to reduce the side effects of drugs and to get proper drug concentration in blood, it is necessary to use one isomer instead of racemic mixture. There are various method applied to separate the enantiomer of chiral drugs viz. Chromatography, Capillary electrophoresis, liquid-liquid extraction, crystallization , complexation, distillation etc. recently a novel carbohydrate derived gemini surfactants were used to encapsulate the poorly soluble drugs, nucleobases, aromatic D- and L- amino acids[43-44] and polycyclic Aromatic Hydrocarbons (PAHs)[45]. These carbohydrate gemini surfactants can be used to separate the enantiomers of chiral drugs, as in case of aromatic α-amino acids, these surfactants encapsulate D- and L- amino acids at different extents. The encapsulation also depends on the chain length of these gemini surfactants. The carbohydrate moiety attached to these surfactants makes them biodegradable, non-toxic and more efficient than surfactant without carbohydrate moiety.

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