12

Physicochemical Properties and Drug Action

For a drug molecule to show its effect, it is necessary that it reaches in sufficient concentration at the site of action and then binds to receptor/enzyme. In order to do this, the drug molecule has to pass various barriers so that it does not get stored at various sites and not get metabolically altered and reaches the site of its action in sufficient concentration. The various factors which affect the transport of the drug molecule from its site of absorption to its site of action include various physicochemical factors such as solubility, partition coefficient, diffusivity, degree of ionization, polymorphism, etc. Not only the physicochemical properties affect the availability of a drug molecule at its site of action but also the dosage form in which it is administered also has an effect on its availability.

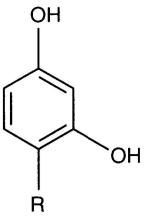
Solubility

The term solubility usually refers to solubility in polar solvents such as water and non-polar solvents such as lipids. Accordingly, the terms hydrophilia or lipophobia refers to solubility in water and hydrophobia or lipophilia to solubility in lipids.

In a homologous series, the lower members which are more water soluble, have lower biological activity. As the length of carbon chain is increased, the lipid solubility increases along with the biological activity until it reaches a maximum. After this any increase in non-polar portion of the molecule results in lowering of the biological activity. The lower activity of lower members is due to their lower lipid solubility, a property required for absoption process. Any increase in lipid solubility results in increase in biological activity also. This increase in biological activity roughly parallels the increase in lipid solubility. However, as indicated above any further increase in lipid solubility results in fall in the biological activity. This decrease in biological activity is due to decrease in solubility in the extracellular fluid (which is polar in character) which serves as a medium of transport.

One of the parameters which reflects a relationship between the solubility in polar and non-polar solvents and biological activity is partition co-efficient between *n*-octanol/water. The *n*-octanol/water system mimics the lipid membrane/water system found in biological system. Water saturated *n*-octanol contains 2·3 M of water and approximates the polar properties of lipid layer whereas the aquous phase which does not contain n-octanol mimics the physiological aqueous compartment.

One of the classical examples illustrating the relationship of biological properties in homologous series is that of 4-*n*-alkylresorcinols (1) in which R differs. Comparision of phenol coefficients of various alkyl resorcinols against *B. typhosus* has shown that as the number of carbon atoms in R (1) is increased, the activity goes on increasing reaching a maximum when the number of carbon atoms is 6 (Fig. 12.1) After this the activity suddenly falls (Fig. 12.1).



(1)

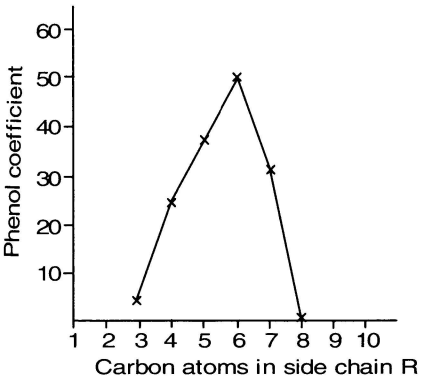


Fig. 12.1 Comparison of phenol co-efficient of various 4-*n*-alkylresorcinols (1)

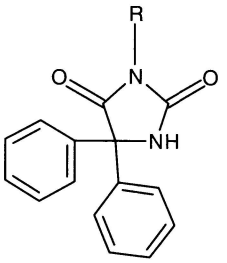
A study of antibacterial activity of alcohols has shown that the antibacterial activity increases as the series is ascended from methyl to octyl. Branched chain alcohols, which are more water soluble than the primary alcohols, have lower lipid/water partition coefficient, are consequently less active as antibacterials. Thus, *n*-hexyl alcohol is twice as active as secondary hexyl alcohol as antibacterial. The higher molecular weight alcohols such as cetyl alcohol, (CH_3 $(CH_2)_{14}CH_2OH$), which has negligible water solubility, is inactive as antibacterial.

Drug Absorption

Most of the drugs are absorbed from gastrointestinal tract by passive diffusion of the unionized form across lipoidal membrane. The absorption of the drug is influenced by the dissociation constant of drug, the lipid solubility of the drug, and the pH of the medium at the absorption site. The various steps involved in the absorption of a drug from an oral dosage form say a tablet dosage form, include disintegration, dissolution and then absorption. Out of these steps, the slowest step determines the rate and extent of absorption. Frequently it is the dissolution step which is the slowest and consequently the rate determining step. Since dissolution precedes absorption, the rate of absorption of a drug is influenced by its dissolution in the medium at the absorption site. The factors that affect dissolution of a drug include its solubility, particle size, surface area, etc.

In addition to dissolution, the absorption of a drug is also affected by formation of complexes in the gastrointestinal tract which results in reduced concentration of the drug at the absorption site.

One of the examples of chemical modification of a drug to improve its absorption is phenytoin (2). It is an anticonvulsant with poor aqueous solubility. As a result it shows erratic and poor absorption on oral administration. In order to improve its solubility, esters (4-6) of 3-hydroxymethyl analog (3) have been synthesized and found to have better absorption.



(2), R = H

(3), R = CH_2OH

(4), R = $CH_2OCCH_2\overset{+}{N}H(CH_3)_2.CH_3SO_3^-$

(5), R = $CH_2OCCH_2CH_2\overset{+}{N}H(CH_3)_2.CH_3SO_3$

(6), R = $CH_2OP(ONa)_2$

Drug Absorption and pH-Partition Hypothesis

Since most of the drugs are either weak acids or bases, their absorption from gastrointestinal tract takes place in unionized form, which is more lipid soluble species. The degree of dissociation, pKa, the negative logarithm of dissociation constant, is calculated from Henderson-Hasselbach equations (Eq. 1 and 2).

In case of acids:

$$RCOOH \longrightarrow RCOO^- + H^+$$

$$pKa = pH - \log \frac{[\text{ionized acid}]}{[\text{unionized acid}]}$$

$$= pH - \log \frac{[RCOO^-]}{[RCOOH]} \qquad \text{(Eq. 1)}$$

In case of bases:

$$RNH_3^+ \longrightarrow RNH_2 + H^+$$

$$pKa = pH - \log \frac{[\text{unionized form}]}{[\text{ionized form}]}$$

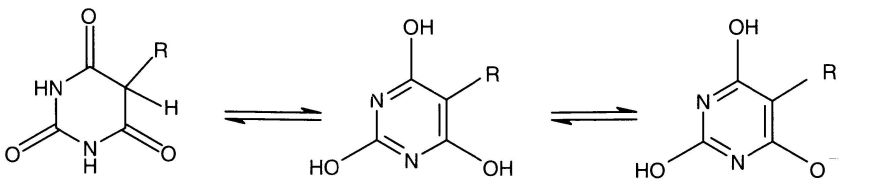
$$= pH - \log \frac{[RNH_2]}{[RNH_3^+]} \qquad \text{(Eq. 2)}$$

The antibacterial activity of benzoic, salicylic, and mandelic acids is greatest in acid media. This is because they remain largely unionzed in acid media and are thus absorbed well. After reaching the site of action they get ionized and show their antibacterial activity. A comparision of intestinal absorption of acids and bases in rat at several pH values (Table 12.1) shows that weak acids are best absorbed at low pH and weak bases at higher pH.

Minor changes in structures of closely related compounds can lead to significant changes in ionization and consequently lead to differences in biological activity. For example, barbituric acid (7) and its 5-monosubstituted (8) derivatives are inactive, while as 5, 5-disubstituted derivatives (9) are CNS depressants. This lack of CNS depressant activity of barbituric acid (pKa 4.0) and its 5-monosubstituted (8) derivatives (5-ethyl, pKa 4.4) is because they are stronger acids. They are able to achieve completely aromatic structure (7a and 8a) which can stabilize the barbiturate ion (7b and 8b) by delocalization of the extra pair of electrons. It has been found that at physiological pH barbituric acid (7) and its

Table 12.1 Percent absorbed of some acids and bases at various pH

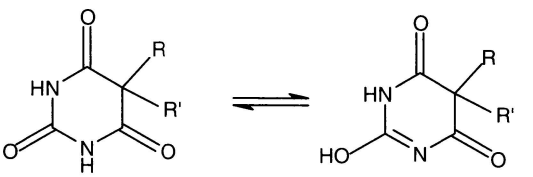
	pKa	*Percent absorbed* pH 4	pH 5	pH 8
Acids				
1. 5-Nitrosalicylic acid	2.3	40	27	0
2. Salicylic acid	3.0	64	35	10
3. Benzoic acid	4.2	62	36	5
Bases				
1. Aniline	4.6	40	48	61
2. Aminopyrine	5.0	21	35	52
3. *o*-Toluidine	5.3	30	42	62
4. Quinine	8.4	9	11	54



(7), R = H
(8), R = alkyl or aryl

(7a), R = H
(8a), R = alkyl or aryl

(7b), R = H
(8b), R = alkyl or aryl

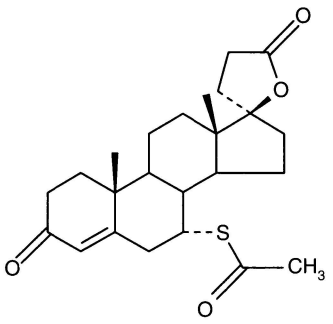


(9), R = R' = alkyl or aryl

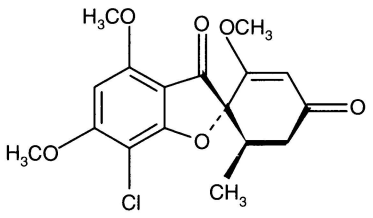
5-monosubstituted (8) derivatives are 99.9 % in ionic form and therefore are not able to cross the blood brain barrier. In contrast, 5, 5-disubstituted barbiturates (9) cannot assume a fully aromatic structure and therefore are much weaker acids (pKa 7.0-8.5). Thus they remain largely in unionized form at physiological pH and are capable of ready passage into the lipoidal tissues of CNS.

Surface Area and Particle Size

Increase in surface area through reduction in particle size results in rapid dissolution. Higher dissolution of many poorly soluble drugs has been achieved through micronization. Thus, the absorption of spironolactone (10), a diuretic, has been increased through micronization. This has resulted in reduction of dose from 500 mg to 25 mg. Similar results have been achieved in griseofulvin (11).



(10)



(11)

Hydrogen Bonding and Biological Activity

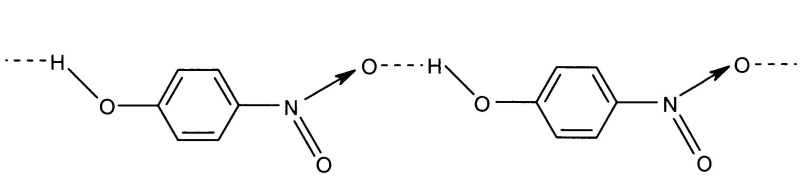
In a hydrogen bond, a hydrogen atom holds two atoms together. The atoms capable of forming hydrogen bond are fluorine, oxygen, and nitrogen. The most common hydrogen bonds are given in Fig. 12.2. Hydrogen bonding could be intermolecular (12) or intramolecular (13). The strength of hydrogen bond varies from 1 to 10 kcal/mole and is usually 5 kcal/mole. It is, thus, a weak bond. Even though it is a weak bond it has a profound effect on biological activity as is evident from the following examples.

O—H----O; O—H----N;

N—H----N; N—H----O;

N—H----F; F—H----F;

Fig. 12.2 Some common hydrogen bonds



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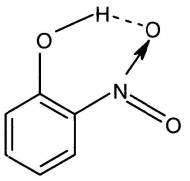
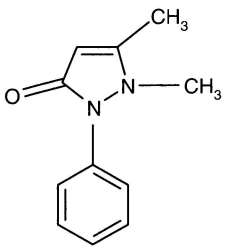


(13)

1. The specific configuration of proteins is because of hydrogen bonding. Denaturation of proteins results in breaking of these hydrogen bonds.
2. 1-Phenyl-2, 3-dimethyl-5-pyrazolone (antipyrine, 14) is a good analgetic while as its 2-desmethyl analog (15) does not possess analgetic activity. The absence of analgetic activity in (15) has been



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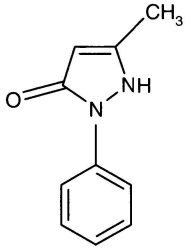


(15)

attributed to intermolecular hydrogen bonding resulting in linear chain formation (Fig. 12.3). As a result it is insoluble in water. The dimethyl analog (14), on the other hand is not capable of forming intermolecular hydrogen bonds and is more soluble in water (1:1) and an effective analgesic.

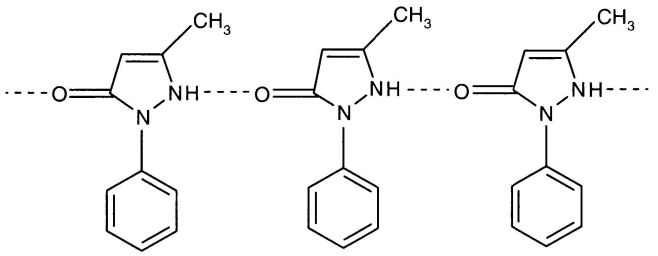
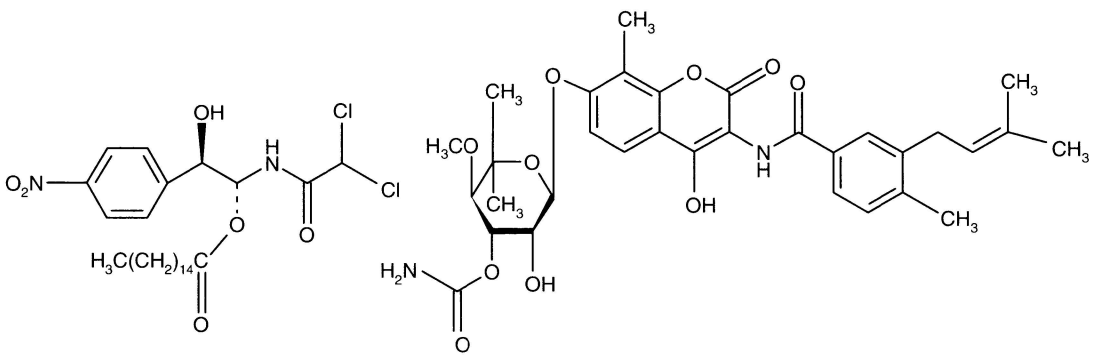


Fig. 12.3 Hydrogen bonding in case of 1-phenyl-3-methyl-5-pyrazolone

Polymorphism

A solid can exist either as amorphous powder or in crystalline form. The ability of a substance to exist in more than one crystalline form with different internal structures is known as polymorphism. Polymorphs are similar in liquid and gaseous state. The polymorphs differ in their physical properties such as solubility, melting point, density, hardness, and compression characteristics. Different polymorphs of a substance are having differing stabilities. The more stable polymorph is in lowest energy state, has highest melting point, and possesses lowest aqueous solubility. The other polymorphs are known as metastable forms. They are in higher energy state, have low melting points and possess higher water solubility. The metastable forms are, thus, preferred forms of polymorphs for the preparation of various dosage forms. Metastable forms readily go to lowest energy state, the stable form. However, when kept dry, they remain stable for long periods. One of the typical example of existence of polymorphic form is in case of chloramphenicol palmitate (16). It exists in 3 polymorphic forms namely A, B, and C. The B-form of polymorph has the best bioavailability. In some cases the amorphous form may have higher water solubility than the crystalline form, example novobiocin (17). The amorphous form is about 10-times more soluble than the crystalline form.



(16) (17)

In addition to the inherent properties of a drug discussed above, the other factors which affect the availability of drug at the receptor/enzyme is the form in which it is administered, i.e. dosage form. The

most common routes through which drugs are administered include, oral and parenteral. The other routes include, topical, buccal, sublingual, etc.

The various dosage forms in which the drugs are administered orally include, tablets, capsules, suspentions, emulsions, powders, solutions, etc. The relative bioavailability of these dosage forms decreases in the order: solutions>emulsions>suspentions>capsules>tablets.

While as tablets require disintegration before dissolution and absorption, capsules, powders and emulsions need only dissolution before absorption. The solution requires absorption step only, thus, the above order of bioavailability. The excipients used in formulation also affect the bioavailability of a drug from its dosage form. More information regarding the bioavailability of various dosage forms can be obtained from any standard book on biopharmaceutics.

FURTHER READING

1. S.H. Curry and K.M. Thakker in "Comprehensive Medicinal Chemistry – Biopharmaceutucs," Vol. 5, C. Hansch, Ed. in-Chief, Pergamon Press, Oxford, 2005, p. 545.
2. Han van de Waterbeemd in "Modern Methods of Drug Discovery," A. Hillisch and R. Hilgenfeld, Eds., Birkhauser Verlag, Switzerland, 2003, p. 243.
3. D.M. Brahmanker and S.B. Jaiswal, "Biopharmaceutics and Pharmacokinetics – A Treatise," Vallabh Prakashan, New Delhi, 1995.