Review Article

Three-dimensional Biopharmaceutics and Clinical Considerations of Drugs for Safety and Efficacy: A Review Study

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ABSTRACT

Background: Several drugs today are described with their molecular structures showcasing symmetrical, dissymmetrical, or asymmetrical configurations. Some drugs showing chirality are racemic or pure enantiomeric forms for clinical practice.

Objectives: This review outlines the mechanistic protocols of kinetic disposition of enantiomers alongside their discriminatory reactions with receptors based on chemical, structural, and conformational orientations that form the objective of this review.

Methods: Articles published from 2001 to 2023 were sorted and reviewed manually from Google Scholar and other scientific databases (e.g. PubMed, Medline, Web of Science, Embase, and Scopus) using words and phrases such as "enantiomer", "racemates", "biopharmaceutics", "enantioselectivity", "three-dimensional drugs", and "molecular inversion".

Results: There is evidence that chirality exists in biological systems as macromolecules (e.g. lipids, amino acids, carbohydrates, phospholipids, nucleosides, glycoproteins, glycolipids, etc.) in the human body's layout. Stereochemistry is gaining greater attention in biopharmaceutics and pharmacotherapy as clinicians are challenged to make informed decisions regarding using either single-enantiomer or racemic drugs. The stereocenter's vivid configurational focus and three-dimensional reactivity are well amplified by the concept of enantioselectivity exhibiting pharmacokinetic and pharmacodynamic implications. Some clinical-toxicological effects have been linked to the other enantiomer in pharmacotherapy. Using racemates continues despite the enantiomeric pharmacokinetic and pharmacodynamic differences of the isomers.

Conclusion: The dramatic transformations of enantiomers alongside their in vitro and in vivo behaviors (i.e. molecular inversion and interconvertibility) are intriguing. The additional protocols of scientific resolution and purification of racemates in drug development may be the spark of more refined three-dimensional biopharmaceutics.

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Introduction

Chirality is currently a top-class focus for academic research and pharmaceutical development. The stereochemistry and basic knowledge of its contribution to drug disposition and activity in biological systems are fundamental to producing clinical outcomes [1, 2]. Clinicians rely on the nature of drugs as a single enantiomer entity or a racemate to make informed decisions during prescribing. Several drugs on the shelves today are mixtures of enantiomers. Biopharmaceutics relates to the absorption of drugs, which is influenced by their physicochemical properties and the formulation alongside the route of drug administration [3]. Cell membranes are selective biological barriers that affect the passage of drugs from the extracellular space into the cell. Absorption protocols may favor either or both enantiomers based on their spatial arrangement. In other words, the spatial arrangement influences the biomembrane permeability. Enantioselectivity may not happen in the passive absorption of enantiomers but may be an issue when the transport-mediated process is involved [4].

Several single-enantiomer formulations have been reported to have greater selectivity for biological targets. They have also demonstrated better pharmacokinetic profiles alongside therapeutic indices than racemic formulations [5]. Literature has not explained in detail, for many drugs, the mechanistic layout of individual disposition of an enantiomer with respect to its mirror image vis-à-vis transmembrane movements. The possibility of interconvertibility from one enantiomer to the other (i.e. self or enzymatic), in vivo transformations, and their enzyme reactivities before the eventual clinical outcome. The pharmacokinetic disposition and pharmacodynamic outcome of administered drugs as pure enantiomeric molecules or as a racemic mixture are the subjects of this review. Published works and reports on drugs and the in vitro and in vivo dispositions were searched in Google Scholar and PubMed from 2000 to 2022. Keywords used in the broad search include stereochemistry, enantiomers, isomers, racemates, drugs, receptors, stereoselectivity, and stereospecificity.

Materials and Methods

Resources and data analysis

This study of drugs was conducted in Nigeria within 3 months (May to July 2023), exhibiting optical activity, their presentation as drug products for pharmacotherapy, enantiomeric disposition, and interaction with biomembranes and receptors based on the considerations of their conformational orientations.

The databases containing peer-reviewed articles were consulted (including PubMed, Medline, Web of Science, Embase, and Scopus) and collated. This information formed the main data source for the study. Keywords such as “enantiomer”, “racemates”, “biopharmaceutics”, “enantioselectivity”, “three-dimensional drugs”, and “molecular inversion”. The inclusion criteria for the articles in the study were peer-reviewed articles written in English, while articles of older status containing duplicated information with another were excluded.

Results

The total number of articles consulted was 93, out of which 75 were relevant to the purpose of this review, as shown in Figure 1.

The distribution of the articles collated is presented in Figure 1. Similarly, the excluded articles were 19.4%.

Discussion

Macromolecules, receptors, and biological environment

The biological system is a network of chiral molecules creating an atmosphere that recognizes the salient difference between the enantiomers of a drug employed in pharmacotherapy [6, 7]. Ordinarily, the enantiomers of a drug have the same physicochemical properties concerning their identity in an achiral system [8]. It suffices to state that the nature of biological systems creates in vivo disparaging behavior. The human olfactory sensory organs are chiral, so the enantiomers R and S isomers of carvone smell differently. The R isomer of carvone smells like spearmint leaves, while the S isomer smells like caraway seeds [9].

The body has numerous homochiral compounds (e.g. levorotatory amino acids). The macromolecules in the body behave as amazingly chiral selectors. They interact with each racemic drug differently and metabolize each enantiomer via a separate pathway, resulting in different pharmacological activities [10].

The fact that enantiomers have the same chemical connectivity of atoms but display marked differences in the observed pharmacokinetics and drug effects is intriguing. Therefore, in the chemical synthesis of chiral drugs, more attention is paid to enantio-separation and purifica-

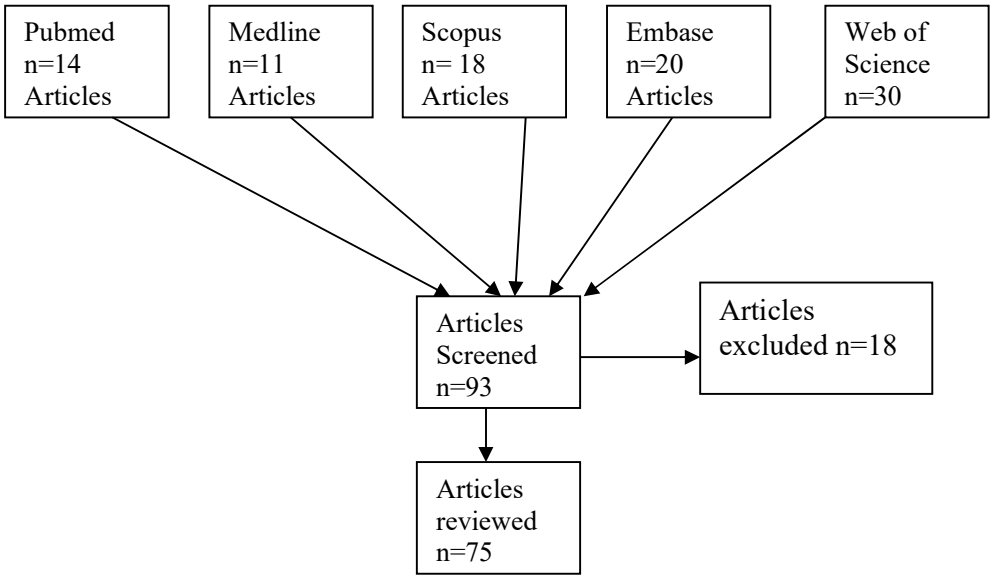

Figure 1. Flow chart of the selected articles

tion [11-13]. The enantiomers of chiral drugs differ in their interactions with enzymes, proteins, receptors, and chiral catalysts. These differences in interactions lead to the observed pharmacokinetics and, in some cases, toxicities. In light of this observation, Rouhi [14] and Pedersen-Bjergaard [15] proposed the three-point drug versus receptor interaction for chiral ligands [14, 15]. In one case, an enantiomer is biologically active; in the other, it is not. This issue is explained by the fact that substituents on the active enantiomer drug require proper alignment to the receptor's binding site [16, 17]. It is the fitting alignment that produces the observed biological effect.

Furthermore, one enantiomer can do this while the other inactive enantiomer cannot due to hitches caused by the optical configuration. Similarly, a particular enantiomer complementary to the receptor site can align within a receptor site. In most cases with biochemical reactions, one stereoisomeric product is formed [18, 19]. The stereochemistry of enzyme-catalyzed reactions, therefore, conforms with the reactive enantiomer.

Proteins are filed into specific 3-dimensional shapes related to the particular recognition of organic molecules they bind. The sensitivity of enzymes to their ligands or substrate stereochemistry postulates a world of drug disposition and effect scenarios. Enzymes, therefore, show discriminatory potentials between enantiomeric substrates or products. Stereospecific/stereoselective enzymes form the basis for pharmacokinetic variations in drugs, especially when administered as racemates.

Chiral bioactive with or without chiral centers

Many molecules with optical activities have been explored for their biological activities. Interestingly, many have a stereogenic carbon with four attachments describing their mirror image identities. Other molecules do not have chiral centers but possess enantiomerism characteristics. Carbon is the major atom that can act as an asymmetric center. Other atoms capable of stereogenic properties are sulfur, phosphorus, and nitrogen. These are found in many therapeutic agents and can sometimes form chiral molecules, as in omeprazole, cyclophosphamide, and methaqualone [20].

Some molecules show optical activity but are achiral. Amines with three different substituents around the nitrogen carrying a lone pair of electrons demonstrate some asymmetric properties. Similarly, sulfur atoms with the influence of the lone pair electrons and different substituents also furnish stereoisomers [21]. The focus about which the activity occurs is called a stereogenic point. It is called a point and not necessarily an atom compared with a chiral atom C, which is in most chiral centers. While chiral carbons are SP^3 hybridized, having essentially single bonds, stereocentres are SP^2 with lone pairs of electrons or double bonds, suggesting that the asymmetric C is not the entire essence of chirality.

Allenes are molecules with C=C=C unit with SP hybridization. These do not possess chiral centers but have optical activity. Allenes are cumulated dienes, unlike other molecules with consecutive (not conjugated)

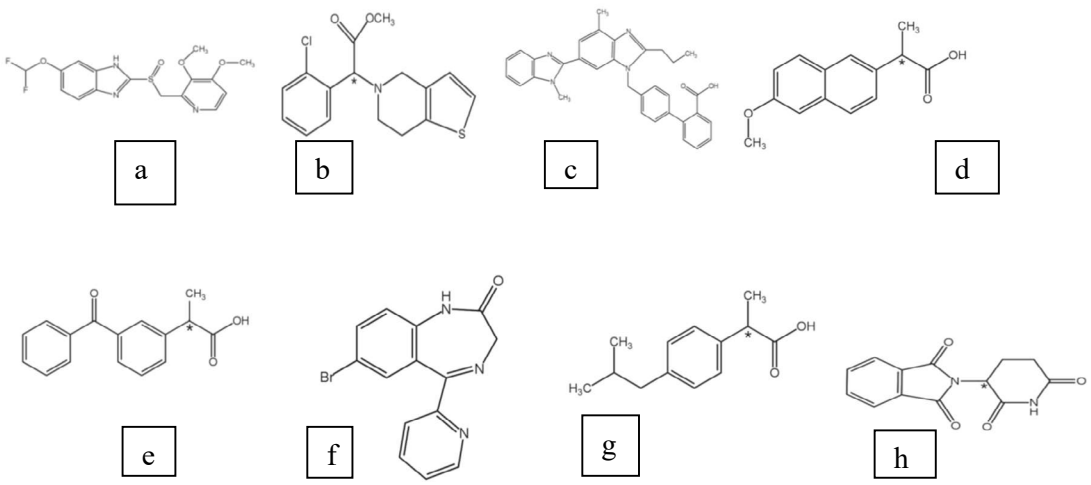

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Figure 2. Drugs with chiral and achiral centers possessing optical activity

Note: Stereocenters are marked with: a) Pantoprazole, b) Clopidogrel, c) Telmisartan, d) Naproxen, e) Ketoprofen, f) Bromazepam, g) Ibuprofen, h) Thalidomide.

double bonds. Since the two pi bonds of allenes are at right angles, the substituents are also configured at 90 °C. Allene has two mirror planes, though they are achiral. Examples of molecules in this category are interesting intermediates and synthetically valuable targets. Over 150 natural products are known to have an allene or cumulene fragment.

Another interesting group of molecules is the biphenyl compounds. The staggered conformation of biphenyl compounds is also observed to have optical activity, though no asymmetric point is observable. Substituted biphenyls show optical isomerism when substituents in the 2-positions are large enough to prevent rotation about the linkage bond joining the two benzene rings. For example, biphenyl-2,2'-sulphonic acid exists in two forms. Biphenyl compounds contain a chiral axis (not a stereo center or a plane). The mirror images here are described to have atropisomerism and are referred to as atropisomers. Examples of biphenyl drugs are found in the ARB (i.e. telmisartan, valsartan) [22]. These molecules have highly strained conformation, so one enantiomer cannot convert to the other, as observed in SP^3 or stereocenters. Figure 2 shows some examples of drugs showing chiral and achiral centers resonating optical activity.

Some drugs are marketed as a pure enantiomer. Enantiomeric excess (EE) measures the degree of purity of a chiral sample when both enantiomers are available in unequal amounts. Usually, the enantiomers are present in equal amounts, which is termed a racemic sample. EE reflects the degree to which a sample contains an enantiomer in excess over the other. A racemic mixture presents an EE of 0% (both enantiomers are present in a 1:1 ratio), while a pure enantiomer has an EE of 100%. If a sample contains 70% of the S isomer and 20% of the R isomer, it will have an EE of 50%. In pharmacotherapy, enantiomer ratio (ER) is also essential as drug discovery and specificity are heightened for safety and efficacy—because while one enantiomer happens to be beneficial, the other enantiomer may be highly toxic [23].

The enantiomer-related toxicity scenario, as observed with the R- and S-enantiomers of thalidomide, explains the importance of enantiomeric preference in drug design and development. The R-enantiomer of thalidomide is an effective sedative, while the S-enantiomer caused teratogenic congenital disabilities in women who took the racemic drug during pregnancy. In light of this argument, the enantiomers can safely be regarded as two drugs with different dispositions when taken by a patient. Exploring three-dimensional biopharmaceutics in drug development may drastically reduce the challenges of unexplained drug toxicities.

Biopharmaceutics and racemic presentations

Molecules with co-enantiomeric presentations used in pharmacotherapy can be divided into three main groups. The first and majority present one major bioactive enantiomer called eutomer and the other inactive or less active, referred to as distomer. The distomer may be

Table 1. Selected examples of drugs in the racemate classes

Classes of Enantiomeric Presentations				References
Class 1 (Eutomer/Distomer)	Class 2 (Bioactive Enantiomers)	Class 3 (Chiral Inversion)		
		Unidirectional	Bidirectional	
Ibuprofen	Carvedilol	Pantoprazole	Lorazepam	[19, 26]
Ketoprofen	Ketamine	Carbenicillin	Oxazepam	[19, 26]
Benxaprophenen	Methorphan	Clopidogrel	Temazepam	[19, 26]
Fenoprofen	Bupivacaine	Ketorolac	Thalidomide	[26]
Amlodipine	Paroxetine	Albendazole		[19, 26]
Propranolol		Omeprazole		[26]

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toxic or exert other desired or undesired pharmacological properties. Another group involves drugs where the two enantiomers are equally active and have the same pharmacodynamics presentation. The last racemic presentation connotes a eutomer with a distomer that could be transformed into its bioactive antipode by chiral inversion [24, 25]. Table 1 presents the classes of possible enantiomeric presentations and commonly prescribed drugs in these classes.

Enantiomeric discrimination, enantioselectivity, and optical configuration inversion

The enantiomeric orientation derived from the spatial display of atoms in drug molecules explains their interactions with macromolecules. This is derived from the mechanistic principles of stereospecificity/stereoselectivity. A stereoselective character describes molecular reaction outcomes, while stereospecificity relates to the mechanism involved in their activities. Molecular reactions can be stereospecific and stereoselective since the terms describe different aspects of the response. These protocols can describe the characteristics of drug molecules as they interact with transport proteins and enzymes. Isomeric specificity is vividly illustrated with methamphetamine and teno-methamphetamine [27].

Position emission tomography describes the specificity of drugs and their pharmacokinetic profile. However, many drugs lack enantioselectivity, as observed in some anticancer and antiviral drugs. This observation has given credence to the optical configuration theory inversion of chiral xenobiotics [28]. The enantiomeric disposition of isomers at the tight active site pockets of transmembrane proteins, as they exhibit chiral inversion, complicates the projections of pharmacokinetic/pharmacodynamic (PK/PD). Any two of the four substituents on the chiral center are exchanged by swapping positions, thereby reverting to the other isomer. This supports the concept of inversion [28]. The swapping concept, or substituent exchange, happens in one enantiomer, causing a reversion to the other. This knowledge is used in the computational modeling of non-reacting substrates to enhance reactivity.

Ligand inversion

Unidirectional enzyme-mediated inversion was previously described only with 2-arylpropionate non-steroidal anti-inflammatory drugs (NSAID), namely ibuprofen, ketoprofen, fenoprofen, benoxaprofen, etc. For this group, only S-enantiomer is active, i.e. it has an analgesic and anti-inflammatory effect. For example, S-ibuprofen is over 100-fold more potent as an inhibitor of cyclooxygenase I than (R)-ibuprofen. In the body, only inactive R-enantiomers can undergo chiral inversion by hepatic enzymes into the active S-enantiomer, which is not vice versa [29].

Bidirectional chiral inversion or racemization of an enantiomer occurs in 3-hydroxy-benzodiazepines (e.g. oxazepam, lorazepam, temazepam) and in thalidomide where either R- and S-enantiomer racemize in vitro by aqueous solution. However, in vivo, this phenomenon occurs with thalidomide but not hydroxyl-benzodiazepines. This is explained by the nature of the substituents around their chiral carbon. The chiral inversion by tautomerization of oxazepam may not proceed in vivo because each enantiomer has a different affinity for albumin. The binding affinities of the enantiomers to al-

bumin may be responsible for the nucleophilic attack by hydroxyl ions (from the aqueous medium) and thus retard the epimerization and racemization in vivo. It has also demonstrated that the in vitro chiral inversion of these benzodiazepine enantiomers was temperature-dependent and was inhibited by lowering the temperature of the aqueous solution to about 10 ˚C [27]—non-optically active molecules with optically active metabolites.

Some drugs may not have the desired optical activity as a molecule but become metabolized to optically active species. Nortriptyline is an achiral molecule and an antidepressant but forms active metabolite E-10-hydroxy nortriptyline exhibiting optical and geometric isomerism. The optically active metabolite, however, has less pronounced toxicity than the parent compound.

Stereoselective toxicities

The relative difference in absorption, bioavailability, and protein binding of the co-enantiomeric components may lead to selective toxicity. Toxicity can reside in the pharmacologically active or inactive enantiomer [30]. The inactive enantiomer may switch to the active and reinforce its activity. Therefore, drug developmental research is directed toward evaluating this phenomenon's possibility. This protocol is a procedure used to transform a known racemic drug into its single active enantiomer. This is a drug developmental design and direction for proven and overriding benefits from a pure enantiomeric entity [31].

Enantiomers on the shelf and their relative activities

NSAIDs are used for the pharmacotherapy of pains and pyrexia. They are primarily marketed as a racemic mixture with the effective enantiomer as S-isoform. This class of drugs binds and inhibits prostaglandin H2 synthase in humans. The R-enantiomer does not bind to this enzyme and usually causes harmful side effects. The R isomer in ibuprofen has been reported to isomerize to the S isomer. Ibuprofen is an inhibitor of many drug transporters [24]. The pharmacology of NSAIDs, including ibuprofen, describes their transport by sodium-coupled monocarboxylate transporter 1 (SMCT 1), a Na+- coupled transporter [32]. Some drugs on the shelf are considered for their pharmacotherapeutic profile. S-ibuprofen is more than 100-fold as potent an inhibitor of cyclooxygenase I than (R)-ibuprofen, while (R)-methadone shows a 20-fold higher affinity than its mirror image for the opioid receptor. Again, (S)-citalopram is more than 100-fold as potent a serotonin reuptake transporter inhibitor than its counterpart. The inactive enantiomer, as it is called, is not necessarily an inert molecule with no effects in vivo.

Furthermore, with bupivacaine, the cardioactivity is mainly associated with the (R)-enantiomer. The psychomimetic effects of ketamine are more exerted with the (R)-enantiomer. Interestingly, (S)-baclofen antagonizes the effects of (R)-baclofen. The beneficial effects of a drug can, therefore, reside in one enantiomer or with its paired enantiomer or possessing antagonist activity against the active enantiomer. The bioavailability of (R)-verapamil was more than twice that of its isomer. This is due to the influence of hepatic first-pass metabolism [33].

Furthermore, the volume of distribution of (R)-methadone is similarly twice that of its isomer. This is premised on the observed plasma binding and increased tissue binding. Similarly, the renal clearance of (R)-pindolol is 25% less than (S)-pindolol due to reduced renal tubular secretion. Research is progressively expatiating on the stereochemistry of pharmacotherapeutic agents to describe the mechanistic details of drug activity. These differences in clearance and volume of distribution translate into differences in half-life [34]. For example, the half-life of (S)-fluoxetine is a quarter that of (R)-fluoxetine. In addition, a prevailing disease can modify these pharmacokinetic properties in a stereoselective manner. Similarly, genetics, ethnicity, age, and concomitantly administered drugs have been reported to influence the pharmacokinetics of enantiomers [35].

Proton pump inhibitors are prodrugs with two inactive enantiomers on enzymatic activation convertible to bioactive moieties. The enantiomers of Proton pump inhibitors have equal effects on the H^+/K^+-ATPase pump [36]. The enantiomers of omeprazole are equipotent; however, they have different metabolism profiles [37]. The diversity in metabolic profiles of these drugs accounts for the variation in their drug disposition.

Presentations of racemates

There are three presentations of racemates in drug formulations based on the properties and activities of the enantiomers. The first class has racemic drugs featuring one major bioactive enantiomer while the other is not of significant activity. This class features essentially cardiovascular drugs. β-adrenergic blocking agents, calcium channel antagonists, and angiotensin-converting enzyme inhibitors have eutomers producing the major bioactivity. Table 2 gives an overview of some classes of drugs

Table 2. Common classes of drugs and current enantiomeric presentation

Class of Drug	Drug Example	Formulation Presentation	Possible Inversion	References
NSAIDs	Ibuprofen	Racemate	Yes	[38]
ARB	Valsartan	Racemate	Yes	[39]
Bronchodilators	Albuterol	Racemate/Enantiopure	Yes	[40]
CCB	Amlodipine	Racemate/Enantiopure	Yes	[41]
ACEI	Lisinopril	Racemate	Yes	[42]
Benzodiazepines	Oxazepam	Racemate	Yes	[43]
β-adrenoceptor	Propranolol Timolol	Racemate/Enantiopure	Yes	[44]
Proton pump inhibitors	Omeprazole	Racemates/Enantiopure	Yes	[45]
B-lactam antibiotics	Amoxycillin	Racemate	Yes	[46]
Macrolide antibacterial	Azithromycin	Racemate	Yes	[47]
Tricyclic antidepressants	Sertraline, Citalopram	Racemate/Enantiopure	Yes	[48]
Psychotropic drugs	Zopiclone, methylphenidate	Racemate/Enantiopure	Yes	[49]

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Abbreviations: NSAIDs: Non-steroidal anti-inflammatory drugs; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers; ACEI: Angiotensin-converting enzyme inhibitors.

and typical examples in the classes with their product presentations [38].

The levorotary-isomers of all β-blockers are responsible and more potent in blocking β-adrenoceptors than their dextrorotary-isomer. S(-)-propranolol is 100 times more active than its R(+)-antipode. Several β-blockers are still marketed in racemic forms, such as acebutolol, atenolol, alprenolol, betaxolol, carvedilol, metoprolol, labetalol, pindolol, sotalol, and so on, except timolol and penbutolol are used as single l-isomer. It is to know that for a racemic drug, each enantiomer possesses pharmacological activities that can be null, similar, different, or opposite [50].

Methadone, a central-acting analgesic with a high affinity for μ-opioid receptors, has been used to treat opiate dependence and cancer pain. Methadone is a chiral synthetic compound used in therapy under a racemic mixture. In humans, R (-)-methadone is about 50-fold more potent as an analgesic than its S (+) antipode [51]. The European Medicines Agency (EMA) and the USA Food and Drug Administration (FDA) have released guidelines concerning the choice of analytical methods for conducting bioequivalence studies for products that contain chiral compounds. The draft document by the FDA recommends the use of achiral bioanalytical methods for the racemates be measured in the cases where the enantiomers exhibit different pharmacokinetics, exhibit pronounced differences in pharmacodynamics, and if the area under curve ratio for the enantiomers is affected by changes in the rate of their relative absorption [52, 53].

The need for bioequivalence studies for different products with enantiomeric character is imperative when one enantiomer is pharmacologically active, and the other is not or has a low impute to activity. It is also essential to consider the issue of the non-convertibility of one enantiomer to the other in vivo. The individual enantiomers are measured in bioequivalence studies when the enantiomers show different pharmacokinetic or pharmacodynamic activities. This is further corroborated where the primary efficacy or safety of the actives in the product is attributed to the minor enantiomer and finally where there is a nonlinear absorption shown by a change in enantiomer concentration ratio concerning change in drug input rate, following up on any of the enantiomers [54, 55]. An alternative protocol is a stereospecific method, where possible, in scenarios where the biological activity is solely in a single enantiomer. The eutomer is rationally analyzed in preference to the other enantiomer.

There are currently many options for stereoselective analytical protocols [56-58]. Accurate and reproduc-

Table 3. Racemic products, projected enantiomers, and pharmacotherapeutic disposition

Racemic Drug	Corresponding Projected/ Preferred Single Enantiomer	Class of Drug	Pharmacological Activity	References
Ketoprofen	S-ketoprofen	Propionic monocarboxylic acid	Analgesic/Anti-inflammatory	[63]
Citalopram	S-citalopram	SSRIs/Antidepressant	SSRIs/Antidepressant	[64]
Cetirizine	Levocetirizine	Selective H1 antagonist	Antihistamine/Anti-allergy	[65]
Sertraline	1S, 4S sertraline	SSRIs/Antidepressant	SSRIs/Antidepressant	[66]
Clopidogrel	(S)-clopidogrel	Thiolactone	Antiplatelet	[67]
Salmeterol	(R)-salmeterol	B2-adrenoceptor agonist	B-agonist and bronchodilator	[68]
Simvastatin	3S, 5S simvastatin	Statins	HMG-CoA reductase inhibitor	[69]
Paroxetine	R and S paroxetine	SSRIs/Antidepressant	SSRIs/Antidepressant	[70]

HMG-CoA: Hydroxymethylglutaryl-coenzyme A; SSRIs: Selective serotonin reuptake inhibitor.

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ible determination of drugs and metabolites in biological fluids involving chiral bioanalytical assay using instruments such as high-pressure liquid chromatography (HPLC), gas chromatography (GC), supercritical fluid chromatography (SFC), nuclear magnetic resonance, and immunoassay have been reported. Among these techniques, chiral chromatography (HPLC, GC, SFC) and electrophoresis (CE) coupled with ultraviolet (UV), fluorescence (FL), and mass spectrometry detection are still the predominant analytical tools [59-61].

Drug development and design

Chemical synthesis of enantiomers is now economical and sustainable, progressively entering the market. With advancements in technological innovations, enantiomer-specific syntheses of drugs have been extensively produced for marketing authorization. The comparative assessment of the efficacy of the produced single enantiomer to the racemic mixture and the consequent choice of which to market is a regulatory concern. With the regulatory authorities and the economic concerns of drug development decisions, there may be a marked reduction in the number of drugs on the shelves sold as racemates [62]. The production of single enantiomers following the patent's expiration of the racemic production referred to as chiral switch, appears to be a new drug development design. Regulatory authorities, therefore, have released guidelines for considering single enantiomers of already marketed racemic drugs based on comparative effectiveness and tolerability. Table 3 presents examples of racemic products, their experimentally projected enantiomers, and the therapeutic classes. The list is progressively increasing because of synthetic and technological advancement.

Levofloxacin is about 128 times more potent than the dextroisomer, as observed in presenting lower MIC90, especially with community-acquired pneumonia [71, 72]. Many single enantiomer products may not be justified if there are racemic mixtures of comparable effectiveness and tolerability. For example, cetirizine and levocetirizine, omeprazole and esomeprazole are products considered for superlative performance but found with similar effects for the single enantiomer and the racemic mixture [73-75].

Conclusion

Three-dimensional biopharmaceutics is becoming more intriguing in light of the physicochemical properties of enantiomers as a single entity and in consideration as a co-enantiomeric presentation. In the future, we will see more chiral switches and metabolite switches. These metabolite and chiral switches and their understanding will provide direction for research in the next decade. Additionally, further research is required to explore the behaviors of enantiomers, whether used as pure or racemates, concerning their activities, interconvertibilities, metabolites and possible pharmacokinetic and pharmacodynamic significance in pharmacotherapy.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this review.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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