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DRUG ENANTIOMERS IN CLINICAL PHARMACOLOGY

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ABSTRACT

The single enantiomers are considered to be safer and better alternatives to racemates, has resulted in a need for developing single isomers as drug products. Most of the drugs in use today are chiral. It is well established that the pharmacological activity is mostly restricted to one of the enantiomers and the individual enantiomers of racemic drugs frequently differ in their biological effects. In many cases, the inactive enantiomer shows unwanted side effects or even toxic effects. A pharmacological study reveals that there is a need for separating and quantifying enantiomers in biological samples to assess the toxic effects of such drugs. Single enantiomer products are being re-marketed by so called the chiral switch process. (Racemate to single enantiomer)

KEYWORDS: *enantiomers, chiral drug, thalidomide, stereoisomers, Racemate.*

I. INTRODUCTION

An enantiomer is one of two stereoisomers that are mirror image of each other that are non-identical. Their isomers have the same chemical formula but with different orientations of the side groups around the central atom. They share the same chemical and physical properties, the same chemical formula, the same bond angles, the same boiling point, and the same melting point. In fact, their only difference lies in the direction in which they rotate polarized light, which are dextrorotary (clockwise rotation) and levorotary (counterclockwise rotation).[1] Due to these changes, sometimes only one of the enantiomers have a therapeutic effect while the other may have an entirely different effect, no effect at all, or even have undesired side effects. Our body can only recognize one enantiomer which in result producing therapeutic effect.[2] This will bind along with its chiral receptor whereas another enantiomerdisturbs the metabolic and regulation process and causes side effect.[3]This problem has been overcome with the production of single enantiomer drug.

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Few separation techniques are introduced and single enantiomer is formulated. Examples of single enantiomer drug used clinically nowadays are omeperazole, propranolol, albuterol etc.In many cases, one enantiomer is the active pharmaceutical ingredient while the other can be benign or even toxic. Thalidomide racemate was one of the first drugs recognized to cause birth defects in humans, which is due to (-)(S)thalidomide. It causes severe side-effects and thousands of babies were born with missing or abnormal arms, hands, legs, or feet. One side of the drug is known to efficacy whereas the other is the cause of side effect which causes teratogenic effect. As the next step in newer generation the scientists introduces the separation technique to prevent the side effects.[4] Here is where the single enantiomers is introduced commercially. Only single-enantiomers are provided in market nowadays.[5]

History of Enantiomers:

Previously, all drugs were made from racemic mixtures or mixtures with equal amounts of both enantiomers. Separation of the two enantiomers thought to be unnecessary due to its high cost. Therefore, enantiomer drugs were given to patients without purification. In 1960s, to inhibit the effects of morning sickness in pregnant woman the drug named Thalidomide is introduced. It is a racemic mixture composed of both R-thalidomide and S-thalidomide. As a result after its release, over 10,000 children of women using this drug were born with severe birth defects such as phocomelia, the development of flipper-like limbs.[6]

Consequently, Thalidomide was sealed as one of the most severe pharmaceutical failures of the 20th century. Research is quickly done by scientists but it was fiasco. However within a few years, scientists discovered the cause of the fatal flaw, it was the nature of enantiomers which was far more complex than ever imagined. The R-form of the enantiomer showed the reputed characteristic of inhibiting morning sickness. It seemed effective in preventing morning sickness and producing desired results. However, the S-form of the organic compound thalidomide produced teratogenic effects which caused the fatal defects in embryonic formation.[7] These effects were believed to result from the increased affinity of S-thalidomide with embryonic cerebrum proteins, which have a direct effect on limb formation. The Thalidomide incident had invested greater interest in a previously recondite and unknown region of the enantiomers.

Pharmaceutical experts spent much of their resources developing better techniques to separate enantiomers in the process of forming a enantiopure drug. Various techniqueswere experimented to separate enantiomers. However the first successful method which is reproducible in separation process was the gas chromatograph, was done in 1966 using an isoleucine lauryl ester mixture as the stationary phase for separating two amino acid enantiomers. Once the racemic mixture was separated into enantiopure mixtures, the optical purity, or the ratio of the two enantiomers, was measured to determine the efficacy of the separating process.[8]

Technique Used for Separation of Enantiomers:

The main techniques of enantiomer separations are capillary electrophoresis, asymmetric biotransformation, liquid-liquid extraction, membranes, sensors, chromatography and crystallization. Enantiomer separation methods, is emphasized on separation by chiral inclusion complexes and crystallization, biological methods, preparative liquid and gas chromatographic methods have been reported. Conventionally optical isomers of racemic compounds can be separated but this has always been difficult and expensive. Hence, chiral separation is used nowadays to produce dual isomer recovery, as well as to generate only single-isomer recovery.[9]

In industry, there are two main categories of techniques that are often applied for enantiomer separation, the classical methods and the modern technology.First of all the classic method, it's the most widely used technique, is the resolution by diastereomeric salt formation. In this method, an acid-base reaction is involved between a racemic drug and a pure single enantiomer called resolving agent. This reaction is responsible for the formation of two diastereomeric salts which have different physical and chemical properties and can be easily separated either by filtration or by crystallization if one is insoluble and the other is soluble. Finally, the pure enantiomer is obtained by salt decomposition by treatment with either acid or base. It can also be separated by classical achiral liquid chromatography. This method has been used in the resolution of -methyl-L-dopa, asparagine and glutamic acid which is widely been using clinically.[10]

Other classical method that is being used is enzymatic or kinetic resolution. In this methodology, formation of resolution is achieved with the biochemical process which destroys one enantiomeric form that causes side effect. Certain microorganisms such as yeasts, molds, bacteria can only degrade one of two isomers of a racemate by enzymatic assimilation. Whereas, the other side which is not digested remains in the solution will be isolated. Enzymatic resolution has been used in the preparation of lorafiban (benzodiazepine), levofloxacin (antibacterial drug), and S-naproxen (anti-inflammatory drug).[11]

The modern technologies, ensures the preparative high-performance liquid chromatography (HPLC) as the method of choice for the enantiomer separation. This method has proven to be one of the best methods for the direct separation and analysis of enantiomers. In chromatographic methods, indirect and direct methodologies are used. The indirect HPLC involves derivatization of samples with a chiral derivatization reagent, for an example a pure single enantiomer, resulting in the formation of two diastereomers which can be separated by a classical reversed-phase column. This indirect HPLC method is rarely used in industry, but due to its high sensitivity, it is frequently performed in biological analysis. Whereas,the direct HPLC utilizes in chiral stationary phases (CSPs) or in the mobile phase called chiral mobile phase additives(CMPA).[12]

Direct chiral separations by CSPs are more predictable, and are more widely used than those using chiral additives in the mobile phase. Among a hundred HPLC CSPs commercially available, only some types of chiral

sorbents following arepresently the most widely used for preparative HPLC in industry. Choosing the right column for the enantioseparation of a racemic compound is difficult. The decision relies mostly on empirical data and experience. However, the understanding of the recognition mechanisms of chiral selectors with enantiomers can help the chromatographists to resolve some problems of resolution and to economize time-consuming.[13]

According to Aboun-Enein and Ali all chiral selectors provide a chiral surface to enantiomers, which form with the selectors temporary complexes, having different bonding energies. The enantiomers differ in their binding energies because they fit differently into the chiral selector structures. Consequently, the two enantiomers can be eluted at different times by the mobile phase and then separately collected. Briefly, in general, the recognition mechanism on a chiral selector is based on a key-and-lock arrangement. However, many other factors such as mobile phase composition (pH, electrolytes, solvent nature), size and length of column, temperature, etc also play a key role for chiral resolution.[14]

There is also a new technique called simulated moving bed (SMB) chromatography is recently developed for industry. Basic concept of SMB technology is the continuous countercurrent movement of stationary and mobile phases in which the movement of a stationary phase is simulated. The small particles in this component are packed into single columns and connected to form a circle. Four external valves allow the addition and subtraction of feed and effluent. The mobile phase is pumped through the circle and when it passes the stationary phase a slight separation occurs, the less absorbable compound running in front and the more absorbable compound staying behind. When steady state is reached, the system can be operated continuously. If all flow rates and the shift time are determined correctly, raffinate and extract fractions can be withdrawn in high purity. An example of a pharmaceutical compound separated by SMB chromatography is tramadol.[16]

To avoid the racemization during chiral drug preparation, an asymmetry synthesis using chiral catalysts has been developed by W.S. Knowles, R. Noyori and K.B. Sharpless, the Nobel Prize in chemistry 2001[17]. Most of the available asymmetric chemical catalysts are organometal types including transition metals such as titanium, and noble metals such as osmium, palladium, and rhodium. Chiral catalysts are like enzymes in that both have a high degree of specificity. They allow stereospecific reactions to take place and therefore avoid the formation of racemates. L-Dopa (anti-Parkinson agent), naproxen (anti-inflammatory drug) are some examples of single enantiomer drugs produced by this catalytic asymmetric synthesis.[18]

Biological activities of enantiomers:

The enantiomers may vary in their interactions with chiral environments such as enzymes, proteins, receptors, etc of the body. These variations may lead to differences in biological activities such as pharmacology, pharmacokinetics, metabolism, toxicity, immune response etc. Biological systems can recognize the two enantiomers as two different substances, and their interaction each other will therefore elicit different responses.

Easson and Stedman has proposed the reason for enantiomers recognition by drug receptors is a three-point interaction of the drug with the receptor site.[19]In this case, one enantiomer is active biologically while the other enantiomer is not active, thereby this fitting interaction can produce an active biological effect. In addition, there is no active response of the inactive enantiomer which cannot bind in the same way with its receptor when it rotates in space.

As a conclusion, the attachment of an enantiomer to the chiral receptor is similar to a hand fitting into a glove or to a key into a lock.Indeed, a right hand can only fit into a right hand glove, therefore a particular enantiomer can only fit into a receptor site having the complimentary shape. The other enantiomer will not fit, like a right hand in a left glove, but may fit into a receptor site elsewhere in the body and cause an eventual unwanted or toxic effect. On the other hand, enantiomers can show different chemical behaviour due to different chiral discrimination by diastereomeric formations with a chiral environment[20].

Uses of enantiomers:

The enantiomers are known to be exhibiting different pharmacological and pharmacokinetic activities because they interact so well with enzymes and receptors consisting of chiral biomoleculesand other amino acids.There are many enantiomers that are formulated as single enantiomers with only having good efficacy without a side effect phase.

For example,DOPA the precursor of dopamine that is effective in the treatment of Parkinson disease, was used under racemic form (d,l- dopa), but knowing to its toxicity (agranulocytosis) of d-isomer, only levoratory form called L-Dopa is being used nowadays in therapeutics.It has been renewed the interest in uses of thalidomide due to its immunomodulatory, anti-angiogenic, and anti-inflammatory effects. In addition, it has a strong inhibition in the tumor necrosis factor alpha.[21]

Thalidomide has given spectacular results in the treatment of erythema nodosum leprosum, aptosis and Behcet's syndrome. Moreover, it has been assayed for organ transplantation, some autoimmune diseases such as chronic lupus erythematosus, rheumatoid arthritis, some forms of cancer, etc. N-hydroxythalidomide which is the derivative of single thalidomide enantiomers were also synthetized by asymmetric technique to study their individual chemical and biological activities.[22]

(S)-albuterol is one of the single formulated enantiomer which is a selective alpha-2 adrenergic receptor agonist used in the treatment of asthma. The other example is (S)-omeperazole, the proton pump inhibitor for the treatment of gastrointestinal tract reflux.[21] Other than that, (S)-citalopram which is primarily responsible for re-uptake of serotonin and act as the antagonism. The drug that responsible for the local anesthetic effect which is (L)-propranolol is also an single formulated enantiomer. Other examples are Ethambutol for treatments of tuberculosis and Naproxen for the treatment of arthritis pain.[23]

II. CONCLUSION

Drug enantiomers are widely being used clinically nowadays. Thus, the enantiomers need to undergo separation methods as this stereoisomers causes side effect which caused by the inefficacy side of the drug. The chiral separation of racemic drugs is a necessary in pharmaceutical industry as well as in clinical therapeutics. However, the usage of a single isomer must be taken after long clinical assessments between the racemate and single enantiomer actions because in some cases, racemates have more therapeutic advantages than single isomers. It is also important to give more information about chiral drugs especially racemic form to healthcare professionals in order to help them for finding an optimal treatment and a right therapeutic control.

REFERENCES

1. **Margaret Guo,** the twin drugs, Journal of youth and science,2011
2. **Davankov, Vadim A.** Analytical Chiral Separation Methods. International Union of Pure and Applied Chemistry, 1997. PDF
3. **Chen J, Korfmacher WA, Hsieh Y.** Chiral liquid chromatography-tandem mass spectrometric methods for stereoisomeric pharmaceutical determinations. Journal of Chromatography B. 2005; 820:1–8.
4. **Lorenz H, Capla F, Polenske D et al,** Crystallization based separation of enantiomers, Journal of the University of Chemical Technology and Metallury 2007: 42: 5-16.
5. **Bojarski J, Aboun-Enein HY, Ghanem A.** What's new in chromatographic enantioseparations. Current Analytical Chemistry. 2005;1:59–97.
6. Boralli VB, Coelho EB, Cerqueira PM, Lanchote VL. Steroselective analysis of metoprolol and its metabolites in rat plasma with application to oxidative metabolism. Journal of Chromatography B.2005;823:195–202.
7. Carvalho,Cass et al,Braz.J.Chem.Eng. vol.23(3)July/Sept. 2006
8. Lien Ai Nguyen, Hua He et al, Int J Biomed Sci. 2006 Jun; 2(2): 85–100
9. Raikumar SV. Thalidomide:Tragedy past and promising future. Commentary. Mayo Clinic Proceedings,PubMed.2004
10. Scott, Raymond PW. "Chiral Gas Chromatography." Chromatography Books Online (free Access Pdfs). Mar. 2011.
11. "Thalidomide." PubMed.gov. National Institute of Health, 3 Feb. 2010.
12. "The Two Enantiomers of Citalopram Bind to the Human Serotonin Transporter in Reversed Orientations." PubMed.gov. National Institute of Health, 3 Feb. 2010.

13. Wisor, Jonathan P., William C. Dement, Lisa Aimone, Michael Williams, and Donna Bozyczko-Coyne. "Armodafinil, the R-enantiomer of Modafinil: Wake-promoting Effects and Pharmacokinetic Profile in the Rat." Pharmacology Biochemistry and Behavior 85.3 (2006): 492-99. ScienceDirect - Home. Nov. 2006.
14. Drayer DE. The early history of stereochemistry. In: Wainer IW, editor. Drug stereochemistry. Analytical methods and pharmacology. 2nd. New York: Marcel Dekker Publisher; 1993. pp. 1–24.
15. Waldeck B. Three-dimensional pharmacology, a subject ranging from ignorance to overstatements.Pharmacology and Toxicology. 2003;93(5):203–210.
16. Davies NM, Teng XV. Importance of chirality in drug therapy and pharmacy practice. Implication for psychiatry. Advances in Pharmacy. 2003;1(3):242–252.
17. Stoschitzky K, Lindner W, Zernig G. Racemic beta-blockers-fixed combinations of different drugs.Journal of Clinical and Basic Cardiology. 1998;1(1):15–19.
18. Darrow, Jonathan J. "The Patentability of Enantiomers: Implications for the Pharmaceutical Industry." Stanford Technology Law Review, 2007. Web. 7 Mar. 2011.
19. Matthijs N, Maftouh M, Heyden YV. Screening approach for chiral separation of pharmaceuticals. IV. Polar organic solvent chromatography. Journal of Chromatography B. 2006;830:114–119.
20. Murphy-Poulton SF, Boyle F, Gu XQA, Mather LE. Thalidomide enantiomers: Determination in biological samples by HPLC and vancomycin-CSP. Journal of Chromatography B. 2006;831:48–56.
21. Staroverov SM, Kuznetsov MA, Nesterenko PN, Vasiarov GG, et al. New chiral stationary phase with macrocyclic glycopeptide antibiotic eremomycin chemically bonded to silica. Journal of Chromatography A.2006;1108:263–267.
22. Bhupinder Singh Sekhon, Enantioseparation of chiral drugs-an overview, International Journal of PharmTech Research 2010 2(2).
23. Mann A, Wermuth CG. Prix Nobel de Chimie 2001: William S. Knowles, Ryori Noyori, K. Barry Sharpless. La catalyse asymetrique. Medecine/Sciences. 2001; 17:1230–1232. (French)