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CHIRAL SWITCH- NEW EXPRESSWAY TO STRATEGIC DEVELOPMENT IN API INDUSTRY

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ABSTRACT

The chirality of drugs has emerged as a major area in API Pharmaceutical Industry. Single enantiomers offer some advantages primarily related to three-dimensional structure and arrangement of atoms in molecule. Enantiomeric purity is achieved either by the switch from an existing racemic drug to the single enantiomer or by the synthetic development of an enantiomerically pure chiral drug. The potential advantages of chiral switch can be related to a higher therapeutic index due to better potency, selectivity and fewer adverse effects, faster onset of action and exposure of the patient to lower drug dosages. Therefore, it is important to promote the chiral separation and analysis of racemic drugs in pharmaceutical industry as well as in clinic in order to eliminate the unwanted isomer and to find an optimal treatment and a right therapeutic control for the patient.

KEYWORDS: Chiral Switch, single enantiomer, Active Pharmaceutical Industry (API), racemic mixture, Chiral separation, Chiral resolution.

INTRODUCTION

The active ingredient in a pharmaceutical drug is called as active pharmaceutical ingredient (API).[1] Generally APIs are either achiral: without any asymmetric centre or are chiral with at least one asymmetric centre. The chiral APIs are used as racemic or in their enantiopure form. Approximately 50% of the small molecules used currently in therapy as APIs are chiral, containing at least one centre of asymmetry in their structure. Although large majority

of these chiral molecules are marketed as racemates, there are about 25% that are used in the form of pure enantiomers.[2-5] One pure enantiomer, due to its specific spatial arrangement may provide considerably higher or better therapeutic effect in the biological system as compared to the other pure enantiomer or its racemate.

A chiral switch may be defined as the development or re-evaluation of a single enantiomer from a previously marketed racemate. Such re-evaluations have resulted in both; expected therapeutic benefits and unpredicted adverse reactions. There is an increasing trend for the API industry to develop and market products containing pure enantiomers. In the period of early 1980s, the most of chiral synthetic APIs on the market were used as racemates and the proportion of single enantiomers was only 12%. After two decades, most of newly launched chiral synthetic APIs were single enantiomers, and only one or two racemates or diastereomers were introduced in a year.[6-7]

The chiral-switching concept goes back to late 90s. when, an in-depth clinical perspective of this debate was presented in 10th International Symposium on Chiral Discrimination in 1998 The definition of the term “chiral switch” was introduced by Agranat and Caner in 1999 and later refined in reference to the development of a single enantiomer from a chiral drug that was developed and marketed, previously as a racemate, or as a mixture of diastereoisomers. Since the 1990, there is a clear trend to develop single enantiomer drugs.[8-11] In 1988, the FDA announced a set of guidelines addressing these stereochemical topics in relation to the submission of new drug applications. Later in the year 1992, the US Food and Drug Administration (FDA) issued a policy statement regarding the development and approval of chiral drugs. This policy adopts a rather strict approach toward chiral drugs, offering detailed guidelines on their assessment. A similar policy was released later in 1993 by the European Union. Both regulatory agencies had indicated rules that explicitly specified that developing an enantiopure medicine should be desired. Since then the pharmaceutical industry has focussed on the single pure enantiomer as compared to the development of racemates. In an analysis carried out in 2006 by the scientists from AstraZeneca, GlaxoSmithKline and Pfizer confirmed this trend, wherein out of the 128 compounds then under development in the three companies, 69 (54%) were molecules containing at least one stereogenic centre, and of the 69 chiral molecules, 67 (97%) were being developed as single enantiomers, and only two as racemates.[12-16] Current regulations still leave the door open to produce racemates as long as there is evidence that the administration of the racemate will lead to therapeutic advantages in

comparison with the single enantiomer.[17-18]

Development of single enantiomers - A pharmaceutical Industry perspective

Till the 1960s, the efficient synthesis of enantiopure chiral API drug was challenged since few enantioselective synthetic methods were known. Therefore, most synthetic API drugs were synthesized as racemates and either tested and used as such or in rare cases resolved via crystallization. In the 1970s, the development of enantioselective synthetic methodologies started in earnest and now there is a plethora of enantioselective synthetic methods available.[19]

Ibuprofen was the first chiral drug of the non-steroidal anti-inflammatory drug (NSAID) class to be switched to the single-enantiomer. It was in the market since 1969 and was well known since 1976 that its (*S*)-enantiomer was the one that is therapeutically active. Later in 1994 (*S*)-(1)-ibuprofen (Dexibuprofen) was launched as a prescription drug in Austria in 1994.[9] The reason for such a switch came from the evidence that the (*S*)-enantiomer was over 100-fold more potent as an inhibitor of cyclooxygenase-1 (COX-1) enzyme than the (*R*)-ibuprofen. Administration of Ibuprofen as racemate undergoes unidirectional chiral inversion from the (*R*)-enantiomer to the (*S*)-enantiomer, the former behaving as a pro-drug for the latter. Therefore, it was thought that the use of the single (*S*)-ibuprofen would give faster onset of action at a lower dosage and would reduce the source of configurational individual variability.[20-23]

Ketoprofen was selected for chiral switching and marketed as the (*S*)-(+)-enantiomer in 1998, the metabolic (*R*) & (*S*) chiral inversion for ketoprofen was shown to be negligible in humans. In case of ketoprofen, the metabolic chiral inversion of (*R*)-ketoprofen into (*S*)-ketoprofen (dexketoprofen) is lower than for ibuprofen (less than 10%). For ketoprofen the chiral switch is more straightforward, dexketoprofen being 2–4 more potent than its racemate.[24-25]

Another important example of chiral switch is omeprazole which is a proton pump (H+/K+-ATPase) inhibitor (PPI). The two enantiomers of omeprazole form the same main metabolites (hydroxy-omeprazole, desmethyl omeprazole and omeprazole sulfone), however their proportion may differ. (*R*)-omeprazole, hydroxylation by CYP2C19 is responsible for 98% of the liver clearance, while (*S*)-omeprazole is for only 70%. The difference between the hepatic metabolism of the two omeprazole enantiomers leads to certain therapeutic advantages of

using (*S*)-omeprazole or esomeprazole over racemic omeprazole such as higher bioavailability in fast metabolizers, and lower exposure in slow metabolizers. The chiral switch of omeprazole to esomeprazole was developed on the premise that less interindividual variation and average higher plasma levels would provide higher dose efficiency.[26-29]

In case of lansoprazole, it was observed that the (*R*)-enantiomer reaches a higher plasma level in both slow and fast metabolizers, and the lower level of (*S*)-lansoprazole (dexlansoprazole) appears to be offset by the more pronounced binding of plasma proteins to the (*S*)-enantiomer.[12,30]

The (*R*)-enantiomer of albuterol, levalbuterol, was introduced in the US market in 1999. The enantiomers are stereoselective at the β2-receptor with a 68-fold greater potency for the (*R*)- than (*S*)- albuterol and racemization after administration of either enantiomer is low, at around 6% and is likely due to acid-catalyzed racemization in the acid environment of the stomach from the swallowed fraction of an inhaled dose. There are no pharmacodynamic differences between the racemate and (*R*)-albuterol. There are pharmacokinetic differences between the entantiomers such that the (*R*)-enantiomer is metabolized 12 times faster than the (*S*)-, leading to higher concentrations of (*S*)-albuterol by all routes of administration and is due largely to the stereoselective metabolism of swallowed drugs.[31]

Formoterol has 2 chiral centres and thus can exist in 4 combinations, but only the (*R*;*R*) (*S*;*S*) racemate is available as the marketed product. As with albuterol, there is stereoselectivity at the β2-receptor with the (*R*;*R*) enantiomer (Arformoterol) having a 1000-fold greater potency than the (*S*;*S*) form. There is no significant inversion of the 2 individual enantiomers to the racemate. Arformoterol, was approved by the FDA in 2006 as a solution for inhalation in patients with chronic obstructive pulmonary disease (COPD). There are little pharmacokinetic data for the (*R*;*R*)- and (*S*;*S*)-enantiomers, but the area under the curve and half-life after single or 14 days of dosing are similar indicating no accumulation of the (*S*;*S*) enantiomer.[31-32]

Cetirizine exists as a racemic mixture of levocetirizine [(R)-entantiomer] and dextrocetirizine [(S)- entantiomer]. Dextrocetirizine appears to be 10-fold less potent than levocetirizine. There are no differences in the pharmacokinetics between cetirizine and levocetirizine and both have a similar volume of distribution suggesting similar penetration through the blood–brain barrier. The potential advantages of chiral switching from the racemic mixture to

levocetrizene include an improved therapeutic index through increased potency and selectivity and decreased side-effects, a faster onset of action, a reduced propensity for drug-drug interactions, and the exposition of the patient to a lower dosage.[31, 33-35]

It cannot be generalized that every product can undergo chiral switch, especially in the pharmaceutical industry, where there is so much unpredictability in the behaviour of the drug in the biological systems. One of such examples is Fluoxetine. Fluoxetine hydrochloride (HCl), the first selective serotonin-reuptake inhibitor (SSRI) and a mainstay medicine for the treatment of depression was invented, developed and launched in 1988 by Eli Lilly and Company and marketed as Prozac. Fluoxetine is a racemate of (R)-(–)- fluoxetine and (S)-(+)-fluoxetine. At the time of the invention, the biochemical and pharmacological activities of each enantiomer were found to be essentially the same. There was little enantiomeric selectivity regarding interactions of fluoxetine with the serotonin-uptake carrier, regardless of the species or pharmacological test. In view of these findings, Eli Lilly did not consider it advantageous to seek patents for the single fluoxetine enantiomers as antidepressants. However, Sepracor obtained US Patent 5,589,511 in December 1996, which claimed (S)-(+)-fluoxetine for the treatment of migraine, and US Patent 5,648,396 in July 1997, which claimed (R)-(–)-fluoxetine for the treatment of depression in humans.

In December 1998, Eli Lilly and Sepracor announced a license agreement that exclusively allowed Eli Lilly to develop and commercialize (R)-fluoxetine globally. (R)-Fluoxetine was in Phase II clinical development in the United States as a potential drug for short washout and increased flexibility in treating depression, and (S)-fluoxetine has been in Phase II clinical development for potential prevention of migraine. In October 2000, Eli Lilly terminated its licensing and development agreement with Sepracor for (R)- fluoxetine, after some patients developed abnormal heart rhythms in Phase II clinical trials. (R)-Fluoxetine, at the highest dose tested, caused a small but statistically significant increase in QTc prolongation (prolongation of the QT interval in the ECG trace). Although Sepracor believed that this cardiac-related side effect was clinically insignificant, development of a lower dose would have delayed the NDA submission by at least two years. Given the risk and timing of the development of (R)-fluoxetine, and after an assessment of the competitive environment, Sepracor decided not to pursue the (R)-fluoxetine programme at that time.[36-37]

Sotalol was another API which was unsuccessful in chiral switch. Sotalol is a nonselective β-adrenergic blocker used as a class III antiarrhythmic, with a chiral carbon atom in its

structure. R-sotalol has both a β- blocker and a potassium channel blocker effect, while S-sotalol has potassium channel blocking activity, its affinity towards β receptors being low. The results of the Survival with ORal D-sotalol (SWORD) study showed that administration of optically pure S-sotalol increased mortality (fatal arrhythmias) in patients with myocardial infarction compared with placebo.[38-39]

In some cases, safety was one of the reasons for chiral switching. For example, the case of the local anesthetic drug bupivacaine, where the (S)-enantiomer (levorotatory) proved to be significantly less cardiotoxic than the (R)-enantiomer and the racemate. Thus, the chiral switching to the levorotatory enantiomer (levobupivacaine), resulted in the development of a local anesthetic drug with a clinical profile similar to that of the previously marketed racemate, but with a decrease in cardiovascular toxicity.[40-42] Dizziness and fainting due to hypotensive episodes are adverse effects of doxazosin, an alpha-1 adrenoceptor antagonist used for treatment of benign prostatic hyperplasia. S-doxazosin is thought to be selective for prostate receptors and at the same time expected to have lower incidence of hypotension[45] The bronchodilator activity of racemic salbutamol resides in its levorotatory R enantiomer whereas the dextrorotatory S enantiomer has been found to be virtually inactive at therapeutic concentrations.

To add to this, later studies have found that the S enantiomer is not completely inert; it rather induces airway hyper-reactivity, eventually contributing to increased morbidity and mortality in patients with asthma. Clinical studies have shown that it is at least twice as potent as the racemate.

There are examples, where chiral switch was not safer, Fenfluramine is a racemic drug used as an appetite suppressant. „Fen-phen,“ the combination of fenfluramine and the achiral anti-obesity drug phentermine was widely used for weight loss. When dexfenfluramine, the S-enantiomer, came to the U.S. market in 1996, Fen-phen also came to mean the combination of dexfenfluramine and phentermine. Vigorous prescription of this new compound with the belief that the dextro-isomer would be safer concealed the fatal adverse effects of fenfluramine which were retained in the dextro-isomer. Both fenfluramine and dexfenfluramine were withdrawn from the market in 1997.[44]

Labetalol is a non-selective β-adrenergic blocker with associated α1-adrenergic blocker effect. there are two chiral centres and hence four stereoisomers of labetalol. The *S,S*-

labetalol and *R,S*-labetalol were found to be inactive. The other two isomers, *S,R*-labetalol and *R,R*-labetalol (named dilevalol) were active, however the possibility of chiral switch was unsuccessful as the development of single dilevalol, was terminated due to adverse effects associated with hepatotoxicity. The product was commercialized as a racemate only.[45]

Recently (2020), during pandemic chloroquine and hydroxychloroquine were chirally switched to (*S*)- enantiomers for repurposing the drugs for the treatment of COVID-19.[63]

One of the attractive benefits of introducing chirality in a drug candidate is that it leads to increased complexity to a specific target, i.e., it gives access to a greater diversity of compounds to be explored.

There are two principal scenarios in chiral drug development: the first is the *de novo* development of an enantiomerically pure chiral drug; the second is a switch from an existing racemic drug to the single enantiomer(s) of that drug. Chiral switches are chiral drugs that are already approved as racemates but that have been redeveloped and launched as single enantiomers.[46-47]

For the de novo development of an enantiomerically pure drug, three main pathways are available for the pharmaceutical industry to access the chiral product: (1) to start from a pure enantiomer of a synthetic product (chiral pool); (2) to employ a stereoselective synthesis (including enzymatic and biological procedures); and (3) to separate a racemate obtained by a non-stereoselective synthetic protocol (chiral resolution). In all the cases, the company must provide detailed specifications for the final product which assure identity, strength, quality, and purity from a stereochemical point of view. At the discovery stage of drug development, when a large number of molecules are required in milligrams amount for initial testing, stereoselective syntheses are not time- or cost-efficient. Moreover, since both the enantiomers of the new drug candidate are needed for biological testing (as required by the FDA's policy statement), the development of a chiral active pharmaceutical ingredient as the racemate can be more suitable, for the pharmaceutical industry, from a commercial and strategic point of view: in fact, the cost for large-scale non-stereoselective reactions is greatly reduced with respect to that affording a single enantiomer; afterwards, the chiral resolution of the racemate can be achieved at any level of the development process (i.e., on starting materials, intermediates or final products), using several methods including crystallization, diastereoisomeric salt or complex formation and enantioselective chromatography. The latter

has become the most time and cost-effective approach for preparative purposes at the discovery stage in the pharmaceutical industry, where it also proved to accelerate drug development and therefore facilitate an earlier regulatory approval. In the later stages of the drug discovery, when the pharmaceutical company decides to focus just on one of the two components of the racemate, the direct production of the desired enantiomer by a stereoselective synthetic route remains a primary target.[48-50]

The term „chiral switches" is preferable to „racemic switches" because the switch is from a racemic drug to the corresponding enantiomer(s). The definition of a chiral switch can be broadened to include chiral drugs that are already approved as mixtures of diastereomers (e.g. epimers) but that have been redeveloped and launched as single enantiomers, or single enantiomers that have been redeveloped and launched as the corresponding enantiomers. Taking into consideration the current FDA and EMA regulations, the current tendency of the pharmaceutical industry favors the development of new enantiomerically pure compounds to the detriment of the chiral switch practice to single enantiomers from already registered racemates.[51-53]

Chiral separation or Chiral resolution in Active Pharmaceutical Ingredients Industry

Chiral separation or chiral resolution, is a procedure used to separate the two isomers of a racemic compound. In API industry, two main categories of techniques are often applied for chiral resolution the classical methods and the modern technologies.[54-55]

In the classical approach, the most widely used technique is the resolution by diastereomeric salt formation. In this strategy, an acid-base reaction is involved between a racemic drug and a pure single enantiomer called resolving agent. This reaction leads to the formation of two diastereomeric salts that now have different physical and chemical properties. These two diastereomers obtained can be easily separated either by crystallization or by filtration if one is soluble and the other is insoluble. Finally, the salt is decomposed by treatment with either acid or base, then the pure enantiomer is obtained. The two diastereomers formed 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.

Another classical approach is the enzymatic or kinetic resolution. In this methodology, resolution is achieved by means of biochemical process that destroys one enantiomeric form. Certain microorganisms such as yeasts, molds, bacteria can only degrade one of two isomers

of a racemate by enzymatic assimilation, the other which is not digested remains in solution, then it is isolated. Enzymatic resolution has been used in the preparation of lotrafiban, levofoxacin, and S-naproxen.

For the modern technologies, preparative high-performance liquid chromatography (HPLC) is the method of choice for the enantiomer separation. Chiral HPLC has proven to be one of the best methods for the direct separation and analysis of enantiomers. In chromatographic methods, two techniques are used: indirect and direct. The indirect HPLC involves derivatization of samples with a chiral derivatization reagent. On the other hand, the direct HPLC utilizes the chiral selector either in chiral stationary phases (CSPs) or in the mobile phase called chiral mobile phase additives (CMPA). The common technique is rarely used in industry because of its high cost and low efficiency. Direct chiral separations using CSPs are more widely used and are more predictable, in mechanistic terms, than those using chiral additives in the mobile.[58-60] Besides the direct chiral HPLC, a new technique called simulated moving bed (SMB) chromatography is recently developed for industry. The basic concept of SMB technology is the continuous counter-current 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.[59]

The single enantiomer introduced in therapy as a result of chiral switch preferably has a similar profile and indications as the “parent” racemate but can present several therapeutic advantages: more predictable pharmacodynamic profile, improved therapeutic index and safety, reduced possibility for drug–drug interactions, faster onset of action and patient exposure to lower dosages. Patients have benefited from a chiral switch in several circumstances, especially when the pharmacological action is concentrated in one of the two enantiomers, such as in case of escitalopram as compared to the racemate citalopram or levofloxacin as compared to ofloxacin. The benefits are also observed when the single

enantiomer is safer than its racemate, for example, levobupivacaine is safer as compared to its racemate bupivacaine.[60-61]

However, there have been cases in which single-enantiomer medications generated from blockbuster racemates had minimal clinical benefit over the racemate (ibuprofen, PPIs), and their release onto the market was likely used by pharmaceutical corporations as a patent-protection tactic against generic competition. Another interesting example is the one of fenfluramine, which was switched successfully to dexfenfluramine but later withdrawn from therapy due to an unfavorable safety profile. Not all of the attempted switches have been successful, and sometimes unanticipated adverse effects were reported, and the chiral switch process was stopped (fluoxetine, labetalol, sotalol).[62]

CONCLUSION

There is no strong requirement in API Pharma Industry for marketing single isomers. There is no requirement from any regulatory authorities for marketing single isomers. However, to reduce the risk of distomer in our body, the pharmaceutical industries are looking for the development of optically pure enantiomers as chiral molecules are huge business for the pharmaceutical industry. A distomer is the enantiomer of a chiral compound that is the less potent for a particular action. It also includes the possibility of other undesired effect or side effect of the distomer.

In this direction, the increasing availability of single-enantiomer drugs promises to offer clinicians with safer, better-tolerated, and more efficacious medications for treating patients. The enantiomers of drugs often behave differently from each other in bioenvironment and the two enantiomers of a racemate can differ in their pharmacokinetic /pharmacodynamic and efficacy/ safety profiles. Pharmacokinetics and pharmacodynamics of chiral drugs with particular reference to bioequivalence determination should be further investigated. Continuous re-evaluation should enable reintroduction of old racemates as single enantiomer products with cleaner pharmacological profiles.

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