PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 3–5

Prolonging drug action: physiological, physical and chemical methods

Educational program “Pharmacy” · 4th year · Al-Farabi Kazakh National University

After these seminars you will be able to

1. Explain how blocking elimination or absorption prolongs drug action
2. Describe physical methods: viscosity, poorly soluble forms, oily depots, crystals
3. Define a prodrug and explain why valacyclovir and enalapril are prodrugs
4. Explain how PEGylation and insulin analogues extend action
5. Choose a prolongation method for a given drug and route

Three ways to make a drug act longer

1

Physiological

Change how the **body** absorbs, distributes or eliminates the drug.

Lidocaine + epinephrine

2

Physical

Change the **dosage form**: slow dissolution or diffusion at the site.

Benzathine penicillin, NPH insulin

3

Chemical

Change the **molecule**: esters, prodrugs, PEG, analogues.

Fluphenazine decanoate, pegfilgrastim

Seminars 3–5 · Classification used in Khlusov et al. (2008) and Aulton’s Pharmaceutics (2022)

The physiological method: act on ADME

Absorption
Slow it at the injection site: vasoconstrictor narrows vessels

Distribution
Binding to plasma proteins or tissues forms a reservoir

Metabolism
Inhibit the enzyme that destroys the drug

Excretion
Block renal secretion, or change urine pH

The drug and its dosage form stay the same; a **second substance** or a **body process** is used to keep the drug at the site of action longer.

Physiological prolongation in practice

Combination	Mechanism	Result
Lidocaine + epinephrine	α-adrenergic vasoconstriction slows removal from the site	Longer local anaesthesia, less bleeding
Penicillin + probenecid	Blocks tubular secretion (organic anion transporters)	Higher, longer plasma levels
Levodopa + carbidopa	Inhibits peripheral DOPA decarboxylase	More levodopa reaches the brain
Nirmatrelvir + ritonavir	Ritonavir inhibits CYP3A4 (“boosting”)	Twice-daily dosing becomes possible
Amoxicillin + clavulanic acid	β-lactamase inhibitor protects the antibiotic	Activity against resistant bacteria

The physical method: slow the release from the form

Viscosity

Gels, polymer solutions (eye drops with HPMC, injectable gels)

Poorly soluble salts

Benzathine and procaine penicillin dissolve slowly in muscle

Crystals, complexes

Insulin–zinc–protamine (NPH) crystals, zinc suspensions

Oily depots

Drug in sesame or castor oil, IM; slow partition into tissue

Coating, matrix

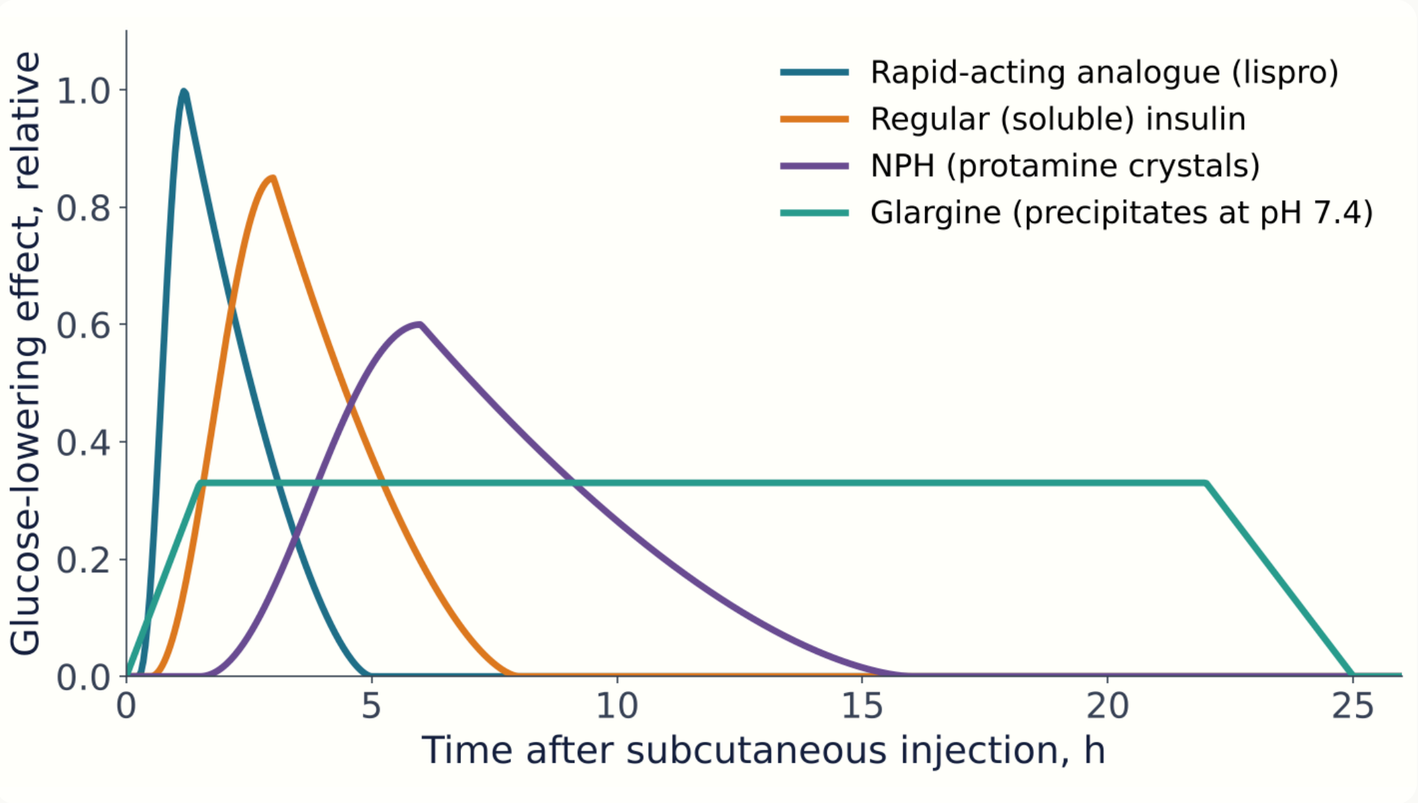
Polymer films and matrices control diffusion in oral forms

Micro-encapsulation

PLGA microspheres: leuprolide, octreotide, risperidone

Common principle (Noyes–Whitney): lower solubility or surface area, or a longer diffusion path → slower release.

One hormone, four durations



Lispro – amino acids swapped: no hexamers, fast

Regular – soluble hexamers

NPH – *physical*: protamine–zinc crystals dissolve slowly

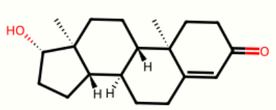
Glargine – *chemical*: pI shifted, precipitates at pH 7.4

PHYSICAL METHOD AT ITS SIMPLEST

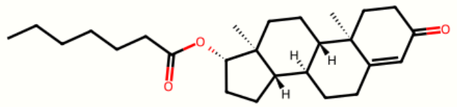
One intramuscular injection of benzathine penicillin G keeps low penicillin levels for 2–4 weeks

Salt of penicillin with a large, poorly soluble base → crystals dissolve slowly in muscle. Used for syphilis and to prevent rheumatic fever.

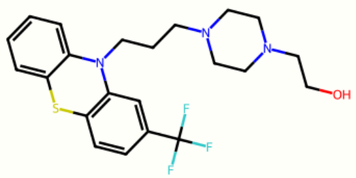
Chemical method: lipophilic esters for oil depots



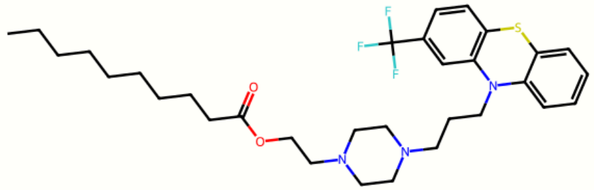
Testosterone



Testosterone enanthate (oil depot)



Fluphenazine



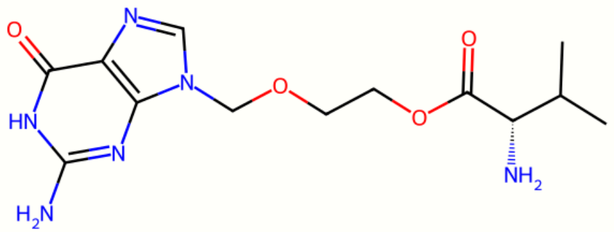
Fluphenazine decanoate (oil depot)

A fatty acid ester on an –OH group makes the drug very **lipophilic**.

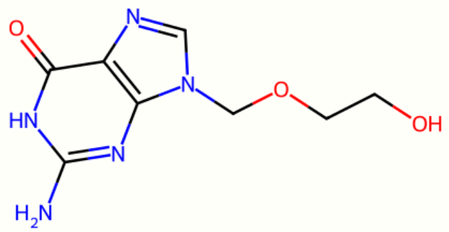
In oil, IM: slow partition into tissue fluid, then **esterases** free the active drug.

Fluphenazine decanoate: every 2–4 weeks instead of daily tablets.

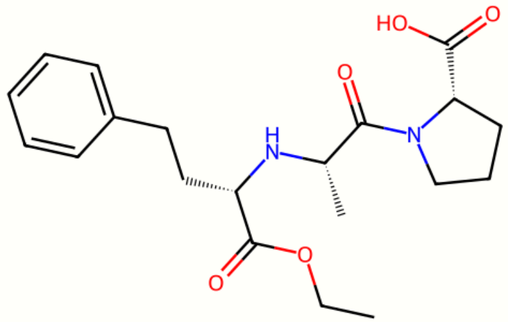
Prodrugs: inactive carriers of the active molecule



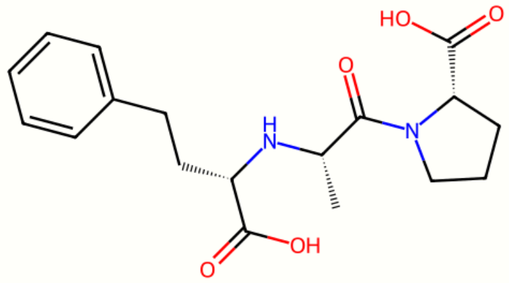
Valacyclovir (prodrug)



Acyclovir (active)



Enalapril (prodrug)



Enalaprilat (active)

Valacyclovir: L-valine ester is carried by the intestinal peptide transporter PEPT1 → bioavailability rises from about 15–20% to about 55%.

Enalapril: ethyl ester is absorbed orally; liver esterases form enalaprilat.

Functional groups used to make prodrugs

Group on drug	Promoiety	Released by	Example
–COOH	Ethyl ester	Esterases	Enalapril, oseltamivir
–OH	Fatty acid ester	Esterases	Haloperidol decanoate
–OH	Phosphate ester	Phosphatases	Fosphenytoin (soluble IV)
–OH	Amino acid ester	Esterases (via PEPT1)	Valacyclovir
Amine, amide	Carbamate, amide	Amidases, CYP	Capecitabine → 5-FU
Whole molecule	Bioprecursor	Metabolism (CYP2C19)	Clopidogrel

PEGylation: a larger molecule stays longer

How it works

- Polyethylene glycol chains attached to the protein
- Larger hydrodynamic size → less kidney filtration
- Water shell hides it from proteases and antibodies

Examples

Native	PEGylated
Filgrastim, daily	Pegfilgrastim, once per cycle
Interferon α, 3× weekly	Peginterferon, weekly
Adenosine deaminase	Adagen (1990)

Limit: some patients form **anti-PEG antibodies**, which speed clearance and can cause reactions.

Comparing the three methods

Feature	Physiological	Physical	Chemical
What changes	Body processes	Dosage form	Molecule
New substance?	Second drug added	No	Yes: new entity
Reversible?	Yes, stop the second drug	Once injected, no	Prodrug reverts in vivo
Main risk	Interactions	Dose dumping, injection pain	Variable activation
Development cost	Low	Medium	High: new safety data

Questions for discussion

1. Why is epinephrine not added to lidocaine for finger blocks in older practice?
2. Which term of the Noyes–Whitney equation does benzathine penicillin change?
3. Is NPH insulin a physical or a chemical method? And glargine?
4. Why does valacyclovir give higher acyclovir levels than acyclovir itself?
5. Why is a decanoate ester given in oil, not in water?
6. Name two disadvantages of PEGylated proteins.

References

1. Rautio J, Meanwell NA, Di L, Hageman MJ. The expanding role of prodrugs in contemporary drug design and development. Nat Rev Drug Discov. 2018;17:559–587.
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5. Rang & Dale’s Pharmacology, 10th ed. Elsevier; 2023.
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7. Khlusov IA, Chuchalin VS, Khoruzhaya TG. Principles of design and functioning of drug delivery systems. Tomsk; 2008 (in Russian).