**MODIFIED RELEASE DOSAGE FORMS**

**PLUTA PHAR323 CEUTICS – EXAM 1**

**DEFINITION:** Delivery of a drug at a predetermined rate to a location according to the needs of the body or disease state for a definite period of time; drug action that is relative constant, extended, & effective

**PROBLEMS WITH CONVENTIONAL THERAPY**
- Toxicity, therapeutic, and ineffective blood levels
- Peak=valleys inconsistent w/drug ½ life (saw tooth)
- Blood levels not in therapeutic range
- Patient non-compliance (too many times per day)

**ADVANTAGES**
#1 benefit: ↑ patient compliance
Other benefits: ↓SE, ↓toxicity accumulation, faster, ↑control, ↑bioavailability, ↓$, no saw tooth effect

**GOOD CANDIDATE**
- Smaller molecules, low MW
- Less protein binding
- Weak acid, base
- Non-ionic, un-ionized
- Solubility relative to dose
- Moderate solubility w/moderate dissolution
- Resists hydrolysis and enzymatic degradation
- Small dose drugs
- Not irritating, not highly potent
- Quick consistent absorption
- Ideal: good solubility, good permeability, low dose

**IN VIVO CONSIDERATIONS**
- Release rate = elimination rate, which depends on Kel, Vd, T/P ratio, and Css,des
- Moderate rate constant for absorption & excretion
- May need priming IR dose
- 2<t½<8
- Treats chronic (not acute) diseases, e.g. hypertension not antibiotics
- Problems:
  - Shouldn’t induce/inhibit enzyme synthesis
  - Variable blood levels due to metabolism
  - Slow/variable absorption
  - Narrow therapeutic window

**DELAYED RELEASE**
- Enteric coating that has a pKa of 5 so that it doesn’t dissolve in the stomach, but when it reaches the small intestine of pH=7, then it releases drug
- Zero→full release
- Take at night→morning blood levels
- Coating formulation has cellulosic polymer w/pH sensitive functional group
- May also function as repeat action
  - Core: conventional tablet
  - 1st coat: DR coating
  - 2nd coat: IR coating w/extra API

**EXTENDED RELEASE**
- Long release; low levels at start w/gradual increase
- Pulsatile: IR + D
- Biphasic: IR + ER + DR + other mixed systems

**MECHANISMS FOR RATE-CONTROLLED DELIVERY**
To deliver drug at define rate for a given time

**CONCEPT:** DIFFUSION
- Mass transfer of individual molecules by random molecular motion w/the concentration gradient as the driving force
- 1. Nonporous media, 2. Solvent filled pores, 3. Fibrous membrane strands

1. **Diffusion**
   - **Matrix:** API distributed throughout the polymer/lipid continuous phase; rate decreases with time, since API in the center has to migrate longer distances
   - **Reservoir:** API surrounded by polymer membrane; Fick’s law governs rate of diffusion (partition and diffusion coefficients, SA, thickness, conc. gradient); zero order/ constant conc. gradient

2. **Dissolution**
   - Polymer must be water soluble/degradable
   - **Matrix:** soluble coating + polymer; release controlled by dissolution of matrix; rate decreases w/time due to decrease in matrix size
   - **Reservoir:** insoluble coating + filler; release controlled by thickness and polymer membrane’s dissolution rate; once coating is dissolved, API is available for dissolution and absorption; zero order

3. **Osmosis**
   - Osmotic pressure is the driving force
   - Semipermeable membrane with a laser cut hole/orifice
Rate of release is proportional to the size of the hole.

Osmotic engine/push layer has lower solute concentration than the liquid drug inside, so as water flows through the semipermeable membrane into the liquid drug area, it pushes the liquid drug through the delivery orifice.

4. Mechanical
Mechanically driven pumps

5. Bioresponsive
Responds to change in the environment/external stimuli (e.g. pH, ionic strength, enzymes)
Influences the swellability of polymeric delivery systems

6. Stimulation systems
Magnetism, electricity, iontophoresis, ultrasound, photoirradiation, thermoresponsive, pH-sensitive

7. Other
Ion exchange, floating systems, bioadhesion, gastric swelling/unfolding

MATRIX SYSTEMS
Extended release matrix systems contain a drug, one or more polymers, excipients; such as fillers or binders, a flow aid (glidant) and a lubricant. Depending on the choice of polymer, a formulator can design a hydrophilic, inert, or hydrophobic matrix. Other functional ingredients such as buffering agents, stabilizers, solubilizers, and surfactants, may also be included to improve or optimize the drug release or the stability of a dosage form. Due to the array of polymers available for use in matrices, drug release can be fine tuned for drugs of low, medium, or high solubility.

TARGETED SYSTEMS
- Colloidal carriers: microparticles, nanoparticles, macromolecular complexes, liposomes, niosomes
- Ligand-mediated: vascular, cellular, or intracellular targets where ligands recognize antigens, receptors, cells on organs or disease sites
- Resealed RBC: API incorporated into RBC by osmotic procedure: osmosis, lysis, drug solution, reseal
- Bioadhesives: adheres to eyes, nose, cheek, intestines, or vagina to increase contact time
- Prodrugs: chemical modification so API liberated by enzymatic or chemical processes (e.g. CYP, esterases, hydrolases, phosphorylases)

ENHANCING PROTEIN DELIVERY
↑absorption, chemical modification, ↓metabolism,
↑t_{1/2}, ↑penetration, protease inhibitors, bioadhesives, nanoparticles

USP TESTING
*Delayed release:* uses basket apparatus with HCl, see how much is dissolved in 2 hours at 2 different pH levels; if API released in stage 1, fail
*Extended release:* uses paddle apparatus to see how much is dissolved in 8 hours (looking for a certain % range at each time interval)

IVIVC
Correlation between in vitro and in vivo
To evaluate predictability, dissolution specifications, and bioequivalence
Level A: predictive mathematical model between in vitro dissolution/release vs. in vivo response time
Approach: formulations with different release rates, in vitro dissolution profiles, in vivo plasma conc. profiles, estimate in vivo absorption/dissolution using math

PHARMACIST COUNSELING POINTS
- Don’t intermittently use IR products
- Don’t change to another ER unless equivalent bioavailability ensured
- Don’t crush/chew w/o careful review
- Nasogastric tube patients can use pelletized products
- “Ghost” shells from hydrophobic matrix products might be visible in stool