Chapter 1

Chirality in pharmaceutical industry

1.1 Introduction

Nowadays, chirality is extremely important in many fields, such as clinical, pharmaceutical, environmental fields, to mention a few [1]. Enantiomers of the same substance proved to behave different in the body or environment, or to be the product of a totally different metabolic system in the body being markers of different diseases.

Due to these different behaviours of the enantiomers of the same chiral molecule, studies were conducted in order to identify the role of each enantiomers and its pathway in the body. Pharmaceutical industry had to consider the re-evaluation of each of the medicines sailed as racemates or with no control of enantopurity. Accordinly, new patents had to be issued for single enantiomers based pharmaceutical formulations.

1.2 Chirality. Terms and definitions

A molecule is chiral if it is not superimposable on its mirror image regardless of how it is contorted. A chiral molecule exist in two forms, called the R and S isomers which are mirror images of each other. The two non-superimposable, mirror images of chiral molecules are referred to as enantiomers. Enantiomers are therefore related to each other through the reflection by the mirror plane, and are not superimposable. Not all mirror-image pairs constitute enantiomers, but only those which are not superimposable after any rotation of the whole molecule or its mirror image. The

existence of enantiomers is usually (but not always) associated with at least one chiral centre. Chiral compounds exhibit optical activity, so enantiomers are also sometimes called optical isomers. Enantiomers have exactly the same energies, and therefore are not differentiated by physical measurements other than optical rotation (rotation of the plane of polarized light). The two enantiomers of a compound may also be classified as levorotary (L) or dextrorotary (D) depending on whether they rotate plane-polarised light in a left- or right-handed manner, respectively. A 50:50 mixture of the two enantiomers of a chiral compound is called a racemic mixture and does not exhibit optical activity [1].

Symmetry refers to a regular occurrence of certain patterns within a molecule or compound. These patterns are generated by the presence of symmetry elements such as centre of symmetry; symmetry axes and symmetry planes. The symmetry of a molecule determines whether it is chiral or not. A molecule is achiral (i.e not chiral) if and only if it has an axis of improper rotation, that is, an n-fold rotation (rotation by $360^0/n$) followed by a reflection in the plane perpendicular to this axis which maps the molecule on to itself. Thus a molecule is chiral if and only if it lacks an improper rotation axis. They are not necessarily asymmetric (i.e. without symmetry), because they can have other types of symmetry, like rotational symmetry. However, all naturally occurring amino acids (except glycine) and many sugars are asymmetric as well as chiral. Enzymes, which themselves are always chiral, often distinguish between two enantiomers of a chiral substrate. Most common chiral molecules have point chirality which centers around a single asymmetric atom (usually a carbon atom). This is the case for chiral amino acids where the α-carbon atom is the stereogenic center, having point chirality. A molecule can have multiple chiral centers

without being chiral overall if there is a symmetry element (mirror plane or inversion center) which relates those chiral centers. Such compounds are referred to as meso compounds. It is also possible for a molecule to be chiral without any specific chiral centers in the molecule. Conformations are temporary positions atoms in a molecule can assume as a result of bond rotation, bending, or stretching as long as no bonds are broken. Configurations are structures of a molecule which are assumed not to be interconvertible under ambient conditions. Enantiomers, and other optically active isomers such as diastereomers, are examples of configurational isomers [2].

1.3 Chiral pharmaceutical compounds

Chirality is a major concern in the modern pharmaceutical industry. A large percentage of commercial and investigational pharmaceutical compounds are chiral and their enantiomers show significant differences in their pharmacokinetics and pharmacodynamics. The importance of chirality of drugs has been increasingly recognized, and the consequences of using them as racemates or as enantiomers has been frequently discussed in the pharmaceutical literature during recent years [3-4]. The biological activity of chiral substances often depends upon their stereochemistry, since the living body is highly chiral environment. The body being amazingly chiral selective, will interact with each racemic drug differently and metabolize each enantiomer by a separate pathway to produce different pharmacological activity. Thus, one isomer may produce the desired therapeutic activities, while the other may be inactive or, in worst cases, produce unwanted effects. For example, the anesthetic ketamine is administered as racemate, and the S(+)-ketamine form is more potent than the R(-) form, the R(-) form being responsible for post-operative effects. A very tragic example is the case of the racemic drug of n-phthalyl-glutamic acid imide that was

marketed in the 1960 's as the sedative Thalidomide. Its therapeutic activity resided exclusively in the R(+)-enantiomer. Only after several hundred births of malformed infants was discovered that the S(-)-enantiomer was teratogenic [5]. Lipitor – one of the most sold drug in the world is delivered as single enantiomers; lipitor is well known for its effect on reducing cholesterol. Zocor – another drug used to reduce the cholesterol in the body is also sold as single enantiomers. While these medicines as well as plavix (used as antithrombotic) and nexium (used as antiulcerant) are sold as single enantiomers, there are medicines that are still sold as racemates: norvasec (used as antihypertensive), seretide (used as bronchodilatator), ogastro (used as antiulcerant) and effexor (used as antidepressant) to mention a few.

The current tendency in the pharmaceutical industry is to prepare drugs based on a single enantiomer, because of the side effects that could be caused by the presence of an undesirable component in a racemic drug. Indeed, to avoid the possible undesirable effects of a chiral drug, it is imperative that only the pure, therapeutically active form be prepared and marketed. However, the production of such drugs through stereoselective reaction or preparative enantiomeric separation can provide impure materials. Hence there is a great need to develop the technology for analysis and separation of racemic drugs.

1.4 Current trends in enantioanalysis of pharmaceutical compounds

Current methods of enantiomeric analysis include polarimetry, nuclear magnetic resonance, isotopic dilution, calorimetry, enzyme techniques as well as chromatographic techniques such as high performance liquid chromatography (HPLC) [6-8], gas chromatography (GC) [9-10], thin layer chromatography (TLC)

[11] and capillary electrophoresis (CE) [12-20]. Capillary electrophoresis is a fact in enantioanalysis. This technique is the most accurate chromatographic techniques used in enantioanalysis. The main disadvantage of it is the low sensitivity.

The utilization of these techniques involves a lot of steps before the actual analysis of the chiral compounds, that includes, the pre-treatement of the analyte sample with different necessary chemicals, separation steps using the chromatographic column. Therefore, the accuracy of the analytical information is not as good as expected.

The utilization of electrochemical sensors in molecular recognition of the enantiomers is not laborious if one compares it with structural and with chromatographic techniques [21]. The reliability of the response characteristics as well as the analytical information obtained by using electrochemical sensors is strictly correlated with the design of sensors [22]. The most reliable design is based on carbon paste. The method is rapid, precise and not expensive. Accordingly, the enantioanalysis using electrochemical techniques became a good alternative for the enantioseparation techniques.

1.5 References

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