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Importance of Physicochemical Properties In Drug Discovery. (Review Article)

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ABSTRACT:

Drug discovery is a complex and demanding enterprise. In recent years there has been a significant discussion on discovery and developmental processes for new chemical entities, wherein various parameters like PK, toxicity, solubility, stability are addressed. The 'Rule of Five', gained wide acceptance as an approach to reduce attrition in drug discovery and development. However, analysis of recent trends reveals that the physical properties of molecules that are currently being synthesized in leading drug discovery companies differ significantly from those of recently discovered oral drugs and compounds in clinical development. The consequences of the marked deviation in the physicochemical properties result in a greater likelihood of lack of selectivity and attrition in drug development. Tackling the threat of compound-related toxicological attrition needs to move to the mainstream of medicinal chemistry decision-making. The impacts of these rules on oral absorption are discussed, and approaches are suggested for the prediction, assessment and communication,of,absorption-related, physicochemical properties in drug discovery and exploratory development.

This review is based on how physicochemical properties of compounds can be optimized for drug discovery.

INTRODUCTION: PHYSICOCHEMICAL PROPERTIES:

Most of the drugs used in medicine behave in solution as weak acids, weak bases, or sometimes as both weak acids and weak bases. The term “physicochemical properties” refers to the influence of the organic functional groups within a molecule on its acid-base properties, water solubility, partition coefficient, crystal structure, stereochemistry, and so on. All these properties influence the absorption, distribution, metabolism, excretion, and toxicity of the molecule. The lead optimization stage of drug discovery usually calls for specific methods that attempt to model properties such as oral absorption, blood–brain barrier penetration, distribution, metabolism and

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its toxicity effects in the individual. Many ADME models include physicochemical properties as descriptors; calculation of these properties has to be widely studied, because success or failure of the drug candidate solely depends on the physicochemical properties of the drug. Christopher A. Lipinski has commented:

'Drug-like is defined as those compounds that have sufficiently acceptable ADME properties and sufficiently acceptable toxicity properties to survive through the completion of human Phase I clinical trials [Lipinski, C. A. (2000)].'

For a discovery project team it is important to focus on both activity and properties of the candidate [Kerns, E. H.et al. (2003)], if the focus is solely on the activity , the team may arrive with a candidate whose properties are worse than the HTS hit. Once a nanomolar activity is obtained it is hard to go back and fix the structural modifications because the substructure may have to be modified again which were added in order to enhance binding affinity. Optimization of drug-like properties like absorption, distribution, metabolism, excretion and toxicity (ADME/T) in addition to pharmacology (e.g. efficacy, selectivity) increases drug discovery success.

The cost of development of new chemical entities is generally high wherein failures of these discovery projects represent major economic losses for the companies. Furthermore years and work on these discoveries and developments are lost. Ultimately, the introduction of a new drug candidate in the market is delayed. PK assessment should be seeded in the late discovery or the predevelopment stage. This testing succeeds in

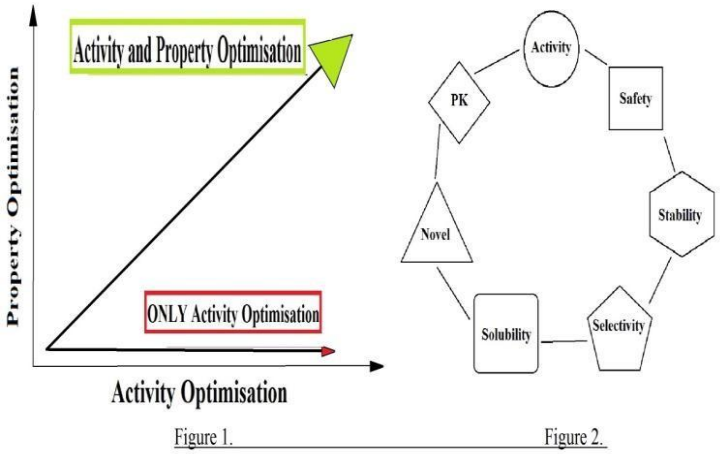

Figure 1. Representation showing optimisation of both Activity and Property. Figure2. Juggling analogy

keeping poor candidates from progressing into development greatly reduces the rates of attrition. Another useful anology is juggling. A proper balance of crucial elements have to be maintained in order to achieve success.

Drug attrition is an alarming situation in recent time. A research carried out by J. Arrowsmith et al., (2013) shows that in 2011-2012, there were a total of 148 failures between Phase II and

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submission (also including Phase I/II studies in patients and major new indications of already marketed drugs). Of these, 105 had reported reasons for failure. The majorities were due to a lack of efficacy (56%) or to safety issues (28%); here, failures that were due to an insufficient therapeutic index were included under the safety parameter.

On comparing by phase bases, for the most recent year range, the proportion of failures due to lack of efficacy was higher in Phase II (59%), but still disturbingly high in Phase III and beyond (52%). The proportion of failures due to safety issues is higher in Phase III and beyond compared with Phase II at 35% and 22%, respectively, which may be due to safety issues that only become apparent in larger numbers of patients and/or longer trials.

When the failure rates are broken down by therapeutic area, oncology and central nervous system (CNS) disorders account for 44% (30% and 14%, respectively) of all the 105 failures between Phase II and submission for which reasons have been reported. However, almost 50% of CNS and endocrinology (diabetes) failures (13 out of 29, and 4 out of 8, respectively) are excluded from these numbers because the reason for the failure has not been disclosed. Figure3 shows various parameters, causes and trends in attrition rates.

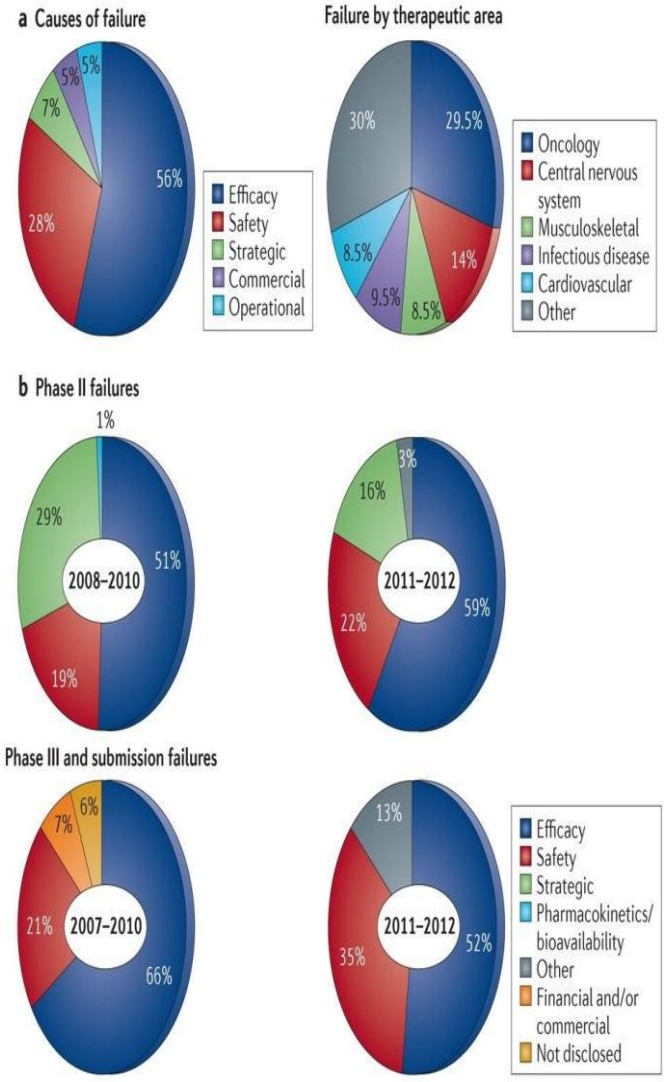

Figure 3. Trends in attrition rates. a. Of the 148 failures between Phase II and submission in 2011 and 2012, reasons were reported for 105; the majority of failures were due to lack of efficacy, as shown on the left. On the right, the 105

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reported failures are broken down according to therapeutic area. b. Comparison of the reasons for failures in Phase II and Phase III trials in 2011 and 2012 with those in earlier periods that we reported previously.

BARRIERS IN DRUG EXPOSURE:

When a drug molecule is administered it has to:

Dissolve in the biological fluids i.e. gastric fluids, intestinal fluids, blood plasma etc.

Survive a range of pH from 1.5 in the stomach to 8.0 until it reaches the large intestine andfurther to the blood.

Survive Intestinal and Gut bacteria.

Permeate through the biological membranes in the GI tract.

Survive Metabolism by the enzymes.

Avoid active transport to bile.

Avoid excretion by kidneys.

Reach the target organ.

Show its therapeutic activity and greater selectivity towards the target receptor.

Reduce partition and binding to unwanted sites.

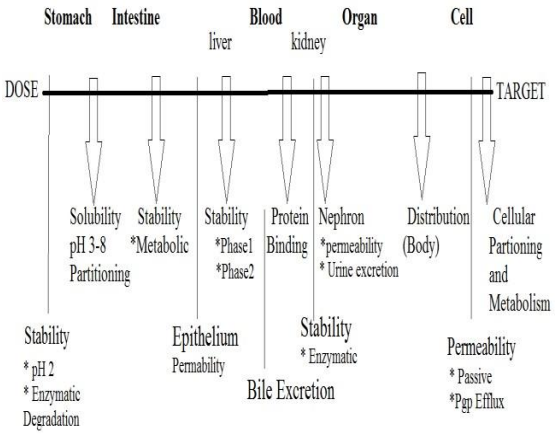

Figure 4. Overview of Barriers in the pathway of Drug Delivery to the target.

Consequences of chirality on barriers and properties:

Chiral compounds show significant stereochemical changes in vivo. Unlike enantiomers, diastereo-isomers exhibit different physicochemical properties, including melting point, boiling point, solubility, and chromatographic behavior. The physicochemical properties of a drug molecule are dependent not only on what functional groups are present in the molecule but also on the spatial arrangement of these groups. This becomes an especially important factor when a molecule is subjected to an asymmetric environment, such as the human body. Proteins and other biological

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macromolecules are asymmetric in nature, how a particular drug molecule interacts with these macromolecules is determined by the three-dimensional orientation of the organic functional groups present. If crucial functional groups are not occupying the proper spatial region surrounding the molecule, then productive bonding interactions with the biological macromolecule (or receptor) will not be possible, potentially decreasing the desired pharmacologic and therapeutic effect. However, if these functional groups are in the proper three-dimensional orientation, the drug can produce its interaction with the receptor. Therefore is very important for the medicinal chemist developing a new molecular entity for therapeutic use to understand not only what functional groups are responsible for the drug's activity but also what three-dimensional orientation of these groups is needed. Interactions with proteins, changes in enantiomeric configuration, affect pharmacodynamics properties of the molecule. Examples are as follows:

Solubility (Crystal forms of enantiomers are different)

Efflux and uptake transport (Binding to transporter)

Metabolism (Binding, orientation of molecules positions to the reactive moiety)

Plasma protein binding (Binding to specific target protein)

Toxicity, such as CYP inhibition, hERG blocking (Binding)

Table 1. Effect of Sterioselectivity on Renal Clearance

Drug	Renal Clearance Enantiomeric Ratio*
Quinidine	4.0
Dissopyramide	1.8
Terbutaline	1.8
Chloroquine	1.6
Pindolol	1.2
Metoprolol	1.2

*ratio of renal clearance of the two enantiomers.

LIPOPHILICITY:

Log P: It is defined as the Log of the partition co-efficient of the compound between an organic phase and aqueous phase at a pH where all the compound molecules are in the neutral form [Rekker et al. (1992)].

$$\log P_{oct/wat} = \log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right)$$

The organic phase used is generally n-octanol and the aqueous phase is unionized water. Log P depends on the partition coefficient of the neutral

molecules between the two phases. Abraham et al. have shown that Log P is affected by several fundamental structural properties of the compound [Mannhold et al (2009)]:

Molecular volume: related to the molecular weight of the compound which affects the size of the cavity in the solvent to solubilize the molecule.

Di-polarity: affects the polar alignment of the compound with the solvent

Hydrogen bond acidity: acceptance of hydrogen bonds of the solvent.

Hydrogen bond basicity donation of hydrogen bonds to the solvent.

Log D: It is defined as the Log of the distribution co-efficient of the compound between an organic phase and aqueous phase at a specified pH (x) where the compound molecules are in the partly in the ionic form and a portion may be in the neutral form [Hansh et al. (2004)].

$$\log\ D_{\mathrm{oct/wat}} = \log\left(\frac{[\mathrm{solute}]_{\mathrm{octanol}}}{[\mathrm{solute}]_{\mathrm{water}}^{\mathrm{ionized}} + [\mathrm{solute}]_{\mathrm{water}}^{\mathrm{neutral}}}\right)$$

Log D depends on the partitioning co-efficient of the neutral portion of the molecule population plus the partioning portion of the ionized portion of the molecular population. Ions generally have greater affinity to the polar aqueous phase than the non-polar organic phase. The fraction of molecules ionized depends on the pH of the aqueous solution, the pK_a of the compound and whether the compound is an acid or a base. For bases the neutral/cations ratio of the molecules in solution increases with increasing pH, hence the Log D value increases with increasing pH. Conversely for acids, the neutral/anion ratio decreases with increasing pH, and Log D also decreases. Thus Log D is directly proportional to the neutral/ion ratio of the molecules in the solution.

Parameters affecting Lipophilicity [Abraham et al. (1997)]

Change in phases: Partitioning between octanol and water is different than that between cyclohexane and water; this is due to the molecular properties of the phases.

pH: Affecting the degree of ionization

Ionic strength of the solvent: Affects polarity, molecular interactions and forms in-situ salts (as counter ions) with drug molecules.

Co-solutes and co-solvents: May change the partitioning behavior of molecules even in smaller concentrations.

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Lipophilicity co-relations [Hansh et al. (2004)]:

Permeability: Increase in lipophilicity increases the permeability through the lipid bilayer hence increase in Absorption:

Distribution: Increase lipophilicity, Increases Plasma protein binding.

Metabolism: Metabolism of Lipophilic compounds occurs faster.

Elimination: Compounds are protein bound, hence elimination and excretion of these compounds is reduced.

Toxicity: Increased stay in the body may result into undesirable side effects.

[Lombardo et al. (2002)] also showed co-relations between the Volume of Distribution (V_d) and lipophilicity. Increase in lipophilicity increases the plasma binding of the drug, increasing the Vd, thus leading to increase in the retention of the drug in the body.

Table 2. Effect of Log P on optimization parameters [Kerns, E. H.et al. (2010)]:

Log P Range	Bioavailability	Nature	Property
Less than 0	Low	More polar	Poor Lipid bilayer permeability
0 to 3	Moderate	Optimal	Good balance of solubility and permeability
More than 3	High	More Lipophilic	Poor Aqueous solubility

Table 3. Effect of Log D on optimization parameters [Kerns, E. H.et al. (2010)]:

Log D	Common impact on properties	Common impact in-vivo
Less than 1	Solubility high Permeability low due to passive trans cellular diffusion If MW less than 200, permeation via Para-cellular diffusion possible Metabolism low	Volume of Distribution low Oral absorption and BBB permeation unfavorable Renal clearance may be high
1 to 3	Solubility moderate Permeability Moderate Metabolism low	Balanced Volume of Distribution Oral absorption and BBB permeation favorable
3 to 5	Solubility low Permeability high Metabolism moderate to high	Oral bioavailability moderate to low Oral absorption variable
More than 5	Solubility low Permeability high Metabolism high	High Volume of Distribution (especially amines) Oral absorption unfavorable and variable

pK_a:

pK_a indicates the ionizability of the compound. It is a function of the acidity or basicity of group(s) in the molecule. pK_a is defined as the logarithmic measure of the acid dissociation constant (K_a). The logarithmic constant, pK_a, is equal to $-\log_{10} K_a$.

For acids:

$HA \leftrightarrow H^+ + A^-$

$pK_a = - \log ([H^+]*[A^-] / [HA])$

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For bases:

$HB^+ \leftrightarrow H^+ + B$

$pK_a = - \log ([H^+]*[B] / [HB^+])$

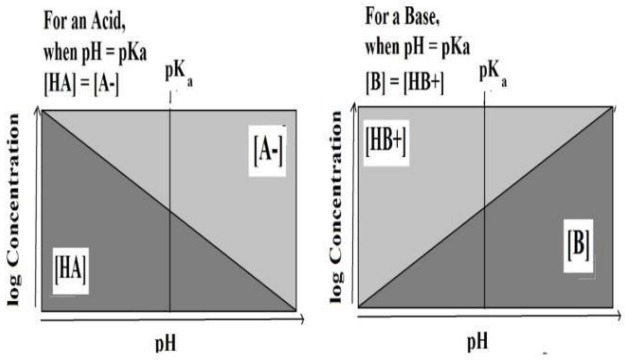

Figure 5. Concentration of neutral and ionic species of acids and bases at pH above and below their pK_a.

To further simplify, acids with lower pK_a value are stronger because as the pH decreases there is a greater concentration of neutral acid molecules (HA) and a lower concentration of anionic acid molecules (A^-) in the solution. Similarly bases with lower pK_a values are weaker because as the pH decreases, there is a lower concentration of neutral base molecules (B) and higher concentration of cationic base molecules (HB^+) in solution [Kerns E H. et al. (2001)].

5.1. The Henderson-Hasselbalch equation [Avdeef et al. (2001)] is a useful relationship for discovery.For acids:

$pH = pK_a + \log ([A^-] / [HA])$

Thus, $[HA/A^-] = 10^{(pKa - pH)}$

For bases:

$pH = pK_a + \log([B] / [HB^+])$

Thus, $[HB^+] / [B] = 10^{(pKa - pH)}$

Using these relationships, concentration of the neutral and ionic species can be calculated at any pH, if the pK_a is known. When pH equals pK_a, there is an equal concentration of ionic and neutral species in the solution.

pK_a is an important parameter because majority of the drugs contain ionizable groups. Most of the drugs are basic, few are acidic and a minor part is non-ionizable.

As pK_a determines the degree of ionization, it has major effect on solubility and permeability. A particular relationship between the permeability and solubility is defined which states that they are inversely proportional. For Acidic molecules, permeability decreases with increasing pH, because as acidity decreases, ionization increases and diffusion of anionic moiety through the membrane becomes difficult, conversely the solubility increases as ionization increases. Similarly for bases, as the pH decreases, ionization increases, permeability decreases and solubility increases. pK_a also affects the activity of a structural series by showing changes in interaction at the active site of the target protein [Martin et al. (1993)].

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SOLUBILITY:

It is defined as the maximum dissolved solute concentration under the given solution conditions. It determines the oral bioavailability and the intestinal absorption. Lipinski et al. stated that solubility is a much larger criterion as compared to permeability in drug discovery [Lipinski et al. (2012)]. The solubility classifications used in drug discovery is given below [Waterbeemd H. (1998); Wu Chi-Yuan et al. (2005)]:

The Biopharmaceutics Classification System:

In order to promote the optimum candidate to development and streamline the transition to development, the BCS was invented. It divides all the drug candidates into 4 classes:

Class I: High Solubility and High Permeability (amphiphilic); the most ideal class for oral absorption. E.g. Metaprolol, Diltiazem, Verapamil.

Class II: Low Solubility and High Permeability (lipophilic); formulation manipulations are used to increase the solubility of these classes of compounds. E.g. Glibenclamide, Acyclovir, Captopril.

Class III: High Solubility and Low Permeability (hydrophilic); prodrug strategies are used for these class of compounds. E.g. Cimetidine, Nifidipine, Ketaconazole.

Class IV: Low Solubility and Low Permeability (risk-philic): development of the compounds of this class is costly and risky. No in-vitro/in-vivo co-relations are expected. E.g. Hydrochlorothiazide, Furosemide, Tobramycin.

5.2. Factors that affect solubility [Rouland M. (2011)]:

Compound structure: More lipophilic, less the polar solubility and more hydrophilic, less the lipid solubility.

pK_a: when the pH of the solution equals the pK_a of the compound its solubility is twice the intrinsic solubility of the compound.

Size: Larger the molecule, less its solubility.

Crystal lattice energy: Greater the energy, lesser its aqueous solubility, due to stronger bonding of the crystal lattice.

Physical state

Solid:

Amorphous: Highly Soluble

Crystalline: Moderately Soluble

Polymorphic: Solubility varies with the compound.

Liquid: Polar liquids more soluble in aqueous solutions than non-polar liquids.

Composition and physical condition of solvents:

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Type of solvents: Polarity

Amount (%) of solvents

Solution components

pH: Acidic compounds more soluble in Basic pH and vice versa.

temperature: Increase in temperature increases Solubility

Medicinal chemists have the ability to alter the solubility by manipulating the structure thus altering the physicochemical properties of the molecule. Yalkowsky and Banerjee have empirically derived a general solubility equation for estimating the aqueous solubility of the compound. The equation demonstrates the effect of lipophilicity and crystal lattice energy on solubility [Yalkowsky et al. (1992)].

Equation: $\text{Log } S = 0.8 - \text{Log } P_{ow} - 0.01(MP - 25)$

Here, S is the Solubility, Log P_{ow} is the octanol/water partition co-efficient (measure of lipophilicity), and MP is the melting point (measure of the crystal lattice strength).

Thus, solubility decreases 10 fold when Log P increases by 1 unit or the melting point increases by 100^{o}C.

Therefore the solubility of a compound at a particular pH is the sum of its intrinsic solubility i.e. the solubility of the neutral species as well as the ionic species portion of the molecules in the solution. This has high implications for the solubility of compounds in various physiological fluids and solutions at different pH. Thus the solubility of a mono- acid or a mono-base is defined as:

$HA + H_2O \leftrightarrow H_3O^+ + A^-$ (Acids)

$B + H_2O \leftrightarrow OH^- + HB^+$ (Bases)

At equilibrium a mono-acid and a mono-base can be described as:

$S = [HA] + [A^-]$ (Acids)

$S = [B] + [HB^+]$ (Base)……where 'S' is Solubility.

A mathematical derivation of the Henderson-Hasselbalch equation provides the insight for solubility as under:

$S = S_o (1 + 10^{(pH - pKa)})$

$S = S_o (1 + 10^{(pKa - pH)})$……where '$S_o$' is the Intrinsic Solubility

Solubility changes linearly with S_o and exponentially with the difference pH and pK_a. Examples are listed in the table. Barbital and amobarbital have same pK_a, but barbital have much higher intrinsic solubility, because of its extra lipophilic chain in amobarbital, thus solubility of barbital is more as compared with amobarbital. Naproxen and phenytoin have somewhat similar intrinsic solubility, but different pKa values; hence their solubility differs

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extensively at pH 9. As the difference in pH and pK_a increases solubility increases exponentially [Lee Y. et al. (2003)]. Examples to prove the above statement:

Table 4. Solubility at a given pH is a given function of the intrinsic solubility of the Neutral portion of the Molecules and solubility of the ionized portion of Molecules [Lee Y. et al. (2003)].

Drug	pK_a	Intrinsic solubility (mg/mL)	Solubility @pH9 (mg/mL)
Amobarbital	7.9	1.2	15
Barbital	7.9	7.0	95

5.3. Effects of solubility:

As the compound dissolves, its concentration in the solution increases, hence its absorption occurs at a faster rate. Compounds with low solubility have low oral bioavailability. Cases of toxicity are also seen with compounds showing low solubility, due to retention of drug in the GI tract E.g. Cocaine, THC etc.

The human GI tract shows a pH gradient along its length varying from strongly acidic to basic. Acidic and basic drugs have different solubility throughout the GI tract. Bases are more soluble in the stomach and the upper part of the intestine due to ionization at acidic pH. Acidic drugs are more soluble in the later section of the small intestine because the region is more basic.

Table 5. Distribution of Drugs Based on the Physiological pH in the Body.

Fluid	pH	Type of drugs
Blood	7.4	Neutral
Stomach	1.3	Basic Drugs Solubilized
Small intestine	5.5-7	Basic and Neutral
Saliva	6.4	Neutral
CSF	7.4	Neutral and Basic
Urine	5.8	Acidic drugs
Muscle tissue	6	Acidic drugs
Adipose tissue		Lipophilic drugs

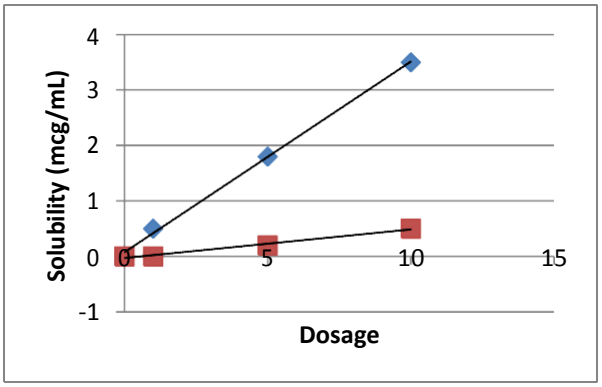

Figure6. Relationship between solubility, permeability and maximum absorbable dose. High-permeable compounds require lower solubility than low-permeability compounds to achieve maximum oral absorption [Bighley L.D. (1995)].

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Lipinski C A. (2000) has developed a useful graphical co-relation of solubility, permeability and dose.

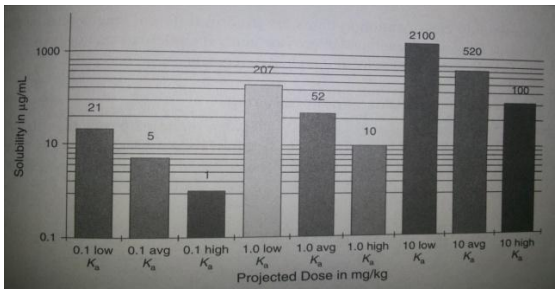

Figure7. Graph for estimating solubility of Discovery Compounds.

In the above example, the compound has average permeability (K_a) and average potency ("1.0" mg/kg considering the dose to be fully absorbed), the compound should have minimum stability of 52mcg/mL to be completely absorbed. In case of non-potent compounds, with a dose of about 10mg/kg and having average permeability, the solubility must be 10 times higher i.e. 520mcg/mL. These estimates help to provide useful guidelines for optimization of solubility parameter during discovery. The following is the classification:

Table 7. Classification of Drugs based on Solubility [Kerns, E. H.et al. (2010)].

Less than 10mcg/mL	**Low Solubility**
10-60 mcg/mL	Moderate Solubility
More than 60 mcg/mL	High Solubility

PERMEABILITY:

The velocity of the molecule passage through a biological membrane barrier is known as permeability [Goodwin J. T. et al. (2001)]. Prediction of in-vitro permeability can enhance a wide range of drug discovery investigations, help with understanding cell based bioassays, and assist prediction and interpretation of in-vivo pharmacokinetic results. Drug molecules encounter several different membrane barriers in the living system [Artursson P. (2002)]. They include Gastrointestinal (GI) epithelial cells, Blood capillary wall, Hepatocyte membrane, Glomerulus, Restrictive organ barriers: Blood Brain Barriers and Target cell membrane.

Permeation through the membranes occurs by five major mechanisms: (a) Passive diffusion, (b) Endocytosis, (c) Uptake transport, (d) Para-cellular transport and (e) Efflux transport [Brahmankar D. M. (2005); Lin J. H. (1997)].

Lipid Bilayer Membrane

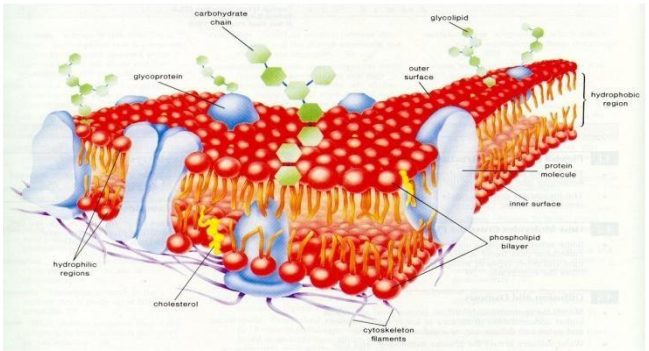

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Figure 8. Complex Model of a Lipid Bilayer Membrane

The phospholipid molecules assemble as a bilayer ranging approximately 490 nm in length, with the hydrophobic portion oriented inwards and the hydrophilic phosphate heads towards the water molecules. Molecules diffuse through this bilayer membrane by breaking the polar hydrogen bonds by shedding the hydrating water molecules and diffuse inside, passing through the tightly packed region of the lipid chains around the glycerol backbone and moves further to the more distorted lipid region of the lipid aliphatic chains in the middle of the membrane. Molecules with lower molecule weight passes through the membrane more easily as compared to the higher molecular weight compounds, due to the tightly packed arrangement. Also, lipophilic molecules pass through the non-polar central core of the membrane more easily than the hydrophilic ones. Molecules then move through the other side chains and polar heads of the other side of the membrane, thus regaining the polar hydrolysable water molecules and form hydrogen bonds again. Membrane permeability differs from tissue to tissue, as composition of different tissues may vary, like Gastro-Intestinal tract v/s the Blood Brain Barrier

Another term that comes into play is the combined or composite permeability, which is the result of dynamic interaction of local conditions and how they affect the various permeability mechanisms. The conditions that may result in change of these parameters are concentration gradient, pH gradient, transport affinity, molecular size and polarity.

BLOOD-BRAIN BARRIER (BBB):

BBB is restrictive for many compounds due owing to the p-glycoprotein efflux, absence of Para-cellular permeation and limited pinocytosis. In order the drug to be administered to the CNS or brain tissue its permeation through the BBB should occur. Many of the compounds generally fail in achieving the desired therapeutic efficacy due to impermeability through the BBB. There are many mechanisms or say a combination of mechanisms that limit the permeability of these drugs through the BBB. The BBB is associated with the micro capillary blood vessels that run throughout the brain in close proximity to the brain cells. These cells provide the necessary nutrients and also take away the excreted products from the brain cells. They possess a surface area of about $12mm^2$. The BBB consist of endothelial cells that form a monolayer lining on the inner surface of the capillaries. The endothelial layer

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consists if mainly astrocyte and pericyte cells, which do not resist drug permeation but can, alter endothelial cell characteristics. CNS drugs must permeate through the endothelial cells to penetrate the brain cells. The mechanism through which drugs permeate through the barrier is shown in the figure.

8.1.Mechanisms that affect the BBB permeation [Kerns E. H. et al. (2006)]:

Restricted physicochemical characters that limit passive diffusion

Physicochemical properties considerations as stated by Pardridge, as well as the compound should have fewer hydrogen bond donors, higher log P, lower PSA and a few rotatable bonds.

High efflux activity

PGp efflux limits the molecules before they can reach the brain cell. Thus an efficient strategy is to reduce efflux by PGp

Lack of sites for Para-cellular permeation and capillary wall fenestrations

Tight junctions between the cells,

Limited pinocytosis

Endothelial cell metabolism and metabolic clearance

Increase in hepatic clearance affects the amount of drug reaching the brain

Uptake transport

Enhancements feature which generally increase the uptake of nutrients like amino acids, peptides, glucose etc. and other endogenous compounds. Uptake enhancement is most commonly delivered by serendipity.

Nonspecific binding to plasma proteins and lipids in the brain tissue

Drug molecules that permeate the BBB are subject to no specific protein binding inside the brain. The free drug hypothesis states that binding of the drug to some other substrate reduces the therapeutic receptor concentration and thus reduce in activity is seen.

Plasma Protein binding

PPB greatly limits the permeation to the brain, because the on/off kinetic models are low to moderate and very little drug is available permeate through the BBB

Clearance of the compound from the ECF into the blood and CSF

The second interface between blood and the brain is choroid plexus. The BBB interfaces with the blood and the ECF of the brain. The choroid plexus interfaces with the blood and the CSF an is hence the blood cerebrospinal fluid barrier (BCSFB)

Limitations of BCSFB is

Surface area is 5000 time smaller than BBB

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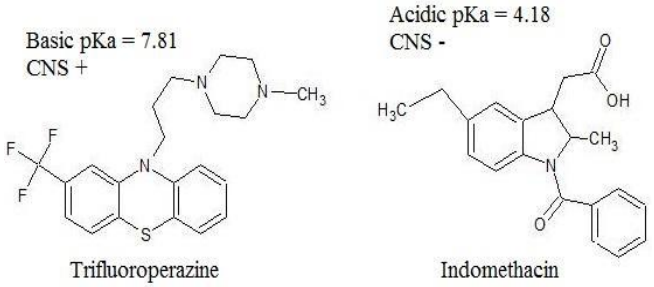
There is little mixing of the components of CSF and ECF

CSF flows very fast from the brain tissue toward the arachnoid villi

CSF is turned over every 5 hours.

Figure9. .Acids Poorly Permeate BBB, whereas Bases have good BBB Permeability [Clark D. E. (2003)].

Amines have favorable interaction with predominantly negatively charged phospholipids head groups in the BBB [Liu X. (2006)]. About 75 % of the prescribed drugs are basic, 19% are neutral and 6% are acidic.



RULES FOR PROPERTY PROFILING FROM STRUCTURE:

Lipinski rules:

The declaration of 'The Rule of 5' as stated in the report of Lipinski et al, opened a new way for the classification of the physicochemical properties of the drug compounds [Lipinski et al. (2012)].

These rules were first used by Pfizer, prior to their publication and since then it has been widely used. The rule states [Lipinski et al. (2004)]:

Poor permeation and absorption are more likely when:

> 5 hydrogen bond donors (expressed as the sum of all OH and NH)

Molecular weight > 500

Log P > 5

>10 hydrogen bond acceptors (expressed as a sum of all the N and O)

Substrates for biological transporters are exception to the rule.

Veber rules:

A study conducted by Veber on rats showed, molecular flexibility, polar surface area and hydrogen bond count are important determinants for oral bioavailability. Rotatable bond also account in the picture, which may be calculated electronically or manually. Calculation of PSA can be done using sophisticated softwares.

Veber rules for good bioavailability in rats [Veber D. et al. (2002)]:

≤ 10 rotatable bonds

≤ 140 PSA

≤ 12 total H bond donors and acceptors

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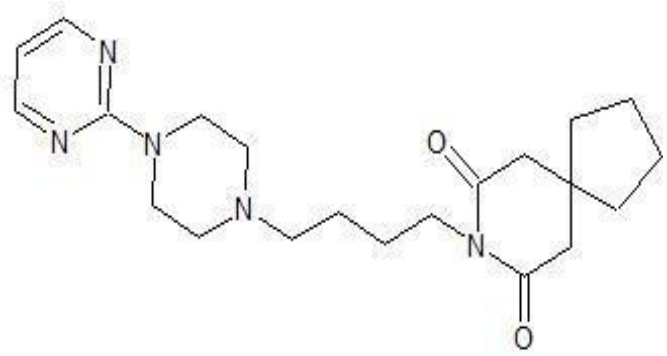

Figure 10. Application of Lipinski and Veber rule Buspirone. Refer Table 8.

Table 8. Calculations for Buspirone

Lipinski Rules	Veber Rules
HBD = 0	Rotatable Bonds = 5
HBA = 7	PSA = 7.0
MW = 385	Total Hydrogen Bonds = 31
ClogP = 1.7	
Good Absorption	Good Oral Bioavailability

Pardridge- rules for BBB permeability:

Physicochemical properties greatly affect BBB permeation. A set of physicochemical rules was first proposed by Pardridge [Pardridge (1995)]. The structure of the compound should have:

Hydrogen bonds (total): < 8 -10

Molecular Weight < 400-500

No acidic moiety.

Sparklin [Maurer T S. et al. (2005)] further suggested that Hydrogen bond acceptors <6 and bond donors >2. This is in agreement that hydrogen bond donors are limiting than hydrogen bond acceptors.

Another set of rules compiled by Clark [Clark D E. (2003)] and Lobell [Lobell et al. (2003)] suggests that the structure should have the following:

$N + O < 6$

PSA < 600 – 700 nm^2

Log D = 1 – 3

Clog P – (N + O) > 0

Opera el al proposed set of rule of 3 for lead-like compounds:

The 'Rule of 3' for lead-like compounds as proposed by Oprea [Opera et al. (2002)]:

Molecular weight ≤ 300

Clog P ≤ 3

Rotatable bonds ≤ 3

Hydrogen bond donors ≤ 3

Hydrogen bond acceptors ≤ 3

Polar surface area (PSA) ≤ 600nm^2

Rules of Thumb for a Given Set Molecular Properties.

A set of simple, consistent structure–property guides have been determined from an analysis of a number of key ADMET assays run within GSK: solubility, permeability, bioavailability, volume of distribution, plasma protein binding, CNS

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penetration, brain tissue binding, P-gp efflux, hERG inhibition, and cytochrome P450 1A2/2C9/2C19/2D6/3A4 inhibition. In-silico models have been developed on almost all the key ADMET assays employed within the pharmaceuticals industry and are reviewed in detail in many researches. Much of the research on in-silico ADMET and QSPR (Quantitative Structure Property Relationship) models is based on more advanced statistical data as reported in the literature. To counter the general reduction in interpretability of QSPR models, an attempt was made to demonstrate a set of simple rules of thumb based on large data sets a range of ADMET assays run within GSK [Gleeson M. P. (2008)].

The results were compiled and a set of rules were formulated wherein qualitatively predict the ADMET issues most likely to be experienced for a molecule based on its ClogP, MWT, and ionization state, without the need for complex computer simulations. The likelihood of a molecule having a particular It is clear that almost all ADMET parameters increase with either increasing MWT and/or ClogP, a single combined ClogP/MWT category has been used for simplicity. Molecules lie in the more desirable category if both MWT < 400 and ClogP < 4, while they are classified as less-desirable should one or more of the parameter lie above the cut-offs.

Figure 11. Indication of How Changes in Key Molecular Properties will affect a Range of ADMET Parameters. a) For Neutral Molecules, b) For Basic Molecules, c) for Acidic Molecules, d) For Amphiphilic Molecules. *a* Expressed relative to the mean value of the data sets. MWT and ClogP cut-offs of 400 and 4, respectively, are used. * Optimum ClogP bin is 3–5 with respect to permeability. ** Average to high volumes rather than high, low, or average generally considered optimum. *** Low CNS considered optimum, although for targets in the brain, this will be reversed. **** Some isoforms show a nonlinear relationship with ClogP and/or MWT. These are guides only.

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neutral molecules	MWT < 400 and clogP < 4	MWT > 400 and/or clogP > 4
solubility	average	lower
permeability*	higher	average/higher
bioavailability	average	lower
volume of Dist.**	average	average
plasma protein binding	average	higher
CNS penetration***	higher/average	average/lower
brain tissue binding	lower	higher
P-gp efflux	average	higher/average
in-vivo clearance	average	average
hERG Inhibition	lower	lower
P450 inhibition****	lower 2C9, 2C19, 2D6 & 3A4 inhibition	higher 2C9, 2C19 & 3A4 inhibition
P450 inhibition****	higher 1A2 inhibition	lower 1A2 inhibition
P450 inhibition****		average 2D6 inhibition

(a)

basic molecules	MWT < 400 and clogP < 4	MWT > 400 and/or clogP > 4
solubility	higher/average	lower/average
permeability*	higher/average	average
bioavailability	average	lower
volume of Dist.**	higher/average	higher
plasma protein binding	lower	average
CNS penetration***	higher/average	average/lower
brain tissue binding	lower	higher
P-gp efflux	average	higher/average
in-vivo clearance	average	higher/average
hERG Inhibition	average/higher	higher
P450 inhibition****	lower 1A2, 2C9, & 2C19 inhibition	lower 1A2 inhibition
P450 inhibition****	average 2D6 & 3A4 inhibition	average 2C9, 2C19 inhibition
P450 inhibition****		higher 2D6 & 3A4 inhibition

(b)

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acidic molecules	MWT < 400 and clogP < 4	MWT > 400 and/or clogP > 4
solubility	higher	average/higher
permeability*	lower	average/lower
bioavailability	average	average
volume of Dist.**	lower	lower
plasma protein binding	average/higher	higher
CNS penetration***	lower	lower
brain tissue binding	lower	higher
P-gp efflux	lower	lower
in-vivo clearance	lower/average	average
hERG Inhibition	lower	lower
P450 inhibition****	lower 1A2, 2C9, 2C19, 2D6 & 3A4 inhibition	lower 1A2, 2C19, 2D6 & 3A4 inhibition
P450 inhibition****		higher 2C9 inhibition

(c

.

(d) zwitterionic molecules	MWT < 400 and clogP < 4	MWT > 400 and/or clogP > 4
solubility	higher	average/higher
permeability*	lower	lower/average
bioavailability	lower	lower
volume of Dist.**	lower	average/lower
plasma protein binding	average/lower	higher
CNS penetration***	average/lower	lower
brain tissue binding	lower	higher
P-gp efflux	average	average
in-vivo clearance	average	average
hERG Inhibition	lower	average/lower
P450 inhibition****	lower 1A2, 2C9, 2C19, 2D6 & 3A4 inhibition	lower 1A2, 2C19 & 3A4 inhibition
P450 inhibition****		average 2C9, 2D6 inhibition

(d)

The rather simplistic modeling used here has the advantage of allowing scientists to make cross comparisons between a large numbers of ADMET assays. It then becomes easy to assess in a qualitative fashion how changes in the key physicochemical parameters will impact each of the different ADMET parameters in a particular program series.

This simplicity can be useful in a lead optimization environment where one does not optimize ADMET parameters in isolation. Such simple rules could also be used in the Hit-to-Lead stage to identify the likely ADMET issues of a given lead, allowing resources to be more effectively directed to the areas identified before the molecule enters lead optimization.

Applications:

These rules aid in the assessment of compounds. They are typically used for the following purposes:

Anticipating of the drug like properties of potential compounds i.e. lead molecules when planning synthesis.

Evaluating the drug-like properties of compounds being considered for purchase from a compound vendor

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CONCLUSION:

Over the years, strategies for reducing failure of lead molecules have been stated and optimization of physicochemical properties has been an important parameter. Figure 44 shows how incorporation of evaluation and optimization of physicochemical properties into drug discovery from target hits to final drug molecule can be fruitful. During lead optimization and parameters such as Absorption, Distribution, Metabolism, Excretion and Toxicity (ADME/Tox) properties should be emphasized throughout the entire discovery process. This approach also helps to improve efficiency, as problematic compounds are removed and delay or failures of candidates are reduced.

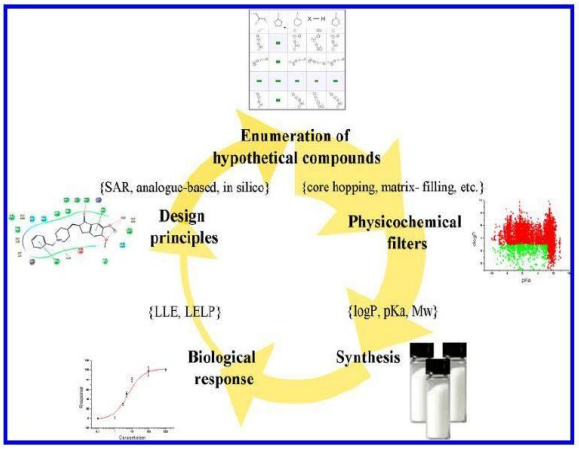

Figure 12. Flowchart for Optimized Drug Discovery

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