Absorption mechanism of drugs from the GI tract: Scientific and intuitive considerations
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For assessing potential absorption behaviour of drugs from the GI tract, the following points may be useful:

1. Drugs are preferentially absorbed as non-ionized (un-dissociated or un-protonated) drug species, therefore, solubility/concentration of the non-ionized species at the site of absorption is to be considered and not that of the ionized (protonated or salt) form. For example, drugs such as diltiazem, metoprolol and propranolol are considered highly water soluble, however, in reality, these are low solubility drugs. The reason for this discrepancy is that these drugs are available and administered as hydrochloride salts, which make them appear highly water soluble. However, following administration in humans, drugs are dissociated from the salt forms depending on the pH of the surrounding environment. They behave according to their native (intrinsic) basic forms, which usually have low aqueous solubilities. In vitro (e.g. for dissolution testing), these drugs may freely dissolve as a salt but in vivo these will behave as native (basic) low solubility drugs. Therefore, in reality in the terminology of BCS, such drugs should belong to the Class II and not Class I, as they are commonly referred to.

2. Similarly, an acidic drug such as a propionic acid based NSAID e.g. naproxen as a sodium salt may provide high in vitro aqueous solubility, but would remain a low solubility drug as a native acid just like others such as ibuprofen and diclofenac.

3. Drugs such as diltiazem (pKa=7.7), propranolol (pKa=9.03), metoprolol (pKa=9.5), and verapamil (pKa= 8.92), which are basic, and drugs such as ibuprofen (pKa=4.43), diclofenac (pKa=4.15) and naproxen (pKa=4.2), which are acidic, should all be considered as low aqueous solubility drugs.

4. All the above mentioned drugs in humans show rapid and very high (> 90%) absorption characteristics with a t_{max} generally between 1 to 2 hours.

5. Similar absorption characteristics and t_{max} values indicate that all the above mentioned drugs are absorbed from the same site. It is commonly accepted that drug absorption mostly occurs from the intestine (link), therefore, it is logical to assume that all these drugs are also absorbed from the intestine.

6. It is important to note that for absorption it is the non-ionized drug which is required. Therefore, these drugs should be available in a non-ionized form in the intestine. Often it is assumed that basic drugs may be in the non-ionized form but acidic drugs will be in ionized (dissociated) form in the intestine as it has a higher pH. So, how would these completely different types (acidic and basic) of drugs are absorbed equally well from the intestine?

7. Before explaining the ionization and absorption processes of these drugs, it is important to understand the equilibrium step for the non-ionized (un-dissociated) and ionized (dissociated) forms. This equilibrium is described by the following equation, commonly known as the *Henderson–Hasselbalch equation*, and is written as follows:

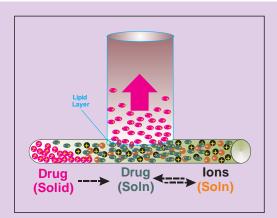$$pH = pKa + \log\left(\frac{[protonated\ or\ dissociated]}{[unprotonated\ or\ undissociated]}\right)$$

8. At a pH equal to the pKa of a drug (acidic or basic), the concentrations of the dissociated and un-dissociated drug will be equal or the ratio of these concentrations will be 1. On the other hand, a different pH value of a solvent/environment than the pKa for drugs will force uneven concentrations of dissociated vs un-dissociated concentrations. Consider such a situation with water as solvent which may have a neutral pH of 7. Water will act as a base for acidic drugs such as ibuprofen (pKa=4.4) and will facilitate ionization. On the other hand, water having a pH of 7 will behave as an acid for basic drugs such as propranolol which has a pKa of 9.

9. A solvent having a pH one unit higher for acidic drugs or lower for basic drugs than the pKa of dissolved drug will increase the dissociation (ionization) of the drugs to 90%, while a 2 pH unit differences from the pKa value will increase the ionization to 99.9%. Therefore, the larger the pH differences between the pKa of a drug and pH of the solvent, the larger the ionization.

10. As the pH of a solvent and pKa of a drug are fixed which provides high dissociated drug, then to maintain the equation balance correspondingly the concentration of an un-dissociated form must also increase. This means that the higher the dissociation, the higher the concentration of the undissociated drug as well i.e. higher ionization favours higher concentration of undissociated drug. This is quite intuitive, however, not usually recognised.

11. Considering that pKa values of the above mentioned drugs are at least one pH unit higher (basic drugs) or lower (acidic drugs), all the drugs will not only preferentially be in the ionic or dissociated form in the intestine assuming a pH of 6 (an average of range of 5 to 7), but will also be ***in equilibrium with relatively larger concentrations*** of non-ionized or undissociated drugs as well.

12. These larger concentrations of non-ionized drugs will be available for absorption.

13. The larger surface area and higher permeability of the intestinal surface provides efficient extraction of the non-ionized drug, thus reducing the concentration of un-dissociated drug in solution form. To keep the equilibrium with ionized drug more drug has to come into solution ***from solid (or un-dissolved)*** in non-ionized form which then get absorbed/extracted by the intestinal layer and the cycle continues until all the un-dissolved or un-dissociated drug is completely absorbed from the intestine (this process is shown in the figure).

14. On the other hand, if all of the drug is in a solution form (dissociated and undissociated) then to maintain the equilibrium, which is disturbed by the extraction of the undissociated drug, dissociated drug (ions) are to move towards undissociated form. Again, these will get absorbed and the cycle continues. Important thing to note is that because of extraction process of intestine, equilibrium favours movement towards undissociated molecules (drug) from both dissociated drug (ions) and/or un-dissolved solid which facilitate efficient drug absorption from intestine for both acidic and basic types of drugs.

15. The following link may be of further help in this regard (http://www.drug-dissolution-testing.com/?p=1746). For pKa values and drug

absorption characteristics see the link (http://www.drugbank.ca/).

Figure 1: Schematic representation of drug absorption (transfer) in the intestine