The Impact of Ionization in Drug Discovery & Development

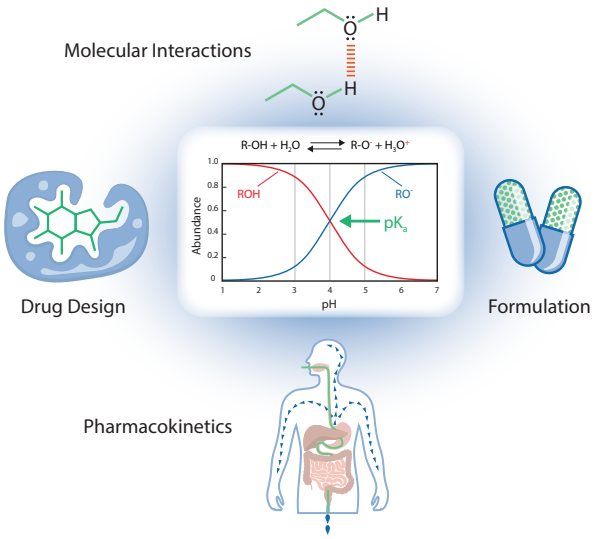


Figure 1: pK_a and the degree of ionization of a molecule impact many aspects of drug discovery and development.

The acid/base profile of a compound directly affects many aspects of drug discovery and development.

Ionization constants (pK_a values) and related properties (log*D* and solubility) are fundamental to the biopharmaceutical characteristics (absorption, distribution, metabolism, excretion, and toxicity—ADMET) of a drug. They influence aqueous solubility and in turn, drug formulation properties.

The charge state (or acid/base profile) of a compound (its acidity or basicity) refers to functional groups that are ionizable at physiological pH and/or pH values encountered during drug formulation. A recent study found the distribution of ion classes for oral drugs—83% contained ionizable groups or are always ionized, while only 11.9% are neutral (Figure 2).

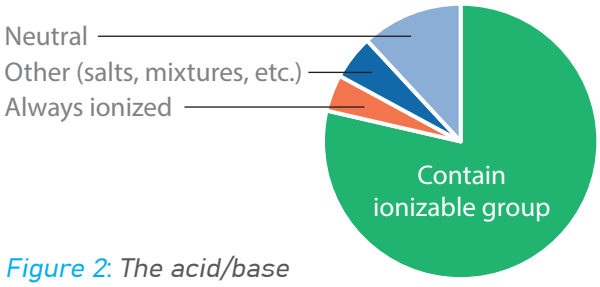
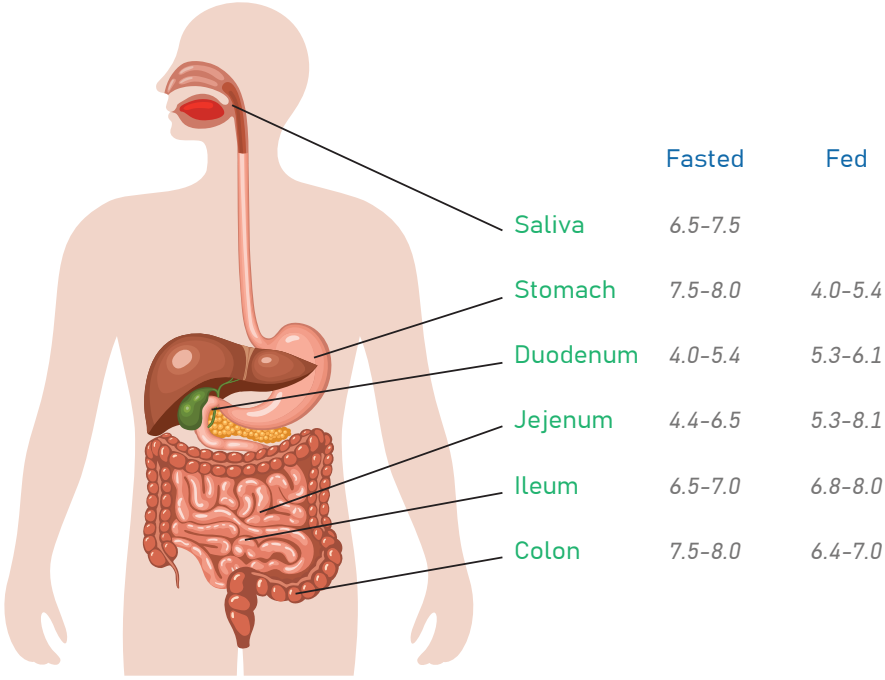


Figure 2: The acid/base profile of orally administered drugs.

The degree of ionization of a molecular entity affects its behavior in the changing pH environments of the human body (Figure 3).



	Fasted	Fed
Saliva	6.5–7.5	
Stomach	7.5–8.0	4.0–5.4
Duodenum	4.0–5.4	5.3–6.1
Jejenum	4.4–6.5	5.3–8.1
Ileum	6.5–7.0	6.8–8.0
Colon	7.5–8.0	6.4–7.0

Figure 3: The pH environments encountered by orally administered drugs.

How Various Properties and Functions Are Impacted by Ionization

Absorption—Acids with pK_a>3 and bases with pK_a<8 are poorly absorbed from the small intestine. Transport of molecules across membranes (permeability) is faster for uncharged species.

Bioavailability—This property is more complex because solubility and clearance must be factored along with ionization. Bioavailability is better for acids than bases, because acids are protonated in the pH of the gastrointestinal (GI) tract. The higher polarity of bases results in reduced lipophilicity, limiting passive absorption across membranes.

Volume of Distribution—Is the drug widely distributed or limited to systemic circulation? Considered with clearance (by the liver and kidneys), volume of distribution (V_d) helps determine the half-life of a drug. Generally, basic compounds have large V_d while acidic molecules exhibit smaller values (this is also true for neutral and zwitterionic compounds).

BBB Permeability—Drugs aimed at CNS targets must pass through the blood brain barrier (BBB) and be available for binding to brain tissue. The ideal pK_a profile for a CNS-targeting molecule is in the range of 5–10. Basic and zwitterionic molecules are the best penetrants (or those to avoid when CNS-related side effects need to be minimized for drugs targeted outside the brain).

hERG—The hERG potassium channel mediates the electrical activity of the heart. Scientists want to avoid inhibiting hERG to avoid cardiac arrhythmias and the potentially fatal QT prolongation. Acidic, Zwitterionic, and neutral compounds show a weaker affinity for the hERG channel than basic molecules and are preferred for cardiac safety.

Clearance, Metabolism & CYP450—Drugs are cleared from the human body via renal and hepatic pathways. The role of ionization state in clearance is related to protein binding. Anionic forms of acids can be highly bound to plasma proteins so they are less likely to be cleared. Bases show higher clearance rates.

Secondary metabolism can generate ionizable functional groups by increasing aqueous solubility for renal clearance. Lipophilic molecules are reabsorbed by the kidneys and must be metabolized for greater water solubility. R&D efforts are taken to reduce metabolism by P450 enzymes to reduce the possibility of toxic metabolites and avoid drug-drug interactions, increase half-life, and reduce dosing schedules.

Drug Receptor Interactions—Drug binding sites contain hydrophobic and hydrophilic regions. Ionizable groups can interact with these pockets through H-bonding or other electrostatic interactions to bind the drug or ligand to the receptor. Medicinal chemists can improve the potency of ligands by modulating the strength and position of ionizable groups.

Off-Target Activity—Acidic neutral and zwitterionic compounds have a lower propensity for off-target activity, while basic compounds often interact with more than one target.

Formulation—pK_a critically influences formulation particularly for drugs administered in solution. Ionized forms are more water soluble. Drugs must be suitably lipophilic to absorb from the GI tract and interact with the target receptor. Solubility can be modulated by the pH of a solution formulation.

Injectables (ideal pH of 4–9) are preferably aqueous and the pH of the medium can help overcome lipophilicity-related limitations when one or more ionizable groups are present. Effective pK_a values for solubility enhancement are in the range of 4–9 to ensure that a good proportion of the ionized drug is adequately water soluble.

pK_a also impacts stability of formulation. Scientists want to avoid oxidizable groups with pK_a near physiologically relevant ranges to prevent accelerated degeneration.

NOTE: The magnitude of the impact of these pK_a ranges is dependent on lipophilicity and dielectric constant. When a low log*P* compound is ionized, it may have a greater modulating ADME effect when compared to a highly lipophilic (high log*P*) compound, i.e., the effect of a single pH-mediated ionization on a greasy molecule is less impactful.

Reference:

Manallack D. T., Prankard R. J., Yuriev E., Opera T. I., Chalmers D. K. (2013). The significance of acid/base properties in drug discovery. *Chem Soc Rev., 42*(2), 485–496. doi:10.1039/c2cs35348b.

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