Drug Discovery, Development and Commercialization, Winter 2013

Key Concepts in Drug Delivery

Brookie M. Best, PharmD, MAS

UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

OUTLINE

What is ADME?

Where can we administer drugs?

What types of dosage forms are available?

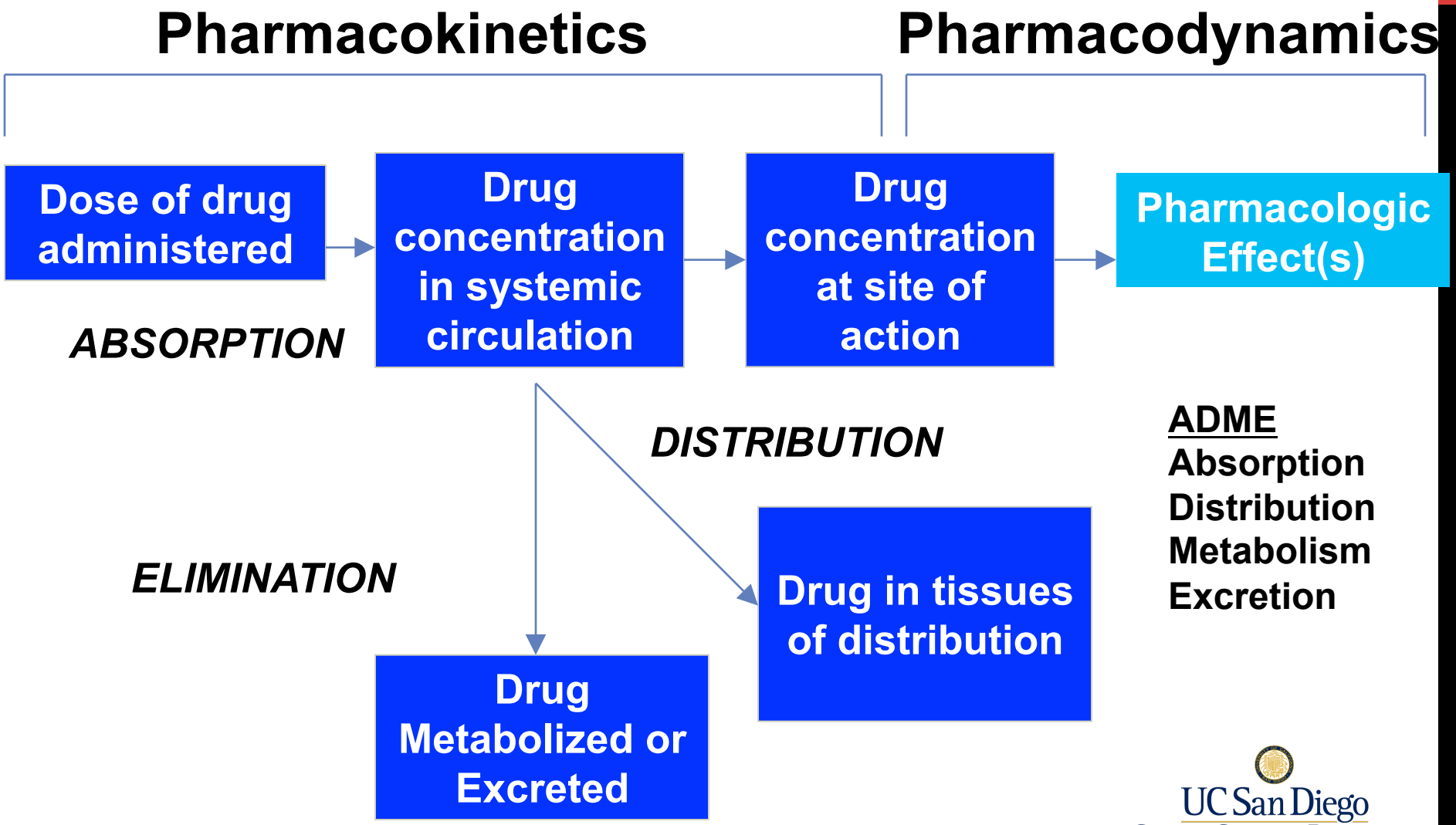
What delivery systems have been developed?

The following presentation was adapted from lectures developed for Biotech Demystified at UC San Diego Rady School of Management and Pharmaceutics courses at UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences.

-Where indicated by website address, images used for illustrations are public domain images licensed for re-use in Creative Commons.

UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

PK/PD Overview



UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

ABSORPTION

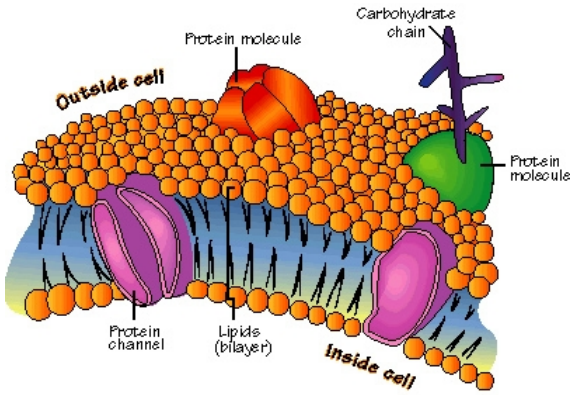
- Most dosage forms are solid, and the drug must first be released before it can be absorbed

Solid Dosage Form

Granules

Fine Particles

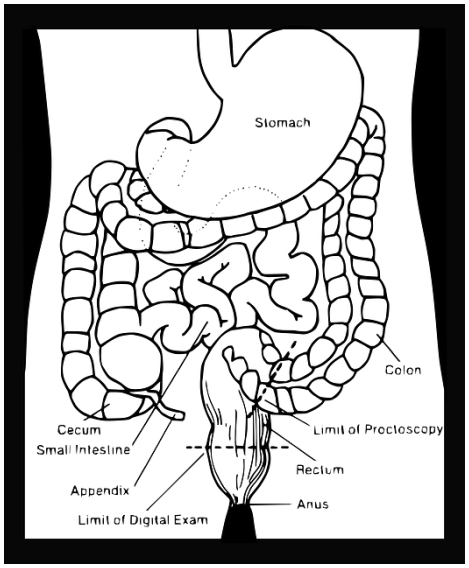
- No matter how the drug is given (other than IV), it must pass through at least one biological membrane before it reaches the site of action



http://www.flickr.com/photos/140264jd/6287300944/sizes/m/in/photostream/

UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

CHALLENGES TO ORAL ABSORPTION



http://pixabay.com/en/black-model-science-diagram-simple-40607/

Stomach	pH = 1 – 3.5
Duodenum Jejunum	pH = 5 – 7
Ileum Colon	pH = 8

- Stable in varied acidic conditions
- Solubility
  - How well/where does it dissolve?
- Permeability
  - How/where does it get through membranes?
- 1st Pass (gut and liver) enzyme stability
  - Does it get broken down by metabolism in the liver or gut?

UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences

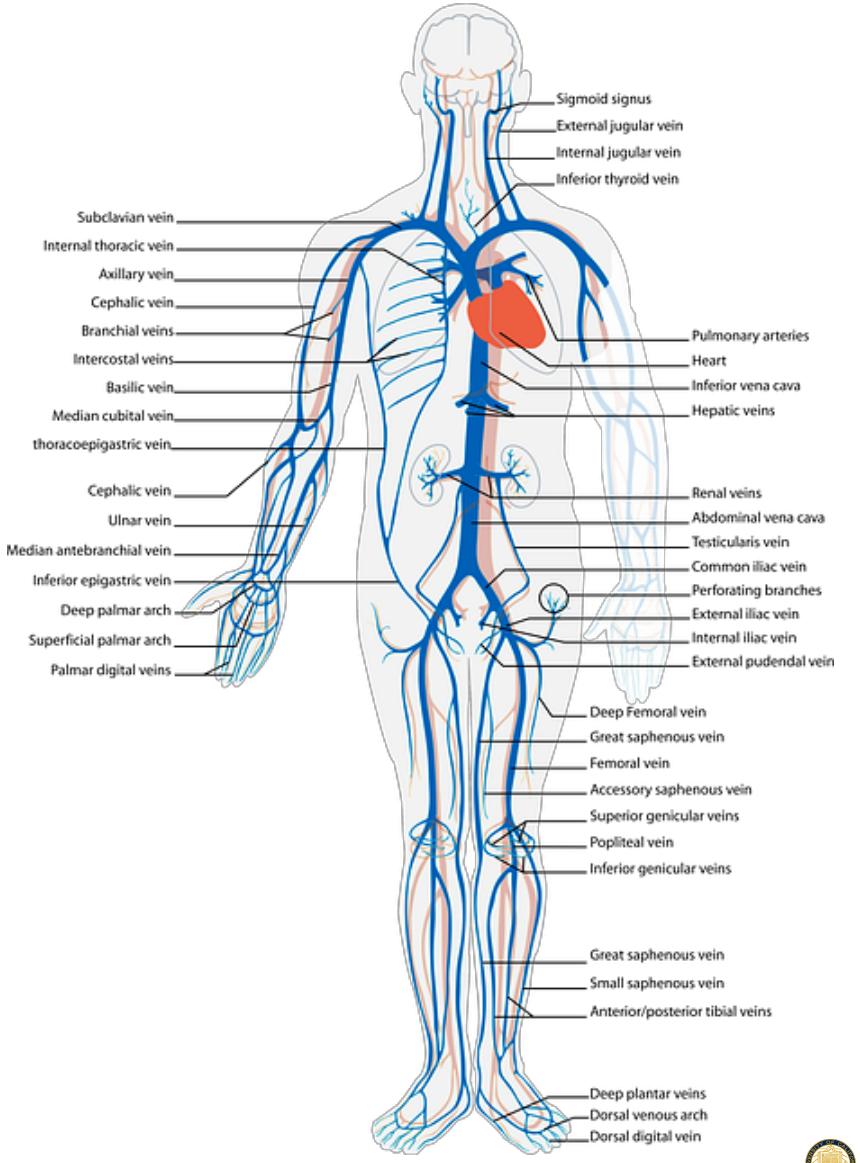
PHYSIOLOGIC FACTORS INFLUENCING ORAL ABSORPTION

- Gastric emptying rate
- Intestinal motility
- Colonic retention
- GI tract perfusion
- Food and diet
- Disease
- Altered anatomy

With any dosage form, the environment for its route of administration must be understood

DISTRIBUTION

- Once drug is in the blood, where does it go next?
  - Protein binding
  - Transport (active and passive)
    - Uptake in intestines, liver, kidney, brain
    - Efflux back into intestine, out of brain
    - Secretion into bile, urine
    - Reabsorption in kidney

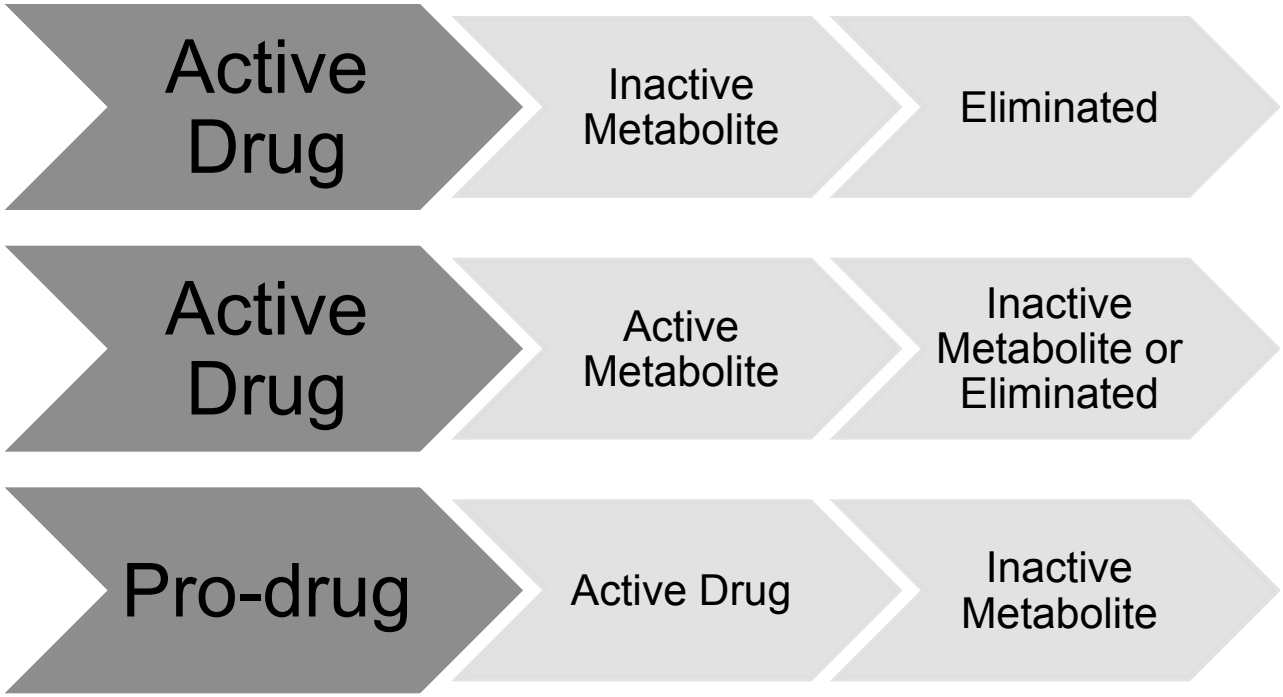


METABOLISM

Phase I - Make more polar (charged; + or -)

Phase II – Attach (conjugate) to compounds to detoxify or excrete

Examples below, all different combinations are seen



UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

PHASE 1 - CYTOCHROME P450 ENZYMES

Major drug metabolism pathways

- UDP-glucuronosyl transferase
- N-acetyl transferase
- Monoamine oxidase
- Flavin monooxygenases
- Cytochrome P450 enzymes (~75%)

Common P450 pathways for metabolizing drugs

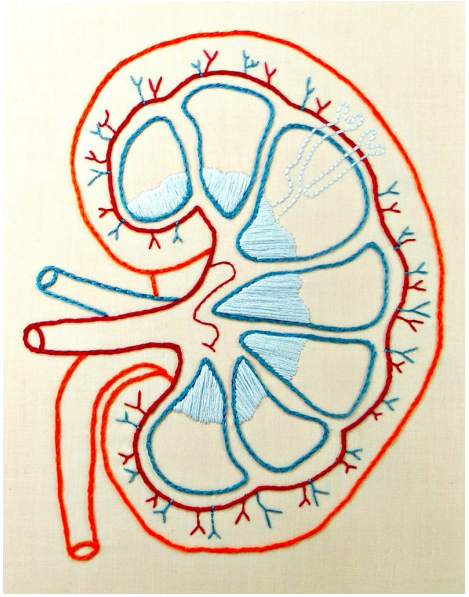
- 3A4(5), 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, 1A1

P450's = Major source of variability in drug response

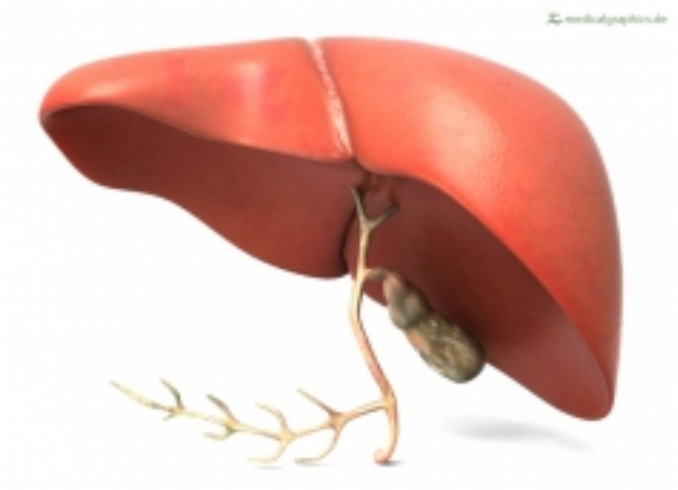
- Enzyme inhibition & induction cause many drug interactions
- Genetic polymorphism
    - Ultrarapid, rapid, intermediate, slow metabolizers

EXCRETION

- Excretion is mainly via urine and feces
- “Elimination” is by metabolism and/or excretion



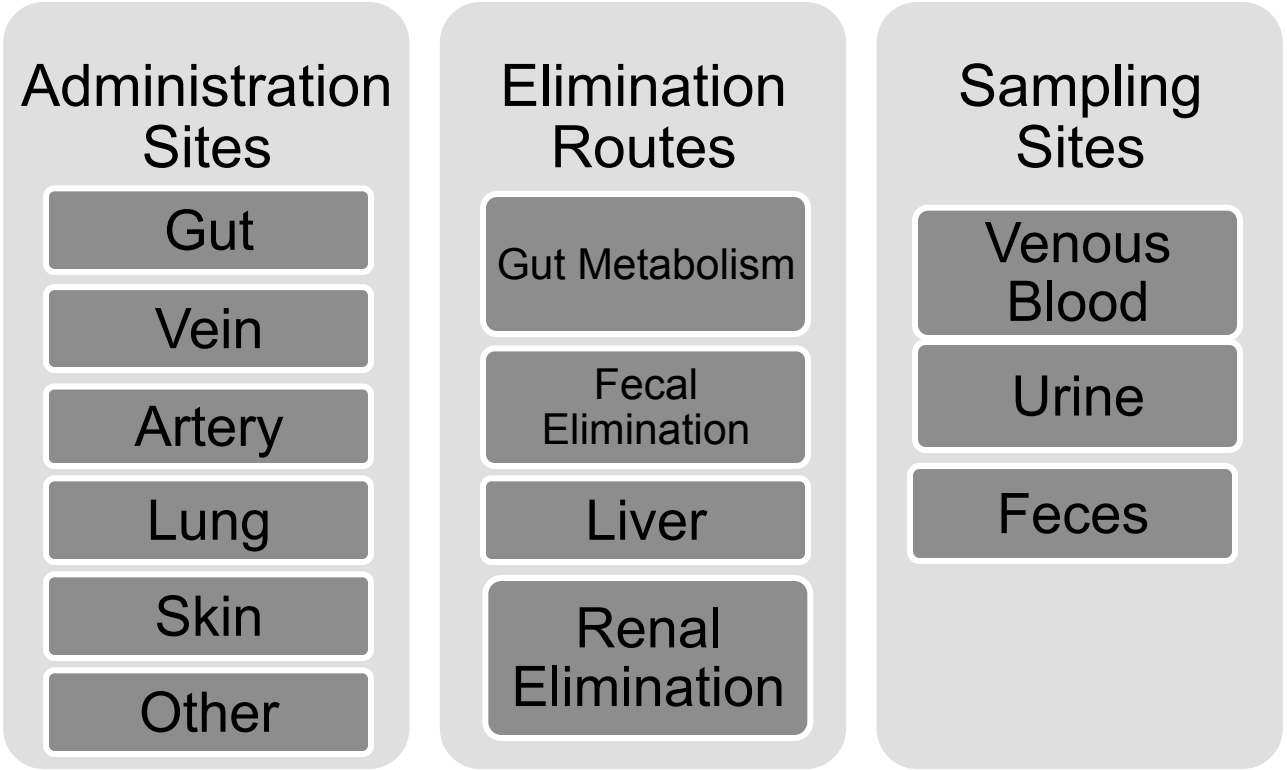
http://www.flickr.com/photos/hey__paul/8316290574/



http://www.medicalgraphics.de/components/com_joomgallery/img_thumbnails/_organs_2/leber_gallenblase_hinten_kl_20120712_2064511122.jpg

UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

SITES OF DRUG ADMINISTRATION



UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

COMMON ROUTES OF ADMINISTRATION

Classification		
Topical (Local)	**Enteral (Systemic)**	**Parenteral (Systemic)**
Transdermal	Oral	Intravenous (IV)
Oral	Buccal	Intramuscular (IM)
Otic (ear)	Sublingual	Subcutaneous (SC)
Ocular (eye)	Rectal	Intrathecal (IT)
Rectal	Nasogastric (via tube)	Pulmonary Inhalation
Vaginal		Nasal
Nasal		Transdermal

FDA recognizes 111 routes of administration:

- http://www.fda.gov/cder/dsm/DRG/drg00301.htm

UC San Diego
SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

DOSAGE FORMS

Mixture of active drug and non-drug components = drug product administered to patients

- Many types depending on route of administration
- Different diseases or patient populations may need different routes of administration of the same drug
- Some medications require certain dosage forms

Solid oral dosage forms are most common (~90% of drug products)

- Preferred by patients

EXAMPLES OF DOSAGE FORMS

Solid Oral	Liquid Oral	Non-Oral
Immediate release	Suspensions	Solutions for injection
Delayed release	Emulsions	Pulmonary
Sustained release	Solutions:	Nasal
Pulsatile release	Syrups	Suppositories
Chewable tablets	Elixirs	Lotions
Lozenges	Infusions	Ointments
Buccal tablets	Decoctions	Transdermal patches
Effervescent tablets	Mouth washes	Plasters
Dispersible tablets	Gargles	Poultices
Solution tablets	Tinctures	Enema
Hard gelatin capsules	Oral Sprays	Implants
Soft gelatin capsules	Spirits	
Pastilles		
Wafer bars		
Sachets		
Lollipop		

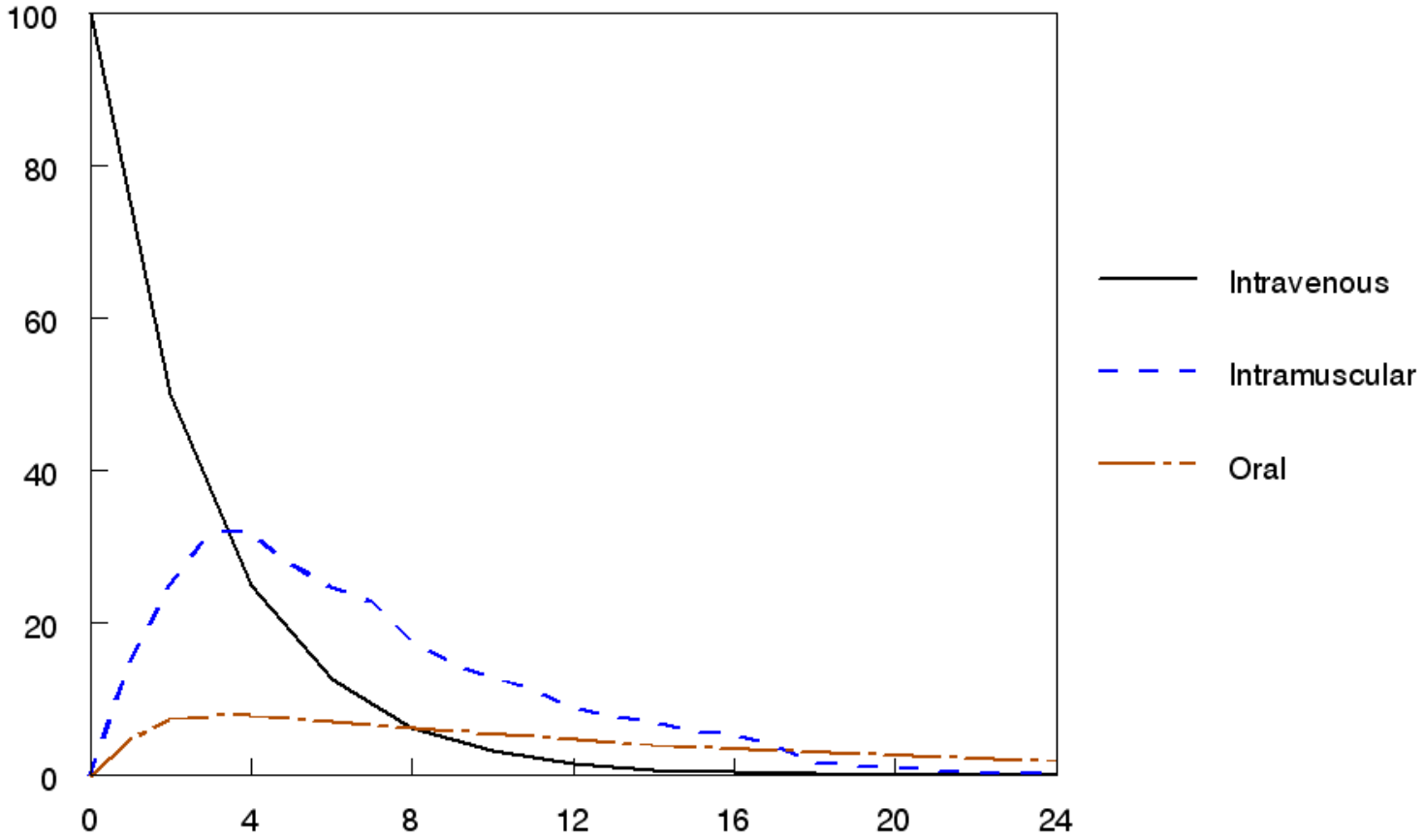
DELIVERY SYSTEMS

Method or process of administering pharmaceutical compounds to achieve a therapeutic effect in patients

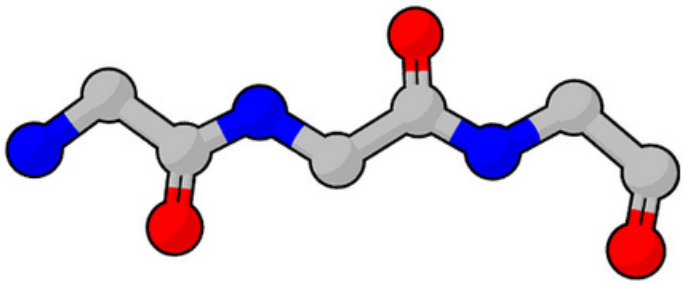
- Might target particular organ, cells or tissues
- Might provide pre-programmed drug release profile (controlled-release drug delivery system (DDS))
- Usually protects drug until it gets to the site of action

Primary objectives are to increase patient adherence and to enhance drug efficacy and tolerability

Example Exposure Profiles



Challenging Properties: Peptides & Proteins



http://www.flickr.com/photos/ethanhein/2756672899/

- Sites of high charge or polarity
  - Blue = nitrogen
  - Red = oxygen

- Unstable in acid (or base)
- Unstable to enzymes
- High polarity causes water association and very low lipid (oil) solubility

PROTEINS AND MACROMOLECULES

- Alternate routes to oral administration
  - Rectal
  - Topical
  - Parenteral
  - Respiratory
  - Nasal
  - Ophthalmic
  - Otic
- Differing dissolution, solubility and permeability characteristics

PULMONARY DELIVERY SYSTEMS

Dry Powder Inhalation

- DPI (Passive & Active)

Soft Mist Inhalation

- (Single breath and breath actuated)

Metered Dose Inhalation (pMDI)

Nebulizers

Portability is preferred

NASAL SYSTEMIC DELIVERY SYSTEMS

Advantages:

- Large surface area
- Rapid absorption, rich blood supply
- Rapid onset
- Non-invasive
- Avoidance of 1st pass loss
- Lower dose/reduced side effects
- Minimal aftertaste
- Self-administration
- New patent coverage for drug formulations
  about to expire

- Disadvantages:
  - Large volumes interfere with normal nose functions
  - Reproducibility of dosing:
    - Patient's method of administration
    - Condition of nasal passage & environmental conditions
  - Irritation, inflammation or toxicity
  - Avoid in patients with:
    - Common cold, Persistent sneezing, Nasal congestion, Nasal inflammation, Allergic rhinitis

TRANSDERMAL DELIVERY SYSTEMS (TDS)

- Systemic Delivery
  - Very effective barrier to penetration of most substances
  - Must penetrate deep dermis for systemic uptake
  - Large surface area to deliver drug if penetration is achieved
    - Avoids first-pass metabolism and digestive degradation of drugs

Reservoir-Based TDS

- Backing, drug depot, rate-controlling membrane & adhesive

Matrix-Based TDS

- Backing, drug in matrix, & adhesive

Drug-in-Adhesive-Type TDS

- Backing, drug mixed in adhesive

IONTOPHORESIS

Charged molecules (drugs in solution) are driven in to the skin using electrical charge gradient

Also used to draw molecules out of the skin (reverse iontophoresis)

Sonophoresis - Ultrasound

- Ultrasound waves cause disruption of lipid layers
- Tingling, no nerves in outer skin layer so not painful
- Skin returns to normal within 24 hours
- Typically used for delivery of lidocaine or a wide variety of skin therapies
- Also under investigation for automated diabetes glucose sampling and insulin delivery

ELECTRICAL CELL ABLATION

Microelectrodes transfer high frequency alternating currents

Creates localized ablation of skin cells, forming microchannels in milliseconds

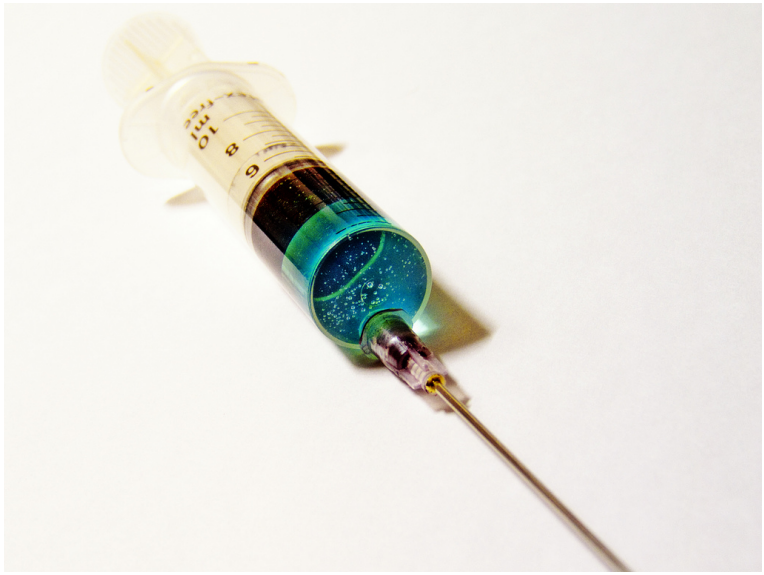
Micro-Needle

- Physically bypass outer skin layer using micro-needles
- Needle tips are hollow or are coated with drug to be delivered
- Ideal for macromolecules- peptides and vaccines
- Can be used in combination with iontophoresis

INJECTABLES: BASIC INJECTION DEVICES

- Injectable systems are more complex and costly than oral dosing
  - Vials and Syringes
  - Pre-Filled Syringes (PFS)

http://www.flickr.com/photos/8499561@N02/2756290144/



http://www.flickr.com/photos/andresrueda/2983149263//

AUTO-INJECTORS

- Definition = pre-filled-syringe-based systems that are usually utilized for single, fixed-dose therapies
  - Re-usable
  - Disposable

Pen Injection Devices

- Solution needs to be stable at room temperature for 1 month
- Device considerations
  - Disposable or re-usable?
  - Dose-titration (dial-a-dose)
  - Needle replacement, supply
  - Possible needle shield

NEEDLE FREE INJECTORS

- Definition = High-pressure systems that use very small holes to produce a fine stream from the formulation, which penetrates the skin without use of a needle
- Used for both chronic and single-dose therapies
  - Re-usable
  - Disposable

Insulin Infusion Pumps

Designed for standard fast-acting insulin formulations

Device considerations

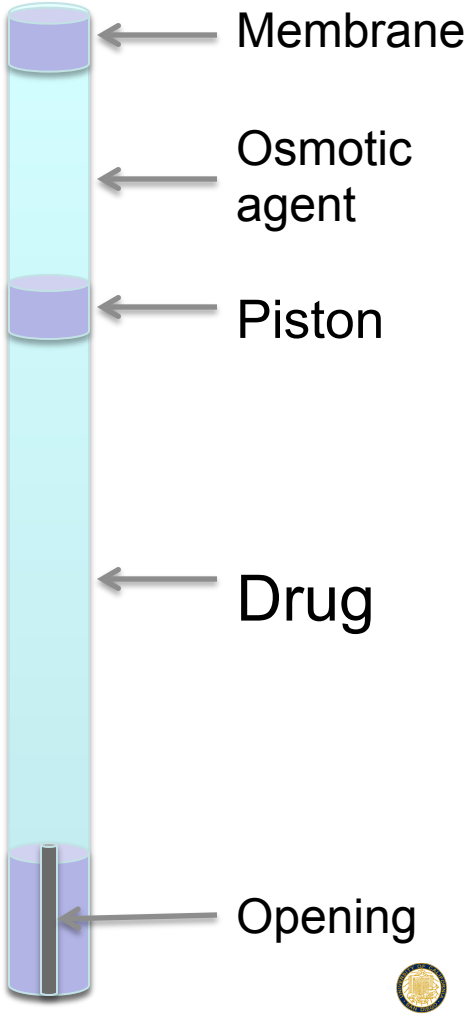
- Device is worn like a pager and has a plastic infusion set attached to a subcutaneous catheter
- Catheter site is changed every three days
- Insulin cartridge is replaced/refilled as needed daily or every few day

Implanted Devices

- Long-term, localized drug therapy
- Example: Medtronic SynchroMed® Infusion System
- Pump is used to obtain high drug concentrations in brain, with very low amounts of drug in blood

OSMOTIC PUMP IMPLANT

- Non-biodegradable (titanium)
  - Insert via trochar (minor surgery), remove by minor incision
  - 12 month drug delivery



Additional Formulation Technologies: Liposomes

- Liposomes are spherical envelopes created by mixing phospholipids and cholesterol
- Lipids gradually diffuse into bodily fluid
- Membrane envelope breaks up and releases drug
- Used for: slowing drug release, targeting delivery, minimizing toxicity

Biodegradable Polymer Systems

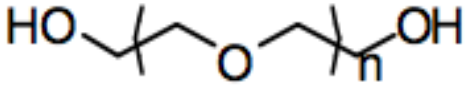
- PLGA or poly(lactic-*co*-glycolic acid) commonly used
- Degrades in body at 98.7°F into lactic acid and glycolic acid which are cleared naturally

NANOSPHERES

- Sub-micron particles (10 – 1000 nm)
- Can cross through GI tract because of small size (though not all of the particles cross)
- Mechanisms not entirely understood
- Possible uses:
  - Diagnostic & genetic tests (Nanospheres, Inc.)
  - Peptide (ligand) – phage (bacterial/viral nanoparticles) combinations
  - Injectable proteins/peptides (Abraxane®)
  - Oral proteins/peptides?
    - Recent rat study showed improved glycemic control with oral double-coated insulin nanosphere formulation
      (Reis, Veiga, Ribeiro et al. J. Pharm. Sci. 2008 Apr 2 Epub)

CONJUGATED FORMS

- Example: PEGylation - Attachment of polyethylene glycol (PEG) chains to a drug or protein
- Many other carriers & penetration enhancers being explored

Neupogen® (G-CSF, or filgrastim) + 

↓ chemical conjugation

Neulasta® (PEG–G-CSF, or pegfilgrastim)

Slow-dissolving Salt Forms

- Salt formation – common way to alter dissolution rate
- Example:
  - NPH insulin is an intermediate-acting insulin formed by adding protamine and zinc

IN SUMMARY

Drug Dosage Forms and Delivery systems are designed to provide the drug

- To the site of action
- At the right time
- In the right amount

…which will ensure efficacy and safety

- And, in a patient-friendly way (easy to use, painless, and affordable)

Questions?

UC San Diego
SKAGGS SCHOOL OF PHARMACY
AND PHARMACEUTICAL SCIENCES