

New York State Oral Pharmaceuticals Course

Principles of Ocular Related Drug Administration (Part 1)

DIANE T. ADAMCZYK, OD, FAAO

PROFESSOR

STATE UNIVERSITY OF NEW YORK

STATE COLLEGE OF OPTOMETRY

No financial disclosures

Ocular Pharmacotherapy

Ocular Pharmacotherapy

Ocular History Considerations

- Use of other ocular medications
- Current ocular conditions: inflammation may have an effect on drug effectivity

Ocular Pharmacotherapy

Medical History Considerations

- Drug interactions
 - MAO inhibitors or tricyclic antidepressants
 - Plus Phenylephrine may result in a cardiovascular effect
- Allergy/drug sensitivity
- Family Hx: POAG + topical steroid may see Δ IOP

Ocular Pharmacotherapy

Medical History Considerations

Systemic Conditions

- Renal/Hepatic Disease
- Cardiovascular Disease
 - Hypertension: Adrenergic agonists (phenylephrine especially 10%)
 - Congestive Heart Disease, bradycardia, AV block: beta blockers

Ocular Pharmacotherapy

Medical History Considerations

Systemic Conditions

- Respiratory Disorders:
 - Beta blockers

Ocular Pharmacotherapy

Medical History Considerations

Systemic Conditions

- Thyroid Disease
 - Adrenergic agonists with vasopressor activity:
 - Because of increased catecholamine activity associated with hyperthyroidism use of phenylephrine may result in increase bp

Ocular Pharmacotherapy

Medical History Considerations

Systemic Conditions

- Diabetes Mellitus

- Systemic hyperosmotics (e.g. oral glycerin used in angle closure): can result in hyperglycemia
- Systemic steroid use exacerbate diabetes
- Pupil dilation (poor dilation)

Ocular Pharmacotherapy

Medical History Considerations

Systemic Conditions

- CNS Disorders
 - Stimulants (may also have opposite effect): cyclopentolate
 - Beta blockers:
 - depression,
 - fatigue,
 - anxiety

Drug Labeling and Population Considerations:

Pregnancy, Lactation, Fertility, Pediatric, Geriatric

Ocular Pharmacotherapy

Medical History Considerations

- Pregnancy

Pregnancy Categories (Prior 2015)

- Category A: no risk to fetus (Vitamin B6)
- Category B: no evidence of risk (Erythromycin, brimonidine)
- Category C: risk to fetus cannot be ruled out (latanoprost)
- Category D: risk to fetus, but benefit outweigh risk (tetracycline)
- Category X: definite fetal risk; avoid
- This category system **over-simplification**
- 2015 updated labeling helps to inform health care providers with:
 - Prescribing decisions and
 - Patient counseling on use of prescription drug

U.S. Food and Drug Administration
Protecting and Promoting Your Health

FDA News Release

FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products

For Immediate Release

December 3, 2014

Effective date: June 30, 2015

Pregnancy and Lactation Prescription Drug and Biological Product Labeling

Updated labeling includes 3 subsections:

- Pregnancy
- Lactation
- Females and Males of Reproductive Potential

Pregnancy and Lactation Prescription Drug and Biological Product Labeling

Subsections must include:

- **Summary of the risks** using drug during pregnancy and breastfeeding
- Discussion of the **data supporting the summary**
- **Prescribing and counseling information** to help health care provider make **clinical considerations**

Updated labeling includes 3 subsections:

- **Pregnancy**
 - **Summary of risk**
 - **Data supporting summary**
 - **Prescribing and counseling info (clinical considerations)**
- **Lactation**
 - **Summary of risk**
 - **Data supporting summary**
 - **Prescribing and counseling info (clinical considerations)**
- **Females and Males of Reproductive Potential**
 - **Summary of risk**
 - **Data supporting summary**
 - **Prescribing and counseling info (clinical considerations)**

Pregnancy and Lactation Prescription Drug and Biological Product Labeling

Pregnancy subsection information includes:

- Potential risks to developing fetus
- *Registry information* must be reported
 - Includes data on how pregnant women affected by drug or biological product
- 3 subheadings - provides detailed information:
 - Risk summary
 - Clinical considerations
 - Data (may include)
 - human and animal data on use of drug
 - adverse reactions for pregnant women

Pregnancy and Lactation Prescription Drug and Biological Product Labeling

Lactation subsection information includes:

- Amount of drug in breast milk
- Potential effects on the breastfed child

- 3 subheadings - provides detailed information:
 - Risk summary
 - Clinical considerations
 - Data
 - Examples:
 - human and animal data on use of drug
 - adverse reactions for lactating women

Pregnancy and Lactation
Prescription Drug and
Biological Product Labeling

Females and Males of Reproductive Potential

subsection information includes the following as it relates to the drug used:

- Pregnancy testing
- Contraception
- Infertility

Pataday

PATADAY™ solution is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis. (1)

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 For topical ocular use only.
 - 5.2 Contamination of Tip and Solution
 - 5.3 Contact Lens Use

- 6 ADVERSE REACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics

- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 14 CLINICAL STUDIES**
 - 16 HOW SUPPLIED/STORAGE AND HANDLING**
 - 17 PATIENT COUNSELING INFORMATION**
 - 17.1 Topical Ophthalmic Use Only
 - 17.2 Sterility of Dropper Tip
 - 17.3 Concomitant Use of Contact Lenses
- * Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

- 1 INDICATIONS AND USAGE**

PATADAY™ solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.
- 2 DOSAGE AND ADMINISTRATION**

The recommended dose is one drop in each affected eye once a day.
- 3 DOSAGE FORMS AND STRENGTHS**

Ophthalmic solution 0.2%: each ml contains 2.22 mg of olopatadine hydrochloride.
- 4 CONTRAINDICATIONS**

Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.

Some of these events were similar to the underlying disease being studied.

- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy**

Teratogenic effects: Pregnancy Category C

- 8.5 Geriatric Use**

No overall differences in safety and effectiveness have been observed between elderly and younger patients.
- 11 DESCRIPTION**

PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is a sterile ophthalmic solution containing olopatadine for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88 and a molecular formula of $C_{21}H_{23}NO_3 \cdot HCl$.

The chemical structure is presented below:

Beovu

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEOVU safely and effectively. See full prescribing information for BEOVU.

BEOVU® (brolucizumab-dbl) injection, for intravitreal use
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Warnings and Precautions, Endophthalmitis and Retinal Detachment (5.1)	6/2020
Warnings and Precautions, Retinal Vasculitis and/or Retinal Vascular Occlusion (5.2)	6/2020

INDICATIONS AND USAGE

BEOVU is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1).

DOSAGE AND ADMINISTRATION

BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks (2.2).

DOSAGE FORMS AND STRENGTHS

Intravitreal injection: 6 mg/0.05 mL solution in a single-dose vial (3).

CONTRAINDICATIONS

- Ocular or Periocular Infections (4.1).
- Active Intraocular Inflammation (4.2).
- Hypersensitivity (4.3).

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachment may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).
- Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported following BEOVU injections. Patients should be instructed to report any change in vision without delay (5.2).
- Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.3).
- There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.4).

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
2.1	General Dosing Information
2.2	Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3	Preparation for Administration
2.4	Injection Procedure
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
4.1	Ocular or Periocular Infections
4.2	Active Intraocular Inflammation
4.3	Hypersensitivity
5	WARNINGS AND PRECAUTIONS
5.1	Endophthalmitis and Retinal Detachment
5.2	Retinal Vasculitis and/or Retinal Vascular Occlusion
5.3	Increase in Intraocular Pressure
5.4	Thromboembolic Events
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
6.2	Immunogenicity
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy

8.2	Lactation
8.3	Females and Males of Reproductive Potential
8.4	Pediatric Use
8.5	Geriatric Use
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.2	Pharmacodynamics
12.3	Pharmacokinetics
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
14	CLINICAL STUDIES
14.1	Neovascular (Wet) Age-Related Macular Degeneration (AMD)
16	HOW SUPPLIED/STORAGE AND HANDLING
16.1	How Supplied
16.2	Storage and Handling
17	PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BEOVU administration in pregnant women.

Based on the anti-VEGF mechanism of action for brolucizumab [see *Clinical Pharmacology* (12.1)], treatment with BEOVU may pose a risk to human embryo-fetal development. BEOVU should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brolucizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are transferred in human milk and because of the potential for absorption and adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with BEOVU.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Females of reproductive potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BEOVU and for at least one month after the last dose when stopping treatment with BEOVU.

Infertility

No studies on the effects of brolucizumab on fertility have been conducted and it is not known whether brolucizumab can affect reproductive capacity. Based on its anti-VEGF mechanism of action, treatment with BEOVU may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of BEOVU in pediatric patients has not been established.

8.5 Geriatric Use

In the two Phase 3 clinical studies, approximately 90% (978/1089) of patients randomized to treatment with BEOVU were ≥ 65 years of age and approximately 60% (648/1089) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is required in patients 65 years and above.



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U.S. Food and Drug Administration [Add Topic +](#)

Animal testing no longer required for drug approval. But high-tech substitutes aren't ready.

Late last year, Congress lifted the requirement that all new drugs be tested on animals. The law marks a triumph for animal rights activists, but what will replace mice, rabbits and primates?



Karen Weintraub
USA TODAY

Published 6:00 a.m. ET Jan. 15, 2023

The FDA Modernization Act 2.0 removes the requirement that all new drugs must be tested in two species – usually mice and a "higher order" mammal like rabbits or primates – before being tried in people. *Handout*

Passed Senate (09/29/2022)

FDA Modernization Act 2.0

This bill authorizes the use of certain alternatives to animal testing, including cell-based assays and computer models, to obtain an exemption from the Food and Drug Administration to investigate the safety and effectiveness of a drug.

The bill also removes a requirement to use animal studies as part of the process to obtain a license for a biological product that is biosimilar or interchangeable with another biological product.

Pharmacokinetics Compartments

OF THE EYE

Pharmacokinetics

An administered drugs course of:

- Absorption
- Distribution
- Metabolism
- Elimination

Compartment Theory

Compartment:

- Region of tissue or fluid through which a drug can diffuse and equilibrate
- Each compartment separated by barrier

Barrier

- Region of lower permeability or restricted diffusion between compartments

Pharmacokinetics

Drug absorption depends on:

- Molecular properties of the drug
- Viscosity of its vehicle
- Functional status of the tissue forming barrier to penetration

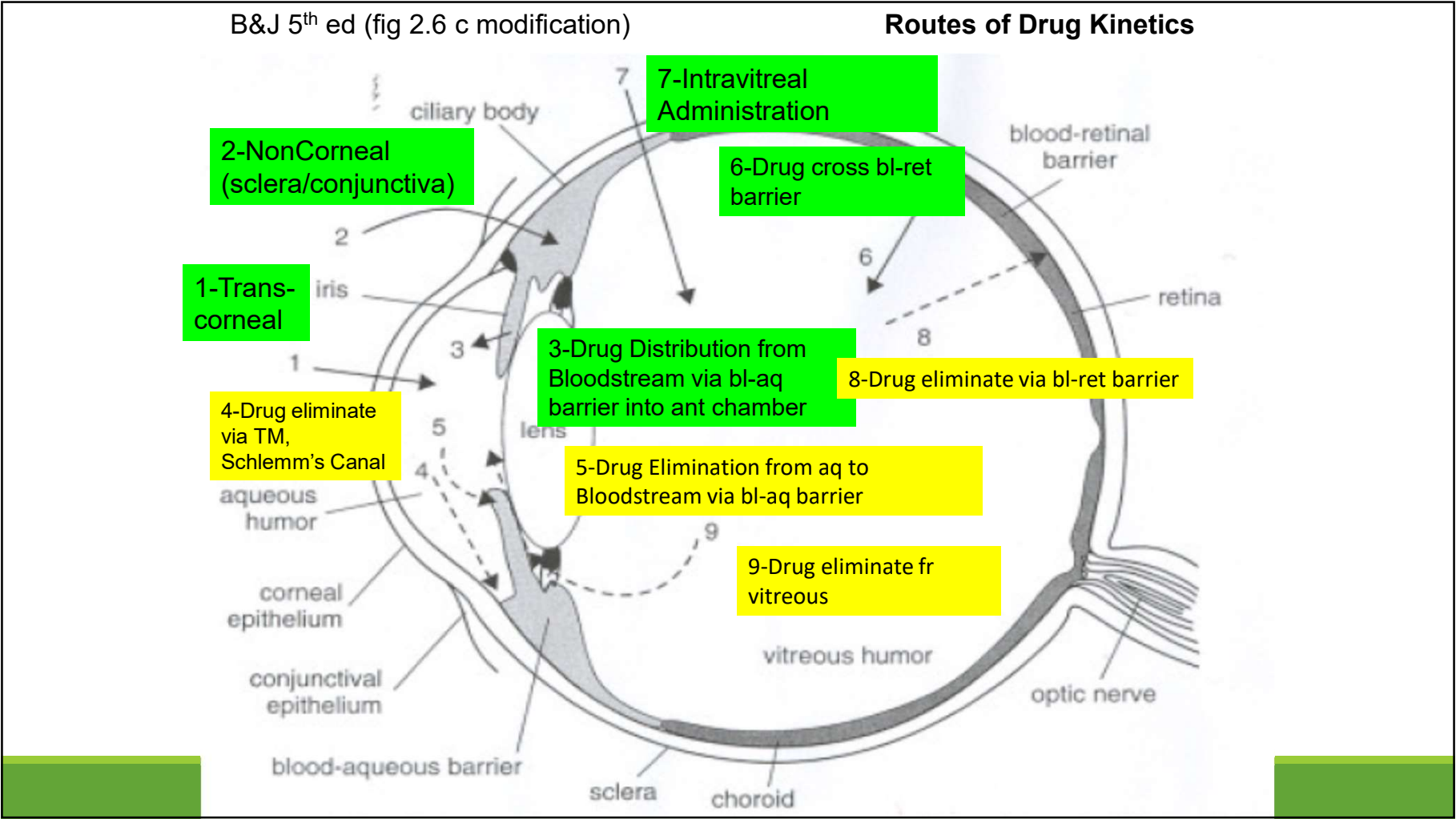
Pharmacokinetics

Drug distribution and bioavailability

- Interrelationships of the compartments and barriers of the eye

Metabolism

- Eliminates drugs and toxic byproducts



Ocular Penetration Routes for Topical Ophthalmic Drug Administration

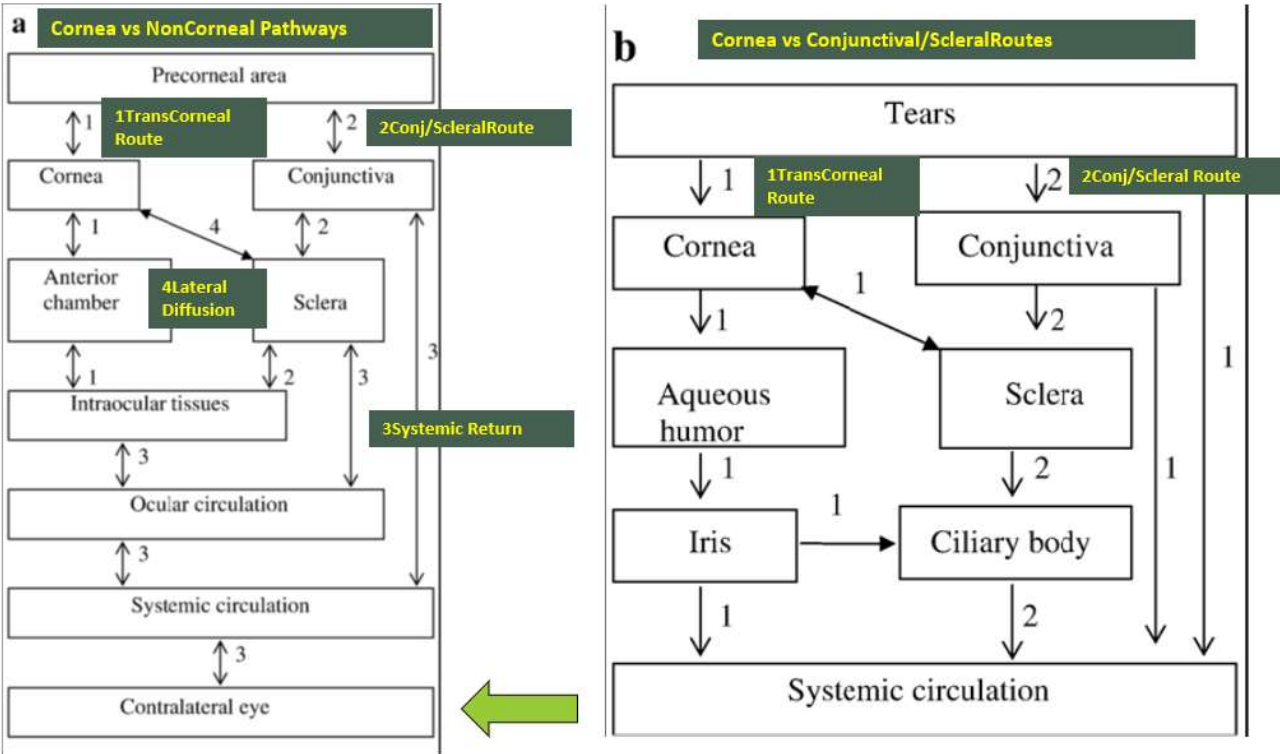


Fig. 3. Ocular penetration routes for topical ophthalmic drugs administration, (a) 1, transcorneal pathway; 2, noncorneal pathway; 3, systemic return pathway; 4, lateral diffusion. (b) 1, corneal route; 2, conjunctival/scleral route.

In situ-forming hydrogels for sustained ophthalmic drug delivery (NanjawadeBK, Manjappa AS) JControlRelease 122(2007)119-34

Ocular Absorption

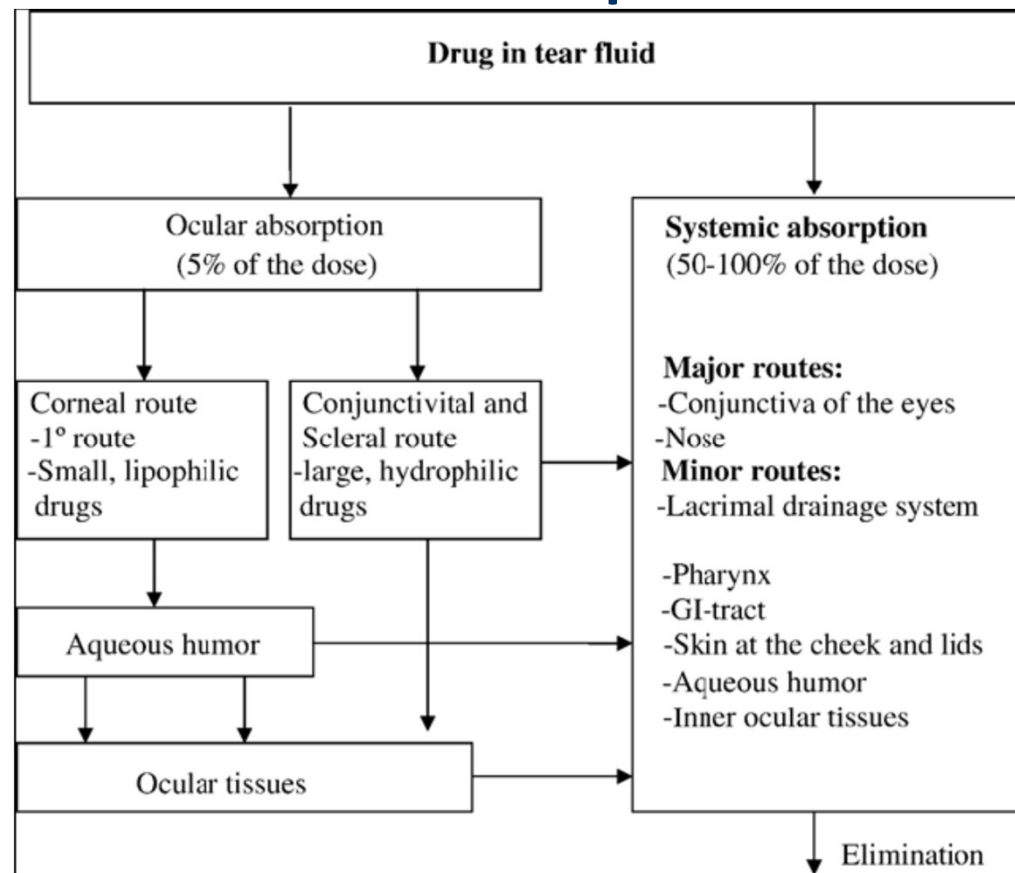
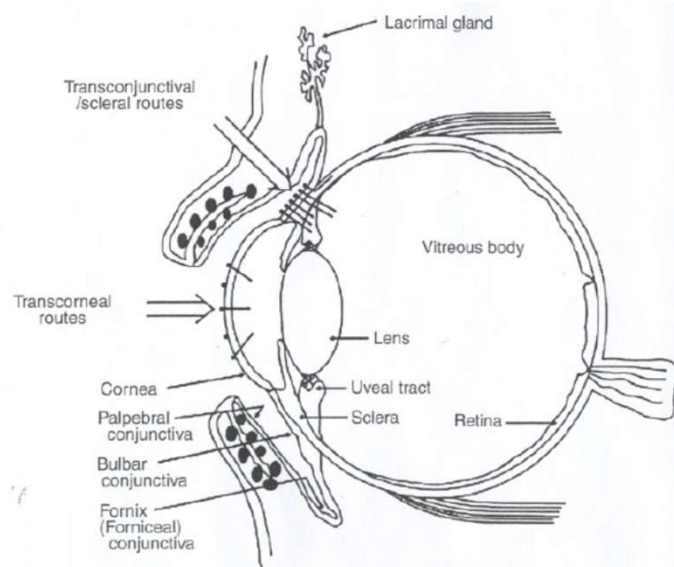


Fig. 2. Schematic diagram of ocular absorption.

In situ-forming hydrogels for sustained ophthalmic drug delivery (NanjawadeBK, Manjappa AS) JControlRelease 122(2007)119-34



Cornea Properties

Major functional barrier to ocular penetration

Major site of absorption

Pharmacodynamics

- Epithelium: lipophilic
- Stroma: hydrophilic
- Corneal penetration: biphasic solubility



Ciliary Body Properties

Ciliary Body is major source of drug metabolizing enzymes

- Drug detoxification
- Drug removal

Systemic drugs enter ant/posterior chambers through CB vasculature

Retina Properties

Zonula occludens of RPE:

- Prevent drug movement from blood to vitreous/retina

Retina capillaries

- Close-walled endothelial cells (blood retinal barrier)

Retina Properties

The barrier

- Protects entry of metabolites, toxins, hydrophilic drugs
- Lipophilic drugs cross barrier easily
 - Retinal toxicity from:
 - Digitalis, phenothiazines, quinine, others
- Systemic hydrophilic drugs do not cross

Drug Kinetics

Molecular property of drug influence:

- Which tissues act as reservoir vs barrier

Drug distribution depends on:

- Rate of passive diffusion
- Barrier resistance

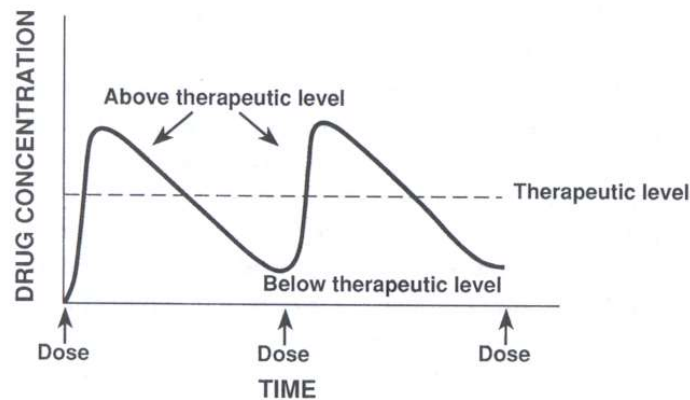


FIGURE 2-8 First-order kinetics of ocular drugs in solution or ointment. This results in periods of overdosage and underdosage. (Modified with permission from Place V, Benson H. Local effects of topically applied steroids. *J Steroid Biochem* 1975;6:717-722. Copyright 1975, Pergamon Press, Ltd.)

Drug Kinetics

First Order Kinetics

- Most common ocular drug movement
- Rate of movement is directly proportional to the concentration difference across the barrier
- Rate changes with time as the concentration differential across the barrier changes

Drug Kinetics

Zero-order Kinetics

- Release of drug is constant over time
- Concentration of drug released over time is independent of concentration
- Lacrisert



Drug Removal

Retinal vessels via active transport

Uveal vessels via bulk transport

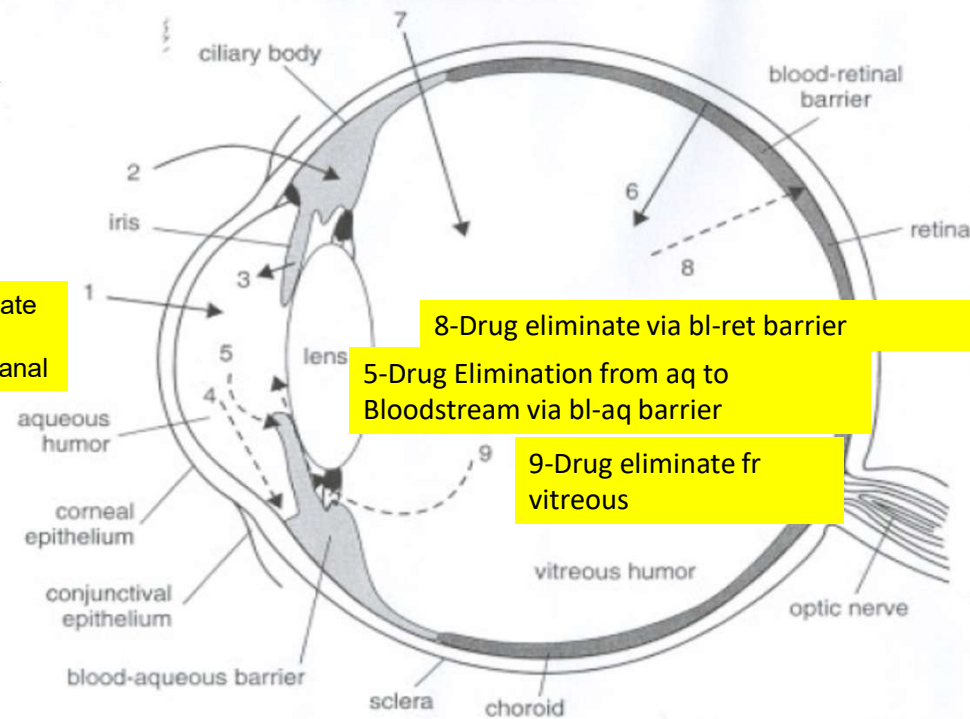
Direct outflow: TM > Schlemm Canal > episcleral vessels

4-Drug eliminate via TM, Schlemm's Canal

8-Drug eliminate via bl-ret barrier

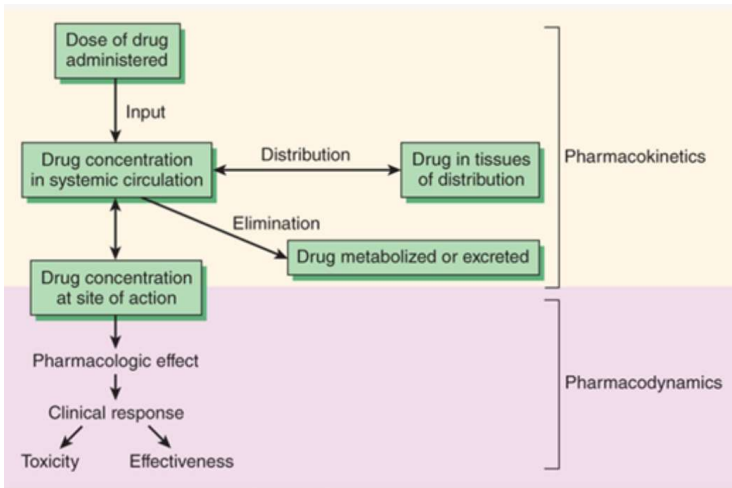
5-Drug Elimination from aq to Bloodstream via bl-aq barrier

9-Drug eliminate fr vitreous

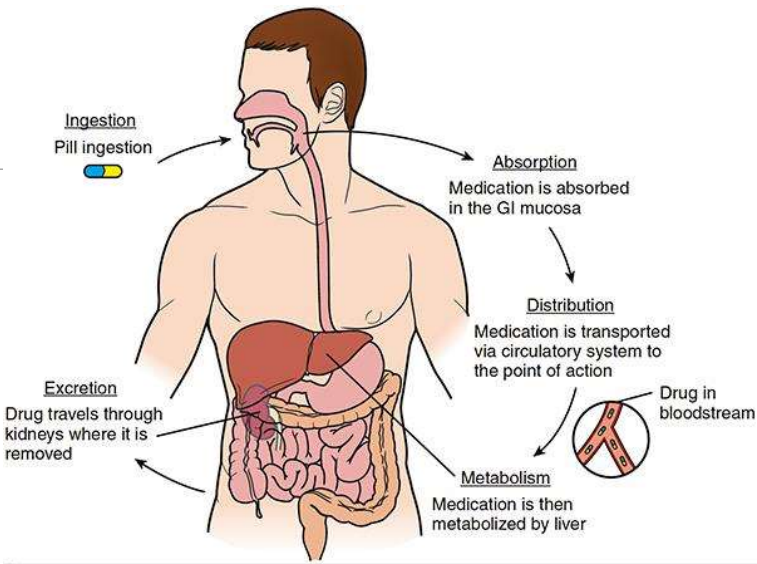




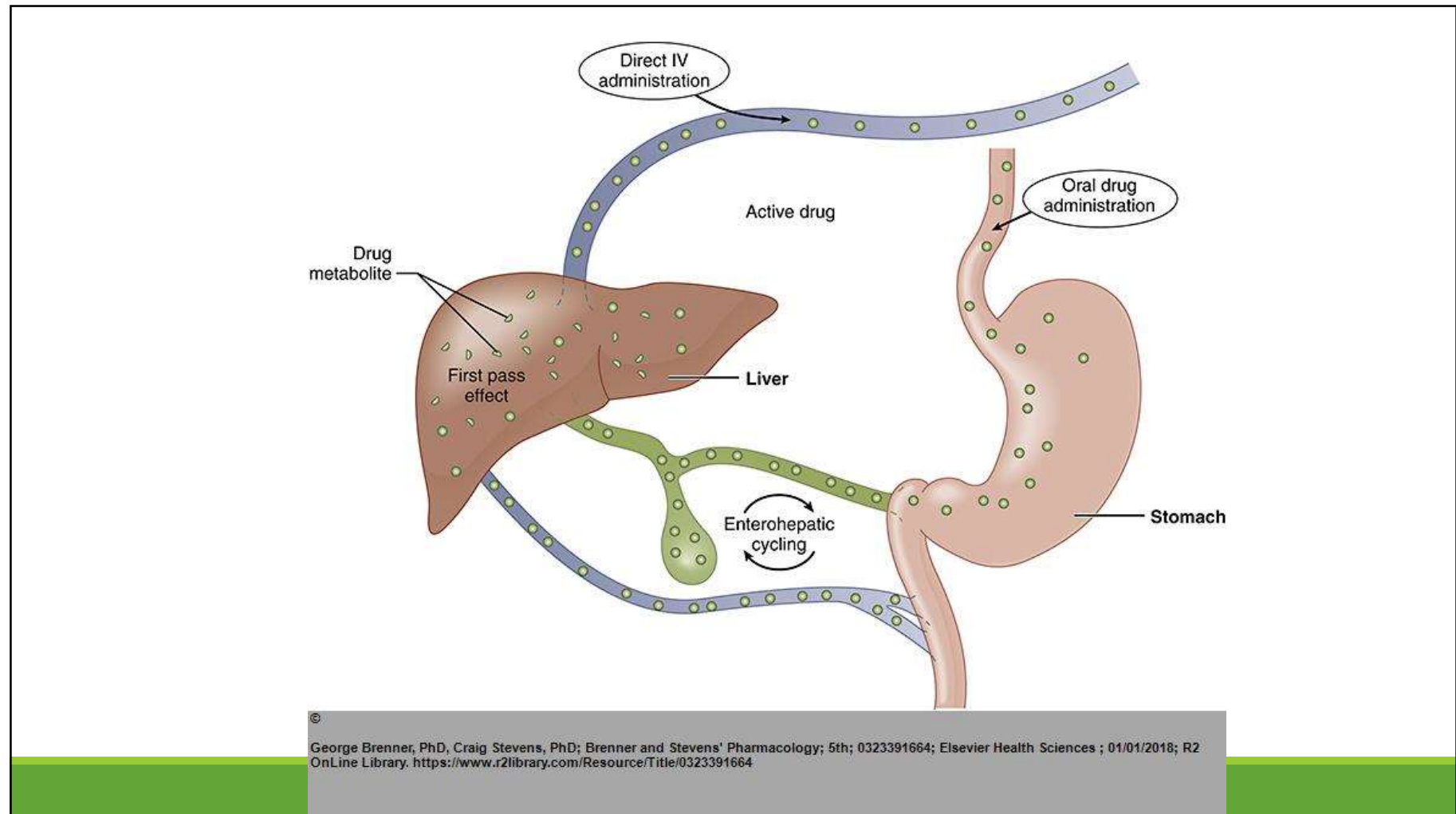
Systemic Drug Pharmacokinetics

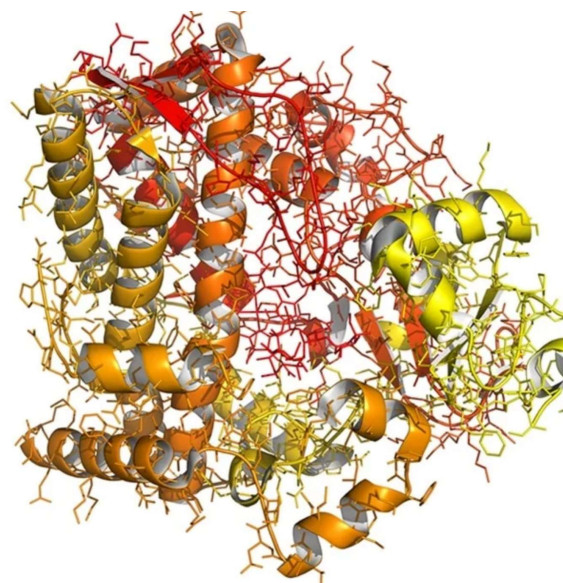


Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition
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Oral Medication Overview





Cytochrome p450 liver enzyme (CYP3A4, human), chemical structure. This liver protein important role in drug detoxification in the human body. Image Credit: molekuul, Shutterstock

Cytochrome P450

Cytochrome P450: a family of isozyme responsible for biotransformation/metabolism of many drugs

- This class has >50 enzymes, 6 metabolize 90% of drugs
- Majority of the isoenzymes are in the liver, extrahepatic metabolism also occurs in the kidneys, skin, GI tract, small intestine and lungs
- Significant inactivation of some orally administered drugs is due to extensive first pass metabolism
- Factors contributing to variable biotransformation: genetic polymorphism, disease (e.g. hepatic), age (newborns or elderly) and gender
- Drugs with CYP activity may be inhibitors, inducers, or substrates for specific CYP enzymatic pathway, altering the metabolism of concurrently administered agents

Cytochrome P450

Drugs with CYP activity may be inhibitors, inducers, or substrates for specific CYP enzymatic pathway, altering the metabolism of concurrently administered agents

- Drugs inhibit enzymatic pathway of CYP: increase concentration of other drugs metabolized by same pathway >>> result in drug toxicity
- Drugs induce enzymatic pathway of CYP may decrease concentration of drugs metabolized by same pathway>>>result in subtherapeutic drug level or tx failure

Cytochrome P450

Interactions

- Substrates of isoenzyme:
 - tacrolimus, cyclosporine, codeine, tramadol, terfenadine, astemizole, acetaminophen, ibuprofen, naproxen, warfarin, erythromycin (CYP3A4)
- Inhibitors of isozyme:
 - erythromycin (CYP1A2), chlorpheniramine, amiodarone, cyclosporine, grapefruit juice, macrolides (not azithromycin)
- Inducers of isozyme:
 - phenobarbital

Table. Cytochrome P450 drug metabolism*						
Function	P450 isozyme					
	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Substrates of isozyme:	caffeine clozapine cyclobenzaprine fluvoxamine imipramine mexiletine olanzapine pimozide propranolol tacrine theophylline warfarin	amitriptyline citalopam clomipramine cyclophosphamide diazepam imipramine lansoprazole nelfinavir omeprazole phenytoin	amitriptyline (demethylation) celecoxib diclofenac flurbiprofen ibuprofen losartan (not candesartan) naproxen phenytoin piroxicam sulfamethoxazole tolbutamide warfarin	amitriptyline clomipramine codeine desipramine dextromethorphan imipramine metoprolol nortriptyline oxycodone paroxetine propafenone thioridazine timolol tramadol venflaxine	acetaminophen chlorzoxazone dapson enflurane ethanol halothane isoflurane isoniazid	alprazolam astemizole buspirone calcium channel blockers carbamazepine cisapride cyclosporine doxorubicin erythromycin etoposide felodipine fentanyl HIV protease inhibitors ifosfamide lovastatin (not pravastatin) midazolam nifedipine pimozide quinidine quinine simvastatin tacrolimus terfenadine triazolam
Inhibitors of isozyme:	cimetidine ciprofloxacin citalopram diltiazem enoxacin erythromycin fluvoxamine mexiletine ofloxacin tacrine ticlopidine	cimetidine felbamate fluoxetine fluvoxamine ketoconazole lansoprazole omeprazole paroxetine ticlopidine	amiodarone fluconazole fluoxetine fluvoxamine isoniazid metronidazole paroxetine phenylbutazone sulfamethoxazole/ trimethoprim sulfaphenazole ticlopidine	amiodarone chlorpheniramine fluoxetine haloperidol indinavir paroxetine propafenone quinidine ritonavir sertraline thioridazine ticlopidine	disulfiram water cress	amiodarone cimetidine cyclosporine danazol diltiazem fluconazole (large doses) grapefruit juice HIV protease inhibitors itraconazole ketoconazole macrolides (not azithromycin) miconazole nefazadone omeprazole quinidine ritonavir verapamil
Inducers of isozyme:	carbamazepine tobacco	carbamazepine norethindrone (not phenobarb.)	phenobarbital rifampin secobarbital		chronic ethanol isoniazid tobacco	carbamazepine rifabutin rifampin ritonavir

Drug interactions due to cytochrome P450. BUMC PROCEEDINGS 2000;13:421–423

Grapefruit Juice

Grapefruit juice decreases cytochrome P450 activity and metabolism of the drug is decreased

- Blood levels of drug may rise

Side effects vary and depend on drug involved and may include:

- abnormal heart rhythms, stomach bleeding, kidney damage, difficulty breathing, sedation, dizziness

Effect of grapefruit juice on medications can last for over 24 hours

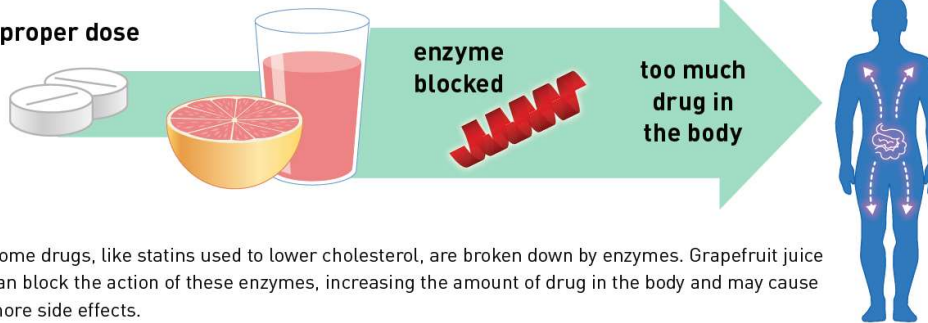
Usually other juices do not have this type of interaction, but orange or apple juice can interact with fexofenadine (Allegra)

- Blood levels with fexofenadine go DOWN and the effectiveness is reduced
- This interaction occurs by a different mechanism than CYP450 3A4 == but still recommend take with water and not fruit juice

How Grapefruit Juice Affects Some Drugs

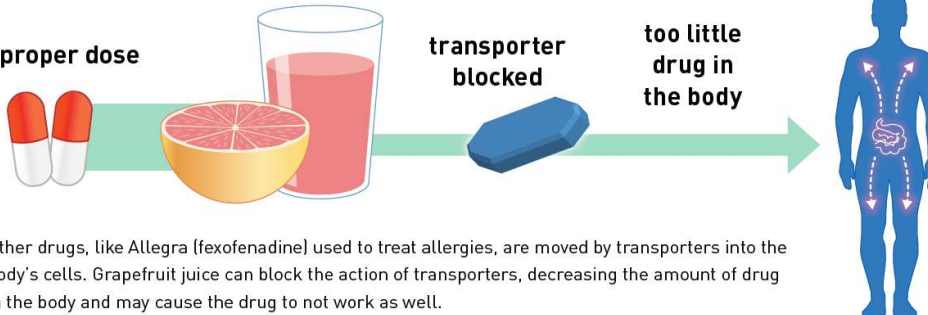
When drugs are swallowed, they may be broken down (metabolized) by enzymes and/or absorbed using transporters in cells found in the small intestine. Grapefruit juice can cause problems with these enzymes and transporters, causing too much or too little drug in the body.

proper dose



Some drugs, like statins used to lower cholesterol, are broken down by enzymes. Grapefruit juice can block the action of these enzymes, increasing the amount of drug in the body and may cause more side effects.

proper dose



Other drugs, like Allegra (fexofenadine) used to treat allergies, are moved by transporters into the body's cells. Grapefruit juice can block the action of transporters, decreasing the amount of drug in the body and may cause the drug to not work as well.

Increasing drug in blood

Grapefruit juice blocks enzyme action >>> Enzyme's ability to metabolize drug is decreased

Amount of CYP3A4 enzyme varies person to person, so grapefruit juice can affect people differently

Decreasing drug in blood (e.g. fexofenadine)

- Instead of changing metabolism, grapefruit juice can affect proteins in body (drug transporters) that help move drug to cells for absorption
- Less drug enters the blood

Prodrugs Soft Drugs Site Specific Drugs

DRUG DESIGNS

Prodrugs

Inactive derivative of drug converted to active form after tissue penetration

Drug metabolite more active at receptor site than the parent form

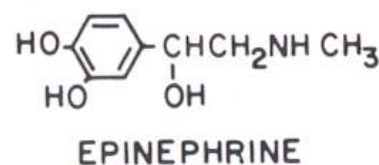
Advantage:

- Better penetration
- Less undesirable effects

Prodrugs

Dipivalyl epinephrine

- Pivalyl groups removed by esterases in cornea > leaving epinephrine to act at receptor
- Epithelial penetration $\wedge 10$ fold
- One tenth concentration = epinephrine
- Decreased systemic absorption



VS

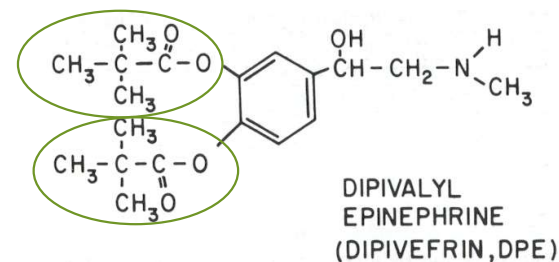


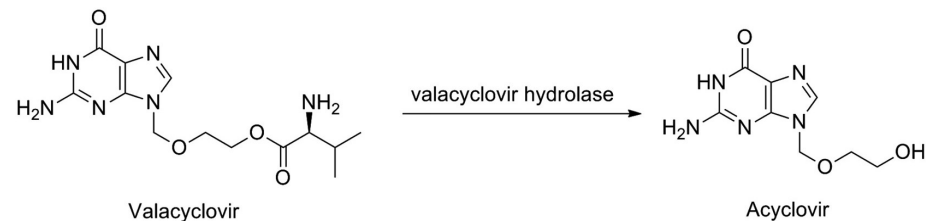
FIGURE 3.10 Molecular structure of dipivalyl epinephrine.

Prodrugs

Latanoprost, travoprost, tafluprost

- Ester-linked group is cleaved off after penetrating cornea
- Free acid remains in aqueous

Valacyclovir prodrug of acyclovir



Prodrug	Hard Drug	Soft Drug	Site Specific Drug
Inactive (or less active) derivative of active drug that is converted (by enzymatic or non- enzymatic reaction) to active drug/metabolite (after tissue penetration)	Non-metabolizable drugs or drugs metabolized to biologically active metabolites (frequently toxic)	Rapidly metabolized by enzyme to inactive metabolite/form	Site specific agent transformed by intrinsic tissue esterases into inactive metabolite after entering target tissue
More active at receptor site than parent drug Absorption, distribution, metabolism, excretion optimized		One step metabolism Metabolized rapidly to non-toxic product after achieving therapeutic role.	May have multiple metabolisms
Fewer side effects	Toxic	Fewer side effects	Fewer side effects
Valacyclovir is a prodrug of acyclovir	Heroin	Loteprednol is analog of prednisolone	

Drug Formulation

Drug Formulation Properties

Biopharmaceuticals

- Optimum dosage forms for drug delivery
 - E.g. Unit dose medications

Bioavailability

- Drug amount present at receptor site

Drug absorption affected by:

- Preservatives, buffers, vehicles

Excipients Defined

Excipients are components of a finished drug product other than the active pharmaceutical ingredient (API) and are added during formulation for a specific purpose. Although listed as inactive ingredients by FDA, excipients generally have well-defined functions in a drug product.

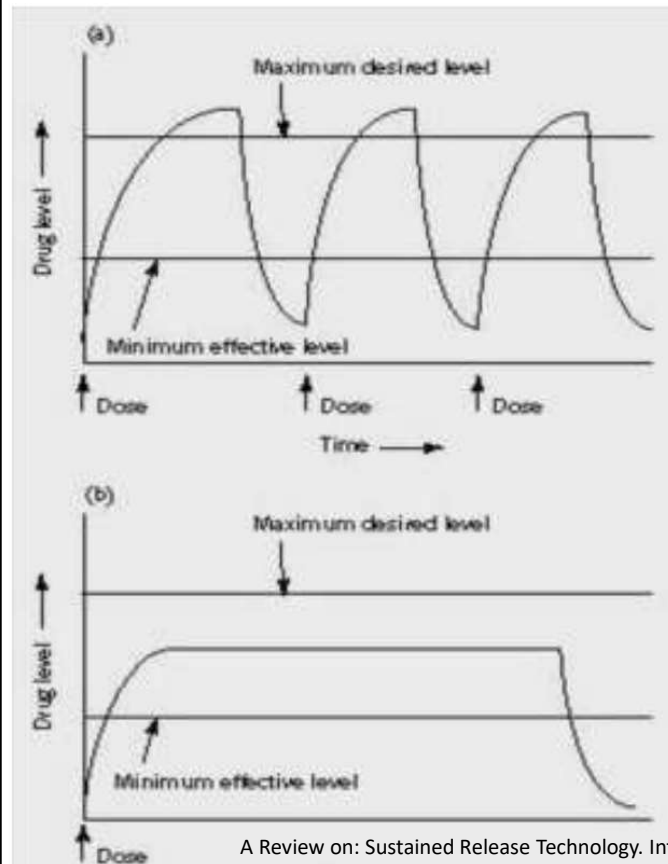
USP Guideline for Submitting Requests for Revision to *USP-NF V3.1 April 2007* U.S. PHARMACOPEIA

Drug Formulation Properties

Vehicles (Excipient)

- Provide proper tonicity, buffering, and viscosity to complement drug action
- Increased viscosity
 - Delay washout, increase drug bioavailability
 - Petrolatum or oil based ointments: longer retention, temporary lipid depot

Fig. 1. Drug levels in the blood with
a) Traditional drug dose systems and
b) Controlled drug delivery dose systems.



A Review on: Sustained Release Technology. *Intrnl J Therapeutic Applications*, Volume 8, 2012, 18 - 23

Extended vs Immediate Release Medications

Immediate release:

- Released within minutes of ingestion/go into the system quickly

Extended release (XR or ER):

- Pill is formulated so drug is released slowly over time (usually 12-24 hours)
- E.g. capsule has beads with some starting to work right away, rest slowly released
- Last longer in the body
- Need less daily doses compared to immediate release
- Potential for fewer side effects since drug level more consistent

Ophthalmic Drug Delivery

Ophthalmic Drug Delivery

Topical Administration

- Most common ophthalmic drug route
- Convenient, noninvasive, simple, self-administered
- Drug loss: diffusion into circulating blood
 - BV of conjunctiva, episclera, intraocular vessels, nasal mucosa, oral pharynx
 - Little benefit posterior segment
- Second passage: liver biotransforms
 - Vs oral meds: metabolized before “first pass” (<toxic than topical drugs)

Advantages & Disadvantages Various Ocular Drug Delivery Systems

	Advantage	Disadvantage-Limitations
Drops	➤ Easy application ➤ Least invasive ➤ Good pt acceptance	➤ Poor ocular bioavailability ➤ Sometimes short duration ➤ Ineffective posterior seg ➤ Potential ocular/systemic toxicity from high concentration or frequent instillation
Suspensions	➤ Prolonged contact time	➤ Shake (pt compliance) ➤ Hx of generic poorly suspend, dropper tip clog
Emulsion	➤ No shake ➤ Improved drug solubility and bioavailability	➤ May be thermodynamically unstable
Gelifying Systems	➤ Enhance drug retention relative to drops ➤ Increased drug absorption ➤ Reduced dosing frequency ➤ Possible better compliance	➤ Duration of drug activity ^ by hours not days or weeks
Nanotechnology	➤ Low irritation ➤ Adequate bioavailability ➤ Ocular tissue compatibility	➤ Potential toxicity

Current & future ophthalmic drug delivery systems. Drug Discovery Today, del Amo EM, Urtti A. 12-2007 (in part reference)

Advantages & Disadvantages Various Ocular Drug Delivery Systems

	Advantage	Disadvantage-Limitations
Injections (Intravitreal, periocular, subconjunctival)	➤Improved drug absorption vs systemic or topical ➤Drug delivery to post seg, no systemic toxicity ➤Drug delivery to target site	➤First order kinetics ➤Short half life (repeat inject) ➤Side Effects: pain, discomfort, IOP[^], intraocular bleed, potential infection, RD, endophthalmitis ➤Patient acceptance
Implants NonBiodegradable Biodegradable	➤Alternate to repeat injections ➤Biodegradable-no removal ➤Zero order kinetics	➤Nonbiodegradable-surgical remove ➤Invasive procedure ➤Side Effects: RD, intravitreal heme
Systemic Administration	➤More effective for post seg diseases vs drops	➤Most do not pass bl-oc barrier ➤Potential systemic toxicity

Current & future ophthalmic drug delivery systems. Drug Discovery Today, del Amo EM, Urtti A. 12-2007. (In part reference)

Pediatric Considerations

Federal Food, Drug and Cosmetic Act defines pediatric persons: Age 21 and younger Neonates: birth to 28 days Infants: 29 days to <2 years Children: 2 years to <12 years Adolescents: 12-21 (up to but not including 22nd birthday) https://www.fda.gov/medical-devices/products-and-medical-procedures/pediatric-medical-devices	Pediatric cohorts Neonates -- birth to < 1 month Infants -- age 1 month to < 2 years Children -- ages 2 to < 12 years Adolescents -- ages 12 to < 17 years https://www.accessdata.fda.gov/scripts/cder/world/index.cfm?action=newdrugs:main&unit=4&lesson=1&topic=5	Pediatric Age Neonates: newborn to 1 month Infants: 1 month – 2 years Children: 2 years – 12 years Adolescents: 12 years – 16 years https://www.fda.gov/drugs/data-standards-manual-monographs/pediatric-exclusivity-study-age-group
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Pediatric Prescribing Considerations

Epocrates

amoxicillin

generic

Adult Dosing ⓘ

Dosage forms: CAP: 250 mg, 500 mg; TAB: 500 mg, 875 mg; ER TAB: 775 mg; CHEWABLE: 125 mg, 250 mg; SUSP: 125 mg per 5 mL, 200 mg per 5 mL, 250 mg per 5 mL, 400 mg per 5 mL

infections, bacterial

[500-875 mg PO q12h]

Alt: 250-500 mg PO q8h; Info: dose, duration vary by infection type/severity

amoxicillin

generic

Peds Dosing ⓘ

Dosage forms: CAP: 250 mg, 500 mg; TAB: 500 mg, 875 mg; ER TAB: 775 mg; CHEWABLE: 125 mg, 250 mg; SUSP: 125 mg per 5 mL, 200 mg per 5 mL, 250 mg per 5 mL, 400 mg per 5 mL

infections, bacterial

[0-3 mo]

Dose: 20-30 mg/kg/day PO divided q12h; Max: 30 mg/kg/day; Info: dose, duration vary by infection type/severity

[>3 mo]

Dose: 25-45 mg/kg/day PO divided q12h; Max: 875 mg/dose; Alt: 20-40 mg/kg/day PO divided q8h; Info: dose, duration vary by infection type/severity

Dosage

Available as the trihydrate; dosage expressed in terms of anhydrous amoxicillin.

Pediatric Patients

General Pediatric Dosage

Oral

Neonates and infants ≤12 weeks (3 months) of age: Manufacturer states dosage up to 30 mg/kg daily can be given in divided doses every 12 hours.

Children ≥3 months of age weighing ≥40 kg: Manufacturer states use usual adult dosage.

Drugs.com

Review Drug Formulation Pertinent Points

LET ME HELP YOU OUT.....



What you need to know about your patients:

- Medical conditions
 - Kidney/liver
 - Cardiac
 - Respiratory
 - Etc.
- Other medications >>Drug Interactions
- Allergies (e.g. sulfa)
- Family history (e.g. POAG)
- Ocular history (e.g. inflammation)



Over-View

History

Pregnancy/Pediatric Considerations

The Drug

Absorption

- Compartments
- Drug Kinetics

Drug removal

Formulation

Delivery



