Physicochemical Properties of Drugs and Drug Disposition

**Stereochemistry (Double the trouble…. or…… double the fun?)**

The vast majority of drugs contain at least one stereo-center or other type of site of asymmetry. All biological receptors and enzymes have complex 3 dimensional structures and are inherently asymmetric. When we study the ADME and therapeutic properties of individual drug isomers we find that they behave differently. Thus when we give a mixture of two stereoisomers we are, in effect, giving a combination of two separate drugs with overlapping properties. Thus when stereoisomers of a drug are given separately the biological response, side effects, protein binding and pharmacokinetics of the isomers are almost always different, sometime strikingly so. Some drugs are given as mixtures of structural or optical isomers however the use of single isomers in drug development is strongly encouraged today. In some cases the therapeutics and safety of old drugs that were given as mixtures of stereoisomers has been improved substantially using single isomers and patent protection extended. The FDA now requires that the properties of stereoisomers of drugs that are intended to be given as stereoisomeric mixtures be determined separately whenever possible.
Note:
When one isomer has a property and the other one does not we use the term **stereospecific**.
When the isomers have a common biological property but different magnitude of effect we use
the term **stereoselective**.

1. **Chiral Centers---Enantiomers:** Most chiral centers in drug and biological structures occur at
tetrahedral sp$^3$ carbon atoms where 4 bonds are formed with distinct chemical groups. These
groups can be arranged in two ways that are “mirror images” of each other and are not superimposable. When there is only one chiral center in the molecule the two possible isomers
are called enantiomers. Sometimes stereocenters can invert or racemize. A **racemate or racemic mixture** is a 50:50 mixture of two isomers.

Note: You should be able to identify chiral centers in a molecule, assign chemical group priority
and deduce stereochemical identifiers (S (left) and R (right) in a structure like alanine shown
below using the Cahn-Ingold-Prelog rules.


1. Compare the atomic number (Z) of the atoms directly attached to the stereocenter; the group
having the atom of higher atomic number receives higher priority.

2. If there is a tie, we must consider the atoms at distance 2 from the stereocenter—as a list is
made for each group of the atoms bonded to the one directly attached to the stereocenter. Each
list is arranged in order of decreasing atomic number. Then the lists are compared atom by atom;
at the earliest difference, the group containing the atom of higher atomic number receives higher
priority.

3. If there is still a tie, each atom in each of the two lists is replaced with a sub-list of the other
atoms bonded to it (at distance 3 from the stereocenter), the sub-lists are arranged in decreasing
order of atomic number, and the entire structure is again compared atom by atom. This process is
repeated, each time with atoms one bond farther from the stereocenter, until the tie is broken.

4. If an atom A is double-bonded to an atom B, A is treated as being singly bonded to two atoms:
B and a **ghost atom** that has the same atomic number as B but is not attached to anything except
A. In turn, when B is replaced with a list of attached atoms, A itself is excluded in accordance
with the general principle of not doubling back along a bond that has just been followed, but a
ghost atom for A is included so that the double bond is properly represented from both ends.

Below for alanine: -NH$_3^+$ = 1; COO$^-$ = 2; CH$_3$ = 3 and the hydrogen (not shown) is 4 (lowest
priority and directed back out of the plane.
- The sequence 1,2,3 clockwise is R.
- The sequence 1,2,3 counterclockwise is S.
Many older drugs still in use are given as racemic mixtures and we see differences in stereoselectivity for pharmacological and ADME properties.

Example: Warfarin (Coumadin) anticoagulant (pKa = 5; Log P = 3.5)

1. Warfarin is given as the racemate. It has a low therapeutic index and individualized dosing with monitoring (INR) is required. PK and pharmacodynamics are very sensitive to drug-drug interactions with CYP2C9 inhibitors and inducers.

2. Stereoselective (not stereospecific) inhibition Vitamin K epoxide reductase

3. The (S) isomer (CYP2C9 substrate) is 3 fold more potent than the (R) enantiomer based on dose (The (R) enantiomer is not a substrate for CYP2C9).

4. Stereoselective half-life for (S) is 24 hours; (R) is 45 hours as well as protein binding

5. Development of single isomers was attempted and failed to improve outcomes.

Example: Fluoxetine (Antidepressant; Prozac; serotonin reuptake inhibitor (SSRI) (pKa = 9; Log P = 3.5)

1. Note the use of a wavy bond to indicate chiral center that is not defined (fairly common).

2. Only SSRI approved for use during pregnancy.

3. N-demethylated metabolite concentrations can exceed parent at multiple dosing due to extremely long half-lives. Metabolites are pharmacologically active and stereoselectively inhibits metabolism of the parent isomers so it is pretty complicated. Parent and metabolites are potent inhibitors of CYP2D6 and CYP2C19. Parent and metabolites accumulate with repeat dosing.
4. Efforts to develop and market the enantiomers failed.

**Ofloxacin (fluoroquinolone antibiotic; topoisomerase inhibitor)**

![Ofloxacin](image)

1. (S) enantiomer (Levofloxacin (Levaquin)) is much more active than the (R) enantiomer and is marketed as a separate drug. Quinolones are infamous for causing spontaneous tendon ruptures. There are two Black box warnings on Levofloxacin (Levaquin).

2. Note that there are multiple ionizeable groups and that the molecule is drawn as the neutral species. It is a zwitterionic (think about it). However bioavailability is good (>95%).

**Omeprazole (Prilosec); Irreversible proton pump inhibitor (PPI) generic**

![Omeprazole](image) ![Esomeprazole](image)

1. Note the unusual chiral center at sulphur which is why I chose it. The lowest priority group here is the lone electron pair and the sulphur does not undergo racemisation. All of the PPI’s (Lanzoprazole for instance) have this structural feature and are chiral.

2. Metabolism is by CYP2C19 which is polymorphic. Evidence suggests that administration of (S) omeprazole (Nexium) provides better AUC and less individual variability. For other PPI’s it is the (R) enantiomer. So there is some PK stereoselectivity

3. Overall controversial whether Nexium (off-patent next year) is worth the extra cost.

4. The PPI’s are unstable to the acid pH in the stomach, are formulated for release in the intestine and are irreversible inhibitors of the proton pump.
Ibuprofen (NSAIDs inhibit cyclo-oxygenase enzyme that produces the prostaglandins)

1. The (S) enantiomer is the active form. (Stereospecific)

2. Efforts to develop the single enantiomer to improve potency were discontinued when it was realized that an acyl-CoA racemase converts the (R)-enantiomer to the (S). Other NSAIDs like ketoprofen also undergo racemization (also called epimerization). In the mechanism of racemization the proton is lost.

Multiple Chiral Centers (Diastereoisomers)

A large number of drugs have multiple chiral centers. The total number of isomers possible is $2^n$ where $n$ is the number of chiral centers.

1. Each isomer has one enantiomer (see below) where the stereochemistry at each chiral center is inverted (R,R -> S,S). (These compounds have identical properties in an achiral environment but act differently as drugs due to the 3-dimensional structures of enzymes and receptors. (-ephedrine and + ephedrine) below are enantiomers because both stereocenters are inverted. Note: the benzylic carbon in (-)-ephedrine is (R) and the other stereocenter is (S). Quickly write in the stereochmestry for the other isomers.

2. The remaining isomers are diastereoisomers so (-) ephedrine has two diastereoisomers which are denoted a pseudo. These various isomers differ in chemical properties as well as in biological activities. Wikipedia entries for ephedrine and pseudoephedrine are interesting.

![Diagram showing the relationship between enantiomers and diastereomers of ephedrine and pseudoephedrine.](image-url)
Multiple stereocenters are common particularly in steroids and drugs that bind to enzyme or receptors of peptides. Often “natural” amino acid sterechemistry will be required.

Perindopril (an ACE inhibitor)
5 stereocenters
8 of 32 possible isomers active
1 isomer chosen

Saquinavir (HIV protease inhibitor)
4 stereocenters
1 isomer marketed

Checklist of things to expect or worry about when isomeric drugs are compared.

1. Different ADME properties are almost always observed since transporter, metabolic enzyme and albumin are complex 3D structures and interact stereoselectively or stereospecifically.

2. Different pharmacology at receptors (you will see cases where one isomer is an agonist and another isomer is an antagonist of the same receptor).

3. Different off-target effects and side effects.

4. Racemization of stereocenters sometimes occurs obviated the need for single isomers.

5. We often see cases where industry markets a mixture (racemate) and later does a follow-on drug of a single isomer. Typically the racemate goes generic first and gets inexpensive. The drug company has to demonstrate that the follow-on single isomer is different enough to

   a. Warrant separate patents
   b. Provide a health benefit for the patient (FDA) over other compounds on the market
   c. Be cost effective (Nexium vs Prilosec).

6. Increasingly it is up to formulary boards at hospitals and other healthcare organizations to make these kinds of evaluations as cost is not an FDA mandate. Pharmacists are right in the middle of it.