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Review article

Drug chirality & its clinical significance evident, future for the development/separation of single enantiomer drug from racemates- The chiral switch.

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Abstract

This review describes the importance and commercial potency of chiral switching of some compounds and their utility. Chiral drugs are made up of molecule with the same chemical structure, but different three-dimensional arrangements. Modern manufacturing has enabled the development of products containing a single molecular arrangement. The development of this single enantiomer from chiral drugs is known as chiral switching**.** Enantiomer of the same drug can have different pharmacodynamic and pharmacokinetic properties. Over the decade the drug chirality, particularly the use of single enantiomer *versus* racemic mixtures, has become an area of considerable interest as a result of advances in the chemical technologies associated with the synthesis, separation and analysis of the individual enantiomers present in a racemates.

In addition to new chemical entities a number of "old" racemates have been re-evaluated as potential single enantiomer products with the possibility for an improved therapeutic profile. However, not all these re-evaluations have resulted in the expected therapeutic benefits and unpredicted adverse reactions have resulted. Recently drug companies are increasingly using chiral switching as a marketing strategy. But, before prescribers switch to single enantiomer drugs they should look for evidence from well-conducted clinical trials that show the chiral switch is cost-effective and improves the outcomes for patients rather than patents.

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Racemate, Chiral drugs, unichiral, Chiral switch

Introduction

Stereoisomers are molecules with one or more "chiral" centre that allow the possibility of forms with the same chemical formula but differing spatial arrangements. Enantiomers are a type of stereoisomer in which the molecules have two non-superimposable mirror image forms. As a hand fits into a glove, only the right or left handed enantiomer may fit a molecular receptor at a drug's desired site of action. A compound containing an equal proportion of each enantiomer is called a racemic mixture. Natural compounds are often single enantiomers (levothyroxine, levodopa, L noradernaline). In contrast, many commercially synthesize drugs are racemic mix (adrenaline, warfarin, fluoxetine, omerprazole). Recent studies with various single enantiomer proved that fewer adverse effects, less doses, many fold more potent therapeutically than its racemates. Over the last ten to fifteen year single enantiomers versus racemic mixtures has become an area of considerable interest as a result of advances in the chemical technologies associated with the synthesis, separation & analysis of the individual enantiomers present in a racemates[1-9]. The chiral switch – in principle, any of the following properties could render single enantiomers preferable due to less complex, more selective pharmacodynamic profile, reduced potential for an improved therapeutical index, less complex pharmacokinetic profile, reduced potential for complex drug interactions & less complex relationship between plasma concentration and effect[10]. In addition to new chemical entities a number old racemates have been re-evaluated as potential single enantiomer products with the possibility for an improved therapeutic profile[11] (thalidomide, citalpram, penicillamine, racemic dopa). Hopefully such re-evaluation will provide agents with a cleaner pharmacological profile, improved safety and efficacy and ultimately therapeutic benefits in addition to commercial advantages.

Advantages of chiral switch[12]

- 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 bio inversion.
- 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.

Chirality- future way of treatment

Many pharmaceutical compounds are marketed as racemates. Some of them need to be used as racemates for optimum activity. (Labetalol & Nebivolol). Many racemates need to be separated into single enantiomers or chirally pure components prefixed as R or S enantiomers.

Drug candidates in which one enantiomer is "active" referred to as "eutomer" and other enantiomer is "inactive" referred as "distomer"; example S-Atenolol β blocking property resides in its S-form, Levocetrizine has antihistaminic profile, while dextro citrizine being essentially inactive; levofloxacin- antibacterial activity resides in the S enantiomer only.

Examples where one isomer is more potent than other are (R, R) methylphenidate approximately ten fold more potent than (S, S)-Methylphendate and many examples from literature indicates where enantiomers have entirely different therapeutic possibilities R-Fluoxetine is useful for

depression while S-Fluoxetine is envisaged for migraine treatment; S-propranolol has β blocking and membrane stabilizing property, its counterpart, R-propranolol, has membrane stabilizing and spermicidal properties and may be useful in hyperthyroidism.

Chiral switch has been proposed to be mean of obtaining safer alternatives to existing racemates. Switching from existing racemates to one of its isomers has provided safer alternatives to drugs ranging from antihistamines like citrizine to anaesthetics like ketamine. Some recent chiral switches have yielded safer/ or more effective alternatives to the existing racemates.

Tab 1. Commercially available some Unichiral drugs

Some of Unichiral drugs have more potent than its racemates	
Levosalbutamol	S-Atenolol
S-Ketamine	S-Metoprolol
Levobupivacaine	S-Omerprazole
S-Zopiclone	S-Pantoprazole
Levocetrizine	R-Ondansetron
S-Amlodipine	R-Fluoxetine

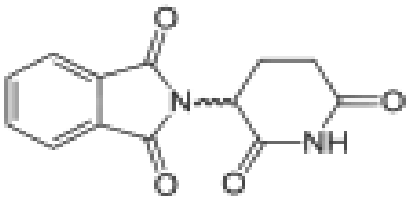
Toxicology

The toxicological properties in a pair of enantiomers can be identical or entirely different. They can reside in the pharmacologically active enantiomer or in the inactive one. Some following drugs are marketed as single enantiomer solely because their toxicities reside almost in one of their two enantiomers[13-17].

Thalidomide

Thalidomide was prescribed to pregnant women to counter morning sickness, led to a tragedy in the 1960's in Europe; studies on the drug later suggested that teratogenicity caused by the S-enantiomer and that the R-enantiomer contained the desired therapeutic activity.

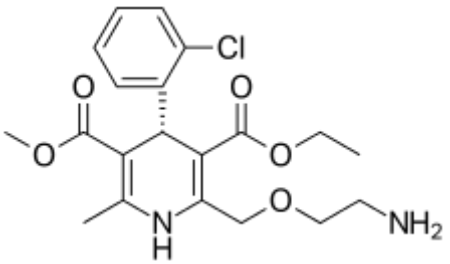
Thalidomide and it analogs have recently been a subject of numerous studies. In 1998 the USFDA approved for use in treating leprosy symptoms & studies indicate some promising results for use in treating symptoms associated with AIDS, behclet disease, Lupus, rheumatoid arthritis inflammatory bowel disease etc[18] .



Thalidomide

Dopa

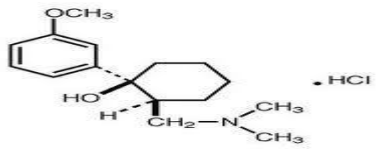
Dopa or dihydroxy-3,4 phenylalanine is a precursor of dopamine that is effective in the treatment of Parkinson disease. Dopa was used under racemic form: d,l- dopa, but owing to the grave toxicity (agranulocytosis) of d-isomer, therefore, only levorotary form called L-Dopa is actually used in therapeutics[19,20].



Levodopa

Tetramisole

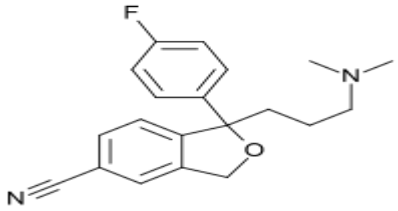
Tetramisole is a nematocide, first used under racemic form. Because of numerous side-effects (vertigo, headache, vomiting, abdominal pain) mainly due to d-isomer, therefore, only l-isomer called levamisole is now used in medicine[21-22].



Tetramisole

Citalopram

In the case of citalopram, the S-enantiomer is primarily responsible for antagonism of serotonin reuptake while the R-enantiomer is 30 fold less potent. S-citalopram appears to have advantages over racemic citalopram and is a good example of the potential benefits of single enantiomer drugs[23].



Citalopram

Chirality in drug delivery formulation[24]

Chirality influences drug delivery because a single enantiomer or a non-racemic blend may have improved solubility, dissolution, and stability. In addition, many available pharmaceutical excipients (cellulose) either naturally occur as single enantiomers or are derivatives of the latter chiral molecules. More attention has been drawn to the influence of chiral excipients on the modification of in vitro release and in vivo disposition of chiral drugs. Chiral excipients have been widely used in pharmaceutical dosage forms. Different chiral excipients and their pharmaceutical applications are given in the Tab 2

Different properties of R and S enantiomers of racemate drugs

Many drugs used in clinical practice are chiral and are administrated as racemate, a 50:50 mixture of complementary enantiomers, but unichiral drugs are increasingly available and promises to provide clinicians with safer, better-tolerated and more efficacious medications for treating patients. It is therefore important for the clinicians to be familiar with the important properties (Tab 3) of individual enantiomers of the racemates used in clinical practice.

Chirality and NSAIDs

The chiral NSAIDs are one of the most studied classes for chirality, includes the Ibuprofen, Ketoprofen, Fenoprofen, Tiaprofenic acid, Carprofen, Pirprofen, Benoxaprofen, Naproxen, Etodolac, and Ketorolac possessing the S configuration that almost exclusively possesses the ability to inhibit prostaglandin activity. Of the chiral NSAIDs, all are traditionally administrated in racemic form except Naproxen, which is given as the single S enantiomer.

Dexibuprofen [S (+) Ibuprofen]

Racemic ibuprofen, which contains equal quantities of R(-) ibuprofen and S(+) ibuprofen, has been used as an anti-inflammatory and analgesic agent for over 30 years. R-Ibuprofen and Dexibuprofen differ in their physicochemical, pharmacological and metabolic properties. S-Ibuprofen or dexibuprofen is the pharmacologically active enantiomer of racemic ibuprofen. Dexibuprofen inhibits both COX-1 and COX-2 enzymes[25].

Tab 2. Shows the chirality role in drug delivery systems

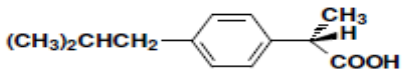
Excipients	Major Applications
Cellulose derivatives	
Carboxymethylcellulose calcium	Suspending agent, stabilizer, coating agent
Ethylcellulose	Binder, coating material viscosity enhancer
Hydroxyethyl cellulose	Viscosity builder, binder, dissolution modifier
Hydropropyl cellulose	Viscosity builder, binder, stabilizer
Hydroxylpropylmethyl cellulose phthalate	Enteric coating agent, taste masking
Microcrystalline cellulose	Binder, diluents, stabilizer, disintegrant
Cellulose acetate	Dissolution modifier film coating agent
Cellulose acetate butyrate	Dissolution modifier film coating agent
Cellulose acetate phthalate	Dissolution modifier film coating agent
Starch, sugar and derivatives	
Alginic acid	Binder, dis-integrant, viscosity enhancer
Carrageenan	sustained release matrix, suspending agent
Cyclodextrins	
β-cyclodextrin	Complexing agent, dissolution enhancer
Hydroxypropyl β-cyclodextrin heptakis	Complexing agent, dissolution enhancer
Acids	
Ascorbic acid	Anti-oxidant
Lactic acid	Acidifying agent
Aminoacids , peptides and derivatives	
Arginine	Stabilizer
Aspartame	Sweeter
Lysine	Stabilizer
Protamine	Stabilizer
Fats, oils,essential oils	
d-limonen	Flavor,
l-menthol	Flavor,
α-tocopherol	Antioxidant

Tab 3. Important properties of R and S enantiomers of the commercially available racemates.

Racemate	Properties of R-enantiomer	Properties of S- enantiomer	Unichiral drugs approved for use
Amlodipine	Inactive as a Ca^{2+} channel blocker but may not be completely inert. Mainly responsible for blunting of precapillary postural vasoconstrictor reflex and for other local changes responsible for peripheral oedema due to racemic amlodipine[39]	Only vasoactive enantiomer of amlodipine longer plasma $t_{1/2.}$ Lesser intersubject variability in the clearance. Negligible incidence of peripheral oedema than the racemate[39].	S-Amlodipine
Atenolol	Relatively stronger activity in blocking β -2 receptors than beta-1 receptors. Responsible for loss of cardioselectivity at higher doses of racemate[40].	Predominantly responsible for cardiac beta blocking activity[41].	S-Atenolol
Bupivacaine	Cardiotoxic effects and toxic effects on the CNS[42].	Less cardiotoxic effects and less toxic effects on the CNS in comparison with both dextrobupivacaine and Bupivacaine itself[42]. Wide safety margin than the racemate[43].	Levobupivacaine
Cetirizine	Smaller volume of distribution, small even than that of Cetirizine-confers improved safety because of low hemato-encephalic barrier passage and low cerebral receptor binding[44-46]. Enhance peripheral receptor binding and improved overall selectivity specific to the H_1 receptor than the racemate[47]. Pharmacokinetic studies indicate improved safety profile.	Inactive nature (larger-scale comparative studies are however, warranted to address the issue)	Levoceirizine

Ketamine	Inhibits the elimination of S-Ketamine in the racemate[48].	Two – three times more potent racemic ketamine[49,50]. Eliminated more rapidly as a single enantiomer than as a component of the racemate. Incidence of psychotomimetic phenomena is negligibly less with S-ketamine in comparison to racemic ketamine[51].	Esketamine
Metoprolol	Relatively stronger activity in blocking β -2 receptor than β-1 receptors[40]. Responsible for loss of cardioselectivity at higher doses of racemate. Clearance is slower than S-metoprolol in poor metabolizers, resulting in higher concentrations of the non-selective R-enentiomer if a racemate is administered[52-53].	Predominally responsible for cardiac β blocking activity[41]. Ensures cardioselectivity even in poor metabolizers as concentrations of only the β-1 selective component would be increased. Avoids some harmful drug-interactions with some drugs like paroxetine,cimetidine, ciprofloxacin and verapamil, which selectively increase the concentrations of non-selective R-metoprolol[54-57].	S-Metoprolol
Omeperazole	Exhibits greater variability than S-isomer in poor versus extensive metabolizers of CYP2C19 substrates. More dependent on CYP2C19. This results in the less active R-enantiomer achieving higher concentrations in poor metabolizers, which may in the long term cause adverse effects like gastric carcinoids and enterochromaffin- like cell hyperplasia[58-59].	Could be metabolized by alternative pathways lie CYP3A4 and sulfotransferases.Clinical more effective than the racemate[60-62].	Esomeprazole
Ondansetron	No QTc prolongation[63]. Less cardiotoxic than either S-Ondansetron[64] or racemic ondansetron. More potent than the S isomer.	Cause QTc prolongation[63-64]	R-Ondansetron
Pantoprazole	Exhibits greater variability than their S isomers in poor versus extensive metabolizers of CYP2C19 substrates.	Could be metabolized by alternative pathways lie CYP3A4 and sulfotransferases.Clinical more	S-Pantoprazole

	More dependent on CYP2C19. This results in the less active R-enantiomer achieving higher concentrations in poor metabolisers, which may in the long term cause adverse effects like gastric carcinoids and enterochromaffin- like cell hyperplasia[58-59].	effective than the racemate[59-61].	
Salbutamol	Bronchodilator activity[65]	Inactive as bronchodilator[65] but not completely inert and can induce airway hyper-reactivity, eventually contributing to increased morbidity and mortality in patients with asthma[66-67].	Levosalbutamol
Zopiclone	More propensity for anticholinergic effects[68]	More active than R-zopiclone at the benzodiazepine receptor complex and is responsible for most of the hypnotic activity of the racemic compound[68-69]. Shorter duration of action, which could minimize or prevent residual hangover effects[70].	Eszopiclone



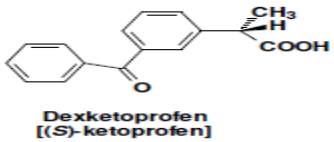
Dexibuprofen [(*S*)-ibuprofen]

Dexibrofen is the S(+)(dextrorotatory)-enantiomer of ibuprofen and accounts for virtually all pharmacodynamic activities of the racemic compound[25,26]. In vitro, dexibuprofen is over 100 times as potent as the R-enantiomer as an inhibitor of prostaglandin biosynthesis. In the therapy, potential advantages of Dexibuprofen over racemic ibuprofen included lesser toxicity, greater clinical efficacy and or less variability in therapeutic effects achieved, and easier dose optimization, all at half the dose of ibuprofen. Several clinical trials and post marketing surveillance studies have been performed to elucidate the efficacy and safety of Dexibuprofen. Many clinical studies have evaluated the efficacy and tolerability of Dexibuprofen. The findings from these studies demonstrate that Dexibuprofen is effective and very well tolerated in patients with osteoarthritis and dental pain[27-30]. These effects are comparable to Diclofenac, Celecoxib and double dose of racemic Ibuprofen.

Dexketoprofen[S (+) Ketoprofen]

Most or all COX inhibitory activity of Ketoprofen is attributed to the S (+)-enantiomer (Dexketoprofen). It has been demonstrated to be an inhibitor of COX-1 and COX-2 activities in experimental animals and humans[31]. The R-enantiomer is 30 to 5000 times less potent as an inhibitor of COX-1 and about 100 times less potent as an inhibitor of COX-2[32]. In addition, S-

Ketoprofen has been found to be significantly less ulcerogenic compared to the racemic ketoprofen[33].

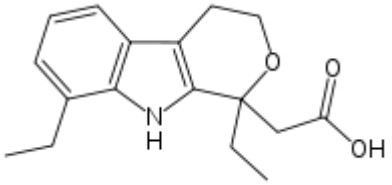


Dexketoprofen
[(*S*)-ketoprofen]

S (+) Etodolac

Etodolac has been shown to inhibit formation of prostaglandin endoperoxides from arachidonic acid. Etodolac is more selective for induced COX-2 (inflammation) over COX-1(cytoprotective)[34]. Etodolac possesses a more favourable therapeutic index between anti-inflammatory effects and gastric irritation as compared to other NSAIDs[35-37].

It is the S-enantiomer of Etodolac that possesses almost all of the anti-inflammatory activity while R-Etodolac is almost inactive. S-Etodolac is 2.6 times more potent than the racemate and 100 times more potent than R-enantiomer[38].



Etodolac

Chirality and Cardiovascular drugs

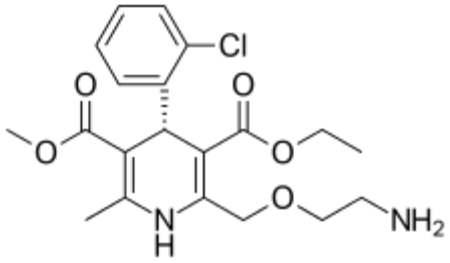
Several cardiovascular drugs in which pharmacokinetic/ pharmacodynamic properties of the enantiomers are distinctly different, therefore Unichiral drug development is important for successful development and clinical use of CVS drugs and their therapeutic applications. Chirality has therefore been visualized as an important factor in cardiovascular research. (Tab 4)

Tab 4. Some of unichiral CVS products

Some of chirally pure CVS products	
β- adrenergic antagonists	S (-) Metoprolol, S (-) Atenolol
Ca^{2+} channel blockers	S (-) Amlodipine, Diltiazem
Antiarrhythmic drugs	Qunindine
ACE inhibitor	Captopril, Enalapril, Rampril, Lisinopril, Benazepril, Fosinopril, Perindrpril
Statins	Atorvastatin, Simvastatin, Pravastatin, Lovastatin,Rosuvastatin
Anti-Platelet	Clopidogrel
Centrally acting antihypertensive	Methyldopa

S-Amlodipine

Amlodipine is an outstanding among other calcium channel blockers has pharmacokinetic and pharmacodynamic profile. Amlodipine is a racemic mixture, composed of S and R enantiomers in equal proportion, but the calcium channel blocking activity is confined only to S-Amlodipine; R-Amlopidine being 1000 fold less active than its S-counterpart. R-Amlopidine is more rapidly eliminated from plasma than S-Amlodipine, with mean terminal half-lives of 34.9 hours (R) and 49.6 hours(S). Thus the attribute of long duration of action of Amlodipine is dependent on its S-enantiomer[71-72].



S-Amlodipine

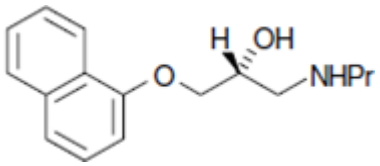
S-Metoprolol[73-74]

Metoprolol is a widely used cardioselective β blocker. It is a racemic mixture of R and S isomers. The β_1 blocking activity (cardioselectivity) of Metoprolol residues in S-isomer while R-isomer exhibits β_2 blocking activity. The needless administration of the non β_1 blocking R-enantiomer that makes up 50% of racemate actually puts the patient at a increase risk of side effects, drug interactions and loss of cardioselectivity with up-titration of dosing. The cardiac β blocking activity of S-Metoprolol is greater than R-isomer with S: R activity ratio 33:1. The β_1 receptor affinity of the S form is about 500 times greater than that of R-form.

S (–) propranolol[75]

Propranolol is a non-selective beta blocker, that is, it blocks the action of epinephrine and norepinephrine on both β1- and β2-adrenergic receptors. It has little intrinsic sympathomimetic activity (ISA) but has strong membrane stabilizing activity (only at high blood concentrations, e.g. overdosage). Research has also shown that propranolol has inhibitory effects on the norepinephrine transporter and/or stimulates norepinephrine release (present experiments have shown that the concentration of norepinephrine is increased in the synapse but do not have the ability to discern which effect is taking place). Since propranolol blocks β-adrenoceptors, the increase in synaptic norepinephrine only results in α-adrenergic activation, with the α1-adrenoceptor being particularly important for effects observed in animal models. Therefore, some have suggested that it be looked upon as an indirect α1 agonist as well as a β antagonist. Probably owing to the effect at the α1-adrenoceptor, the racemic and the individual enantiomers of propranolol have been shown to substitute for cocaine in rats, with the most potent enantiomer being S-(–)-propranolol. In addition, some evidence suggests that propranolol may function as a partial agonist at one or more serotonin receptors (possibly 5-HT1B).

Both enantiomers of the drug have a local anaesthetic (topical) effect, which is normally mediated by blockade of voltage-gated sodium channels. Few studies have demonstrated propranolol's ability to block cardiac, neuronal, and skeletal voltage-gated sodium channels, accounting for its known "membrane stabilizing effect" and anti-arrhythmic and other central nervous system effects.



Propranolol

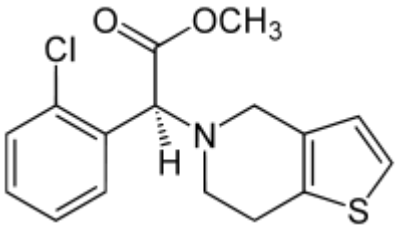
On the other hand, without changing the protein binding, high po doses generate zero-order kinetics and more profoundly depress (*S*)-(−)-propranolol metabolism, producing stereoselective differences in the rates of elimination of the enantiomers. Finally, high iv doses, generating zero-order kinetics, 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.

S-Atenolol[77]

It is active β1 blocker component only, half the racemate dose, and lesser side effects on switch-over from racemate to entomer. The pharmacokinetics of R- and S Atenolol after IV administration of racemic Atenolol were studied in 3, 12 and 24 month old rats and 3 month old rats with renal failure induced by uranyl nitrate. In all age groups, the area under the plasma concentration-time curves is higher for R than S atenolol; volume of distribution, total clearance are lower for r-atenolol than for S Atenolol, but the differences are small. The total amount of the both enantiomers excreted in the urine is decreased in the rats with renal failure. Therefore there is no stereoselective effect of treatment of the rats with urany nitrate.

Clopidogrel[78-83]

Clopidogrel is a potent antiaggregant and antithrombotic drug; it demonstrated superior efficacy versus aspirin in preventing thrombotic events (myocardial infarction, stroke and vascular death) in high risk patients. Clopidogrel has an absolute S configuration at carbon 7. The corresponding R enantiomer is totally devoid of antiaggregating activity, thus indicating the importance of the configuration of this asymmetric carbon for the biological activity. In experiments, incubation of clopidogrel with rat hepatic microsomes was found to generate 2-oxo-clopidogrel, through a CYP450-dependent pathway of metabolism. Similar results were obtained using human liver microsomes. Despite being not active in vitro, 2-oxo-clopidogrel can demonstrate an antiaggregating activity ex vivo, thus indicating that the formation of the active metabolite of clopidogrel occurred downstream to the formation of 2-oxo-clopidogrel. The structure of active metabolite of another thienopyridine, CS-747, was reported. In another report, these authors indicated the precise absolute configuration to express the biological activity, since only one among the four optical isomers showed activity in inhibiting platelet aggregation.



Clopidogrel

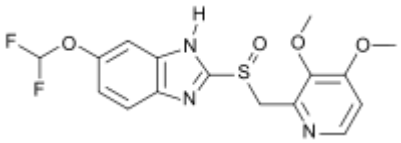
Chirally pure proton pump inhibitors

Proton Pump Inhibitors (PPIs) inhibit gastric acid secretion by inhibiting the final step of acid synthesis, the hydrogen-potassium-ATPase pump, in the parietal cell canaliculi. In the parietal cell canaliculus, PPIs get protonated to

form the active sulfenamide moiety, which is achiral. This sulfenamide molecule binds to the cysteine residues of the proton pumps and causes irreversible inhibition of the $H^+ K^+$ ATPase pump. Chemically, PPIs are substituted benzimidazole and chiral compounds, i.e. their spatial orientation is asymmetrical with a sulphur atom as the chiral centre, in most cases. These drugs are currently available as racemic mixtures of the (R) and (S) enantiomers in equal proportions. The individual isomers show variations in PK, PD properties and differences in safety, toxicity profiles and can prove to be superior to their racemic counterparts as has been demonstrated with the development of esomerprazole, S-Pantoprazole and dexrabeprazole.

S-Pantoprazole[58-59]

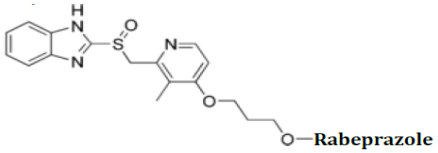
The S-isomer of Pantoprazole was found to be a better at inhibiting acid related lesions because of its stronger inhibition of acid secretion in the pylorus ligation induced ulcer and histamine induced ulcer model in rats and guinea pigs. A randomized, double blind, multicentric, parallel group, comparative clinical trial (n=369) evaluated S-Pantoprazole versus racemic Pantoprazole, demonstrated statistically significant between group difference. Absolute risk reductions for heartburn, acid regurgitation, and bloating were approx 15% on day 14and 10% on day 28.



S-Pantoprazole

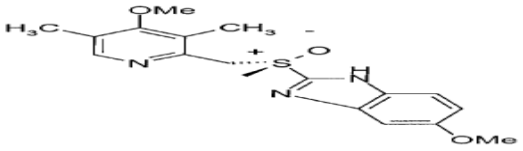
Dexrabeprazole[84]

Rabeprazole is available as a racemic mixture of two isomers, R (+) isomer and S(-) isomer in 1:1 proportion. The chirally pure dexrabeprazole, a study done on Wister rats demonstrated that R (+) Rabeprazole was more effective than S(-) Rabeprazole and racemate rabeprazole in preventing acid related gastric lesions. The dexrabeprazole group showed a higher incidence of improvement/healing of esophagitis and relief from symptoms of regurgitation as compared to the rabeprazole group.



Esomeprazole[60-62]

Omeperazole is a gastric anti-secretory proton pump inhibitor, a unichiral S (-) enantiomer form is esomerprazole based on the premise that therapeutic benefit would be achieved by less inter-individual variation, (slow versus rapid metabolizers), and that average higher plasma levels would provide higher dose efficiency in patients.

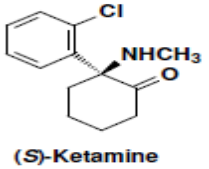


Esomeprazole

Others unichiral drugs

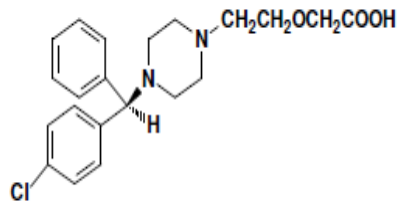
Esketamine[48-50]

(S)-Ketamine has a greater analgesic and anaesthetic potency than the *R*-enantiomer in both animals and man. Two – three times more potent racemic ketamine, eliminated more rapidly as a single enantiomer than as a component of the racemate. Incidence of psychotomimetic phenomena is negligibly less with S-ketamine in comparison to racemic ketamine.



Levocetrizine[44-47]

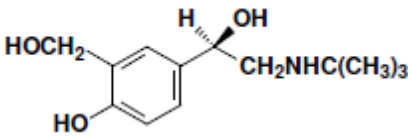
Cetirizine is a H_1-receptor antihistamine. *R*-Enantiomer of cetirizine; K_i values against H_1--receptors 3.2 and 6.3 nM for the *R*-enantiomer and racemate respectively. Clinical studies have indicated the equivalence of a 2.5 mg dose of the single enantiomer compared to 5 mg of the racemate, the *S*-enantiomer being essentially inactive.



Levocetirizine
[(*R*)-cetirizine]

Levalbuterol[85]

Racemic and (*S*)-salbutamol induce airway hyper responsiveness in sensitised animals; use of the racemate is associated with some loss of bronchodilator potency, decreased protection against bronchoprovocation and increased sensitivity to allergen challenge and bronchoconstrictor stimuli. Studies in humans have indicated that inhalation of (*R*)-salbutamol produces significantly greater bronchodilatation than the equivalent dose of the racemate.



(*R*)-Salbutamol
[levalbuterol]

FDA's Policy for the development of new stereoisomeric drugs [86-90]

USFDA recognised the growing importance of chirality in drugs and published its policy statement for the development of new stereoisomeric drugs in the year 1992.

For the product development following information should be considered.

- Appropriate manufacturing and control procedures should be used to assure stereoisomeric composition of a product, with respect to identity, strength, quality and purity. Manufacturers should notify compendia of these specifications and tests.
- Pharmacokinetic evaluations that do not use a chiral assay will be misleading if the disposition of the enantiomers is different. Therefore, techniques to quantify individual stereoisomer in pharmacokinetics sample should be available early. If the pharmacokinetics of the enantiomers are demonstrated to be the some or to exist as fixed ratio in the target population an achiral assay or an assay that monitors one of the enantiomers may be used, subsequently.

Policy in general

The stereoisomeric composition of a drug with a chiral centre should be known and the quantitative isomeric composition of the material used in pharmacologic, toxicologic, and clinical studies known. Specifications for the final product should assure identify; strength, quality, and purity from a stereochemical viewpoint.
Pharmacokinetic evaluation should be done unless it proves particularly difficult; the main pharmacologic activities of the isomers should be compared in vitro systems, in animals and or in humans. Toxicological study should be carried of the isomers. If, however, there are toxic findings other than those that are natural extensions of the pharmacologic effects of the drug, and especially if they are unusual or occur near the effective dose in animals or near the planned human exposure, toxicologic evaluation of the individual

isomers in the study where the toxicity was detected should be undertaken. All information developed by the sponsor or available from the literature that is relevant to the chemistry, pharmacology, toxicology, or clinical actions of the stereoisomers should be included in the IND and NDA submissions.

Developing a single stereoisomer after the Racemate is studied

To develop a single stereoisomer from a mixture that has already been studied non-clinically, an abbreviated, appropriate pharmacology/toxicology evaluation could be conducted to allow the existing knowledge of the racemate available to the sponsor to be applied to the pure stereoisomer. Ongoing studies would usually include the longest repeat-dose toxicity study conducted (up to 3 months), and the reproductive toxicity segment II study in the most sensitive species, using the single enantiomer. These studies should include a positive control group consisting of the racemate. If there is no difference between the toxicological profile of the single stereoisomeric product and the racemate, no further studies would be neede. If the single enantiomer is more toxic, the explanation should be sought and the implications for human dosing considered.

Biopharmaceutical and Clinical

Where little is observed in activity and disposition of the enantiomers, racemates may be developed. In some situations, development of a single enantiomer is particularly desirable (e.g., where one enantiomer has a toxic or undesirable pharmacological effect and the other does not). A signal that should trigger further investigation of the propertied of the individual enantiomers and their active metabolites is the occurrence at clinical doses of toxicity with the racemate that is not clearly expected from the pharmacology of the drug or the occurrence of any other unexpected pharmacologic effect with the racemate. These signals might be explored in animal in animals but human testing may be essential.

It should be appreciated that toxicity or unusual pharmacologic properties might reside not in the parent isomer, but in an isomer-specific metabolite. In general, it is more important to evaluate both enantiomers clinical and consider developing only one when both enantiomers are pharmacologically active but differ significantly in potent, specificity, or maximum effect, than when one isomer is essentially inert. Where both enantiomers are fortuitously found to carry desirable but different properties, development of a mixture of the two, not necessarily the racemate, as a fixed combination might be reasonable.

If a racemate is studied, the pharmacokinetics of the two isomers should be studied in phase 1. Potential interconversion should also be examined. Based on phase 1 or 2 pharmacokinetic data in the target population, it should be possible to determine whether an achiral assay or monitoring of just one enantiomer where a fixed ratio is confirmed will be sufficient for pharmacokinetic evaluation.

If a racemate has been marketed and the sponsor wishes to develop the single enantiomer, evaluation should include determination of whether there is significant conversion to the other isomer, and whether the pharmacokinetics of the single isomer are the same as they were for that isomer as part of the racemate.

Commercial impact of chirality drugs

In an analysis of all single enantiomer drugs launched as a percentage of chiral molecules, the ratio increased from 31.6% in 1985-1988 to 89.8 % in 2001- 2004. It is estimated that sales of Unichiral drugs reached $ 200 billion in 2008. A

number of factors have contributed to the introduction and popularity of Unichiral products since 1980 and more so 1992 onwards. According to data from ORG-IMS, out of the 15 top cardiovascular molecules sold in India, seven are single enantiomers (Table 5).As a number of commercially highly successful drugs are chiral the economic significance of stereochemistry to the pharmaceutical industry is obvious. The chiral switch process provides a strategy to extend the profitable life of a pharmaceutical 'bestseller", and may result in extended patent protection and provide an advantage against generic competition.

Tab 5. Shows commercial impact of chiral drugs

Top 10 single-enantiomer products belong to billion-dollar club

BRAND NAME	GENERIC NAME	MARKETER	THERAPEUTIC AREA	2002 SALES ($ BILLIONS)
Lipitor	Atorvastatin calcium	Pfizer	Cardiovascular	$8.0
Zocor	Simvastatin	Merck	Cardiovascular	5.6
Pravachol, Mevalotin	Pravastatin sodium	Bristol-Myers Squibb and Sankyo	Cardiovascular	4.0
Paxil	Paroxetine hydrochloride	GlaxoSmithKline	Central nervous system	3.1
Plavix	Clopidogrel bisulfate	Sanofi Synthelabo and Bristol-Myers Squibb	Hematology	2.9
Zoloft	Sertraline hydrochloride	Pfizer	Central nervous system	2.7
Advair, Seretide	Fluticasone propionate and salmeterol xinafoate	GlaxoSmithKline	Respiratory	2.4
Nexium	Esomeprazole magnesium	AstraZeneca	Gastrointestinal	2.0
Augmentin	Amoxicillin and potassium clavulanate	GlaxoSmithKline	Antibiotic	1.8
Diovan	Valsartan	Novartis	Cardiovascular	1.7
TOTAL				$34.2

Conclusion

The increasing availability of a single enantiomer drugs promises pharmaceutics scientists to formulate safer, better tolerated, and more efficacious medications for treating patients. Therefore, the development of new chiral separation techniques is and will be a topic subject in academic research as well as in industrial advance. In addition to new chemical entities a number of "old" racemates have been re-evaluated as potential single enantiomer products with the possibility for an improved therapeutic profile. However, not all these re-evaluations have resulted in the expected therapeutic benefits and unpredicted adverse reactions have resulted. It is also important to give more information about chiral drugs especially racemic form to healthcare professionals in order to help them for finding an optimal treatment and a right therapeutic control.

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