Learning outcomes
On completion of this article, you should be able to:

- Describe the general principles of how the body handles drugs (pharmacokinetics)
- Describe the basic principles of drugs action (pharmacodynamics)
- Discuss the pharmacokinetics of ophthalmic drugs.

Introduction
The science of pharmacology is concerned with the effects of drugs on the function of living tissues (Greek: Pharmakos = drug, Logos = study). Since modern medicine relies heavily on drugs as the principal tool for the treatment and prevention of disease, it is important that all clinicians possess a basic understanding of the pharmacological principles that govern their clinical use. These include the mechanisms by which the body handles drugs, so that the optimal dose can be delivered to the target tissue, coupled with an understanding of how drugs act at a cellular or molecular level so as to predict adverse reactions and interactions.

A large number of drugs, including both topical and systemic preparations, are used in the treatment of eye disease. However, the eye presents a particular challenge for drug delivery due to the various barrier mechanisms that have evolved to protect the delicate ocular tissues from noxious substances. These barriers often make it difficult to maintain a sufficiently high drug concentration to achieve the desired therapeutic effect. Although the use of high drug concentrations can sometimes be used to overcome these barriers, this needs to be balanced with the susceptibility of the eye to drug toxicity and the risk of systemic adverse effects. The aim of this module is to provide an overview of the general principles of pharmacology and specifically address the factors involved in ocular pharmacokinetics.

GENERAL PHARMACOLOGICAL PRINCIPLES
Pharmacokinetics
The way in which the body handles drugs is described by the term pharmacokinetics. Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs. These parameters are important when choosing an appropriate route of administration for a particular drug and pharmacokinetic factors can also be a cause of inter-individual variability in therapeutic response.

Drugs may be administered by a variety of routes (Figure 1). In most cases the oral route (enteral) is preferred, partly for convenience but also since strict sterility need not be observed. Alternative routes (perenteral) are chosen if a drug is poorly absorbed from the gut, causes gastrointestinal irritation or if a specific local action is required (as with ophthalmic drugs or inhaled drugs to treat asthma).

For a drug to reach its target tissue it must first be absorbed from its site of administration. The rate of absorption is largely determined by lipid solubility, which governs penetration across cell membranes. Non-polar (unionised) compounds readily penetrate cell membranes by diffusion; however most drugs are weak acids or bases, which can exist in ionised or unionised forms. The ratio of these two forms is determined by the surrounding pH and the dissociation constant (pK), which represents the pH at which the drug is 50% ionised.
For a weak acid the ionisation reaction can be represented by:

\[ \text{HA} \xrightleftharpoons{K_a} A^- + H^+ \]

The degree of ionisation can be calculated from the Henderson-Hasselbalch equation:

\[ \text{pH} = \text{pKa} + \log \left[ \frac{[A^-]}{[HA]} \right] \]

Similarly for a weak base:

\[ \text{BH}^+ \xrightleftharpoons{K_b} B + H^+ \quad \text{pH} = \text{pKb} + \log \left[ \frac{[B]}{[BH^+]} \right] \]

The ionised species BH\(^+\) or A\(^-\) have low lipid solubility and will be not cross cell membranes (unless a specific carrier mechanism exists). By contrast, the uncharged species B or HA are lipid soluble and will potentially pass through the plasma membrane. However, the rate of membrane diffusion will additionally depend on the molecular size and chemical structure of the drug. For example, aminoglycoside antibiotics are uncharged but contain a number of hydrogen-bonding groups, which renders them effectively hydrophilic.

The term bioavailability refers to the fraction of the dose that proceeds unaltered from the site of administration and becomes available at the site of action. For systemic drugs it is measured as the area under the curve of log plasma concentration versus time. Bioavailability is to a large extent dependent on the rate of absorption, but in the case of orally administered drugs other factors are involved. For example, a proportion of the administered drug can become chemically altered e.g. broken down by the acid conditions of the stomach, or biotransformed by enzymes within the gut wall or liver before it reaches the plasma compartment (Figure 2). This latter effect is termed first pass metabolism and explains why, for example, glyceryl trinitrate (GTN), a drug used for the treatment of angina, is effective sublingually but not when swallowed. Topical ophthalmic drugs, that undergo systemic absorption across the nasal mucosa,
escape first pass metabolism. As a result, bioavailability is high with a greater risk of systemic adverse effects.

Once in the bloodstream, the drug can be distributed to the tissues. However, distribution is frequently not uniform, due to factors such as the physicochemical properties of the drug, differences in blood flow between tissues or degree of ‘leakiness’ of the blood vessels within a particular tissue. Furthermore, the drug may have an affinity for a particular tissue component e.g. melanin or fat. Plasma protein binding is another important variable. Drugs travel in the plasma, partly in solution (unbound drug), or bound to plasma proteins (bound drug). It is the unbound drug that is pharmacologically active. Albumin is the major plasma protein for drug binding and binds mainly acidic drugs e.g. warfarin and non-steroidal anti-inflammatory drugs (NSAID). Other plasma proteins, e.g. α acid glycoprotein, bind mainly basic drugs such as propranolol. Protein binding potentially reduces the availability of the active form of the drug and protein-bound drugs show a restricted tissue distribution. Less commonly, protein binding can form the basis of certain drug interactions as one drug displaces another from its protein-binding site.

The elimination of drugs from the body occurs by two processes: metabolism (biotransformation) and excretion. Metabolism involves the enzymatic conversion of the drug into another chemical entity, whereas excretion consists of the elimination of the unchanged drug (or its metabolites). The body has evolved a variety of mechanisms to detoxify foreign chemicals, which are utilised in the biotransformation of drug molecules. Drug metabolism involves two types of chemical transformation, which are termed phase I and phase II reactions (Figure 3).

Most drugs leave the body in the urine either unchanged or as polar metabolites. Other drugs are secreted into bile via the liver followed by loss of the drug via the faeces. The rate of renal clearance is variable: some drugs are lost in a single transit whilst others are cleared more slowly. Three fundamental processes account for renal excretion: glomerular filtration, tubular secretion and passive diffusion across the renal tubule. Glomerular filtration is possible for those drugs that are not bound to plasma proteins and is dependent on the glomerular filtration rate. However, only about 20% of the drug is lost across the glomerulus and the remainder passes to the capillaries surrounding the tubules. From here, the drug may be actively secreted into the tubule lumen by drug transporters or may diffuse passively across the tubule. Lipid soluble drugs are extensively reabsorbed and are therefore not...
efficiently cleared. For those drugs that are excreted without biotransformation, drug action can only be terminated by renal elimination. These drugs therefore need to be prescribed with special care in the elderly and in those with altered renal function.

Most drugs are administered as a fixed dose given at regular intervals. The duration of drug action is governed by its half-life, which is a function of its tissue distribution and clearance. A drug with a short half-life needs to be administered more frequently with the potential for non-compliance. For example, the calcium channel blocker nifedipine, which is used in the treatment of hypertension, has a short half-life (approximately two hours) and needs to be administered four times per day. Prolongation of the half-life can be achieved by chemical modification or using a sustained release formulation.

Principles of drug action: pharmacodynamics

Drugs are effectively chemicals that alter the physiological function of cells in a specific way. Most drugs exert their effects by binding to specific target protein molecules (Figure 4). These targets include:

- Receptors
- Enzymes
- Transporters
- Ion channels

Receptors: Many therapeutically important drugs act on receptors (Table 1). Receptors have evolved to allow endogenous chemical signals (e.g. neurotransmitters, hormones) to affect cellular function. Most receptors are situated on the surface of cells and therefore the interaction between drug and receptor occurs at the cell surface. However, drugs binding to intracellular receptors (e.g. steroids) must be lipid soluble since they have to cross the plasma membrane.

Enzymes: some drugs alter cell function by interacting with enzymes. Typically, the drug is a substrate analogue, which acts as a reversible or irreversible inhibitor. Alternatively, drugs can act as false substrates, which are converted into a product, which subverts a normal metabolic pathway. Some drugs require enzymatic transformation to convert them from an inactive form (pro-drug) to an active form.

Transporters: these molecules normally transport ions or small organic molecules across the cell and contain recognition sites for the particular carrier species that are often the target for drugs.

Ion channels: these transmembrane proteins contain a central channel through which particular ions can flow when the channel is open. Some channels incorporate a receptor and open only when an agonist occupies the receptor. Drugs can either physically block the channel (e.g. local anaesthetics acting on voltage-gated sodium channels) or the drug can interact with the receptor site.

For a drug to be useful as a therapeutic tool it must act selectively on particular cells and tissues i.e. it must show a high degree of specificity in terms of its binding site. However, specificity is rarely absolute and a drug can affect targets other than the principal one and lead to unwanted side effects, particularly in the case of those drugs where the toxic dose is similar to the therapeutic dose. Such drugs e.g. digoxin are said to have a narrow therapeutic index and patients need to be monitored closely for side effects.
Basic and ocular pharmacology

<table>
<thead>
<tr>
<th>Target</th>
<th>Effector 1</th>
<th>Effector 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-adrenoceptor</td>
<td>Noradrenaline</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Muscarinic Ach receptor</td>
<td>Acetyl choline</td>
<td>Cyclopentolate</td>
</tr>
<tr>
<td>Histamine (H1 receptor)</td>
<td>Histamine</td>
<td>Cetirizine</td>
</tr>
<tr>
<td>Histamine (H2 receptor)</td>
<td>Histamine</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Dopamine (D2 receptor)</td>
<td>Dopamine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Oestrogen receptor</td>
<td>Oestradiol</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine esterase</td>
<td>Neostigmine</td>
<td></td>
</tr>
<tr>
<td>Carbonic anhydrase</td>
<td>Acetazolamide</td>
<td></td>
</tr>
<tr>
<td>Reverse transcriptase</td>
<td>Zidovudine (AZT)</td>
<td></td>
</tr>
<tr>
<td>Transporter molecules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺ K⁺ ATPase</td>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Na⁺ K⁺ Cl⁻ cotransporter</td>
<td>Furosemide</td>
<td></td>
</tr>
<tr>
<td>Ion channels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage gated sodium channels</td>
<td>Local anaesthetics</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Examples of targets for drug action

Although binding of a drug to its receptor can be measured directly using radioactive isotopes, it is more usual to look at a biological response as an indirect index of receptor occupancy. This is often plotted as a dose response curve (Figure 5). From the curve, the maximum drug response ($E_{\text{max}}$) and the concentration of the drug to produce a 50% ($EC_{50}$) maximal response can be calculated. A drug can be characterised in terms of its efficacy and its potency. The efficacy represents the maximal response a drug can give whereas the potency describes the amount of drug to give a desired response. Drugs can either stimulate receptors (agonists) or bind to receptors without stimulating them (antagonists). Agonists can be divided into full agonists that produce a maximal response when all receptors are occupied, or partial agonists, which produce a sub-maximal response. Antagonists can be competitive or non-competitive. With competitive antagonists e.g. beta-blockers, the drug effect can be overcome by increasing the agonist concentration. By contrast, increasing the agonist concentration has no effect on the action of non-competitive antagonists.

OCULAR PHARMACOLOGY

Ocular pharmacokinetics

The structural constraints and diffusional resistances that regulate the movement of drugs within ocular tissues are summarised in Figure 6a. Dashed lines denote indicates tissue barriers with a lower diffusional

Figure 5: A dose response curve

Figure 6:

a. Pharmacokinetic model of the eye
b. Compartment model of the eye used to predict variation in drug concentration with time. a = aqueous, c = cornea, d = tear reservoir, h = posterior chamber, i = iris, l = lens, p = plasma, s = sclera, v = vitreous, z = ciliary body

Adapted from Maurice and Mishma (1984)
resistance. Continuous lines represent cellular barriers with a higher resistance and the thickness of the line denotes the resistance. It is important also to consider the vascular system: particularly the relative permeability of the blood vessels in each tissue. Although the system is complex it can be modelled fairly simply as a series of interconnected compartments (Figure 6b) and this technique is frequently used in drug development to calculate changes in drug concentration over time.

Various methods are available to deliver therapeutic agents to ocular tissues including:

- Topical administration
- Local injection
- Systemic administration (ingestion or perenteral injection).

**Topical Administration**

Topical application of drugs is the method of choice for most eye diseases and solutions or suspensions administered as eyedrops account for the majority of ophthalmic formulations. These include drugs that act at the surface of the eye e.g. antimicrobials for superficial infection, as well as those that pass through the cornea to reach intraocular targets as in the case of anti-glaucoma drugs. One of the main problems with a topical route of delivery is the rapid and extensive pre-corneal drug loss. A single drop from a conventional dropper bottle is 40-50μl, which overwhelms the capacity of the conjunctival sac to contain it and following a blink only about 10μl of the original volume remains.

The rate of tear turnover has a major influence on pre-corneal drug retention time. Radioactive suspensions instilled into human eyes show a two-thirds reduction in radioactivity within two minutes, followed by complete elimination after 15 minutes. The loss of an instilled drug from the precorneal area is the net result of nasolacrimal drainage, tear turnover, binding to tear proteins and extracorneal uptake (Table 2). Drainage of a drug through the nasolacrimal duct is more rapid than its rate of absorption across the cornea. Higher rates of drainage are found with larger drop sizes (Figure 7a).

For most drugs, increasing the drop size above 20μl does not significantly increase bioavailability and could potentially increase the risk of systemic toxicity (Figure 7b). Furthermore, if a drop of one medication is followed rapidly by a drop of another, a substantial washout occurs with a lessening of its effect. However, after an interval of five minutes almost no washout occurs.

Reducing the loss of the instilled drug from the pre-corneal area represents a key strategy for improved bioavailability, and various techniques have been proposed to improve the pre-corneal drug retention time e.g. adding polymers such as polyvinyl alcohol or methylcellulose to increase viscosity.

The cornea represents the major route for drug entry into the anterior chamber. Anatomically, the cornea consists of five tissue layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium (Figure 8). In terms of drug penetration, only the epithelium, stroma and endothelium represent

---

**Pre-corneal factors influencing ophthalmic drug bioavailability**

- Volume of drug instilled
- Drug formulation
- Tear turnover
- Tear protein binding
- Tissue absorption

**Table 2: Pre-corneal pharmacokinetics**
Basic and ocular pharmacology

Figure 8

A. Transverse histological section through the cornea. The stroma represents 90% of the corneal thickness and is bounded by the epithelium (asterisk) and endothelium (arrow). The transcorneal movement of the ionised and unionised forms of a weak base is shown.

B. Detail of the corneal epithelium. Three types of cells are seen: basal cells (asterisk), wing cells (arrow head) and squamous cells (arrow). The most superficial cells are linked together by tight junctions. BM=Bowman's membrane.

C. Detail of the corneal endothelium, which consists of a single layer of squamous cells (arrow). DM=Descemet's membrane.

significant permeability barriers. The epithelium is the primary penetrant barrier, and therefore drug lipophilicity is one of the most important determinants of drug permeability. Lipophilicity is measured by the partition coefficient of the drug between an organic solvent (octanol) and an aqueous solution. Generally, the greater the partition coefficient of a drug, the greater its corneal penetration. However, the hydrophilic nature of the stroma means that it can become rate limiting for highly lipophilic compounds, which become retarded at the epithelial:stromal interface. Formulations, which possess an optimal balance of hydrophilic and lipophilic properties, can therefore more readily permeate the cornea (Figure 9). For example, many ophthalmic preparations are weak acids or bases, which exist in both, unionised and ionised forms. A simple representation of the ocular penetration of a weak base is shown in Figure 8. In its unionised form (R3N) the drug can readily cross the epithelium, and upon conversion to its ionised form (R3NH+) it can be transported through the stroma. For a particular drug, the ratio between ionised and unionised forms is determined by the pH and the dissociation constant. The endothelium is made up of a single layer of squamous cells and is therefore a low resistance barrier. Like the epithelium, it favours lipophilic compounds (such as R3N), although hydrophilic agents can cross the endothelium by a paracellular route.

Although the cornea is the primary route for drug entry into the eye, the conjunctiva and sclera should not be ignored. Drug penetration across the conjunctival epithelium is likely to be more rapid than across the corneal epithelium, although the rich vascularity of the conjunctiva means that there is considerable scope for systemic absorption. The co-administration of vasoconstrictors could potentially reduce this possibility. For most drugs, the rate of trans-scleral permeability is similar to the corneal stroma.

The rate at which a drug is absorbed is affected by ocular disease. Infection, inflammation and trauma can significantly alter pharmacokinetics by increasing corneal permeability or breakdown of blood-tissue barriers.

Drug metabolism and excretion

Knowledge of the pathways by which drugs are metabolised is essential for predicting drug clearance and detoxification. Several enzymes that are involved in drug metabolism have been identified within the eye. These include: esterases, peptidases, ketone reductase, monoamine oxidase, N-acetyltransferase, oxidoreductase, and catechol-O-methyltransferase. Some drugs are broken down by the tissues during intra-ocular penetration, which may limit their

Figure 9: Optimal corneal penetration occurs for drugs which have a balance between hydrophilic and lipophilic properties
effectiveness. However, these pathways can be exploited in the development of pro-drugs, where the breakdown product is more efficacious than the parent compound. For example, the anti-glaucoma drug latanoprost is metabolised by esterases on its transit through the cornea.

Following corneal penetration, drugs are distributed into, and then eliminated from the aqueous humour. The aqueous is continuously secreted by the ciliary epithelium at a rate of 2-5μl/min, and drains by two routes: a conventional route via the canal of Schlemm, and a non-conventional pathway through the connective tissue of the ciliary muscle (uveo-scleral pathway) (see blue arrows in Figure 10). Drugs are eliminated from the anterior chamber by a combination of aqueous turnover and absorption into the tissues of the anterior uvea. Drug binding to the pigmented tissues of the iris and ciliary body is an additional factor, which can influence bioavailability and may predispose to toxicity. For example, the mydriatic and cycloplegic effects of cyclopentolate and tropicamide are slower in onset in heavily pigmented irides due to melanin binding.

Systemic administration

Systemically administered drugs may enter the bloodstream from where they can reach ocular structures across the limbal, uveal and retinal vasculature. Although relatively few ophthalmic drugs are administered via this route, it is important to consider these pathways from the point of view of potential drug toxicity. Several factors determine the delivery of systemic drugs into eye including the physicochemical characteristics of the drug and the integrity of the blood-ocular barriers (Table 3).

![Figure 10: The blood aqueous barrier (black arrows) limits the passage of hydrophilic drugs into the anterior chamber (AC). The barrier is formed by tight junctions between ciliary epithelial cells and vascular endothelial cells of the iris. This barrier can be breached by leakage across connective tissue at the iris root (red arrow). Drug access to tissues behind the iris is prevented by tight junctions within the iris epithelium (green arrow). PC=posterior chamber, VC=vitreous cavity, ev=episcleral veins.](image)

**Factors influencing ocular penetration of systemic drugs**

- Protein binding
- Molecular size
- Lipid solubility
- Active transport
- Integrity of blood-ocular barriers

**Table 3: Intra-ocular drug penetration from the systemic circulation**

The delicate internal tissues of the eye are protected from the general circulation by two barrier systems: the blood-aqueous (BAB) and the blood-retinal (BRB) barriers. Both show a high selectivity for the transfer of solutes from the blood. The blood-aqueous barrier has two structural components: an epithelial barrier within the ciliary body, and an endothelial barrier within the iris. Experiments using a variety of tracers injected into the vasculature have shown that tight junctions between adjacent non-pigmented (inner) ciliary epithelial cells, and between the endothelial cells of iris blood vessels provide the major barrier to the free diffusion of molecules from the blood into the aqueous. Recent studies have shown that small quantities of plasma-derived proteins can "leak" into the anterior chamber from the stroma of the ciliary body across the iris root. However, they are prevented from entering the posterior chamber by the tight junctions of the iris epithelium and the unidirectional flow of aqueous from the posterior to anterior chambers (Figure 10). Under normal circumstances the integrity of the BAB serves as a selective partition between the retina and the circulation (Figure 11). It maintains the highly specialised environment that is essential for optimal neural function. The retina has two sites where there is a direct interface with the blood: at the level of the retinal vasculature and at the chorioretinal interface. Tight junctions between adjacent capillary endothelial cells, and between retinal pigment epithelial cells, form a continuous and almost impermeable barrier that limits the passive influx of all but the smallest of lipid-soluble molecules (Figure 12).

The factors influencing drug penetration into the retina are not fully understood. Mechanisms other than passive diffusion are likely to be involved in retinal drug delivery, for example facilitated or active transport systems. Several influx and efflux drug transport proteins, which have been well characterised in peripheral tissues, have been identified at the BRB e.g.
P-glycoprotein and members of the organic anion transport system. Efflux carriers provide a protective function by removing drugs from the retina and transferring them back into the systemic circulation. Furthermore, drug-metabolising enzymes within the BRB play a role in the detoxification of potentially harmful pharmacological agents. Despite these protective mechanisms, several drugs are associated with significant retinal toxicity e.g. cardiac glycosides, phenothiazines and quinolone preparations. The ability of these drugs to enter the retina may be the result of several factors such as the absence of BRB characteristics in some blood vessels at the optic nerve head, or the absence of appropriate retinal efflux transporters.

Another factor affecting drug toxicity is the degree of melanin blinding e.g. chloroquine binds to melanin and is taken up by the retinal pigment epithelium, which may account for the retinopathy that can occur during prolonged use of this drug.

**Conclusion**

In this article, the way in which the body handles drugs (pharmacokinetics) and the basic principles of how drugs act (pharmacodynamics) have been discussed. In particular, the factors influencing the absorption, distribution, metabolism and excretion of ophthalmic drugs have been explained. This information will provide a foundation for an understanding of the action of therapeutic agents used in ophthalmology.

**FURTHER READING**


---

**Figure 11: Anatomy of the blood-retinal barrier.**

(A). Inner blood-retinal barrier is formed by vascular endothelial cells (EC) joined together by tight junctions. (B). Outer blood-retinal barrier is formed by tight junctions between adjacent retinal pigment epithelial cells (RPE). Influx and efflux drug transporters (arrows), located at both sites, further regulate drug entry into the retina. L=lumen.

**Figure 12: Demonstration of the blood-retinal barrier**

A. Reference histological section through the retina and choroid

B. Following an intravascular injection of sodium fluorescein there is widespread leakage in the choroid (asterisk). The RPE prevents access of the dye into the retina. Within the inner retina fluorescein is confined to the capillary lumen (arrows)
Basic and ocular pharmacology


MULTIPLE CHOICE QUESTIONS

1. What is the primary determinant of the rate of drug absorption?
   a. Route of administration
   b. Dose
   c. Molecular size
   d. Lipophilicity

2. What is ‘first pass metabolism’?
   a. Biotransformation of a drug by gut wall or liver enzymes prior to entry into the plasma compartment
   b. Direct entry of drugs into the plasma compartment
   c. Passage of a drug through the liver without being chemically altered
   d. An increase in the water solubility of a drug to facilitate excretion

3. What is the dissociation constant (pK) of a drug?
   a. The pH at which the drug is 50% ionised
   b. $-\log_{10}[H^+]$
   c. A variable whose value depends on the surrounding pH
   d. A measure of a drug's stability in an aqueous environment

4. Which plasma protein is primarily responsible for drug binding?
   a. Globulin
   b. Albumin
   c. Alpha glycoprotein
   d. Low density lipoprotein

5. What is phase I metabolism?
   a. Metabolism of a drug by liver microsomal enzymes to facilitate its excretion
   b. Conjugation of a drug to increase its lipophilicity
   c. Addition of hydrophilic groups to increase a drug's solubility
   d. Biotransformation of a drug on its transit through the kidney

6. Which is the principal organ for the excretion of drugs?
   a. Liver
   b. Intestine
   c. Pancreas
   d. Kidney

7. Which of the following groups of drug act upon ion channels?
   a. Steroids
   b. Beta blockers
   c. Local anaesthetics
   d. Cardiac glycosides

8. Which of the following drugs acts as an enzyme inhibitor?
   a. Chlorpromazine
   b. Furosemide
   c. Acetazolamide
   d. Propanolol

9. Which of the following statements regarding the absorption of topical ophthalmic drugs is true?
   a. Increasing the volume of an eyedrop leads to increased absorption
   b. Hydrophilic drugs readily penetrate the corneal epithelium
   c. Increasing pre-corneal retention time increases absorption
   d. 70% of the administered dose is available for absorption

10. Which of the following is an example of a pro-drug?
    a. Adrenaline
    b. Dorzolamide
    c. Latanoprost
    d. Timolol Maleate

11. Which of the following drugs binds to melanin and produces a characteristic retinopathy?
    a. Digoxin
    b. Chloroquine
    c. Vigabatrin
    d. Tamoxifen

12. What is the barrier that limits entry of hydrophilic drugs into the retina?
    a. Retinal efflux transporters
    b. Tight junctions between RPE cells and retinal vascular endothelial cells
    c. Anterior vitreous face
    d. Internal limiting membrane