Oral Controlled Release Formulations

Sheri Shamblin

ALEURITES Consulting

We provide premium technical consulting services for the design and development of immediate-release and controlled release medicines. Our primary focus is on small molecule oral drug products.

Sheri L. Shamblin, PhD

- Principal consultant for Aleurites.
- Over 28 years working in drug development at Pfizer Inc.
- Expertise in the design and development of oral controlled release formulations and formulations to increase solubility and bioavailability.

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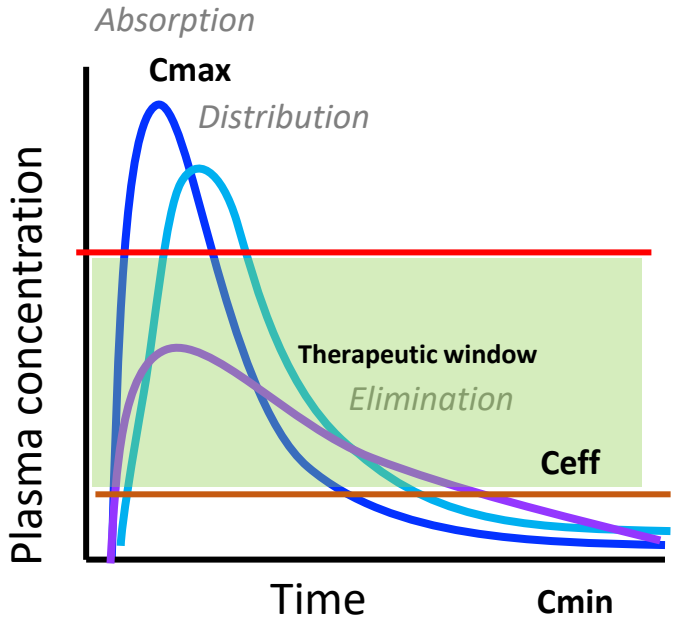
What you will learn

- Typical drivers for use of oral controlled release (CR) formulations.
- An overview of standard oral CR technologies.
- What CR technology is appropriate for your drug.
- Tips and tools for formulation development and clinical evaluation.

Drivers for Controlled Release

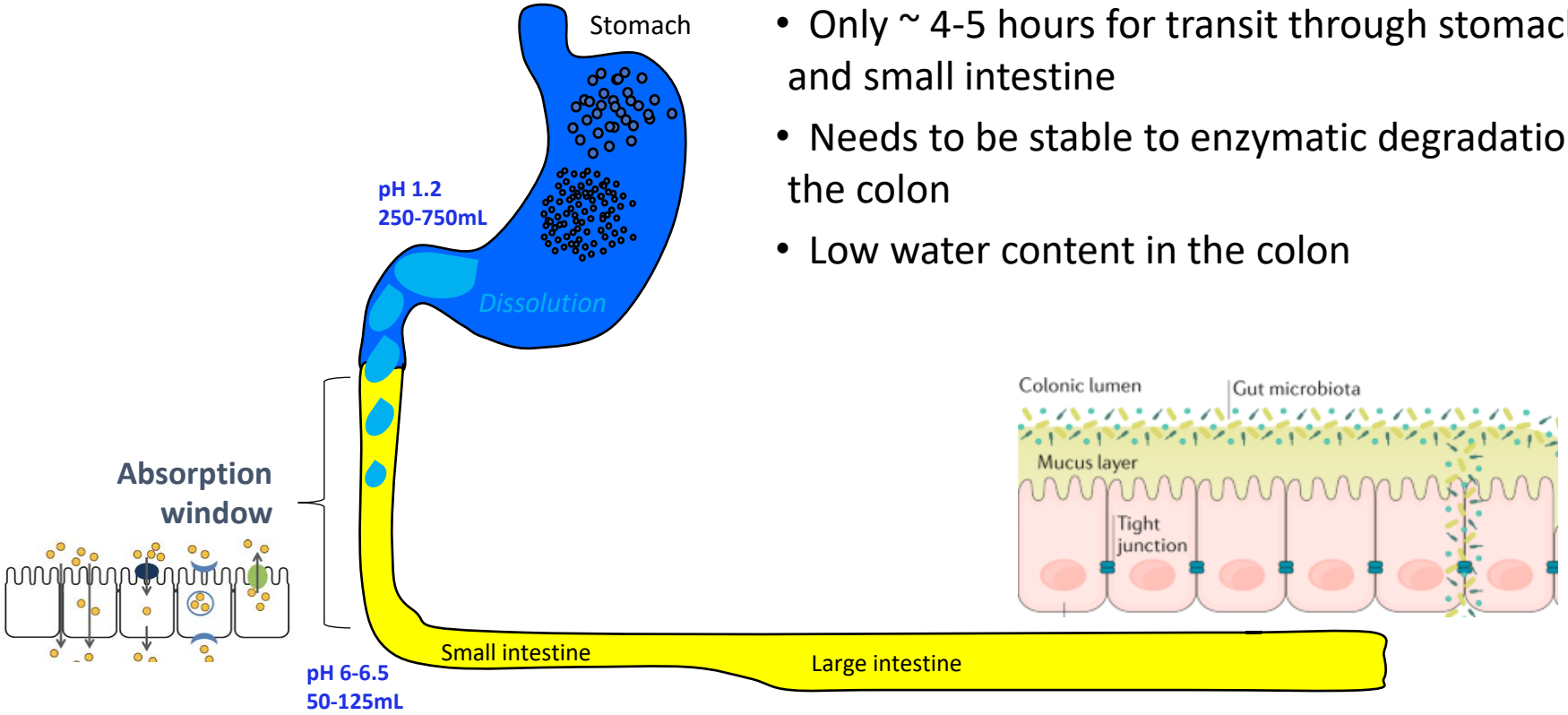
- Reduce the frequency of dosing
  - TID (3 times a day) to BID (2 times a day) or QD (once a day)
- Reduce side-effects
  - Local, e.g., irritation in GI
  - Systemic
  - reduce “rate of rise” of plasma levels
  - reduce Cmax/Cmin
- Increase efficacy
- Decrease drug degradation in stomach
- Delivery to OR around a specific region in the GI tract



Oral CR Delivery and GI Physiology

$$\text{Dose Volume (mL)} = \frac{\text{Dose (mg)}}{\text{Solubility } \left(\frac{\text{mg}}{\text{mL}}\right)}$$

- Colonic absorption is **LIKELY** needed for most CR dosage forms
- Only ~ 4-5 hours for transit through stomach and small intestine
- Needs to be stable to enzymatic degradation in the colon
- Low water content in the colon



Boegh, M. & Foged, Camilla & Müllertz, Anette & Nielsen, Hanne. (2013). Mucosal drug delivery: Barriers, in vitro models and formulation strategies. Journal of Drug Delivery Science and Technology. 23. 383.

Long duration = more challenging

Before you begin formulating: Controlled Release Feasibility

Solubility	• Dose, solubility and duration • Role of pKa and pH for ionizable drugs
Permeability	• Differences in regional absorption along the GI tract • Efflux mechanisms, PGP
Stability	• Chemical stability (polymers for matrix and functional coatings) • Enzymatic stability (in vivo)
Metabolism	• Rate of elimination ($t_{1/2}$) • Mechanism of elimination and extent of first-pass

Thombre, A. G. (2005). Assessment of the feasibility of oral controlled release in an exploratory development setting. *Drug Delivery Today*, *10*(17), 1159–1166.

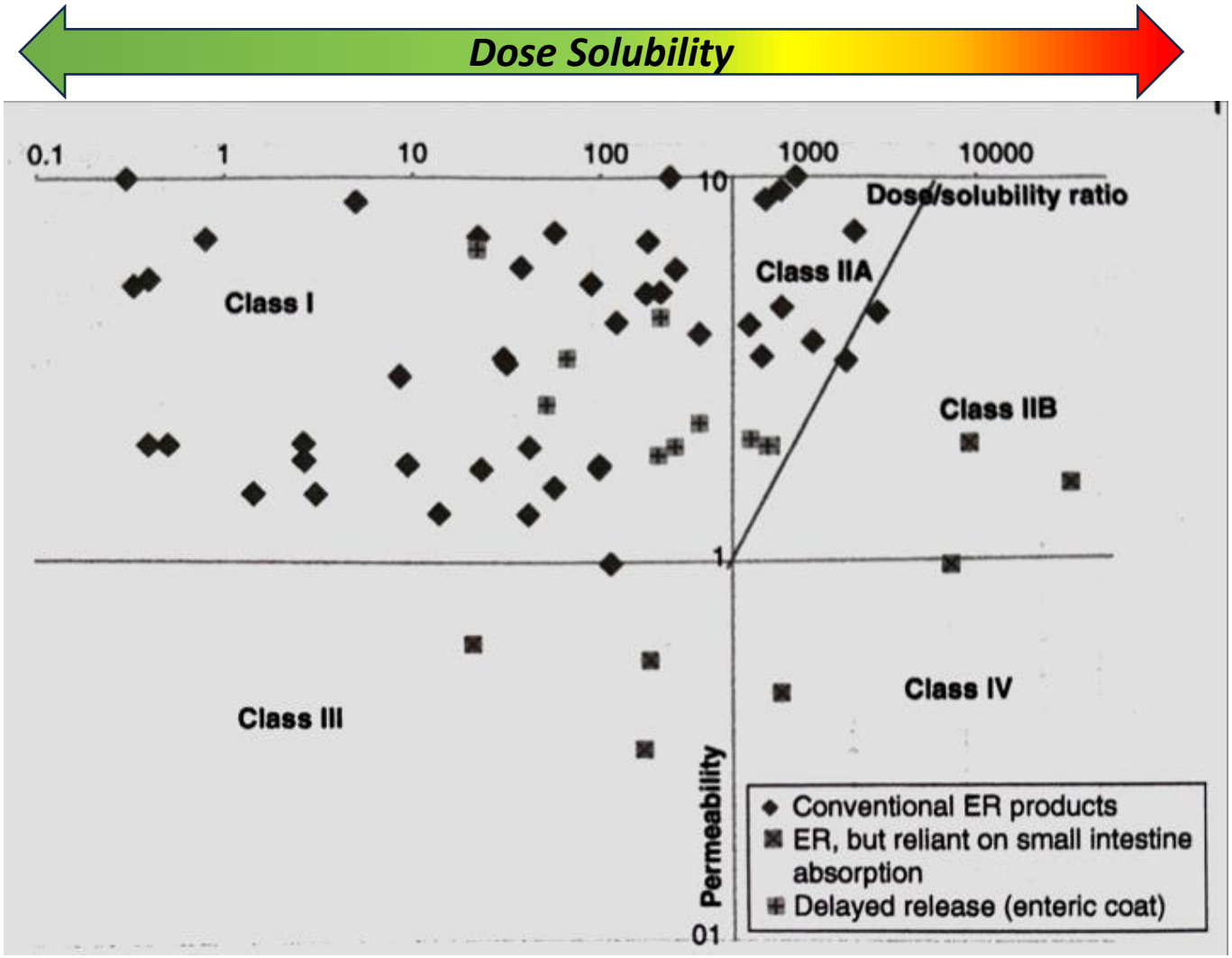
Assessment of Clinical Success with CR

Factor	
Dose	<1mg
	10-250mg
	>>250-300mg
Dose:Solubility (Dose volume)	<1mL
	100-1000 mL
	>1000 mL
	>10,000 mL
Regional Permeability	Good- P_{app} >10^{-5} cm/s
	Moderate P_{app} 10^{-5} -10^{-6} cm/s
	Poor P_{app} < 10^{-6} cm/s
PK or PD half-life	>>10h
	2-10 h
	<1-2

Stability, absorption pathways, role of efflux and metabolic pathways are also critical

Thombre, A. G. (2005). Assessment of the feasibility of oral controlled release in an exploratory development setting. *Drug Delivery Today*, *10*(17), 1159–1166.

Developability Classification System and Commercial MR Products



Feasibility based on Thombre, 2005.

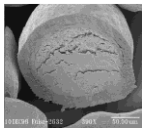
Butler, J.M., "The Application of Biopharmceutics Classification Systems to Modified-Release Formulations", *in Oral Drug Delivery for Modified Release Formulations, First Edition*, 2022, Wiley & Sons.

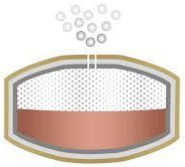
Oral Controlled Release Technologies

Increasing complexity

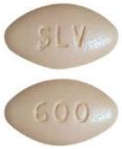
- Matrix Tablet
  - Polymer matrix controls drug release
  - Most common oral CR technology used for marketed drugs
- Multiparticulates
  - Particulates ranging from 0.2 – 3.0mm
  - Includes beads, granules, minitablets microspheres
  - Control through multiparticulate and/or functional coating

- Delayed Release (enteric coated)
  - Tablets (IR or CR)
  - Multiparticulates (bead or minitablets)





- Osmotic Pump
  - Constant rate of delivery driven by flux of water across a semi-permeable membrane
- Gastric Retentive
  - Polymers that expand or swell
  - Large size prevents passage through pylorus



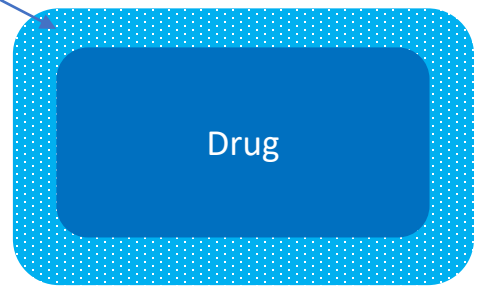
Controlling release by controlling diffusion

Fick's First Law

$$\frac{dQ}{dt} = \frac{DAk}{h}(C_x - C_o)$$

D = diffusion coefficient (depends on viscosity, size of diffusing species
A = surface area of membrane
k = partition/permeability coefficient
h = membrane thickness
Cx-Co = concentration difference

Barrier to diffusion created by gel, coating, porous membrane



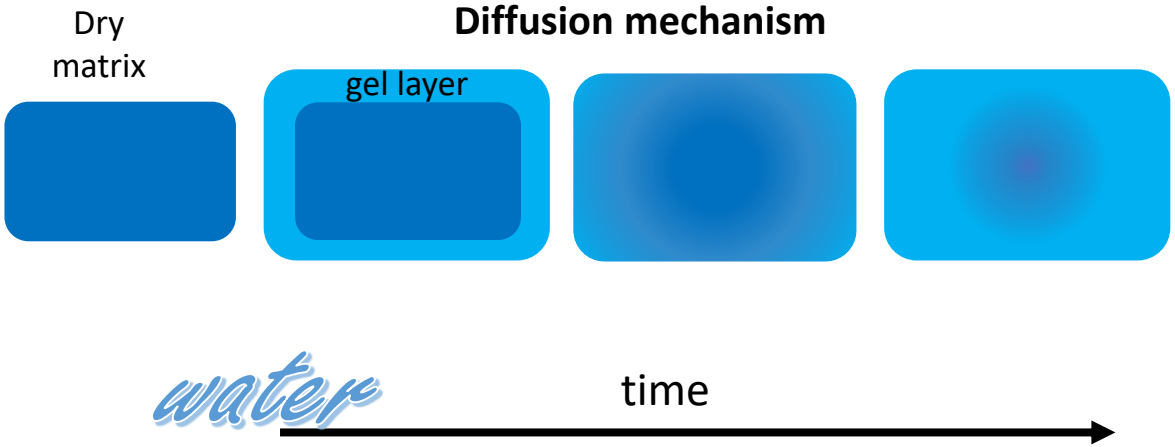
Controlling drug diffusion

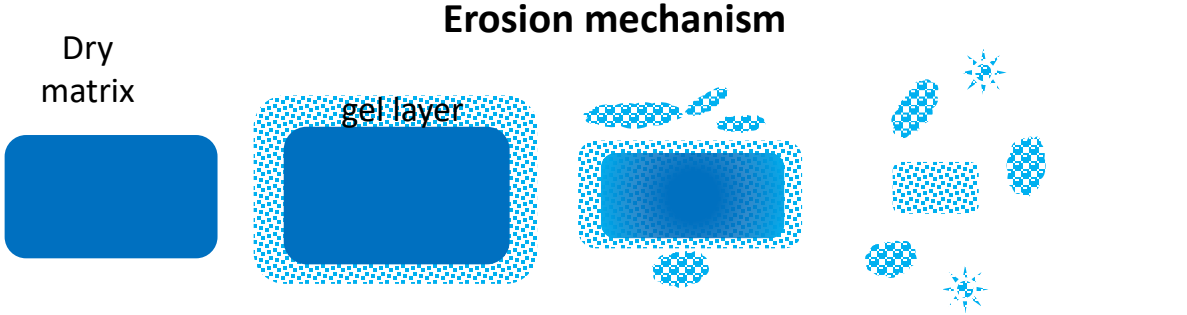
- Diffusion of drug across a membrane
- Diffusion of drug through a viscous matrix or gel
- Porous diffusion through a hydrophobic matrix (multiparticulate bead, granules)
- Controlled diffusion of water into a tablet through a semi-permeable membrane to create an osmotic pump that delivers drug

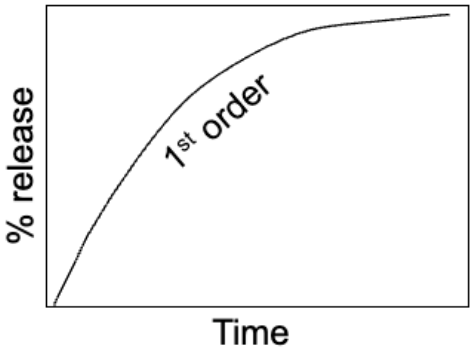
Matrix Tablets

Matrix Tablets: Mechanism of Control

Homogeneous blend of drug, hydrophilic or hydrophobic polymers, soluble and insoluble excipients







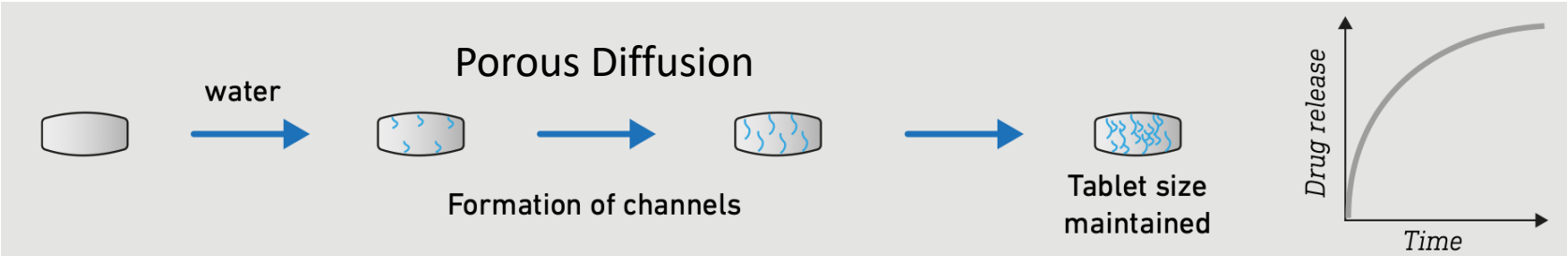
$$\frac{dM}{dt} \approx C_d A l D_{eff}$$

Drug dissolves and diffuses through viscous gel created by polymer matrix

$$\frac{dM}{dt} \approx kA$$

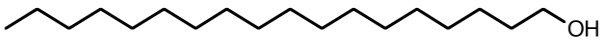
Undissolved drug weakens polymer gel resulting in erosion of the hydrate matrix

Wax Matrix: Mechanism of Release



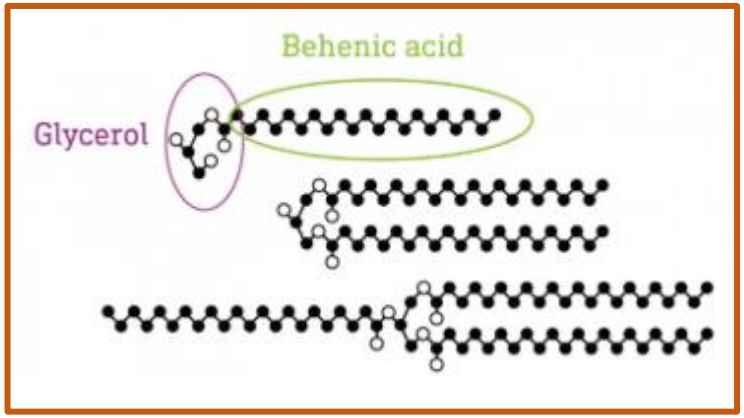
Fast release

Stearyl alcohol



Slow release

Glyceryl behenate



Matrix Tablets

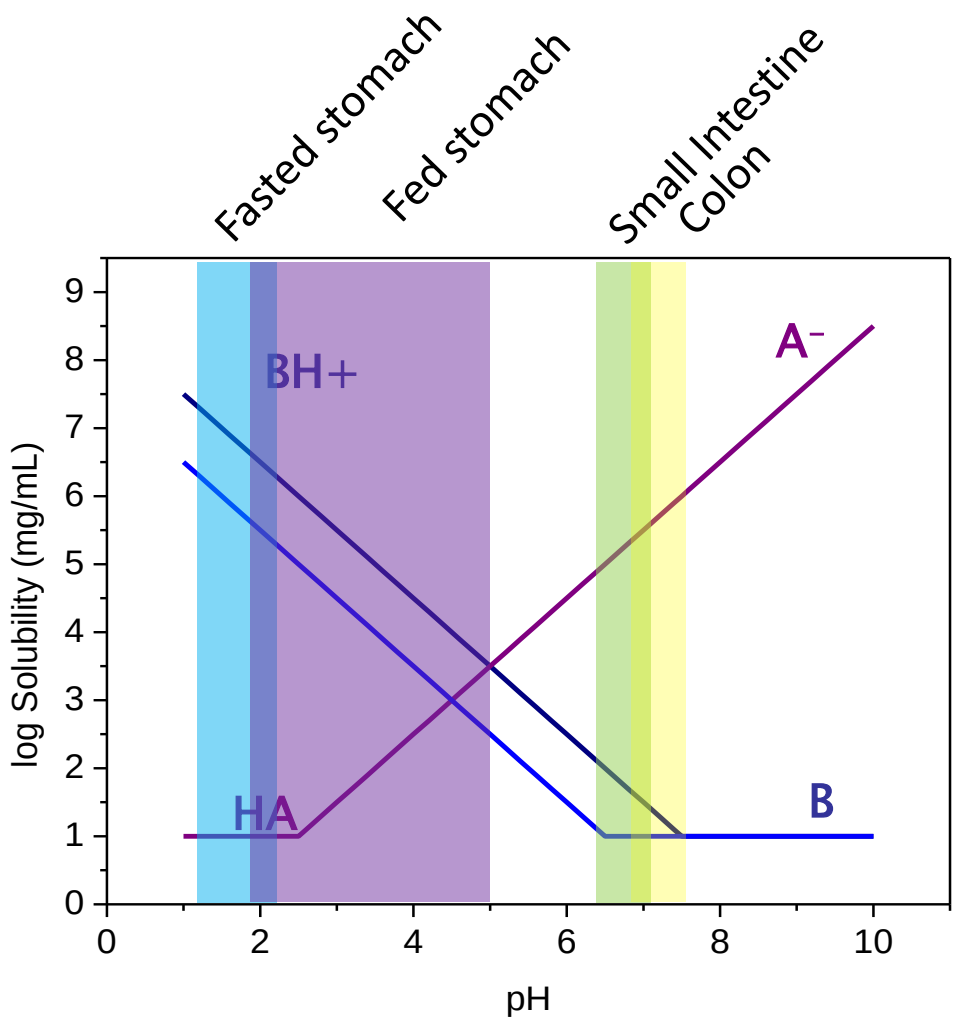
Attributes

- Simple to manufacture
- Wide-selection of polymers and waxes available
- No functional coatings required
- Can be coated to provide a delayed CR profile.

Challenges

- Release rate depends on drug solubility in aqueous environment
- Variable release for ionizable drugs
- Eroding matrix tablets are sensitive to food/digestion and can have a food effect
- In vitro release rate may not be predicted of in vivo release and performance

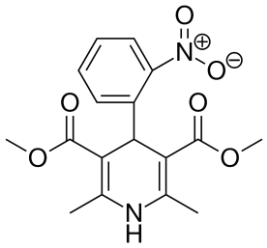
Ionizable Drugs and Solubility



- Ionizable drugs have pKa's from 3-7, drug solubility will change as the drug/dosage form move through the GI tract.
- For matrix tablets, the change in drug solubility will cause a change in release rate, and even mechanism.

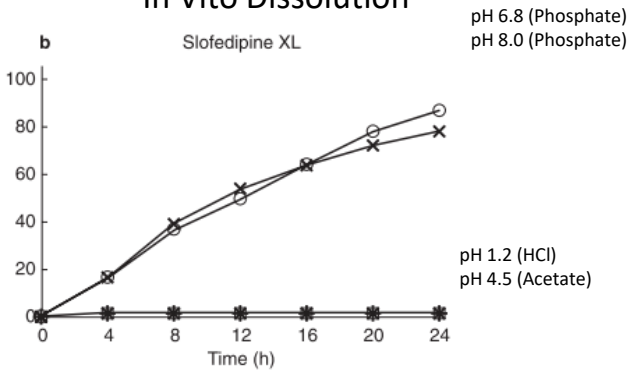
Li, X., Jasti, B. "Design of Controlled Release Drug Delivery Systems", McGraw-Hill, 2006

Controlled Release of Nifedipine

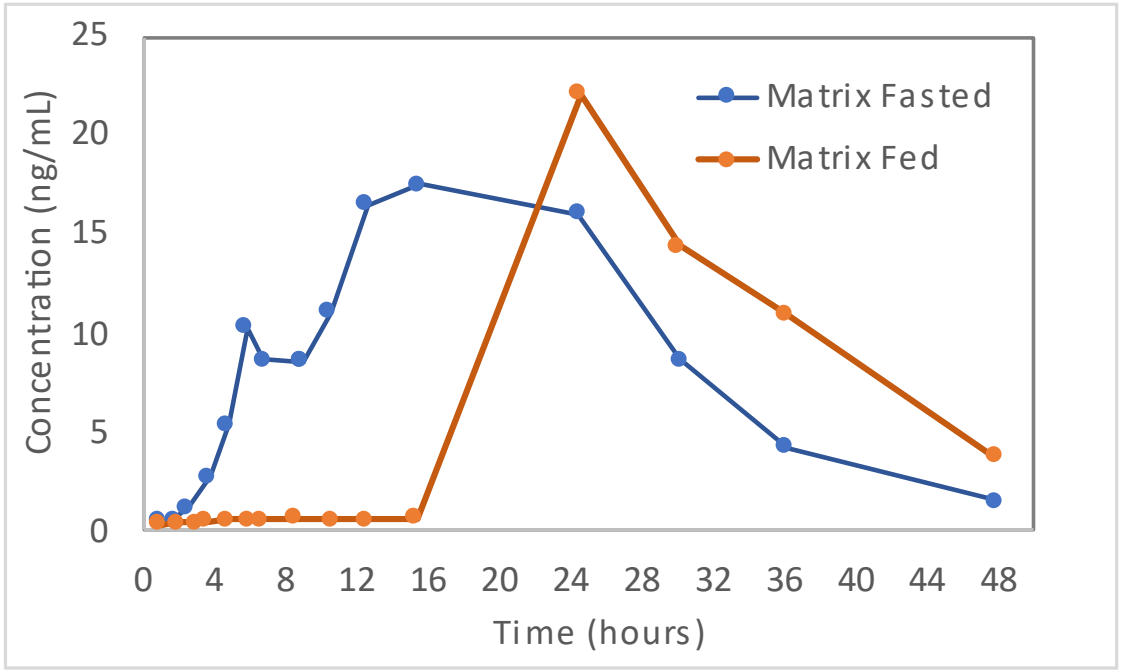


pK_a = 3.93 (weak acid)
10ug/mL (water)

In Vito Dissolution



PK Profile of Nifedipine in Humans (n=24)



Friedrich, H. (2004). Improvement of solubility and stability of poorly soluble drugs. In: Ph.D. Dissertation. Berlin, Germany: Freie Universitä̈t Berlin.
Freidrich et al (2005). **Drug Dev and Ind. Pharmacy, v31, 8, p 718-728**

Multiparticulates

Multiparticulates: Flexibility and versatility

Types of multiparticulates:

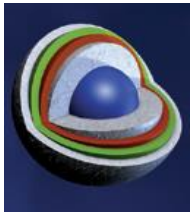
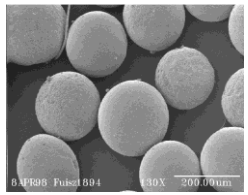
- Wax/polymer matrix beads
- Drug layered bead
- Granules
- Minitablets
- Coated or uncoated

Presentations to the Patient

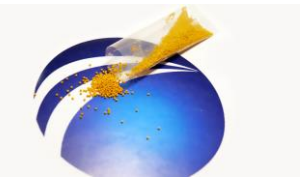
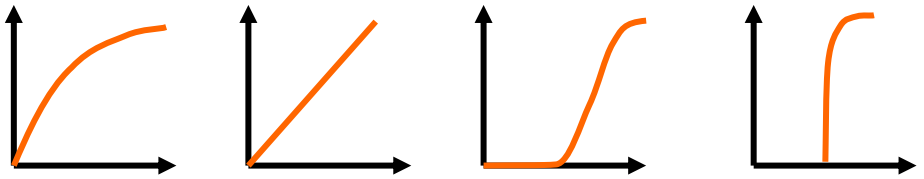
- Capsule
- Sachet
- Stick pack

Coatings:

- Enteric (pH release)
- Time release
- Semipermeable (osmotic)



Multiparticulates

Attributes

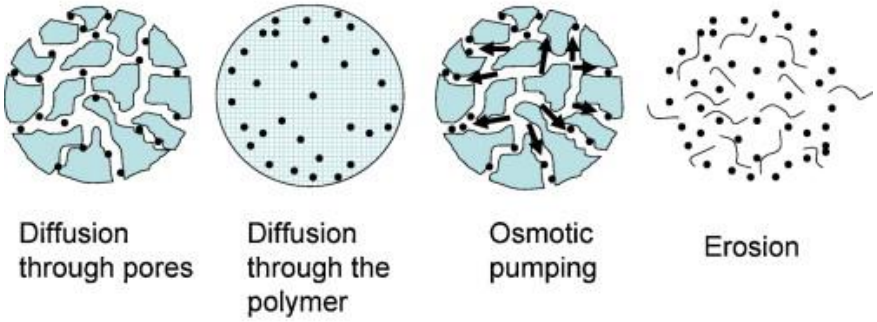
- Broad category that includes many types of particulates (0.2mm – 3.0mm)
- Reproducible GI transit (more consistent with or without food)
- Wide range of release profiles possible: Delayed (enteric), Sustained, Pulsed, or IR+CR
- Well-suited for combination drugs
- Pediatric/geriatric dosage form
- Offers versatility in release profile
- Flexibility in dose and presentation

Challenges

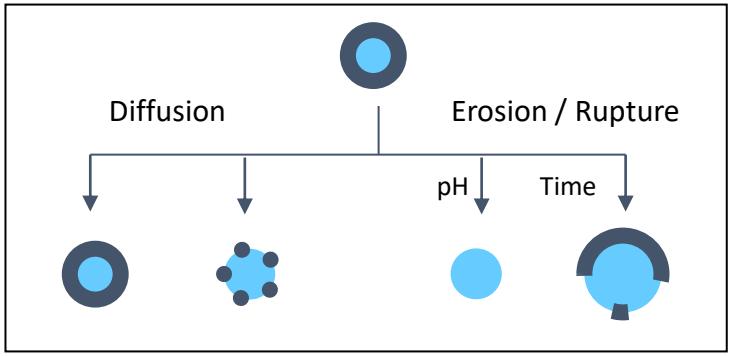
- Complex manufacturing compared to monolithic matrix tablets
- Drug loadings are on the low side, typically <30%

Multiparticulates: Mechanisms of drug release

CR Multiparticulates

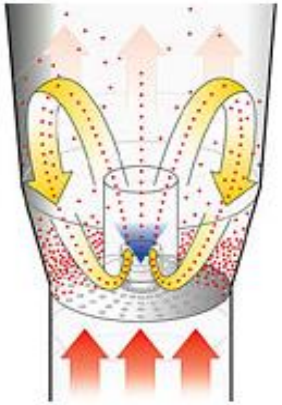


Film coated beads



Manufacturing Multiparticulates

Fluid Bed



Cellets
(microcrystalline cellulose beads)

Photo: Cellet.com

- CR granules
- Drug layering on inert beads
- Functional coating of beads, granules, minitablets

Extrusion

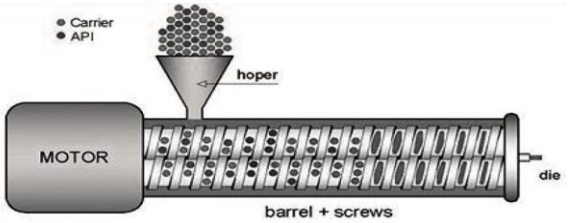


Image: Aleksovski et al, 2016, Macedonian pharmaceutical bulletin

- CR granules or pellets
- Feed for congealing

Compression of Minitablets

Photo: Tabletsandcapsules.com

- CR granules or pellets
- Feed for congealing

Congeal Spin or Spray

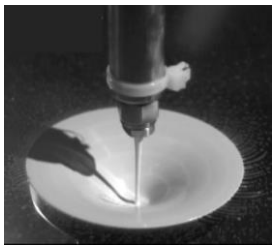


Photo: SWRI

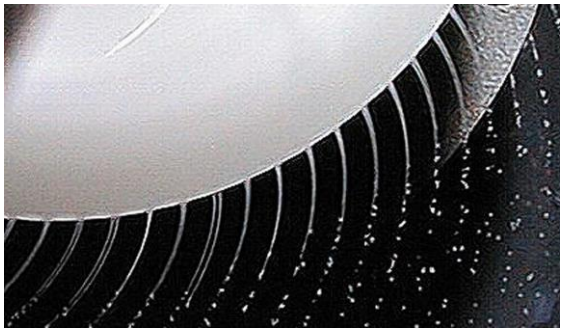


Photo: SWRI

- Microspheres – 200-500 um (spinning disk)
- Microspheres – 500-1000 um (spray-congeal)

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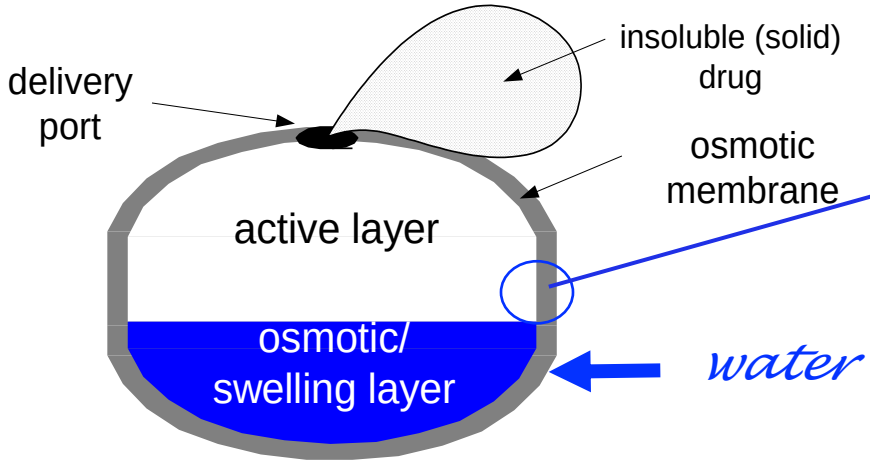
Osmotic Tablets

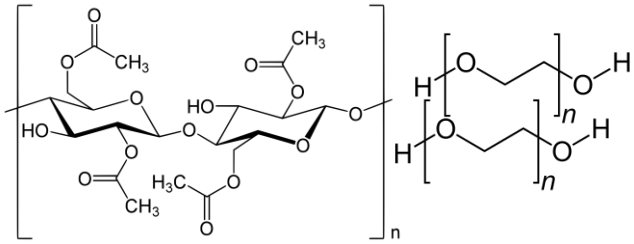
Osmotic Tablet Technology

Bilayer Osmotic Tablet

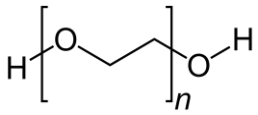


Drug release is controlled by the semi-permeable osmotic membrane and an osmogen (NaCl)

Cellulose acetate and polyethylene glycol

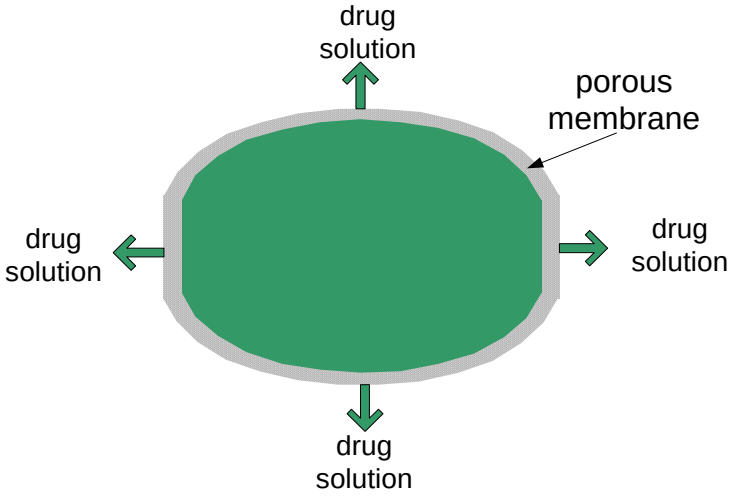


Active layer:
- Drug
- Polyethyelene oxide (2M



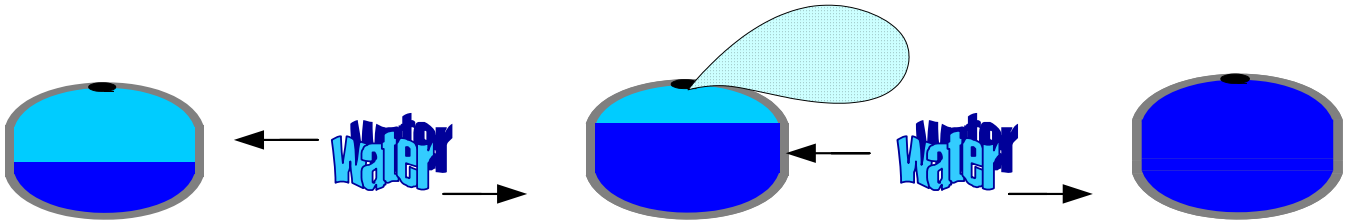
Swelling layer:
- NaCl
- Polyethyelene oxide (5M)
- Blue Lake #2

Monolithic Osmotic Tablet



Shamblin, S. L. (2010). Controlled release using bilayer osmotic tablet technology: reducing theory to practice. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, 129–153.

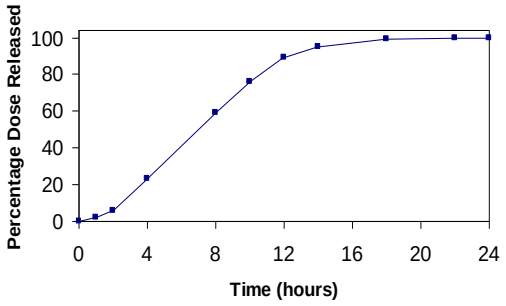
Generic Mechanism of Delivery For Osmotic Drug Delivery Systems



Initial
Initially water diffuses through film- coating
Hydrates bilayer core

During Delivery
Solvation of osmogens creates a constant osmotic pressure difference, $\Delta\pi$
Hydration causes a decrease in viscosity
Drug is extruded or "pushed" via a hydrostatic pressure and/or swelling mechanism

Final
Sweller layer expands, filling void as drug layer extrudes
Intact tablet shell is excreted



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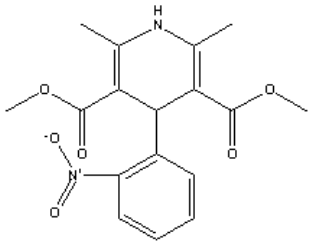
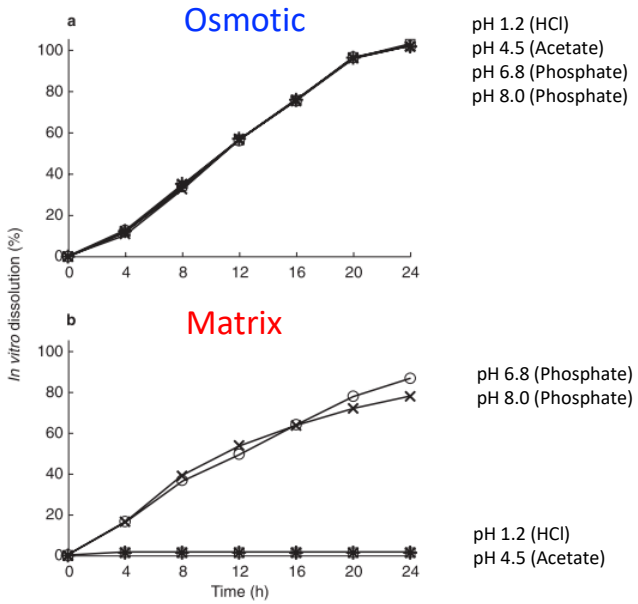
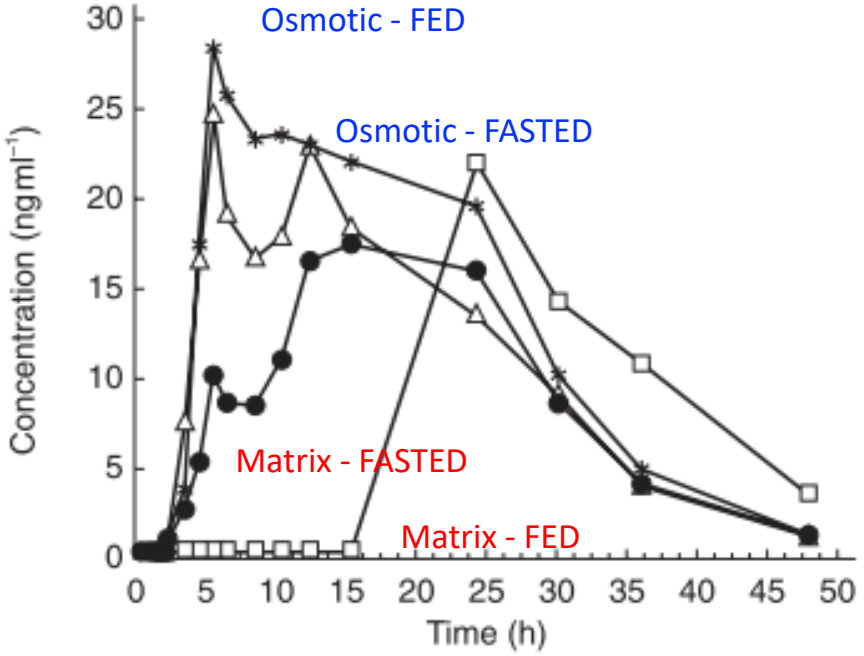
Nifedpine: Osmotic vs Matrix Tablet





PK Profile of Nifedipine in Humans (n=24)



Osmotic Tablets

Attributes

- Delivers drug via osmotic potential typically in a zero-order fashion
- Drug release independent of pH/ stirring even for low solubility and ionizable drugs
- Applicable to drugs independent of their solubility
- Good in-vitro/in-vivo predictive tests – speed development and minimize iterations

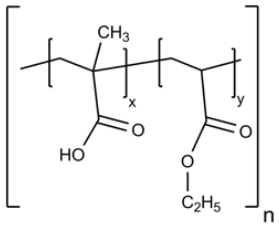
Challenges

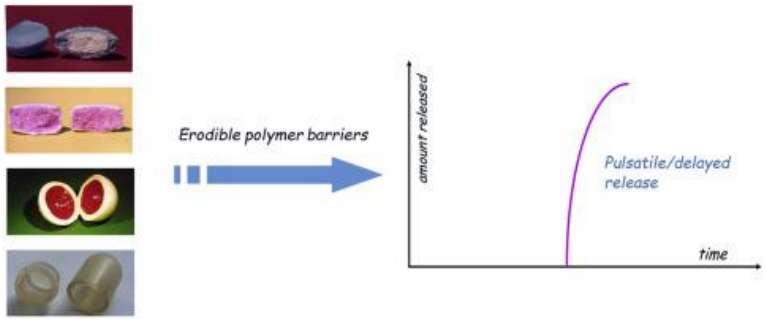
- Complex manufacturing Solvent coatings
- May require laser-drilling and requires solvent coating capability
- May require layered tablet cores and hole(s) in coating.
- Drug loadings are on the low side, typically <30%
- Can have a lag time to initial drug delivery
- Not well suited to multiple profiles or combination therapies.

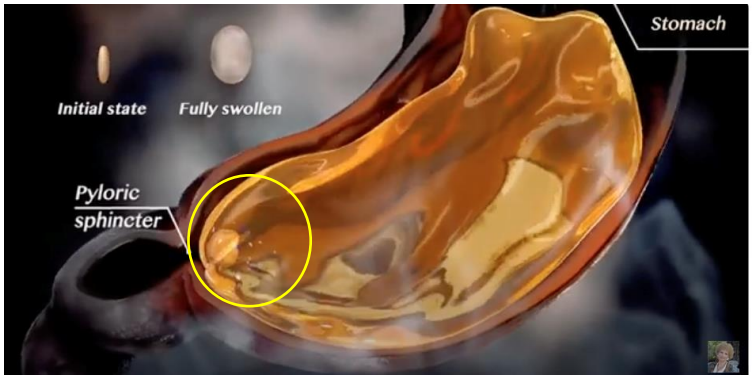
Additional ways to control drug release

- Delayed drug release (pH, time)
  - Enteric polymer coatings prevent drug release in the stomach
  - Reverse enteric polymer coatings that prevent drug release in neutral environment in the mouth.
  - Use of erodible polymer coatings/barriers to slow or delay release
  - Control obtained using coating type and thickness
- Gastric-retentive
  - Designed to remain in stomach using swelling, density or muco-adhesion
  - Control of drug release using polymers, hydrogels to slow drug release
  - Limits drug absorption to the duodenum

EUDRAGIT® L 30 D-55

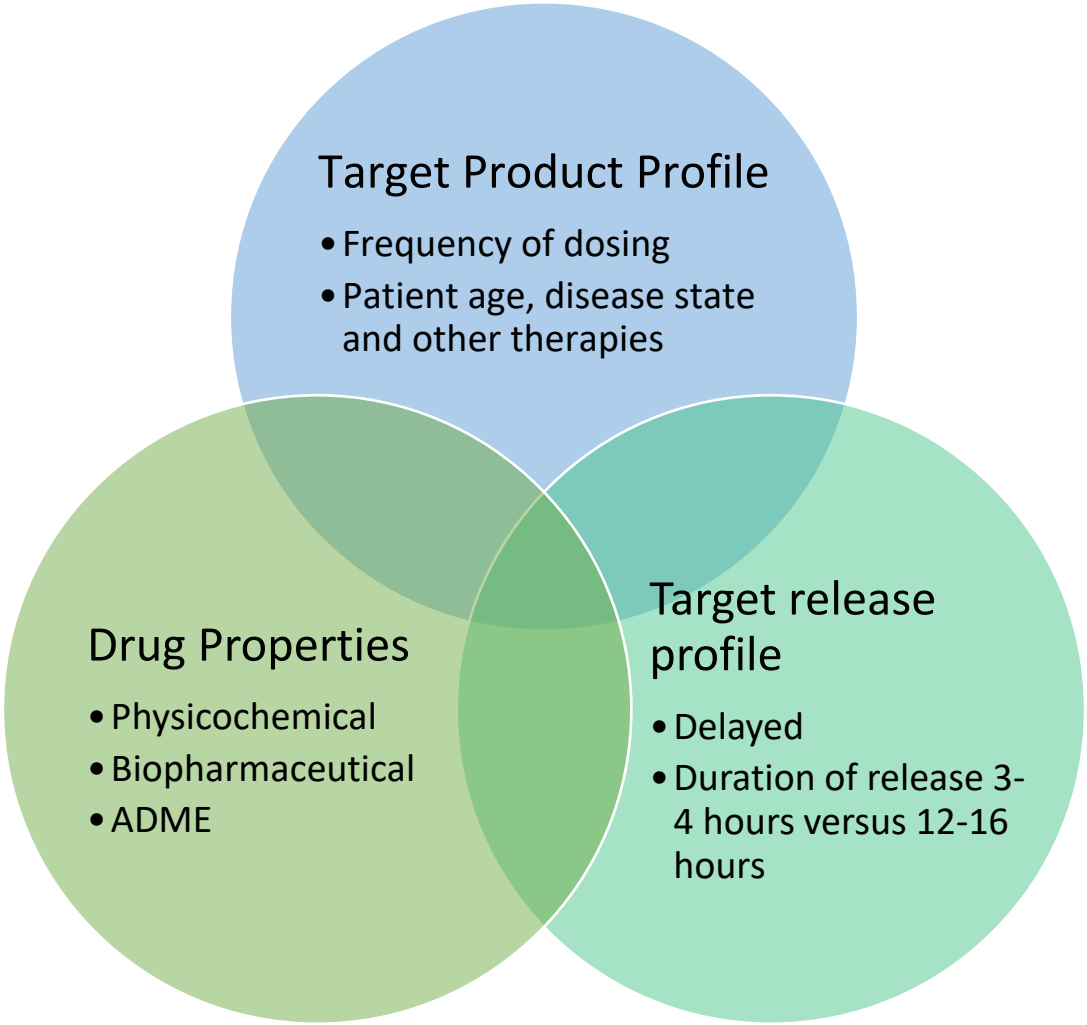




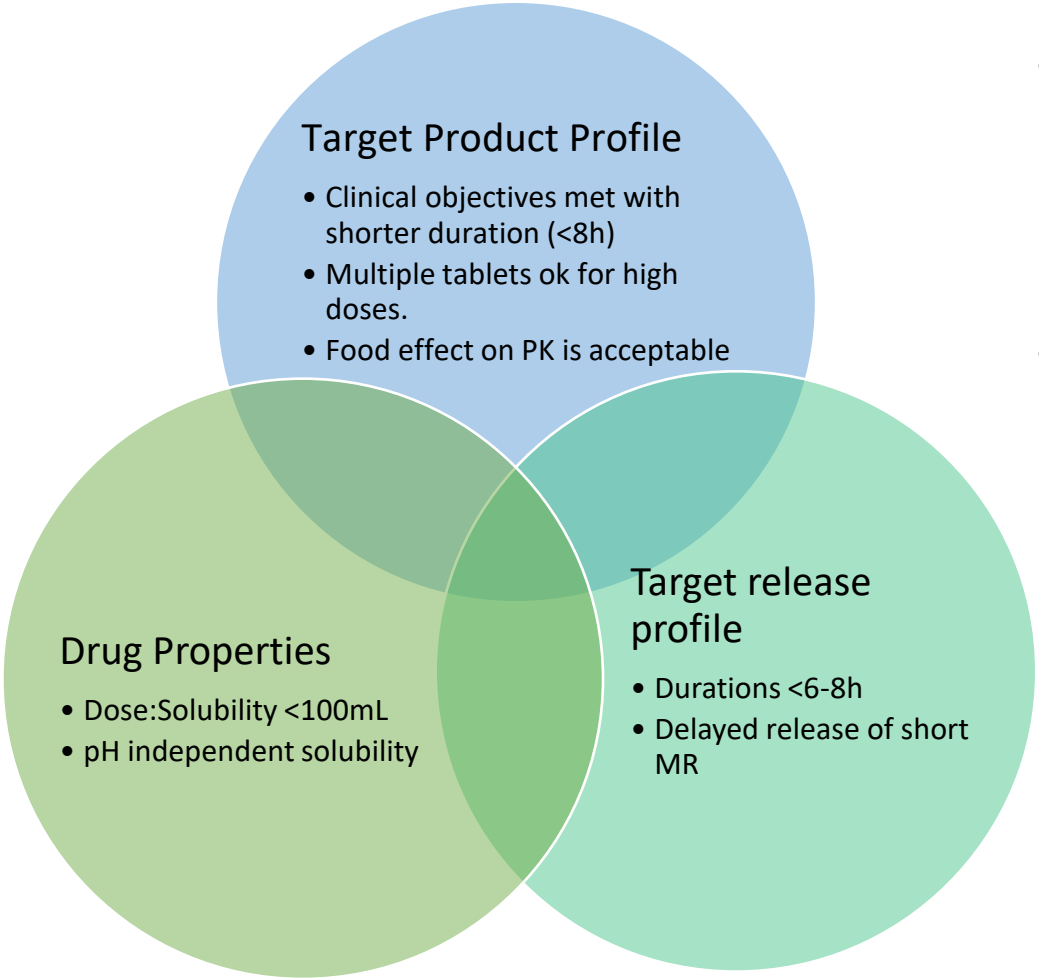


GRALISE® (gabapentin) Pharmacokinetic Mechanism of Action - YouTube

Selection of a CR Technology

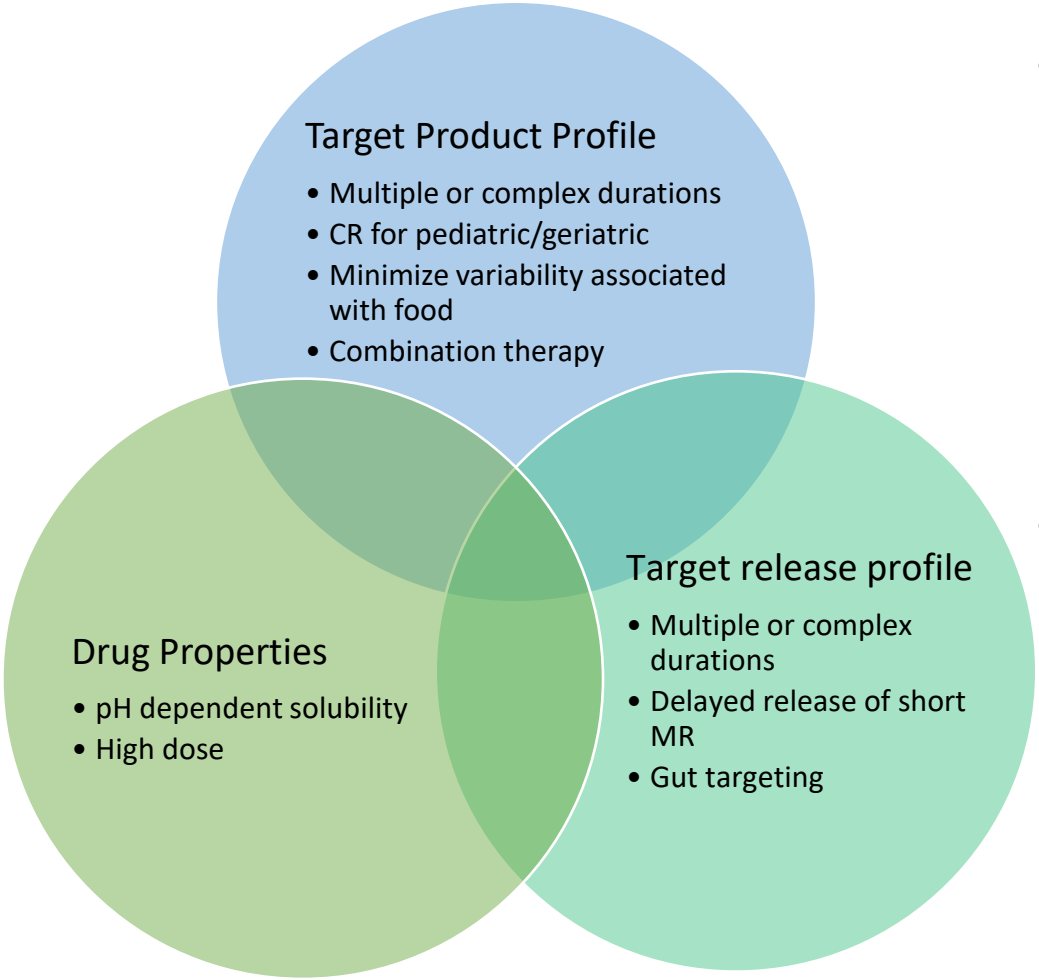


When to use a matrix tablet



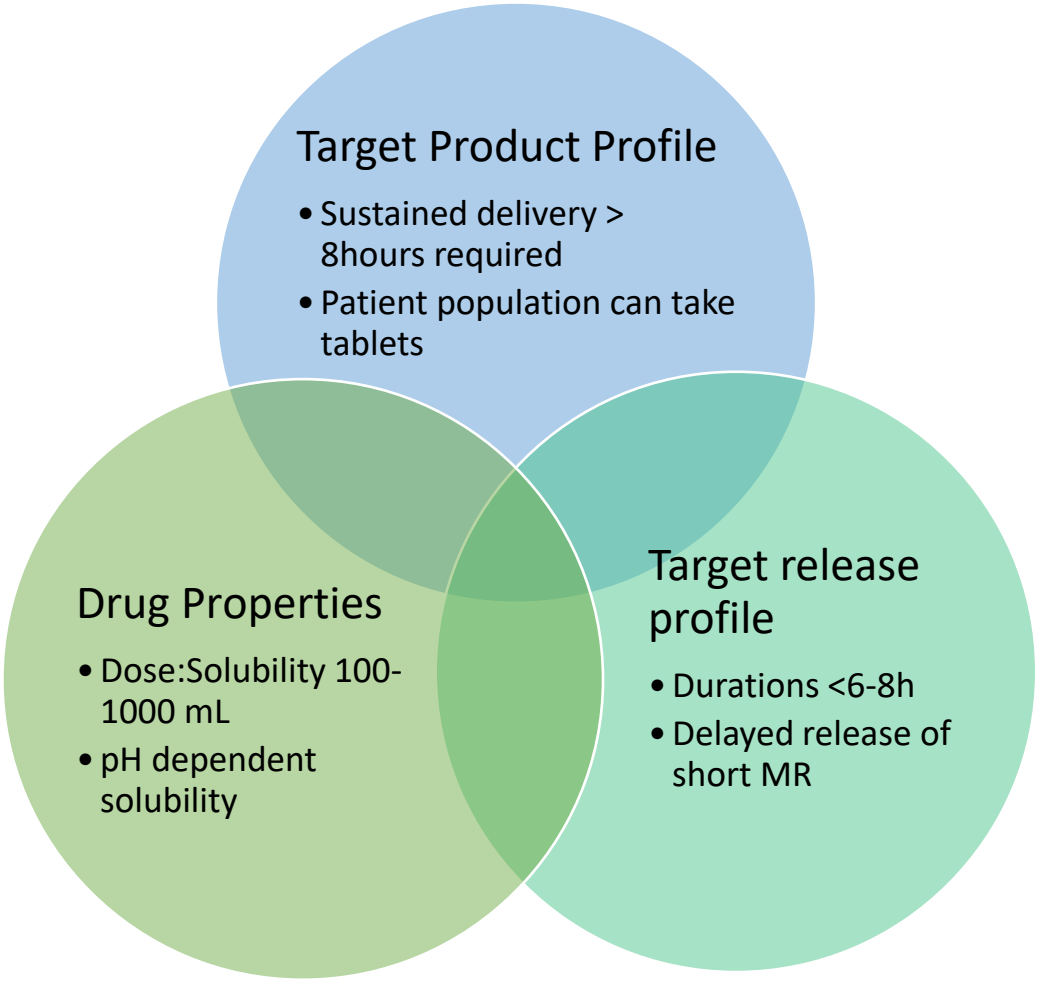
- Matrix tablets are a good starting point:
  - Simple to manufacture
  - Most common marketed CR/MR technology
- Why you might not want to use a matrix tablet:
  - Low drug solubility
  - pH dependent solubility over physiologic range
  - Pediatric/geriatric patients
  - High dose (tablet burden)
  - Combination product

When to use multiparticulates



- Multiparticulates are flexible and versatile:
  - Wide range of profiles
  - Suitable for low and high dose
  - Amenable to different presentations
  - Commercial precedence
- Why you might not want to use multiparticulates:
  - More complex to manufacture than a simple matrix
  - Slower throughput, not continuous (yet)

When to pursue osmotic delivery



- The complexity of an osmotic tablet is worth it when:
  - Narrow therapeutic window
  - Long durations are required to achieve QD dosing
  - Need to minimize iterations of CR design and protype testing
- When not to use an osmotic tablet:
  - When a simpler technology can achieve the clinical objectives and meet TPP
  - For some geriatric patients and those under 12 years
  - High doses that require multiple tablets

CR Formulation design and optimization tips

- Identify stability/compatibility issues as early as possible
- Start analytical method development early
- Extraction/potency methods can be challenging
- Use sink conditions for formulation optimization
- Low potency is very common due to:
  - Challenges with extraction from blends, granules and tablets
  - Potential for residual drug in tablets
  - Loss of drug during processing

Development and clinical strategy considerations

- Development of CR dosage forms is iterative
- Initial PK studies to establish in vitro and in vivo relationships should use multiple release durations/formulations that bracket design space
- Plan for multiple PK studies to finalize the formulation
- Use of an IR (or IV) as a reference for multiple MR durations in PK studies is recommended
- For drugs with moderate-to-high PK variability, consider the number of subjects/patients for pivotal BA/BE studies

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