Stereoselective Pharmacodynamics of Chiral Drugs with Special Reference to Ibuprofen

Shiwani Sharma[1], DrAtulPratap Singh[2]
[1, 2] Department of chemistry, University Institute of Sciences (UIS), Chandigarh University, Mohali, Punjab, India
[1] shiwiattri12@gmail.com, [2]atulpiid@gmail.com

Abstract

Chiral drugs constitute an enormous portion of the pharmaceutical industry. Nearly 56% of drugs manufactured today are chiral and most of them are marketed as racemates consisting of equimolar concentrations of the two enantiomers. Stereoselective pharmacodynamics and metabolism are the striking features of these chiral drugs, an interesting example of which is Ibuprofen 2-(4 isobutyl phenyl) propionic acid. It is a non-steroidal anti-inflammatory drug (NSAID) possessing analgesic, antipyretic, and antiplatelet (blood-thinning) properties. This article attempts to elucidate the stereoselective pharmacodynamics and toxicology of ibuprofen.

Index Terms Chiral drugs, NSAIDs, ibuprofen, chiral separation.

DOINumber:10.14704/nq.2022.20.8.NQ44722 **NeuroQuantology2022;20(8):6964-6974**

INTRODUCTION

Since the evolution of early human society, medicines have played a key role in guiding the overall well-being of humans. Many ancient civilizations incorporated natural plant parts and herbs into the treatment of a variety of ailments, the quintessence of which is the ancient Ayurveda; a profound field in medical sciences. Perhaps the "medicines" in the ancient era were not analyzed in terms of toxicology. With the initiation of the printing press in the 1500s, rationality was established in the uses and misuses of these folk remedies. It was until the 1800s that the inclusion of purified natural products in therapies marked its onset. As the demand and production of medicinal drugs increased, it was followed by many revolutionary developments in the drug industry including the discovery of chirality in drugs. The concept of chirality in drugs was discovered by Louis Pasteur; a French chemist and biologist in the year 1848 when he successfully separated the two enantiomers of sodium ammonium tartrate. Since then, chirality is playing a key role in determining the spatial arrangement of chiral drugs and their stereoselective nature of the action. Almost all naturally occurring compounds like proteins, enzymes, amino acids, carbohydrates, nucleosides, and most alkaloids are chiral. It is interesting to note that all-natural amino

*e*ISSN1303-5150

acids occur as l-isomers (levorotatory) whereas all-natural sugars exist as d-isomers (dextrorotatory). This phenomenon is termed homochirality. Now reaching this far in the article, one might wonder what exactly is chirality and why chirality is so crucial in drugs? [1]

In simple words, chirality is the property of a molecule to form a non-superimposable mirror image. Chirality is often termed as "handedness" since our hand is the supreme example of chirality. The two non-superimposable mirror images are termed enantiomers. We can say that enantiomers are the isomers with the same chemical formula and properties but the different spatial arrangements of molecules. The presence of chirality in a molecule is usually attributed to the presence of an asymmetric carbon attached to four different functional groups. Apart from carbon, some elements like sulfur, phosphorus, and nitrogen can also be chiral as seen in omeprazole, cyclophosphamide, and methaqualone respectively. An essential property of chiral molecules is their remarkable ability to move a plane-polarized light in a particular direction. While discussing the chiral nature of the biomolecules, we identified them as dextrorotatory and levorotatory. This information is relevant while studying the rotation of plane-polarized light by the chiral molecules. A dextrorotatory isomer is the one that rotates the plane-polarized light in the right direction, it is denoted by a (+) sign. Levorotatory is the one that moves the plane-polarized light in the left direction (-). The nomenclature of the enantiomers in terms of their 3-dimensional spatial arrangement is done under the rules of the Cahn Ingold Prelog (CIP) convention. According to the rules of the CIP convention, a molecule is designated as R (rectus or right) or S (sinister or left) as per the position of priority atoms (clockwise or anti-clockwise) in the molecule. R and S enantiomers can move the plane-polarized in the right or left direction meaning they can exist as R(+) or R(-) and S(+) or S(-). Both the enantiomers can have different physiological actions in the body depending on their stereoselective action (discussed a little later in the article). Sometimes, it is also possible for the enantiomers to exist as an equimolar mixture of both the R and S isomers (50:50). In such a case the mixture is called a racemic mixture and is optically inactive.[2]

ROLE OF CHIRALITY IN DRUGS

It is of utmost importance to study drug chirality as well as chiral separation of drugs in the pharma industry to avoid the ambiguities in the production as well as the functioning of one particular enantiomer. The stereoselective pharmacodynamics holds the same place in terms of importance as the biological effect of the drug action because both the stereoisomers of a chiral drug vary profoundly in their biological action and consequent hazards. For example, racemic ibuprofen constituting equal quantities of R(-)-ibuprofen and S(+)-ibuprofen is being put into use as an anti-inflammatory and analgesic agent. Perhaps their capabilities are remarkably different. The S (+)-enantiomer acts as a cyclooxygenase (COX) inhibitor, R (-)-enantiomer doesn't have much effect. R (-)-ibuprofen is inculcated into triglycerides in the pathway of lipid metabolism.[3]

IBUPROFEN

2-(4-isobutylphenyl) propionic acid or ibuprofen is a well-acquainted drug in today's era working against pain, fever, inflammation, menstrual cramps, and rheumatoid arthritis. As mentioned earlier, it belongs to the class of non-steroidal anti-inflammatory drugs (NSAID) but is a weaker anti-inflammatory agent than other NSAIDs. It is consumed orally or intravenously and takes around an hour to begin its action. As

already discussed, it exists in two isomeric forms; R (-) ibuprofen and S (+) ibuprofen. While ibuprofen has become a crucial drug in the pharmaceutical industry, its stereoselective mode of action makes it a little less universal in terms of its usage. Due to the dissimilarity between two of the enantiomers in terms of their action and hazards, the study of ibuprofen becomes a rather interesting one. Another very relevant concept to this discussion is the concept of 'metabolic inversion'. An adequate amount of racemic ibuprofen when incorporated, the R (-) ibuprofen undergoes inversion to generate S (+) ibuprofen. To produce a clinical effect that corresponds to the racemic form, a dose of S (+) ibuprofen must be 75% of the racemate, which will be discussed in detail in the pharmacodynamics section. [4]

3.1 Discovery

The journey of ibuprofen is traced back to 1953 when pharmacist and pharmacologist Stewart Adams and chemist John Nicholson working at Boots Pure Drug Company Ltd set on a hunt to find a referent of aspirin for the long-term treatment of rheumatoid arthritis with comparatively less gastric implications. Clinical trials of ibuprofen were initiated in 1966 in six patients suffering from rheumatoid arthritis in Edinburgh. Ibuprofen with the market name Brufen was first launched in 1969 in the UK with a prescribed dose of 600-800 mg per day with fewer gastrointestinal adversities than aspirin. Later it became available in the United States in 1974. Ibuprofen is an NSAID that was made accessible over the counter (OTC) in the UK (1983) and USA (1984). By the year 1985, ibuprofen became a familiar medicine for over 100 million individuals in 120 countries. The use of ibuprofen progressed well over the coming 10 years. A study revealed that the administration of ibuprofen worked miraculously for patients with lung ailments. It was revealed that ibuprofen was able to do it by preventing the lysosomal enzyme secretion and further preventing the neutrophils from migrating, adhering, or clustering. In 1996, ibuprofen gained the status of General Sale List (GSL) which enabled its sale without the prescription of a pharmacist. In the year 2005, it was revealed that the long-term dose of ibuprofen was increasing the risk of breast cancer in women by 51%. Long after, in the year 2008, it was concluded that the long-term dose of ibuprofen could curb the chances of having Alzheimer's disease by 44%[5]

3.2 Metabolism

The study of ibuprofen is an interesting area of research, however, the information available regarding its metabolism is very limited. Ibuprofen is metabolized into its metabolites by a pathway that involves glucuronic acid. The administered ibuprofen gets fused with glucuronic acid which is preferably selective for the S (+) enantiomers and consequently results in the formation of two major metabolites, 2-hydroxy ibuprofen, and carboxy ibuprofen. This fusion of the hydroxy and carboxy metabolites is proven to take place at the propanoic acid position. Moreover, some other trivial oxidation products have also been identified; 1-hydroxy-ibuprofen is found in human urine, and 3-hydroxy-ibuprofen is found in dialysis fluid when ibuprofen is given to nephrectomized patients. In addition to these, a taurine conjugate of ibuprofen has also been detected in urine up to 1.5%. The major metabolites 2-hydroxy ibuprofen and carboxy ibuprofen are excreted through urine preferentially in dextrorotatory form. This crucial observation established the idea of chiral inversion in ibuprofen.

3.3 Pharmacodynamics

As we have earlier discussed in this article, ibuprofen is an important agent when it comes to the inhibition of cyclooxygenase

eISSN1303-5150

(COX1, COX-2) enzymes. The mechanism of inhibition of cyclooxygenase by ibuprofen is considered non-selective as well as reversible. However, it is also important to mention that both the enantiomers have different potency when it comes to COX inhibition. S-ibuprofen is stronger in this regard as compared to R enantiomer. The main function of COX-1 and COX-2 is to act as a catalyst in the production of prostaglandins in the body which further are indulged in many crucial pathological phenomena.[6] The pharmacodynamics of NSAIDs is studied by analyzing their C_{max} (whichis the maximum plasma concentration of the drug) over Tmax (time to achieve C_{max}). When C_{max} is plotted against T_{max}, the area under the curve is termed AUC and is used to study the comparative pharmacodynamics of different formulations of a drug. [7] The pharmacological activity of a drug is highly dependent on its protein binding ability. Talking about ibuprofen, both its enantiomers have a high protein binding affinity, more than 99% as per therapeutic drug concentration standard. At a high concentration of protein binding, there is an occurrence of saturation. The binding of ibuprofen is considered to be highly enantioselective as well as competitive. This can be explained by the presence of two binding sites (low and high affinity) for both the enantiomers. The binding site with high affinity is the same for both the enantiomers which lead to a competitive aspect of protein binding. The problem here is that the R enantiomer has a higher binding affinity (2.6 times more) to that site than its S counterpart. The less binding potential of the S enantiomer is mainly responsible for its transport to the synovial fluid which is the site for its pharmacological activity.[8]

Recent studies have shown that the concentration of the unbound S enantiomer is very much dependent. The fraction of unbound S-ibuprofen in the plasma was greater than R-ibuprofen by 40-60%. The trend was the same for the administration of racemic ibuprofen (800mg) to healthy individuals where the unbound concentration of R enantiomer was 0.0042 and S enantiomer was 0.0064. Due to the binding of enantiomers being concentrated dependent, one enantiomer was able to displace its counterpart from the binding site in plasma. This was the possible explanation as to why the unbound concentration of R-ibuprofen was more in the plasma. There must have been competition among the enantiomers since one site with higher affinity was common for both**.** In addition to COX inhibition, there are some other biological actions produced by ibuprofen in which the efficiency of both the enantiomers is equal. These include activation of neutrophils, oxidative phosphorylation, and oxidation of fatty acids in the mitochondria. All these processes carried out by ibuprofen are non-stereoselective. As discussed earlier, the pharmacodynamics of S-ibuprofen differs in some aspects from the R-enantiomer as the R-ibuprofen is involved in the mechanism of lipid metabolism. It gets attached to the triglycerides by replacing the fatty acids from it. These newly transformed triglycerides are thus stored in the adipose tissues and consequently, a 'factory' is formed and the enantiomer is gradually released in the due course of time.[9]

The anti-inflammatory action of ibuprofen is basically due to the inhibition of COX. Despite this, there are certain other modes of action by which it generates its anti-inflammatory mode of action. These modes include its ability to inhibit the clustering of leucocytes and curb their expression, the inflammation produced by leucocytes is controlled by ibuprofen, and inhibition of prostaglandins as a result of which the afferent and efferent neural pathways causing pain are reduced. A native analgesic

*e*ISSN1303-5150

called anandamide is produced in the Central Nervous System that gets hydrolyzed into arachidonic acid. Ibuprofen is known to inhibit its conversion by prohibiting the action of the enzyme that brings about this conversion. Another striking feature of ibuprofen is its ability to reduce fever (antipyretic). Ibuprofen regulates the interleukins that are produced by leucocytes or prohibits the production of native pyrogens secreted via the hypothalamus. Another very important aspect of ibuprofen pharmacodynamics is its interaction with other drugs. One such interaction exists between ibuprofen and aspirin. A low dose of aspirin is considered to be an effective cardioprotective drug. Since both ibuprofen and aspirin compete for the binding site of COX-1, ibuprofen works against the action of aspirin. For encountering myocardial infarction or stroke, a low dose of aspirin is considered an ideal antiplatelet agent. [10]

Being an anti-platelet agent, when ibuprofen is incorporated with other anti-coagulants, it increases the risk of bleeding. For example, when ibuprofen is administered alongside warfarin, there was a significant increase in the risk of bleeding. The international normalized ratio that governs the capacity of blood clotting was exceeded by this combination.

One of the most important aspects of ibuprofen pharmacodynamics is the concept of chiral inversion. As we have discussed earlier, when an active racemate of ibuprofen is administered, the R enantiomer is most likely to undergo chiral inversion into its S form. The site where this inversion takes place affects the extent of inversion in one way or the other. Studies have shown that if the chiral inversion takes place in the gastrointestinal tract, the extent of inversion is most likely to increase. The concept of chiral inversion in ibuprofen dates back to 1973. It is interesting to note that the R-ibuprofen to get indulged in the metabolism of lipids by getting incorporated into the triglycerides, has to undergo chiral inversion into its S form. [11]

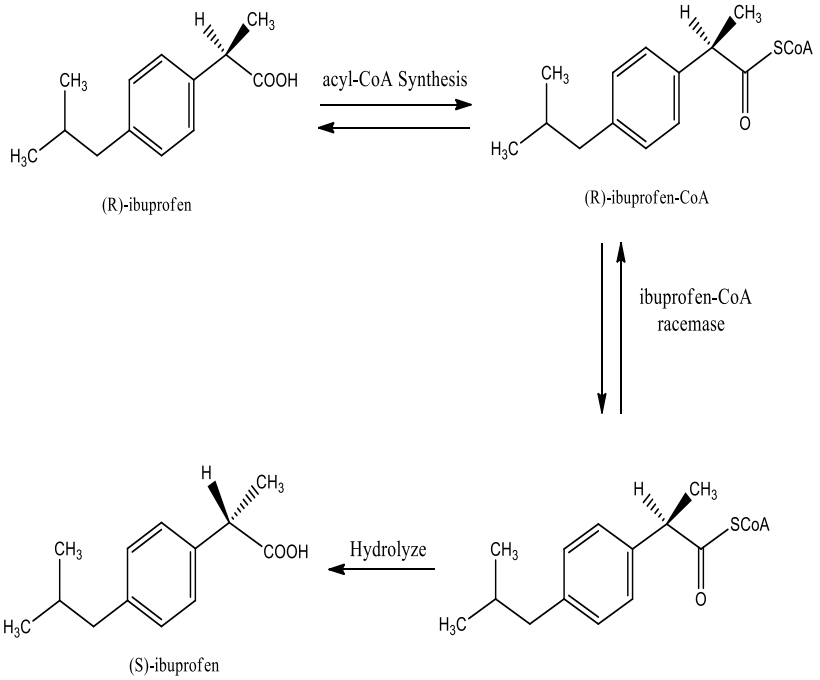

Fig.1 Diagrammatic representation of chiral inversion of (S)-ibuprofen to (R)-ibuprofen.

*e*ISSN1303-5150

Ibuprofen and COVID-19

In 2020 when COVID-19 was peaking in the world, there was a perception of the potential risk of worsening COVID-19 because of NSAIDs, particularly ibuprofen. French Govt was the first to warn against the potential risk although there was no well-established research to prove the same. Initially WHO released the statement along the same path but later denied the occurrence of the relation between NSAIDs and COVID-19. The main idea put forward to assert the assumption of ibuprofen related to COVID-19 was based on the ACE-2 expression. However, there was no scientific research to establish this hypothesis. The existing assumption came from some studies on animals but no proper research on human individuals. Most of the research papers written in this aspect have established no fundamental effect of ibuprofen or other NSAIDs on COVID-19.[12]

3.4 Clinical effects

Dental pain is one of the most severe pains in the body. Ibuprofen has been proven effective against dental pain following extraction or removal of the third molar. It is also notable that as compared to other NSAIDs, ibuprofen is more effective in relieving dental pain. It is also preferred over other NSAIDs because of its less harmful effects than others.

Another very common effect of ibuprofen in the body is general pain-relieving properties at the OTC doses. Recent studies have shown ibuprofen (400mg) to be the go-to drug for headaches or migraine without any formal prescription. Not just pain relief, ibuprofen is very much effective in fighting against fever. Some infections in association with the lungs are also believed to be eradicated by ibuprofen.

It is also used in the long-term treatment of osteoarthritis in many countries. Since ibuprofen has fewer gastrointestinal implications than aspirin, it is considered to be more effective for a prolonged time.

Not only in adults, but the analgesic effects of ibuprofen are also very much profound in children as well. Since ibuprofen can enter the CNS, it proves to be effective against headaches in children. The analgesic effect of the active form (s enantiomer) is considered to be greater than those of R-ibuprofen.

Although the popularity of paracetamol as an anti-pyretic is more than ibuprofen, many pediatricians have suggested the combined administration of paracetamol and ibuprofen for the treatment of fever in children in severe conditions. However, the combined use is not considered a safe option due to its potential liver and kidney implications, and also lack of many studies in this field makes it a little controversial. The most important area of supremacy for ibuprofen is in the treatment of rheumatoid arthritis. As opposed to this statement, aspirin has been famously incorporated for this treatment but several studies implying its gastric implications are a concern.[13]

3.5 Toxicology

A study of the toxic effects of ibuprofen was done on various animal species and the most common adverse effect concluded was in the gastrointestinal tract, a very common toxic effect of the NSAIDs. The dosage composition that led to the adversities was 180mg/kg/day in the case of rats and 8mg/kg/day in the case of dogs. The study also established the presence of GI in rats was limited to the intestine while in dogs, it was in the pylorus. Studies were also conducted in the laboratory to analyze the potential liver dysfunction caused by the precursor of ibuprofen called ibufenac. An administration of ibuprofen for 6 months in the rats showed the potential risk of liver adversities although there was no sign of complete damage to the liver. In humans, we have so far discussed the clinical effect of ibuprofen which mainly

occurs due to their activity of COX inhibition. It is interesting to note that most of the toxic effect of NSAIDs is due to the same reason. Some of its major hazards include gastrointestinal implications, uncoupling of oxidative phosphorylation in the mitochondria, the permeability of mucosa in the stomach making it susceptible to pathogens, etc.[14] Let us discuss all these effects in detail.

In terms of GI damage, there has not been a proper relation to establishing the direct attack of ibuprofen or other NSAIDs. Since their action mainly includes the inhibition of COX-1, it is believed to affect the GI system as it prohibits the secretion of carbonates of mucosal formation which may lead to pain in the abdomen, and nausea but the adversities are not to an extent where they can be considered as toxic. [15]

COX-2 is an enzyme contributing to pain, injuries in tissues as well as inflammation. Prostaglandins are an important factor involved in the healing of bones after an injury especially PGE2. Since NSAIDs work antagonistic to prostaglandin, it interferes with the healing process of bones, tendons, or ligaments. [16]

NSAID toxicity has also been linked to the liver. Prolonged usage of these NSAID drugs like ibuprofen has been associated with minor liver disfunction due to a serum called aminotransferase. Another form of liver damage is more severe and can even lead to liver damage. However, the chances of these complications arising in an individual are rare since there has been no establishment of a proper mechanism to prove the above implications. although a broad idea as to how these hepatic hazards may occur has been put forward. It is most likely that the implications occur due to an injury in the mitochondria, a condition of cholestasis, or the metabolite of the drug forming a protein adduct. [17]

The mouth-like part of the nephron in the kidney through which ultrafiltrate enters it is called glomeruli and the rate with which the ultrafiltrate enters it is called glomerular filtration rate (GFR). The prostaglandins especially PGE2 are an important factor in regulating this GFR and as already discussed NSAIDs prohibit the activity as well as secretion of prostaglandins which disturbs the GFR and can potentially lead to renal adversities. Another worse condition is seen in children, called Tubulointerstitial Nephritis (TIN) caused by NSAIDs. A study concluded that out of the 27 children having acute kidney injuries, 6 cases were of TIN caused by NSAIDs. [18]

In patients that are being treated with coumarin, extra caution needs to be taken because of the antiplatelet effects of NSAIDs. Although there has not been a fundamental relationship between the drugs and coumarins, cases of stomach irritation and GI bleeding are prevalent. In pregnant women, NSAIDs can cause a delay in labor and heavy bleeding due to the inhibition of prostaglandins by these drugs. Along the same line, the inflammation caused by intrauterine devices can be curbed by these non-steroidal anti-inflammatory drugs. [19]

Ibuprofen and dysmenorrhea

Menstrual health is an unsung but equally crucial phenomenon of the human body. It is not a very forwardly talked about issue. From the biological to chemical aspect, it is kept behind curtains. But thanks to our growing awareness of biology and chemistry, it is gradually coming forward as a mainstream issue faced by every woman. Nevertheless, we will focus on the pharmaceutical perception of it. Menstrual cramps or primary dysmenorrhea is the excruciating pain caused by the release of endometrial prostaglandins during menstruation. It leads to a contraction in the uterus, reduction in the flow of blood, and uterine hypoxia. NSAIDs are known to cure primary dysmenorrhea by their

potential to curb prostaglandins ($PGF_{2\alpha}$). Drugs like acetaminophen(500mg) are also known to work against cramps but studies have proven ibuprofen(400mg) comparatively better in this regard. Studies by Chan, Morrison, and Larkin have also concluded the effect of ibuprofen against dysmenorrhea. However, the lack of proper methodology and explanation did not establish the finding as accurate. To be more precise, it did not mention the level of pain and the method to measure it for each individual. Since it lacked a strong methodology, it cannot be considered reliable. The reason why it's a little tricky to enumerate menstrual pain is that it usually happens with a lot of other complications like fainting, nausea, vomiting, and headache that are very subjective. Needless to mention the superiority of ibuprofen over naproxen sodium and acetaminophen.

Using NSAIDs for menstrual main relief has not always worked wonders. Studies have shown that these drugs can cause gastrointestinal implications as mentioned earlier in the toxicology section. To avoid implications, a herbal replacement for this medication to reduce dysmenorrhea is ginger. Surprisingly, ginger is proven to be equally effective as ibuprofen for this purpose. However, there is a lack of proper research to conclude the reason for ginger's action but it can be its ability to inhibit the prostaglandin synthesis in the cyclooxygenase pathway that can make it an important anti-inflammatory and analgesic agent. The use of ginger can also avoid the side effects of NSAIDs. Regardless, more research is needed in this field because natural plant products hold an ocean of potential in curing several diseases. They just need a deep dive into their mechanisms, application, and properties. Since we discussed the potential side effects caused to our bodies by NSAIDs like ibuprofen, the question that comes to our mind is how can they be reduced? [20]

CHIRAL SEPARATION OF DRUGS

We are well aware of the fact that the clinical effect of a drug in our body is entirely dependent on its pharmacodynamics and pharmacokinetics. As we discussed in ibuprofen, the active enantiomer is S(+) ibuprofen. Therefore, it becomes a necessity to avoid the toxic effect of R enantiomer. For this, we need to incorporate ibuprofen which is purely one active enantiomer. Since chiral inversion of R ibuprofen to S ibuprofen is a very popular property of ibuprofen, biological screening of the drug is a crucial test during the early course of drug production. The time and cost required for this enantioselective analysis are more than that of a non-enantioselective analysis. Since FDA's guidelines mention the safety analysis of both the enantiomers, it becomes a soul duty for the pharmaceutical industries to produce that is safe from a very early stage of manufacture. [21]

4.1 High-Performance Liquid Chromatography (HPLC)

When it comes to chiral separation, HPLC is considered to be the most applied technique. The chromatographic techniques are based on the adsorption capacity of different compounds in the stationary phase. The common stationary phase used for this purpose is cellulose or amylose. The use of chromatographic techniques for chiral separation has been gaining popularity after the development of the Chiral Stationary Phase (CPSs). However, an important thing that needs to be made sure of while selecting the CPSs is enough knowledge about the enantiomers for an accurate separation. The availability of these CPSs also plays a crucial role during the separation. Additionally, mobile phase selection is also an important part of the procedure. A mobile phase must be easily accessible, not too expensive, and most importantly environment-friendly. Thus, with the proper knowledge about the

eISSN1303-5150

properties of a racemate drug, we can choose CPSs and mobile phase accordingly and separate them using HPLC.[22]

4.2 Enantioselective Liquid-Liquid Extraction (ELLE)

This technique has also been gaining a lot of popularity in terms of its application in chiral separation. The advantage of this technique is its affordability and convenience. In ELLE, the major role is played by the chiral extractants. The main chiral extractants used these days are cyclodextrins, tartaric acid derivatives, and crown ethers. It works on a "three-point interaction" principle. There is a formation of stable complexes between extractant and the enantiomers using hydrogen bonding, π-π interaction, or dipole-dipole interaction. One of the two enantiomers efficiently binds with the extractant (in the case of ibuprofen, it is the R enantiomer) and leaves the other one separated from the mixture. Thus, with the selection of an appropriate extractant, chiral separation can be carried out effectively.[23]

The effectiveness of a drug can be determined using its absolute configuration (AC). In this regard, a toolbox called "chiral technology" was developed which included a set of techniques or tools to depict the absolute configuration. Not only that, these techniques enabled efficient chiral separation at a preparative level. With the regulations of the FDA, the purity selection of drugs has become a crucial step during the early preparative stage of the drug. [24]

No matter how much we eulogize these techniques, they still are very time-consuming and cost a lot and generate a lot of chemical waste that might be hazardous. Hence there is a need for techniques that are easy, cost-friendly, and environmentally stable. A lot of techniques like electrochemical sensors, gravimetric sensors, and nanoparticles are incorporated. however, these techniques have still not gained much popularity over the traditional methods. [25]

The study of chiral drugs is an ocean of opportunity. Not only it is crucial or sometimes hazardous for the well-being of humans but also potentially harms the environment. It is very important to conduct a diverse range of research on their potential health and environment and try to inculcate advanced technologies to curb their toxic effects as a measure to provide optimum health and wellness to today and future generations.

CONCLUSION AND FUTURE SCOPES

We have come a long way with the development and revolutions in drug chemistry, especially chirality. It cannot be denied that every enantiomer in a racemate drug has its own merits and demerits. But the demerits of one enantiomer over the activity of another cannot be denied. The safety of a drug should not be overlooked just for the sake of therapy. From the start of the development of a drug till its manufacture, the stereochemical aspect must be religiously kept in mind. Since chiral drugs constitute such an enormous portion of the pharmaceutical industry, their production needs to be as safe as possible. To ensure safety, there is a need for chiral drug production to be purely enantioselective. Chiral switching should essentially be practiced with techniques that are environmentally friendly, safe, and enantioselective. The development of new drug synthesis must consider the safety of the people as well as inculcate the concept of green chemistry. While reviewing this topic, one of the biggest research gaps for me was the lack of enough research on the toxicological aspect of NSAIDs. It may be attributed to their intrinsic modes of action but we cannot deny the fact that these drugs are part of everyday medication for millions of people. Hence, it is of utmost importance that we devote as much effort as we can to evaluating their toxicological

eISSN1303-5150

effects. Usage of medicines especially chiral drugs in today's world is exclusive. Every human some way or the other needs medication, especially a common drug like ibuprofen. Thus, it becomes a duty for the pharmaceutical industry to produce the drug ethically and for analytical chemists to ensure its safety in terms of stereoselective side effects. Hence, it's very important to understand every aspect of medicines to a level deep enough so that in the future, we can produce drugs that can ensure absolute safety for the people.

"Wherever the art of medicine is loved, there is a love for humanity."

References

[1] Eric. Francotte and W. (Wolfgang) Lindner, Chirality in drug research. Wiley-VCH, 2006.

[2] W. H. Brooks, W. C. Guida, and K. G. Daniel, "The Significance of Chirality in Drug Design and Development HHS Public Access," 2011. [Online]. Available: www.pdb.org

[3] A. M. Evans, "Clin Rheumatol (2001) (Suppll):S9-S14 Clinical Rheumatology Comparative Pharmacology of S(+)-Ibuprofen and (RS)-Ibuprofen," 2001.

[4] K. D. Rainsford, "Ibuprofen: From invention to an OTC therapeutic mainstay," International Journal of Clinical Practice, vol. 67, no. SUPPL. 178. Blackwell Publishing Ltd, pp. 9–20, 2013. doi: 10.1111/ijcp.12055.

[5] A. M. Evans, "Clin Rheumatol (2001) (Suppll):S9-S14 Clinical Rheumatology Comparative Pharmacology of S(+)-Ibuprofen and (RS)-Ibuprofen," 2001.

[6] H. Hao, G. Wang, and J. Sun, "Enantioselective pharmacokinetics of ibuprofen and involved mechanisms," Drug Metabolism Reviews, vol. 37, no. 1. Taylor and Francis Inc., pp. 215–234, 2005. doi: 10.1081/DMR-200047999.

[7] H. Hao, G. Wang, and J. Sun, "Enantioselective pharmacokinetics of ibuprofen and involved mechanisms," Drug Metabolism Reviews, vol. 37, no. 1. Taylor and Francis Inc., pp. 215–234, 2005. doi: 10.1081/DMR-200047999.

[8] E. Journa and A. M. Evans, "42:23%256 Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs," 1992.

[9] A. M. Evans, "Clin Rheumatol (2001) (Suppll):S9-S14 Clinical Rheumatology Comparative Pharmacology of S(+)-Ibuprofen and (RS)-Ibuprofen," 2001.

[10] L. L. Mazaleuskaya et al., "PharmGKB summary: Ibuprofen pathways," Pharmacogenetics and Genomics, vol. 25, no. 2, pp. 96–106, Feb. 2015, doi: 10.1097/FPC.0000000000000113.

[11] K. D. Rainsford, Ibuprofen: Pharmacology, Therapeutics and Side Effects. Springer Basel, 2012. doi: 10.1007/978-3-0348-0496-7.

[12] N. Moore, B. Carleton, P. Blin, P. Bosco-Levy, and C. Droz, "Does Ibuprofen Worsen COVID-19?," Drug Safety, vol. 43, no. 7. Adis, pp. 611–614, Jul. 01, 2020. doi: 10.1007/s40264-020-00953-0.

[13] S. S. Adams, R. G. Bough, E. E. Cliffe, B. Lessel, and R. F. N. Mills, "Absorption, Distribution and Toxicity of I buprofenl," 1969.

[14] J. L. Goldstein and B. Cryer, "Gastrointestinal injury associated

eISSN1303-5150

with NSAID use: A case study and review of risk factors and preventative strategies," Drug, Healthcare and Patient Safety, vol. 7, pp. 31–41, Jan. 2014, doi: 10.2147/DHPS.S71976.

[15] F. Buttgereit, G. R. Burmester, and L. S. Simon, "Gastrointestinal Toxic Side Effects of Nonsteroidal Anti-Inflammatory Drugs and Cyclooxygenase-2-Specific Inhibitors," 2001.

[16] N. Ghosh et al., "Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Their Effect on Musculoskeletal Soft-Tissue Healing: A Scoping Review," JBJS Reviews, vol. 7, no. 12. Journal of Bone and Joint Surgery Inc., 2019. doi: 10.2106/JBJS.RVW.19.00055.

[17] S. A. Schug, "Do nsaids really interfere with healing after surgery?," Journal of Clinical Medicine, vol. 10, no. 11. MDPI, Jun. 01, 2021. doi: 10.3390/jcm10112359.

[18] U. A. Boelsterli, "Mechanisms of NSAID-Induced Hepatotoxicity Focus on Nimesulide."

[19] A. Bensman, "Non-steroidal Anti-inflammatory Drugs (NSAIDs) Systemic Use: The Risk of Renal Failure," Frontiers in Pediatrics, vol. 7, Jan. 2020, doi: 10.3389/fped.2019.00517.

[20] J. C. Morrison et al., "Analgesic Efficacy of Ibuprofen for Treatment of Primary Dysmenorrhea*."

[21] P. O. Carvalho, Q. B. Cass, S. A. Calafatti, F. J. Contesini, and R. Bizaco, "REVIEW-ALTERNATIVES FOR THE SEPARATION OF DRUG ENANTIOMERS: IBUPROFEN AS A MODEL COMPOUND," vol. 23, no. 03, pp. 291–300, [Online]. Available: www.abeq.org.br/bjche

[22] M. M. M. Pinto, C. Fernandes, and M. E. Tiritan, "Chiral separations in preparative scale: A medicinal chemistry point of view," Molecules, vol. 25, no. 8. MDPI AG, Apr. 01, 2020. doi: 10.3390/molecules25081931.

[23] T. J. Ward and K. D. Ward, "Chiral separations: A review of current topics and trends," Analytical Chemistry, vol. 84, no. 2. pp. 626–635, Jan. 17, 2012. doi: 10.1021/ac202892w.

[24] A. Calcaterra and I. D'Acquarica, "The market of chiral drugs: Chiral switches versus de novo enantiomerically pure compounds," Journal of Pharmaceutical and Biomedical Analysis, vol. 147. Elsevier B.V., pp. 323–340, Jan. 05, 2018. doi: 10.1016/j.jpba.2017.07.008.

[25] H. Y. Aboul-Enein, N. Bounoua, M. Rebizi, and H. Wagdy, "Application of nanoparticles in chiral analysis and chiral separation," Chirality, vol. 33, no. 5. John Wiley and Sons Inc, pp. 196–208, May 01, 2021. doi: 10.1002/chir.23303.

*e*ISSN1303-5150