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Review Article

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# CHIRAL INTERACTIONS AND CHIRAL INVERSIONS – NEW CHALLENGES TO CHIRAL SCIENTISTS

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## ABSTRACT

The interest in chirality and its consequences is not a new phenomenon. However, during the last decade it has raised increasing expectations due to scientific and economic reasons, the pharmaceutical industry being the main contributor and driving force. Advances in chemical technologies connected with the synthesis, separation, and analysis of pure enantiomers from racemates, together with administrative regulatory measures, have resulted in an increase in the number of newly registered chiral drugs containing only one of the enantiomers. Though the advantages of using single enantiomer like least possible side effects, reduced metabolic/renal/hepatic drug load and reduced drug interactions with an improved efficacy are so attractive the problems associated with the development of single enantiomer drugs are so challenging and many of them are left unsolved even today. In this article we mainly stressed upon chiral interactions, chiral inversions and impact of *in vivo* chiral interactions in every stage of the kinetics leading to stereoselective absorption, distribution, metabolism and excretion. Discussion about the rational use of chiral excipients which can enhance the eutomer/distomer ratio of enantiomer release versus time of a racemic drug was made. Finally we also mentioned the list questions which are gradually turning into unsolved challenges and threatening the future research in the chiral area.

**Keywords:** Chirality, chiral excipients, stereospecific drug delivery, enantioselective drug interactions, chiral drugs and chiral formulations.

## INTRODUCTION

### Why chirality is important

The importance of chirality has been appreciated and addressed by the pharmaceutical industry for decades. A number of scientific meetings, involving academic, industrial and regulatory scientists, were held in the late 1980s – early 1990s with the specific objective of discussing the new technologies and the significance of chirality in pharmacology and therapeutics.[1-3]

As technologies for measuring and making enantiopure materials have improved, the production of enantiopure pharmaceuticals, many of the top selling drugs in the world are now being sold in enantiopure form. Consequently, the subject of chirality and the pharmaceutical industry is a topic of considerable recent interest and importance. The issue of chirality in drugs increasingly is interacting with other issues facing the drug industry and its suppliers. These issues include drug delivery systems, defenses against generic competition by drug innovators, Food & Drug Administration approval requirements, education of physicians, supply agreements, and production. Firms that have stakes in chirality in Drugs-such as ChiroTech Technology, Chirex, Sepracor, and Oxford Asymmetry—must increasingly factor these issues into their business plans.[4-7]

The chiral nature of living systems has evident implications on biologically active compounds interacting with them. On a molecular level, chirality represents an intrinsic property of the "building blocks of life", such as amino acids and sugars, and therefore, of peptides, proteins and polysaccharides. This is what the reason for why only L-amino acids & D-glucose are only absorbed into our body. Therefore metabolic and regulatory processes mediated by biological systems are sensitive to stereochemistry and different responses can be often observed when comparing the activities of a pair of enantiomers.[8-9]

Stereoselectivity is often a characteristic feature of enzymatic reactions, messenger- receptor interactions and metabolic processes; it can vary interspecifically and even from one individual to the other. Therefore, stereochemistry has to be considered when studying xenobiotics, such as drugs, agrochemicals, food additives, flavours or fragrances but unfortunately the terminology used in "stereochemistry involved chiral drug delivery" is difficult to comprehend for most of the formulation scientists working in non chiral areas.[10] Therefore for the comfort and convenient understanding of this article, all important terms and their definitions are mentioned in Table **1**.

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**Table 1. Glossary of selective terms in Stereochemistry**

| Terminology | Definition |
|---|---|
| Chiraliy | It is a property of an object which is non-superimposable with its mirror image |
| Homochirality | It is the biological chirality in which all biologic compounds have the same chirality such as all amino acids are levorotary isomers. |
| Chiral switch | It is a procedure used to transform an old racemic drug into its single active enantiomer |
| Chiral molecules | Molecules whose mirror images are not superimposable upon each other |
| Achiral compounds | Molecules whose mirror images are superimposable on each other |
| Stereoisomers | Compounds that have the same atoms connected in same order but differ from each other in the way the atoms are oriented each other in the way are oriented in space. |
| Enantiomer | Stereoisomer whose mirror images cannot be superimposed |
| Enantiomers | Chiral molecules that are structurally different from each other only in the left and right-handedness of their orientations |
| Levo- | Isomer that rotates the plane of polarized light to the left |
| Dextro- | Isomer that rotates the plane of polarized light to the right |
| Racemates | The two enantiomers that comprise a racemic mixture |
| Absolute configuration | Indicates the actual arrangements of the substituents in the chiral compound |
| Diastereomers | Stereoisomers with multiple chiral centers that are not enantiomers |
| Meso compound | Diastereomer with two or more chiral centers where the four groups on each of the chiral carbon atoms contains a plane of symmetry within the molecule |
| Chiral inversion | Conversion of one enantiomer into its mirror image |
| Distomer | Refers to the enantiomer with lower pharmacological affinity or activity |
| Eutomer | Refers to the enantiomer with higher pharmacological affinity or activity |
| Epimers | Diastereomers which have a different configuration at only one chiral center are called epimers. |
| Isomers | Compounds that have identical molecular formulae but differ in nature or sequence of bonding of their atoms or in the arrangement of their atoms in space |
| Constitutional isomers | Isomers that have the same number and kinds of atoms but differ in terms of the arrangement of atoms in the molecules. |
| Racemic mixture | A mixture of equimolar amounts of enantiomers |
| Racemization | Conversion of an enantiomer to its racemate |
| Conformation | This term is used to refer to any one of an infinite number of arrangements of atoms in space that result from the rotations about any of the bonds in the molecule. |
| Configuration | This term refers to the relative position or order of the arrangement of atoms in space that characterizes a certain stereoisomer. |
| Absolute configuration | This term refers to the actual order of the arrangement of atoms about a chiral center. |

Today every industry is recognizing the importcance of producing single enantiomer drugs even for the existing racemic drugs where ever it is possible i.e. importcnce of chiral switch is growing day by day.[11] Racemic switches are chiral drugs that have already been approved as racemates which have been redeveloped as single enantiomer.[12-14]There are several advantages and driving forces for this chiral swith.[15-18]

**Advantages**[19]

- Removal of unwanted pharmacodynamic side effects and toxic effects if these reside exclusively in one enantiomer.
- Exposing the patient to lower dose with same therapeutic effect, thus reducing metabolic/renal/ hepatic drug load compared to racemic drug administration.
- Easier assessment of physiology, disease, and drug co-administration effects.
- Reduce drug interactions.
- Prevents enantiomer–enantiomer drug interactions if present.
- Avoids the probability for bioinversion.
- Easier assessment of efficacy and toxicity through pharmacokinetic/pharmacodynamic monitoring of the stereochemically pure active enantiomer.
- If the enantiomers are sufficiently different in pharmacological effects, it may be possible to get a patent on one or both.

This article we mainly stressed upon chiral intractions, chiral inversions and impact of invivo chiral interactions in different stages of the kinetics leading to stereoselective absorption, distribution, metabolism and excretion.

Chiral interactions: The two enantiomers of a racemic drug may interact with each other or they may interact with other enatiomers of concomitantly administered chiral drugs. Sometimes enantiomers of a racemic drug may interact with the chiral excipients with which they are formulated and lead to stereospecific or enantioselective drug delivery.[20-23]

***In-vitro* chiral interactions**

In the last decade, attention has been paid to the release of enantiomers of different drugs from formulations containing the racemate. Eventhough the scope for this kind of interactions is very less; we just can't ignore our research from this point of view. It is useful in the prevention of unwanted conversion of active enantiomer of the drug molecule to inactive enantiomer in invitro due to chiral drug-excipient interaction.

The study of chiral interactions from invitro point of view, gives us an opprtunity to select such chiral excipients which do not bring the chiral inversion from distomer to eutomer. With rational use of chiral excipients we can also enhance the eutomer/distomer ratio of enantiomer release versus time of a racemic drug.

The *in-vitro* Chiral interaction studies are based on the hypothesis put forward by Duddu et al in 1993[24] which assume that chiral excipients may interact preferentially with one enantiomer leading to stereoselective release from a formulation containing a racemate. Solinís MA et al studied the release of salbutamol[25-26] and ketoprofen[26-27] enantiomers from matrices formulated by direct compression with hidroxypropylmethyl cellulose (HPMC) K100M, a chiral excipient commonly used in pharmaceutical technology and from their studies they

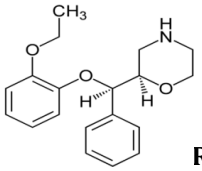
observed a small stereoselective release for ketoprofen but not for salbutamol sulphate. However, diffusion tests[28] confirmed the existence of a chiral interaction between salbutamol and HPMC K100M and they also studied the release of salbutamol enantiomers from HPMC matrices elaborated by wet granulation and found that the use of wet granulation techniques, will allow a major interaction beweeen a chiral drug and chiral excipient showing a stereoselectivity in the release of enantiomers.

***In-vivo* chiral interactions**

***Stereoselectivity of chiral drugs at different stages of their pharmacokinetics:*** The reason for discussing the stereoselectivity of chiral drugs at different stages of their pharmacokinetics like at absorption, distribution, metabolism and excretion is that all these alterations in the kinetics is again because of invivo chiral interactions of chiral drugs.

The major cause for the invivo chiral interactions might be the selectivity and specificity of the metabolisisng enzymes to different enantiomers of same drug molecule. We can observe the impact of *in-vivo* chiral interactions in every stage of the kinetics leading to stereoslective absorption, distribution, metabolism and excretion.[29-31]

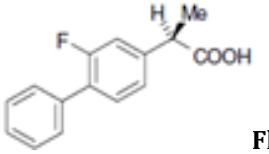
Reboxetine, (RS)-2-[(RS)-α-(2-ethoxyphenoxy) benzyl] morpholine methanesulphonate, is a racemic compound and consists of a mixture of the (*R*,*R*)-(–)- and (*S*,*S*)-(+)-enantiomers. Reboxetine is an antidepressant drug used in the treatment of clinical depression and panic disorders. Reboxetine has two chiral centers. Thus, four stereoisomers may exist, the (*R*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, and (*S*,*R*)-isomers.



**Reboxitine**

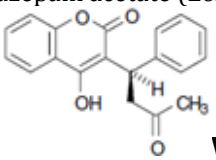
In a study Margherita Strolin et al[32] determined brain and plasma levels of both enantiomers in mice and rats after oral administration of reboxetine at doses (1.1 mg/kg, mouse; 20 mg/kg, rat) twice the respective $ED_{50}$ values in the antireserpine test. In mice and rats, brain and plasma levels of the (R,R)-enantiomer were always higher than those of the (S,S)-enantiomer. After normalization for dose, the mean $AUC_{0-\infty}$ values of both (R,R)- and (S,S)-enantiomers in mouse brain were about 23 and 32 times higher than in rat brain, respectively. In plasma, the corrected mean $AUC_{0-\infty}$ values were about 5 (R,R) and 10 (S,S) times higher in mice than in rats. Their results provide evidence for the higher bioavailability and/or lower clearance of both enantiomers in mice than in rats, and for a higher penetration of both enantiomers into mouse brain compared to rat brain. From this we can state that stereospecific kinetics may be species specific.

Flurbiprofen is a chiral nonsteroidal anti-inflammatory drug. Flurbiprofen exhibits stereoselectivity in its pharmacokinetics. Stereoselectivity is exhibited at the level of protein binding and metabolite formation. Flurbiprofen binds extensively to plasma albumin, apparently in a stereoselective manner.[33]



**Flurbiprofen**

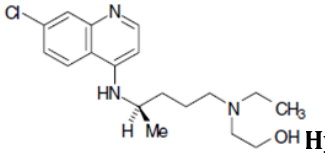
Warfarin is an anticoagulant. A few years after its introduction, warfarin was found to be effective and relatively safe for preventing thrombosis and embolism. Ilona Fitos et al performed the kinetic and equilibrium binding studies on the interaction of warfarin enantiomers with human serum albumin (HSA) in the absence and presence of lorazepam acetate (LoAc) enantiomers.



**Warfarin**

The binding of (R)-warfarin displayed an exponentially increasing fluorescence, satisfying the two-step mechanism reported previously for the racemate, i.e., a diffusion controlled pre-equilibrium is followed by a slower rearrangement of the complex. In the case of (S)-warfarin, the signal was biphasic: a fast fluorescence enhancement was followed by a slow decline. The different kinetic features indicate that the equilibrium conformations of the [(S)-warfarin-HSA] and [(R)-warfarin-HSA] complexes are achieved via different mechanisms. The phenomenon was seen in buffers of different pH and compositions. Equilibrium binding measurements indicated significantly lower molar intrinsic fluorescence for the (S)-warfarin complex, suggesting differences in the microenvironments of the bound enantiomers. In the presence of (S)-LoAc, the allosterically enhanced binding of (S)-warfarin manifested itself in accelerated relaxation kinetics.[34]

Hydroxychloroquine is used in the treatment of acute attacks of malaria due to *Plasmodium vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis. Andrew J. McLachlan et al investigated the disposition of hydroxychloroquine enantiomers in patients with rheumatoid arthritis following administration of a single dose of the racemate.

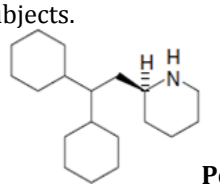


**Hydroxychloroquine**

Blood concentrations of (-)-(R)-hydroxychloroquine exceed those of (+)-(S)-hydroxychloroquine following both an oral and intravenous dose of the racemate. Maximum blood concentrations of (-)-(R)-hydroxychloroquine were higher than (+)-(S)-hydroxychloroquine after oral dosing (121 ± 56 and 99 ± 42 ng/ml, respectively, $P = 0.009$). The time to maximum concentration and the absorption half-life, calculated using deconvolution techniques, were similar for both enantiomers. The fractions of the dose of each enantiomer absorbed were similar, 0.74 and 0.77 for (-)-(R)- and (+)-(S)-hydroxychloroquine, respectively ($P = 0.77$). Their experimental data suggested that absorption of hydroxychloroquine is not enantioselective. Finally they concluded that the stereoselective disposition of hydroxychloroquine appears to be due to enantioselective metabolism and renal clearance, rather than stereoselectivity in absorption and distribution.[35]

B. J. Gould et al determined blood plasma and urine excretion pharmacokinetics of the (+) and (-) enantiomers of perhexiline which is a prophylactic antianginal agent after oral single-dose studies in human volunteers, and

compared with the pharmacokinetics of the racemate drug in the same subjects.

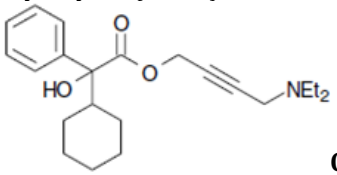


**Perhexiline**

They found that the (-) enantiomer is more rapidly metabolized and eliminated, and is stereoselectively hydroxylated to the *cis*-monohydroxy-perhexiline. The peak plasma concentrations of unchanged perhexiline is greater, while that of the *cis*-monohydroxy-perhexiline metabolite is lower, after administration of the (+) enantiomer than after the (-) enantiomer or the racemate. Similarly, the *AUC* values for unchanged perhexiline and for the *trans*-monohydroxy-perhexiline metabolite are greatest and the *AUC* value for the *cis*-monohydroxy-perhexiline metabolite is lowest for the (+) enantiomer. The three stereoisomeric forms of perhexiline all had the same times to peak plasma concentration of the unchanged drug or of the *cis*-metabolite, and all three forms had a similar plasma elimination half-life for unchanged perhexiline.

Metabolism of racemic perhexiline to the *cis*-monohydroxy metabolite is the major mechanism of elimination of the drug in man and has been shown to be polymorphic in human populations. The (−) enantiomer which shows stereoselective metabolism to the *cis* metabolite might therefore show a greater polymorphic effect. From their studies it is observed that DA strain of rats exhibited slower rates of hydroxylation *in vitro* than Wistar or Lewis strains of rats. From this we can conclude that there is some species dependent stereospecific metabolism.[36]

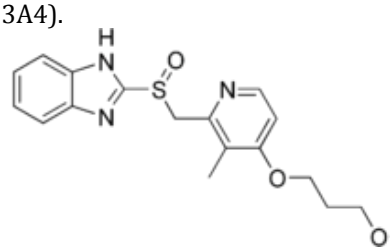
*In-vitro* studies and the multiple applications of an oxybutynin (OXY) transdermal delivery system to Japanese healthy volunteers were conducted by mizushima et al to characterize the stereoselectivity in the pharmacokinetics of oxybutynin and its metabolite, *N*-desethyloxybutynin (DEOB).



**Oxybutynin**

In human liver microsomes, (*R*)-OXY and (*R*)-DEOB were eliminated slightly slower than the corresponding (*S*)-enantiomers. The production of DEOB from OXY for the (*R*)-enantiomer was also slower than that for the (*S*)-enantiomer. In human P450-expressing liver microsomes, OXY was metabolized mainly by CYP3A4 among five cytochrome P450s (CYPs) tested (CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5) and the kinetics were slightly different for the enantiomer. The unbound fraction of (*R*)-OXY in plasma was almost two times higher than that of (*S*)-OXY, whereas (*R*)-DEOB was bound to plasma protein more than (*S*)-DEOB. No differences were observed in the blood–plasma concentration ratios for the enantiomers. After multiple applications of the transdermal delivery system, the plasma concentrations of (*R*)-OXY were lower than those of (*S*)-OXY. This data indicates that for the stereoselectivity of OXY, the unbound fraction of each OXY enantiomer was a major factor and the metabolism in liver had a minimal effect.[37]

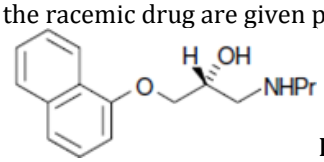
Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. Masatomo Miura et al designed a study to confirm the stereoselective metabolism of rabeprazole and to identify the enzyme(s) involved in the metabolic breakdown of rabeprazole-thioether to rabeprazole by incubating the rabeprazole-thioether with human liver microsomes and several recombinant cytochrome P450 (CYP) enzymes (CYPs 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4).



**Rabeprazole**

Their study results proved that rabeprazole is reduced mainly non-enzymatically to rabeprazole-thioether, which is further stereoselectively re-oxidized by CYP3A4 mainly to (*R*)-rabeprazole. The difference in the enantioselective disposition of rabeprazole is determined by stereoselectivity in CYP3A4-mediated metabolic conversion from rabeprazole-thioether to rabeprazole.[38]

Jean-Francois Marier et al studied the effects of increasing doses of propranolol on the stereoselective kinetics of its enantiomers and they proved that the kinetics of propranolol enantiomers are stereoselective when high doses of the racemic drug are given per oral (po).



**Propranolol**

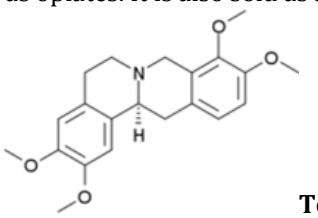
To document whether the dose and/or the route of administration determines the stereoselective kinetics of propranolol enantiomers, they conducted a study on rabbits. In conclusion, their *in-vitro* studies show that in the intestine the stereoselective kinetics of (*RS*)-propranolol are secondary to differences in the intrinsic clearances of the enantiomers, whereas in the liver there is preferential saturation of the metabolism of (*S*)-(−)-propranolol. *In-vivo,* low doses of (*RS*)-propranolol administered iv or po do not generate stereoselective kinetics of the enantiomers of propranolol, possibly because the contribution of the liver overshadows the contribution of the intestine.

On the other hand, without changing the protein binding, high po doses generate zero-order kinetics and more profoundly depress (*S*)-(−)-propranolol metabolism, producing stereoselective differences in the rates of elimination of the enantiomers. Finally, high iv doses, generating zero-order kinetics, induce small stereoselective differences in the elimination of the enantiomers of propranolol, but in this case (*S*)-(−)-propranolol is eliminated more rapidly than (*R*)-(+)-propranolol.

Therefore at low po (per oral) and iv (Intravenous) doses, the kinetics of the propranolol enantiomers were identical. Propranolol enantiomers plasma protein binding was not stereoselective and at low po or iv doses the kinetics of (*RS*)-propranolol are not stereoselective as the liver is dominating the effect of the intestine, and at high po doses the kinetics of propranolol enantiomers are stereoselective because of hepatic saturation of (*S*)-(−)-propranolol clearance.

Tetrahydropalmatine (THP) is an alkaloid found in several different plant species, mainly in the *Corydalis* family. The pharmaceutical industry has synthetically produced the

more potent enantiomer Levo-tetrahydropalmatine (Levo-THP), which has been marketed worldwide under different brand names as an alternative to anxiolytic and sedative drugs of the benzodiazepine group and analgesics such as opiates. It is also sold as a dietary supplement.

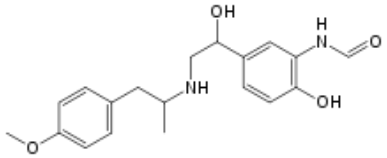


**Tetrahydropalmatine**

Zhanying Hong et al studied the stereoselectivity in excretion of tetrahydropalmatine enantiomers by rats and identified the metabolites of racemic tetrahydropalmatine (*racemic*-THP) in rat urine. Urine and bile samples were collected at various time intervals after a single oral dose of *racemic*-THP. The mean cumulative amount of (-)-THP was significantly higher than that of (+)-THP both in urine and bile samples. However, the enantiomeric (-/+) concentration ratios in rat urine and bile were significantly lower than those ratios in rat plasma. They finally suggested the excretion of THP enantiomers was stereoselective rather than a reflection of chiral pharmacokinetic aspects in plasma and (-)-THP was preferentially excreted in rat urine and bile.[39]

Yamaguchi et al were studied the stereoselective distribution, metabolism, and excretion of 2-phenylpropionic acid (hydratropic acid, HTA) by giving racemic HTA (20 mg/kg) to intact, bile duct-cannulated, bile duct-ligated, and nephrectomized and bile duct-cannulated rats. Their results suggested that the step regulating stereoselective excretion of hydratropic acid in rats is that of its excretion from the liver into bile and blood. There is no or very little stereoselectivity in the step of hydratropic acid excretion through the kidney into the urine.[40]

Mei Zhang et al studied the stereoselectivity of urinary excretion of formoterol and its glucuronide conjugate after oral dosing of human volunteers with racemic formoterol. They found that the unchanged (S; S)-formoterol excretion was significantly greater than that off unchanged (R; R)-formoterol and (R; R)-formoterol glucuronide excretion was significantly greater than that of (S; S)-formoterol glucuronide.



**Formoterol**

The total RR-formoterol (unchanged drug plus glucuronide) excreted was significantly greater than the total (S; S)-formoterol. Finally they concluded that the urinary excretion of formoterol in male humans after oral administration of racemic formoterol is stereoselective with preferential excretion of the active (R; R)-formoterol as unchanged drug and glucuronide.[41]

## CHIRAL INVERSIONS

2-Arylpropionic acid derivatives are probably the most frequently cited drugs exhibiting the phenomenon that is best known as chiral inversion. One enantiomer of drug is converted into its antipode either in the presence of a solvent or more often in inner environment of an organism. Mechanistic studies of the metabolic chiral inversion were carried out for several drugs from NSAIDs, and a model of this inversion was suggested and subsequently confirmed. The chiral inversion of NSAIDs has been intensely studied in the context of the pharmacological and toxicological consequences. However, the group of NSAIDs is not the sole group of drugs in which the inversion phenomenon can be observed. There exist several other drugs that also display chiral inversion of one or even both of their enantiomers. These drugs belong to different pharmacotherapeutic groups as monoamine oxidase inhibitors, antiepileptic drugs, drugs used in the treatment of hyperlipoproteinemia or drugs that are effective in the treatment of leprosy.

As the process of chiral inversion is affected by several factors, so the intensity of chiral inversion of individual substances and at different conditions can differ considerably. Interspecies differences and types of tissue are reported to be the main factors that were recognized to play the key role in the process of chiral inversion. Some of more recent studies have also revealed that several other factors, such as the route of administration or interaction with other xenobiotics, can influence the enantiomeric conversion.

Chiral inversion does not seem to be a phenomenon connected with only several drugs from some unique group of 2- arylpropionic acid derivatives: it is also observed in drugs with rather different chemical structures and is much more frequent than it can be realized.[42] Profen drugs represent a significant share of the present pharmaceutical market. Virtually all examples of profens are currently marketed as racemates. Racemic profen drugs are a good illustration of so-called “racemic switches.” Racemic switches are chiral drugs that have already been approved as racemates which have been redeveloped as single enantiomer.

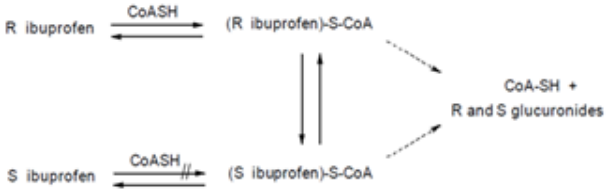
### *In-vivo* behaviour of different profen drug enantiomers

The enantiomers of profens differ substantially in both their pharmacodynamics and pharmacokinetic properties. It is generally recognized that the S profens are the enantiomers that inhibit prostaglandin synthesis. The absolute configuration, as well as the conformation of this isomer is important for the interactions with the cell receptors responsible for the therapeutic anti-inflammatory activity. In practice, the profens are generally administered as racemic mixture. *In-vivo*, however, some of the profens can undergo, to a certain extent, a unidirectional inversion from the R to the S form, leading to an enantiomeric excess of the S form when a racemate of the drug is administered. This unique process was supposed to enhance the effectiveness of profen racemates as chiral drugs.

The most wideley accepted mechanism for this inversion (Figure **1**), originally proposed by nakamura et al., is a three step process which commences with the enantiospecific enzymatic formation of a thioester between the R enantiomer of the 2- arylpropionic acid and coenzyme a (CoA). This thioester may be hydrolysed to regenerate the R enantiomer or may undergo epimerization to yield the thioester in which the 2-arylpropionyl moiety has the s configuration. Subsequent hydrolysis of this (S)-CoA thioester completes the inversion process. The epimerization step may proceed non-enzymatically, due to the acidic nature of the proton connected to the alpha carbon of the 2-arylpropionic acid

substituent of the thioester. This process is clinically important because it generates an active cyclo-oxygenase inhibitor (S- profen) from a relatively inactive precursor (R-profen).

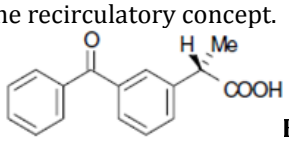
**Figure 1. Mechanism of Ibuprofen inversion**




Ketoprofen, a potent nonsteroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class, has been used clinically for over 15 years in Europe, and has recently been introduced in the United States. Although it possesses a chiral centre, with only the S-enantiomer possessing beneficial pharmacological activity, all ketoprofen preparations to date are marketed as the racemate. Ketoprofen exhibits little stereoselectivity in its pharmacokinetics. The enantiomers have similar plasma time-courses and do not seem to interact with one another. The absorption of ketoprofen is rapid and almost complete when given orally. Ketoprofen binds extensively to plasma albumin, apparently in a stereoselective manner. Substantial concentrations of the drug are attained in synovial fluid, the proposed site of action of NSAIDs. It is eliminated following extensive biotransformation to inactive glucuroconjugated metabolite. There is about 10% R to S inversion upon oral administration. Conjugates are excreted in urine, and virtually no drug is eliminated unchanged.[43]

Flurbiprofen is a chiral nonsteroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class. Although it possesses a chiral centre, with the S-(+)-enantiomer possessing most of the beneficial anti-inflammatory activity, both enantiomers may possess analgesic activity and all flurbiprofen preparations to date are marketed as the racemate. Conversion from R to S is noticed after oral administration but it is found at insignificant level.

Ketoprofen, (RS)2-(3-benzoylphenyl)-propionic acid is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. The stereoselective enterohepatic circulation (EHC) and the synchronous chiral inversion of ketoprofen enantiomer in rat were evaluated by moment analysis based on the recirculatory concept.



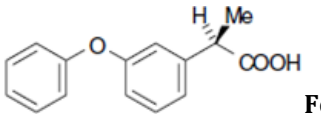

**Ketoprofen**

(S)-Ketoprofen was generated by the chiral inversion from (R)-ketoprofen, whereas (R)-ketoprofen was not generated from (S)-ketoprofen. Within 30 min after intravenous administrations, the plasma time courses of R- and S-enantiomers were almost the same between rats with laparotomy and those with bile-duct cannula. After 30 min, the plasma concentrations in rats with laparotomy were significantly higher than those in rats with bile-duct cannula. The recirculation ratios of (R)- and (S)-ketoprofen for the single EHC were estimated to be 15.4% and 63.6%, respectively. The absorption ratios of (R)- and (S)-ketoprofen for the absorption process from the gastrointestinal tract into the systemic circulation were 87.0% and 83.8%, respectively. The biliary excretion ratios of (R)- and (S)-ketoprofen for the disposition process through the systemic circulation into the bile were 17.7% and 75.8%, respectively. The chiral inversion ratio from (R)-ketoprofen into (S)-ketoprofen was 59.5%. All the above results clearly indicated the stereoselective enterohepatic circulation.[44]

The R enantiomers of some of the 2-arylpropionic acid non-steroidal antiinflammatory drugs (NSAIDs) are known to undergo metabolic chiral inversion to their more pharmacologically active antipodes. This process is drug and species dependent and usually unidirectional. The S to R chiral inversion, on the other hand, is rare and has been observed, in substantial extents, only for ibuprofen in guinea pigs and 2-phenylpropionic acid in dogs. After intra peritonial administration of single doses of racemic ketoprofen or its optically pure enantiomers to male CD-1 mice and subsequent study of the concentration time-course of the enantiomers, they noticed substantial chiral inversion in both directions. Following racemic doses, no stereoselectivity in the plasma-concentration time courses was observed. After dosing with optically pure enantiomer, the concentration of the administered enantiomer predominated during the absorption phase. During the terminal elimination phase, however, the enantiomers had the same concentrations. Therefore a very importan observation of Jamali et al is the presence of reversible chiral inversion for ketoprofen enantiomers in mice.[45]

Baillie et al studied the metabolic chiral inversion of R-(-)-ibuprofen in human subjects by means of specific deuterium labeling and stereoselective gas chromatography-mass spectrometry methodology. The results of their analysis indicated that: 1) conversion of R-(-)- to S-(+)-ibuprofen takes place with complete retention of deuterium at the beta-methyl (C-3) position; 2) chiral inversion of R-(-)-[2H3]ibuprofen is not subject to a discernible deuterium isotope effect; and 3) replacement of the beta- methyl hydrogen atoms by deuterium has no effect on any of the serum pharmacokinetic parameters for R-(-)- or S-(+)-ibuprofen. These data indicate that the process whereby R-(-)-ibuprofen undergoes metabolic inversion in human subjects does not involve 2,3-dihydroibuprofen as an intermediate, and that the underlying mechanism cannot, therefore, entail a desaturation/reduction sequence.[46]

Fenoprofen is a non-steroidal anti-inflammatory drug. Fenoprofen calcium is used for symptomatic relief for rheumatoid arthritis, osteoarthritis, and mild to moderate pain. San martin et al studied the influence of clofibrate on the stereoconversion of fenoprofen (FPF) in guinea pigs.

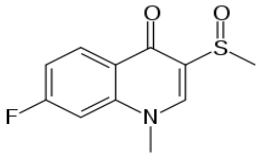



**Fenoprofen**

This hypolipidaemic agent has been related to some biochemical changes in the liver leading to an increase in the chiral inversion process. Pretreatment with clofibrate increased the chiral inversion of (*R*)-FPF in favour of thepharmacologically active (*S*)-FPF enantiomer.[47]

Flosequinan is a quinolone vasodilator. It has direct relaxing effects on peripheral arteries and veins. It is administered orally in cases of congestive heart failure in patients who are not responsive to digitalis or ACE inhibitors. Chiral inversion at a sulphoxide position of flosequinan enantiomers [(±)-7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone] occurred in conventional rats but not in either genn-free rats or rats treated with

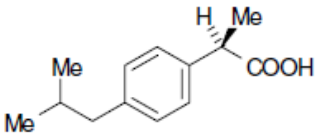
antibiotics after an oral administration of each enantiomer. Thus, it was postulated that the chiral inversion occurred by mechanisms mediated by intestinal bacteria.



**Flosequinan**

The intestinal content isolated from conventional rats reduced *R*(+)- and *S*(−)-flosequinan to produce the sulphide, while intestinal content from rats treated with antibiotics did not reduce the drug. Several strains of facultative anaerobes possessed a high flosequinan reducing activity. *Escherichia coli, Klebsiella oxytoca* and *Klebsiella pneumoniae* reduced *R*(+)-flosequinan to the sulphide stereoselectively. On the other hand, *Enterobacter aerogenes* and *Micrococcus agilis* exclusively reduced *S*(−)-flosequinan. The sulphide, which could be produced by intestinal bacteria from *R*(+)- and *S*(−)-flosequinan, was readily absorbed upon an oral administration to rats, and was oxidized fairly rapidly to *R*(+)- and *S*(−)-flosequinan and further to the sulphone form. Based on their data, they confirmed that chiral inversion at the sulphoxide position of flosequinan enantiomers occur via stereoselective reduction of sulphoxide by intestinal bacteria to form the sulphide, followed by oxidation of the sulphide in the body to produce *R*(+)- and *S*(−)-flosequinan.[48]

Sanins SM et al studied the oxidative metabolism and chiral inversion of ibuprofen in freshly isolated rat hepatocytes. R(-)-Ibuprofen underwent metabolic chiral inversion to the S(+) enantiomer, whose formation was dependent on incubation time, cell density, and substrate concentration.



**Ibuprofen**

S(+)-Ibuprofen, on the other hand, was not converted to R(-)-ibuprofen in rat hepatocytes. When cells were incubated with a mixture of unlabeled R(-)-ibuprofen and R(-)-[3,3,3-2H3]ibuprofen, the resultant S(+) enantiomer consisted only of unlabeled and trideutero molecules (formed in the same ratio as the corresponding species of R(-)-ibuprofen), indicating that 2,3-dehydroibuprofen did not serve as the symmetrical intermediate in the chiral inversion reaction. Collectively, their results demonstrate that freshly isolated rat hepatocytes represent a convenient and reproducible *in vitro* model system for studies on the metabolism to prove the chiral inversion of ibuprofen.[49]

## DISCUSSION

Till now only one thing is well proved that "The stereospecific drug release and enantiospecific drug absorption is possible only when the mechanism of drug release or drug absorption is by diffusion process. But till now nobody has proved molecular level driving force for this enantiomeric discrimination in the drug release as well as absorption. But the possible hypothetical assumed mechanism we want to propose is "There might be some steric or chiral interactions between some chiral enantiomers and chiral excipients." Further we want to assume that the chiral centre of a particular enantiomer might be susceptible for the chiral interaction by a particular chiral excipient. Hence that particular enantiomer as a result of chiral interaction is either driven from the dosage form fast or hindered or it may be absorbed fast or its absorption may be hindered.[50]

## CHALLENGES

About 50% of the drugs what are present in the current market are racemic drugs with chirality and even today we do not have their complete pharmacokinetic and pharmacodynamic profiles as an individual enantiomer. In the currently existing racemic drugs, are both the enantiomers of all the racemic drugs are equally active? Or one enantiomer is highly active and other is less active? Or one of the two enantiomers is completely inactive? Or one is active and other is toxic? Or if both the enantiomers are active, are those enantiomers active in only racemic state or even when they are administered individually? If one enantiomer is active and other is inactive, is that active enantiomer active when it is formulated as single enantiomer? If it is active as single enantiomer is it stable or undergoes any invitro or invivo chiral inversion into its inactive form? Are all the chiral excipients compatible or not? Which chiral excipients produce which kind of stereospecific drug release with existing chiral drugs? Is this chiral discrimination possible with all the chiral excipients and chiral drugs? If only with few, what are those few chiral drugs and excipients? For howmany racemic drugs we have the solutions for the above list of questions? These are all the challenges which are presented infront of all the chiral scientists all over the world expecting an immediate attention.

## CONCLUSION

The study of chiral interactions and chiral inversions has a great significance. It is useful in the prevention of unwanted conversion of eutomer to distomer either *in-vitro* or *in-vivo*; however the scope for the conversion in invitro is less.

The study of chiral interactions and chiral inversions also gives us an opprtunity to select such chiral excipients which do not bring the chiral inversion from distomer to eutomer. Using suitable chiral excipients we can also enhance the eutomer/distomer ratio of enantiomer release versus time of a racemic drug.

In case of cardiovascular risks, the release of eutomer rather than the distomer is very essential to elicit required pharmacological effect. This is made possible with use of suitable chiral excipients. If the enantiomers are sufficiently different in pharmacological effects, it may be possible to get a patent on one or both. It is evident, however, that it is far better to use the specific active enantiomer in view of dosage and economic considerations to give a better pharmacological benefit to the patients.

As current regulatory guidelines also stress the importance of investigating Pharmacokinetic and Pharmacodynamic studies of drugs with a chiral centre because the enantiomers of drugs often display different pharmacological and toxicological profiles we feel that there is lot of scope need to extend research in this chiral area with an immediate attention.

## ACKNOWLEDGMENT

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