Multiparticulates: Flexible Oral Solid Dosage Formulations

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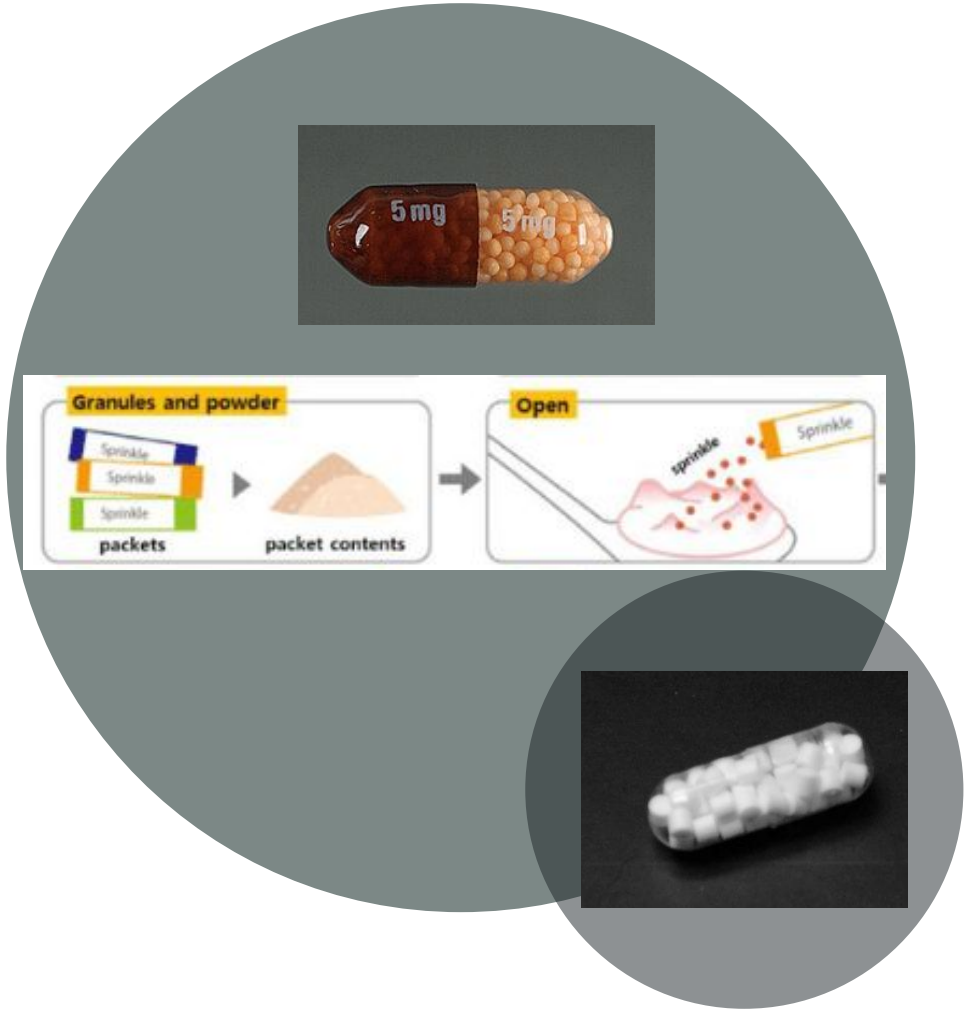
Overview

- What are Multiparticulates?
- Are Multiparticulates the best choice for all products?
- How do you make them?
- What makes multiparticulates more flexible than tablets?



What are Multiparticulates?

- Dosage form where the total dose is spread across many subunits (typically beads or minitablets)
- First FDA approved SR multiparticulate product was Dexedrine Spansules in 1952
- 1960's- OTC cold medicine – Contac –
- 6 different API's, 12 hr profile

Sprinkle photo from review article by Han Lee et all, Asian Journal of Pharm. Sci 2019

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Are Multiparticulates always the right choice?

- No. They are a tool which is extremely useful in the development of drug products which include:
  - Multiple API's
  - Pediatric and adult doses
  - Complex drug release profile needed
    - IR and SR combination
    - Pulsatile
  - Can simplify SR development when dose and/or SR profile is not defined

How do you choose the type of oral solid dosage (OSD) to develop?

- Know your Target Product Profile
  - Dose & PK profile
  - API characteristics
  - Patient population
- What are your program constraints?
  - Time / API availability / budget
  - Clinical Phase

Simple examples of OSD choice

- Example 1
  - Phase I study
  - Estimated doses for dose range finding studies: 50-500mg, IR
  - 500g R&D API & ~ 1kg GMP API available
  - Clinic date in 6 months
  - API slightly soluble

Simple examples of OSD choice

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- OSD: IR capsules, 50mg and 150mg
  (Common blend ~ 50% drug load, size 3 and 00 capsules)
  - Multiparticulates would require larger amounts of API per batch, and more complicated than required for this study

Simple examples of OSD choice

- Example 2
  - Phase III study ongoing with 150mg IR tablet (500mg tablet weight)- TID dosing
  - Pediatric indication to be added in ~9 months: need doses ranging from 25-100mg for children ages 2+
  - API very bitter, not stable in solution

Simple examples of OSD choice

- Example 2
  - Phase III study ongoing with 150mg IR tablet (500mg tablet weight)- TID dosing
  - Pediatric indication to be added in ~9 months: need doses ranging from 25-100mg for children ages 2+
  - API very bitter, not stable in solution
- OSD: Taste-masked sprinkle on food (multiparticulate)
  - 10-25% drug load to provide beads that can be filled into a capsule at any potency up to 100mg/capsule: opened to put on food for dosing

Simple examples of OSD choice

- Example 3
  - Phase II studies planned in 6 months; need a dose 750mg, BID
  - Phase I formula was 250mg capsules (dry blend in size 00 shell)
  - API prone to hydrolysis

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  - Phase I formula was 250mg capsules (dry blend in size 00 shell)
  - API prone to hydrolysis

- OSD: 750mg tablet, made by roller compaction (target ~70% drug load/1070mg tablet)

- 750mg dose is extremely high for multiparticulates, and there is only one API, IR release desired

Simple examples of OSD choice

- Example 4
  - Line extension: SR product, 2 API's
  - Commercial products are a 50mg IR tablet (Compound A), dosed 4x's/day, and a 75mg SR tablet, dosed once/day
  - Clinical target is a morning loading dose of Compound A, followed by sustained release throughout the day of both products, and full elimination overnight
  - Both API's are slightly soluble

Simple examples of OSD choice

- Example 4
  - Line extension: SR product, 2 API's
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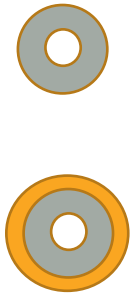
- OSD: Multiparticulates
  - Separately develop IR beads and SR coated for compound A, and SR coated beads for compound B; combine all 3 into single capsule

How do you make multiparticulates?

- Beads or minitablets in capsule
  - Drug loading
  - Polymer coating
  - Encapsulation



Picture by Natoli

Drug Loading

- Compression of minitabs
- Extrusion & spheronization
- Top spray
- Solid Coating pan

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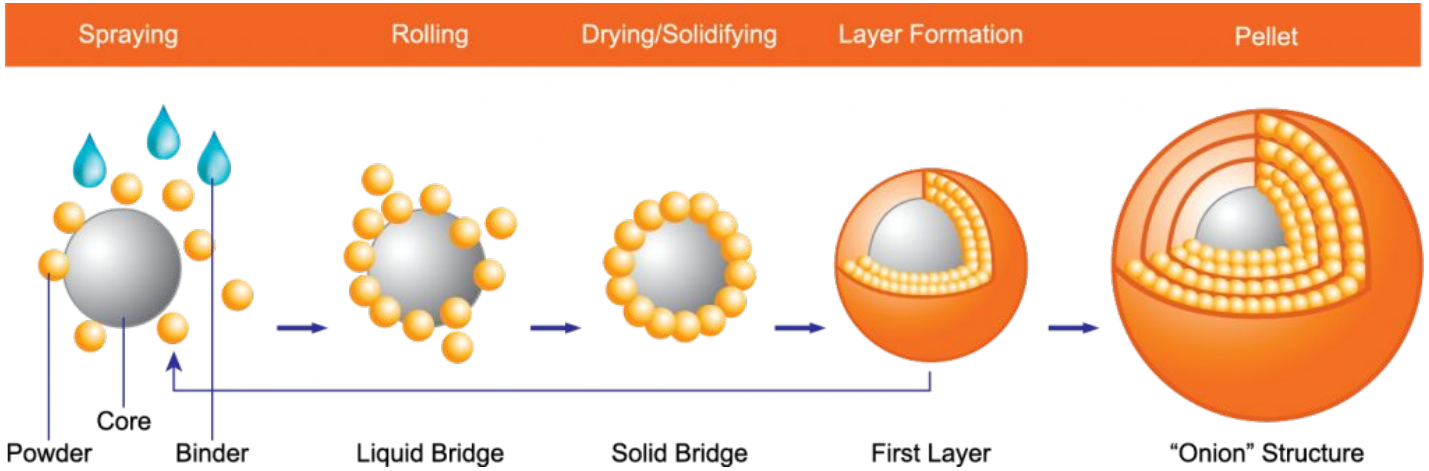
Drug Loading

- Powder Layering / rotor granulation
  - Add the active as a powder
  - Higher drug loads and shorter processing times compared to bottom spray



Figures from Freund-vector website

Drug Loading

- Fluidized bed
  - Wurster column (bottom-spray)
  - Dissolve or suspend the API in solvent (water or organic)
  - Layer onto sugar or MCC sphere
  - Typically coat 1-3X weight gain for the API layer
  - Very high drying capacity

Figure from Glatt website

Bottom Spray Drug Loading

- Basics of the formulation
  - Substrate (Sugar sphere or MCC sphere)
    - Type and size
  - Drug
  - Binder
    - Hypromellose low viscosity (E6)
    - Povidone K30
  - Anti-adherent
    - Talc or silicon dioxide
  - Processing Solvent
    - Water
    - Solvent (ethanol, IPA, acetone)

Bottom Spray Drug Layering

- Processing Parameters
  - Column height, air distribution plate, filter bag, spray nozzle
  - Air volume
  - Air temperature
  - Dewpoint
  - Spray rate & atomization air
- If parameters are not chosen properly, the following can occur
  - API does not adhere to the substrate and reverts to powder
  - Beads stick together forming agglomerates

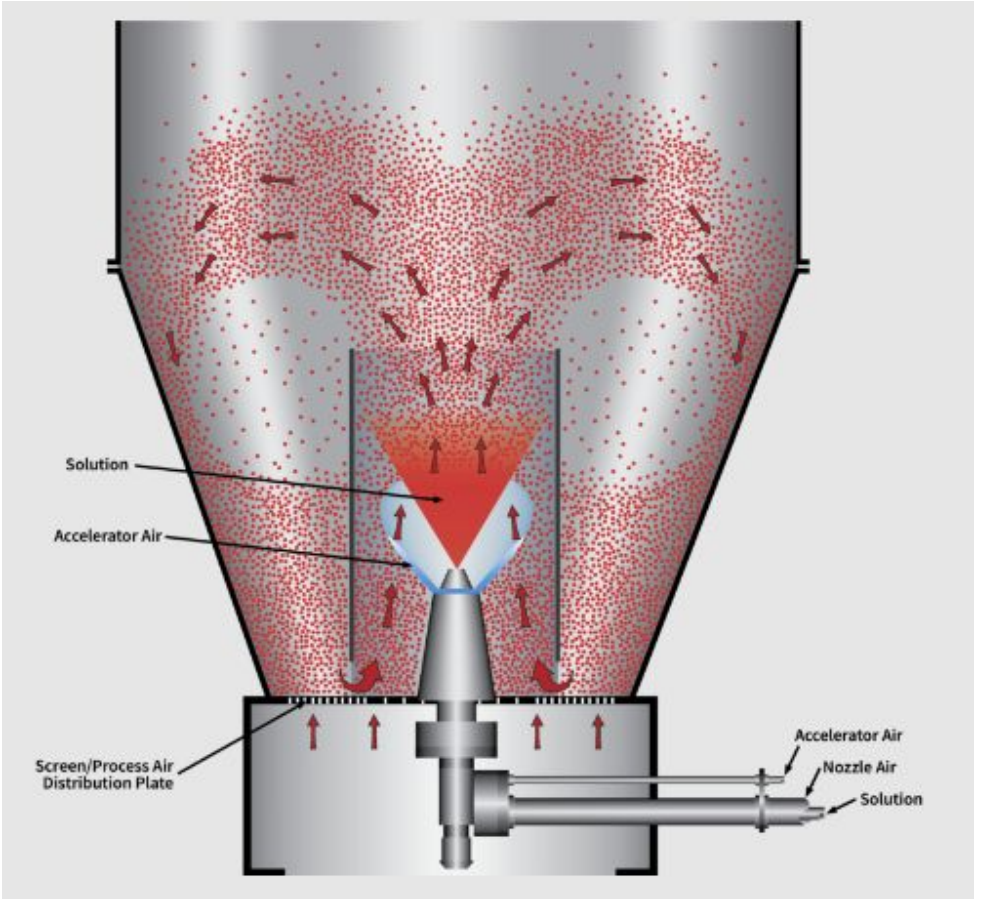
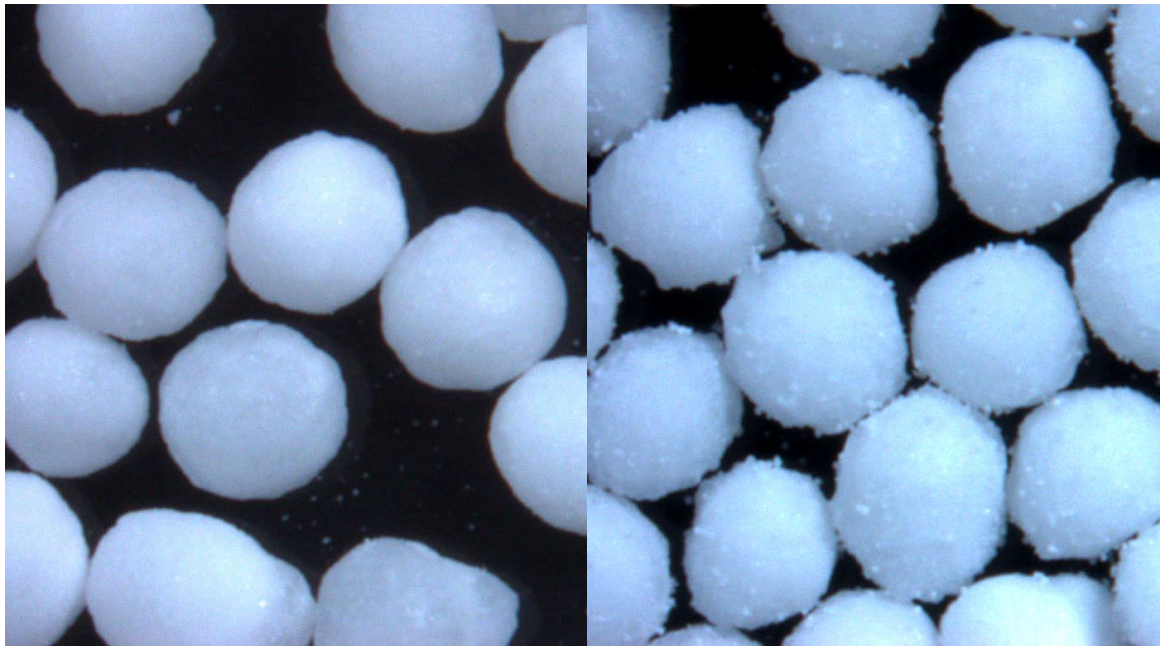


Figure from Vector website

Drug Loading process	Bottom Spray	Rotor Granulation	Extrusion/ spheronization	Mini-tablet
				
Nominal particle sizes	0.2 - 1.0 mm	0.3 – 1.5 mm	0.5 - 1.5 mm	1.5 – 3 mm
Typical drug loading	1 - 50%	10 - 75%	10 - 75%	10 - 85%
Considerations when choosing drug loading process	Number of processing steps required, equipment available, drug loading required, surface area.			

Drug Loading

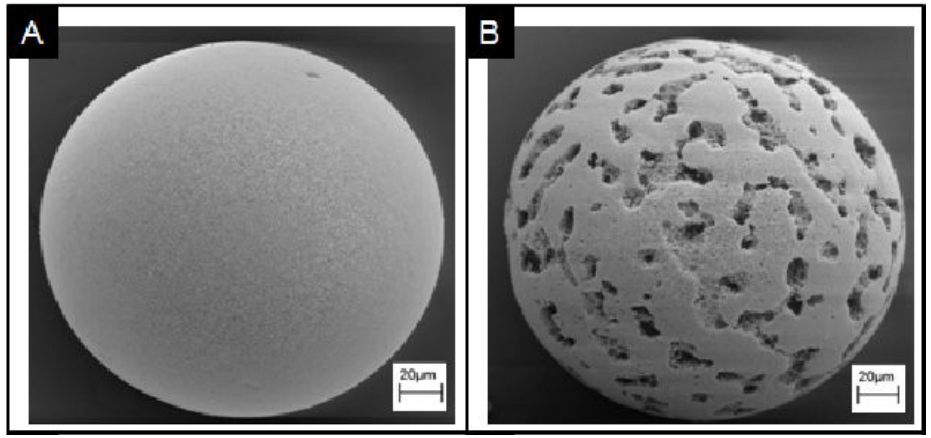
- End goals
  - Surface of the drug layered bead/minitab must be:
    - Smooth
    - Dense
    - Dust-free
    - Low friability
- Seal coating of the drug layered bead can help smooth out surface imperfections

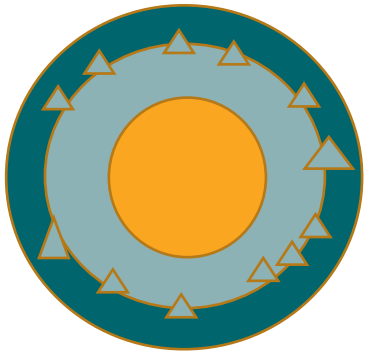


Good Dusty

Drug Loaded Beads

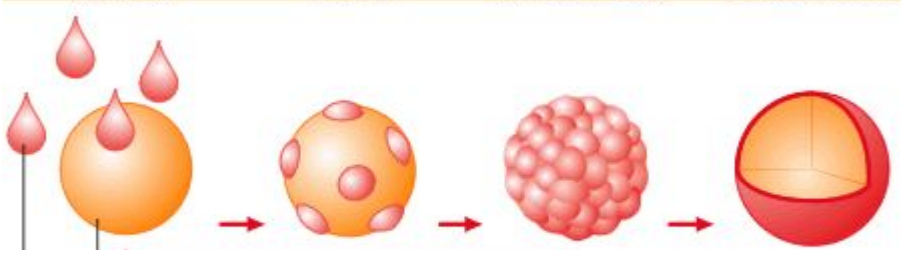
- If the surface of the drug loaded bead is not smooth, the polymer coat will not be as effective
  - Rough surfaces and sharp require more coating to achieve the same minimum thickness and/or may leave thin spots in the coating, affecting dissolution
  - Porous surface will absorb the coating
  - A friable surface could cause the product to fail





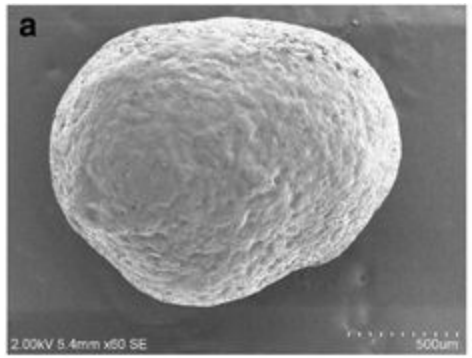
Polymer coating

- Typically, Bottom spray
- Process the same concept as drug loading
  - Film quality and thickness key to product performance
  - Need about a 30 micron thickness for a robust coat
  - The film must be fully coalesced around the substrate. If using aqueous polymer systems, this requires curing
  - Coating flaws include:
    - Dusting, orange peel, cracking, peeling, bubbles, inclusions

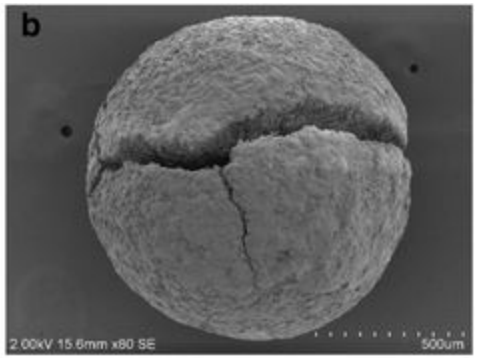


Coating flaws

Smooth (SEM)

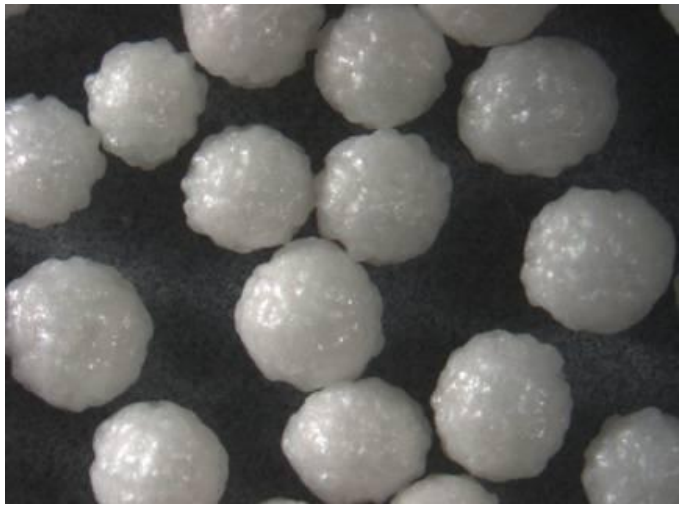


Cracking (SEM)



Smooth (microscope)

Orange-peel (microscope)



SEM: Erroneous Formulation of DR omeprazole capsules. M. Rahman et al, BMC Pharmacology and Toxicology May 2017

Polymer coating (bottom spray)

- Be sure to use the formulation to control the performance
- Use process to drive productivity
- Extensive choice of polymers / systems to tailor your drug release profiles

- Note: the smaller the drug loaded core, the higher the surface area. Higher surface area requires more polymer coating to achieve the same coating thickness.

Encapsulation

- Volumetric fill of the beads or minitablets into capsule shells
- Multiple populations of beads can be blended and filled into a capsule shell
- Equipment available to fill separate bead populations into a capsule shell

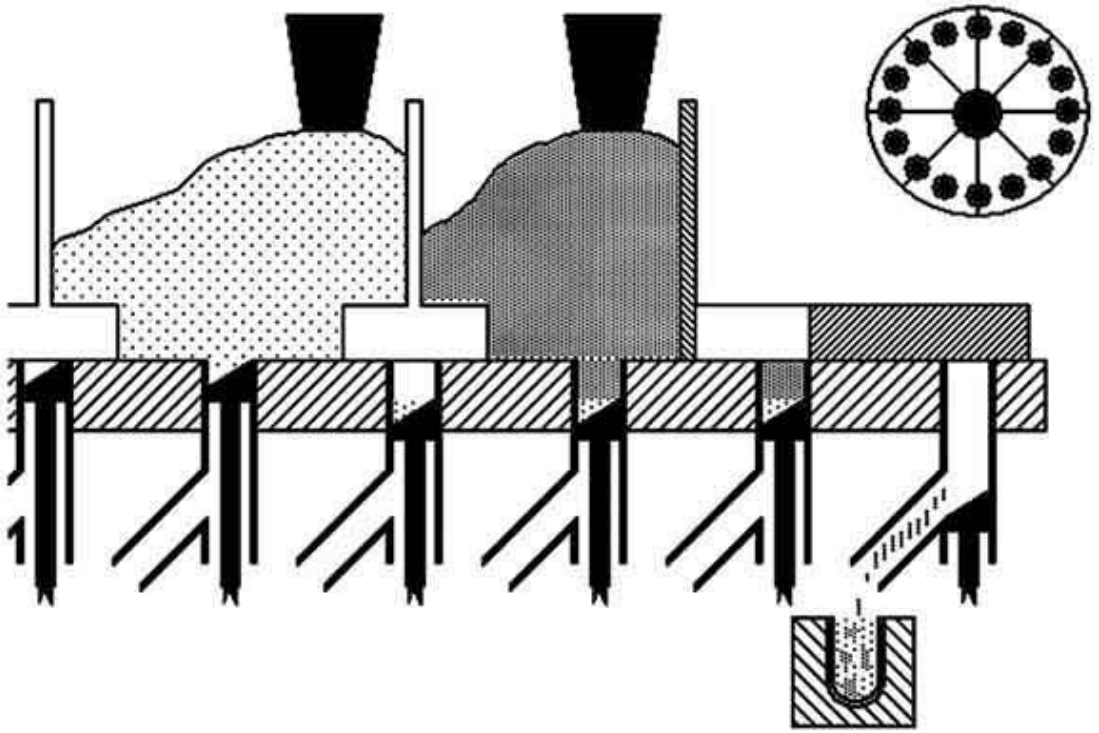


Figure from MG America website

Filling the Capsule

- Fill weight depends on your bead density and size
  - Minimum fill weight is ~30mg
  - Bulk density is ~0.7-0.8 g/mL of coated beads, so max fill weight is around 700mg

Capsule Size	Volume (mL)
00e	1.02
00	0.91
0e	0.78
0	0.68
1	0.50
2	0.37
3	0.30
4	0.21
5	0.10

Size 00 capsule

3 mm modified-ball tablets | 2.5 mm tablets | 30-35 mesh sugar spheres

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What MR polymer coating do you use?

- What release profile do you want?
  - First-order
  - Zero-order
  - Delayed release, Pulsatile
- What is the API's solubility?

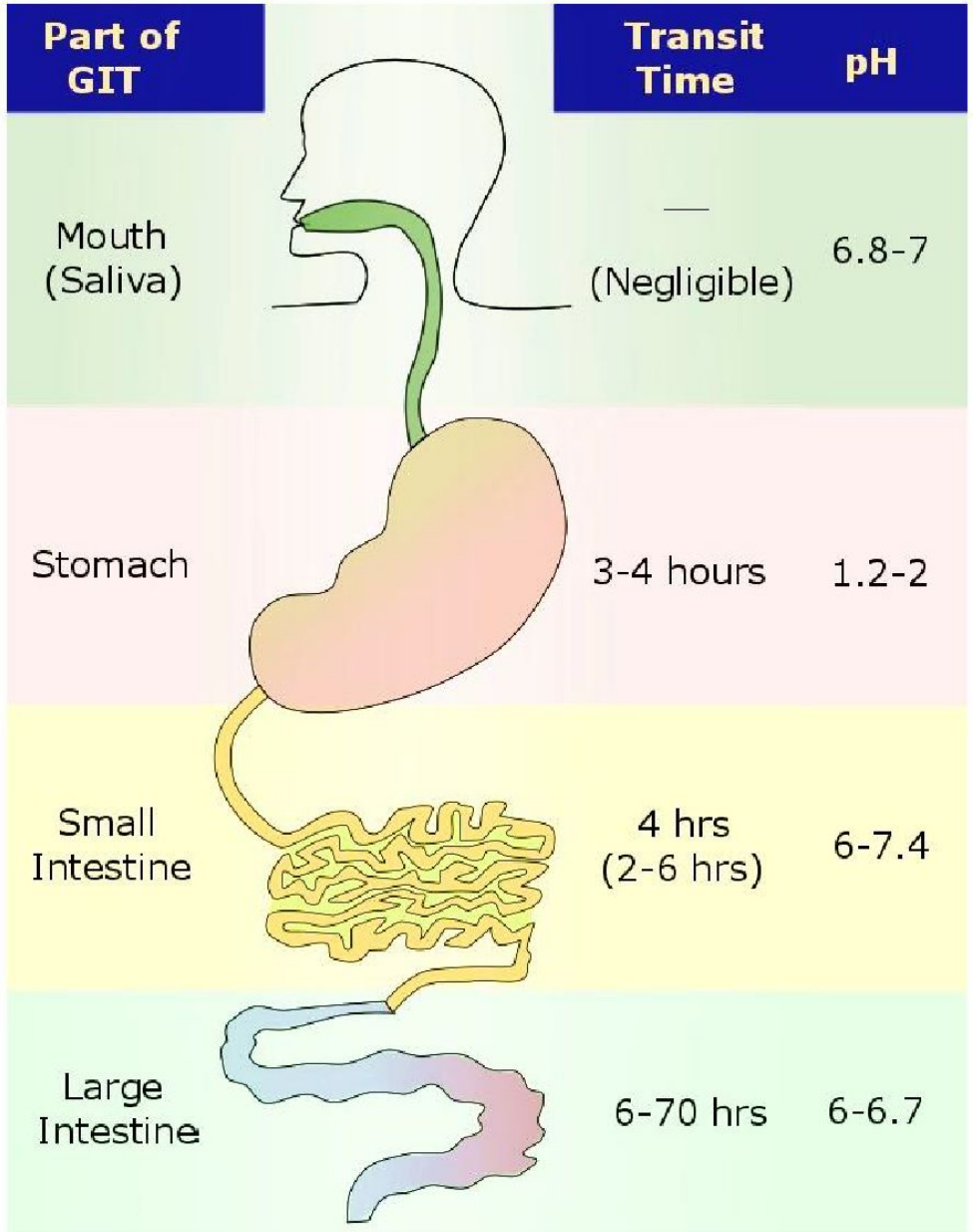
What MR polymer coating do you use?

- What release profile do you want?
  - First-order Diffusion Coating
  - Zero-order Osmotic system or combination Matrix core and diffusion
  - Delayed release, Pulsatile Erodible coating

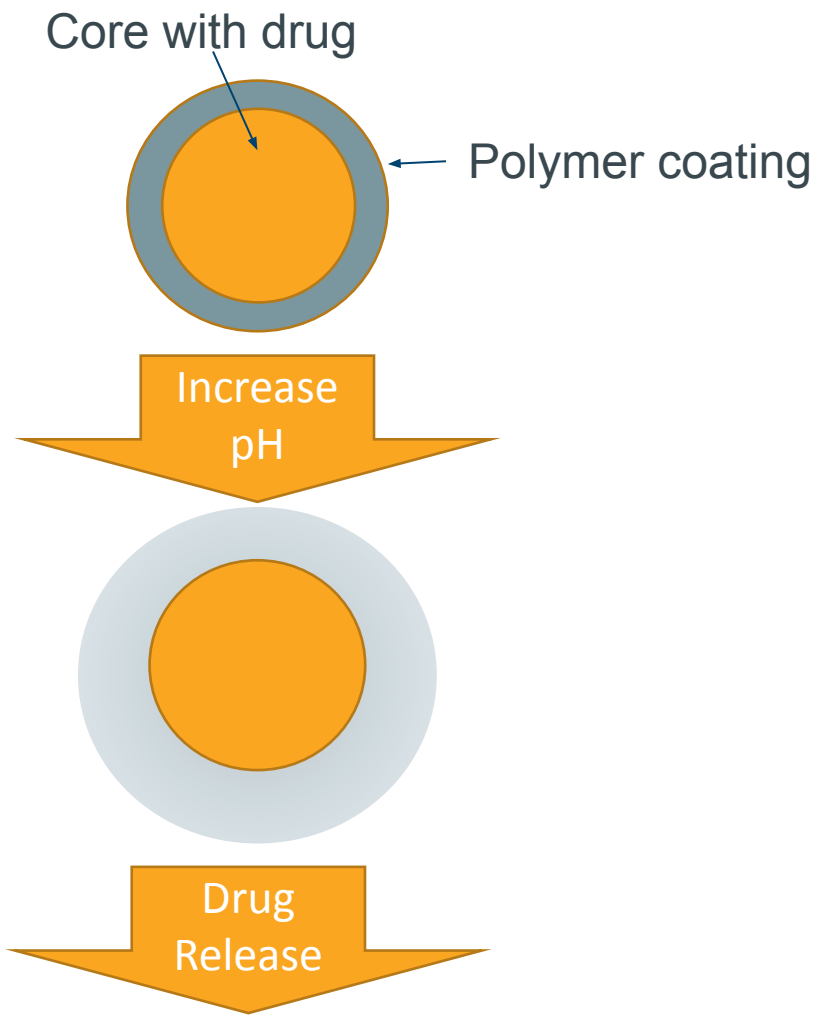
- What is the API's solubility? highly soluble drugs tend to diffuse
  - poorly soluble drugs do not diffuse (need osmotic pressure or erodible coating)

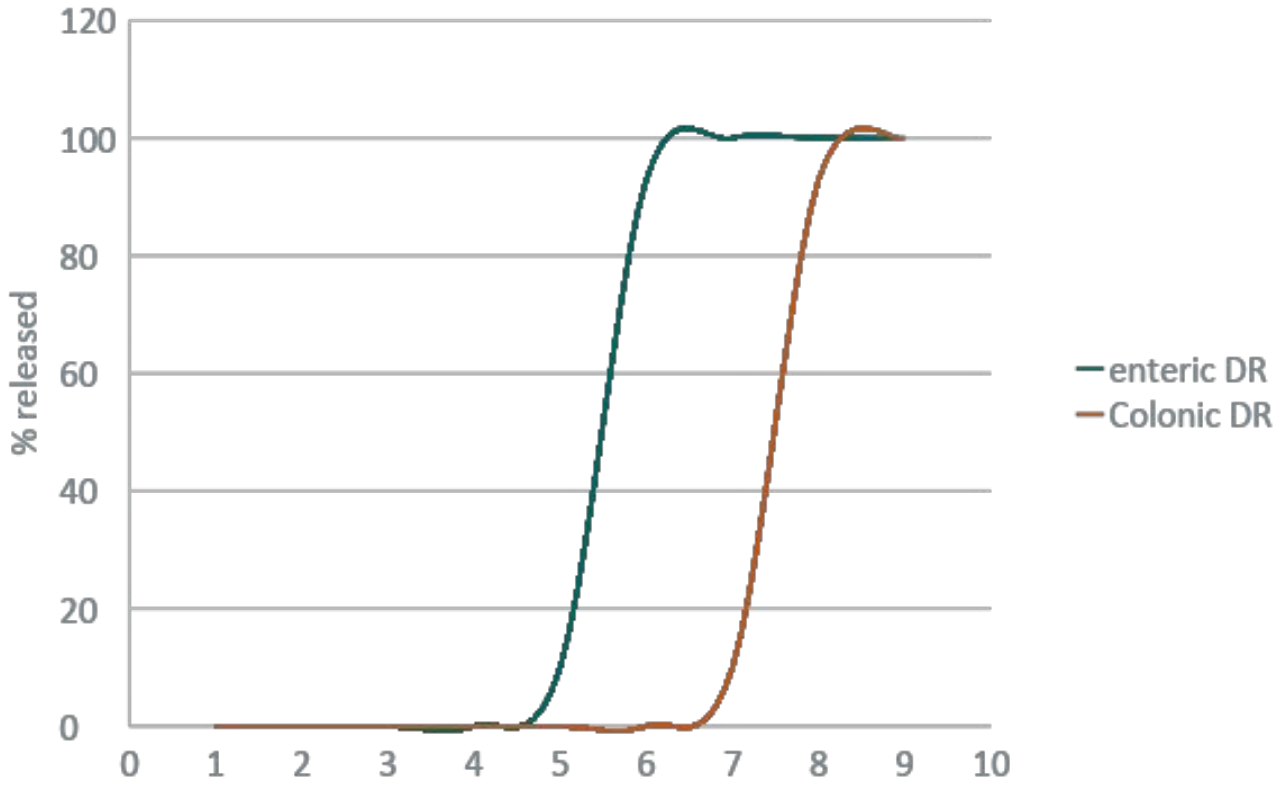
Erodible Coating

- pH dependent delayed release
  - Taste mask (soluble below pH 5)
    - Will dissolve in the stomach for IR
  - Enteric (soluble above pH 5)
    - Delayed release until product reached small intestine
    - protect from stomach irritation or acidic degradation
  - Colonic (soluble above pH 7)
    - delay release until the product reaches the large intestine



Delayed Release Dissolution





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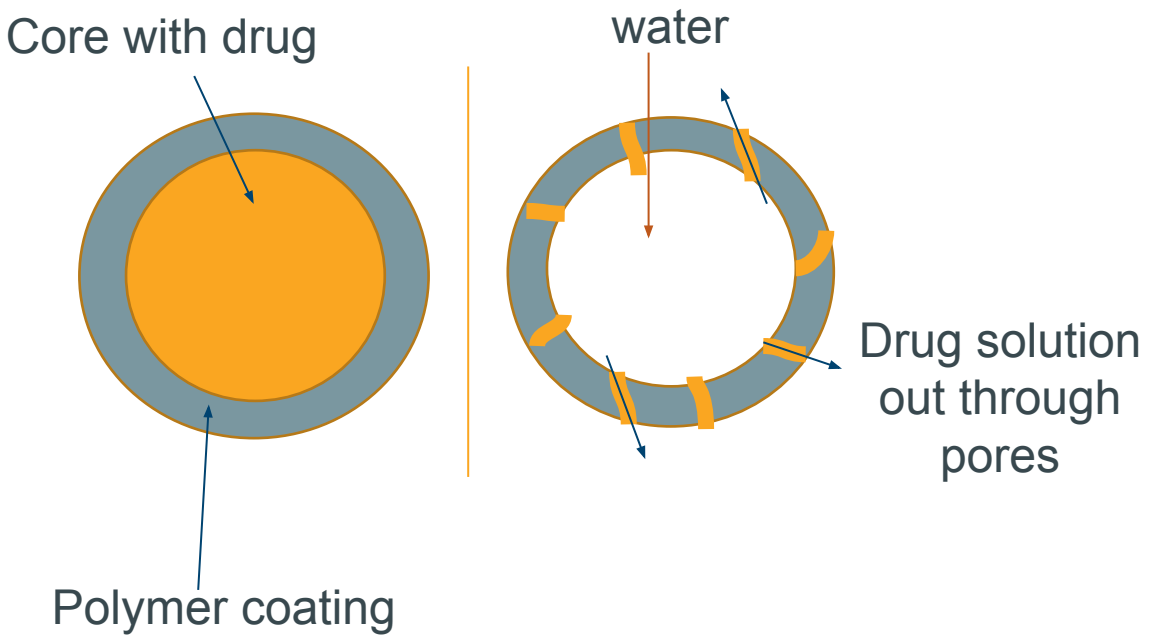
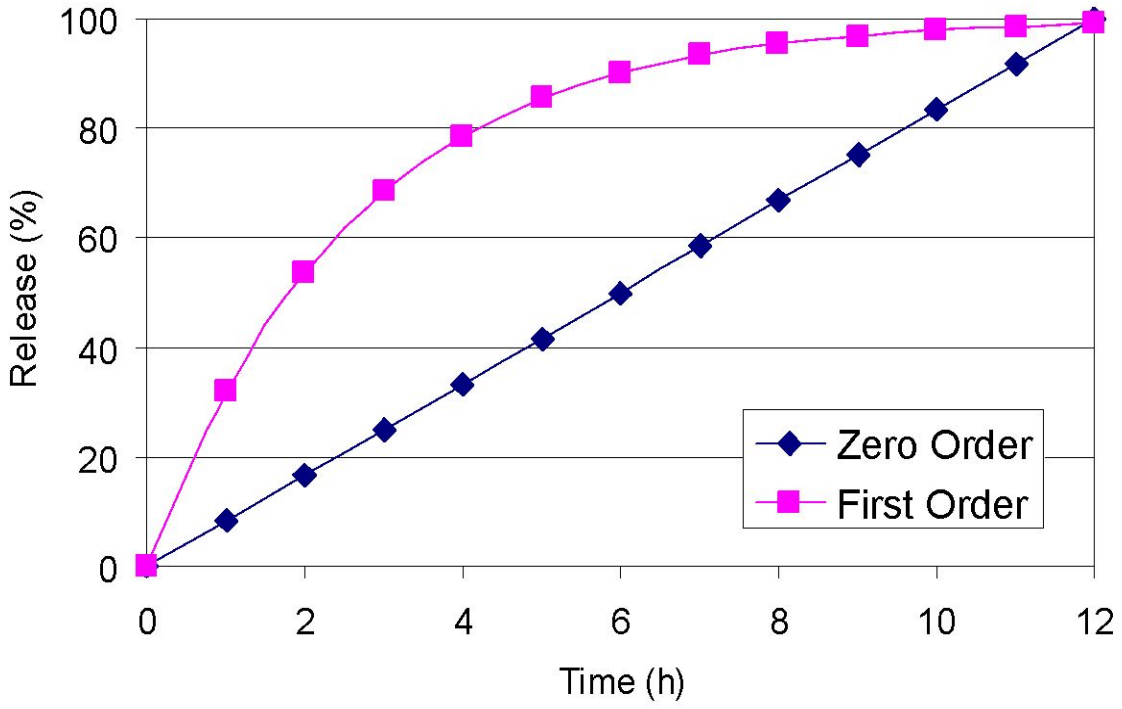
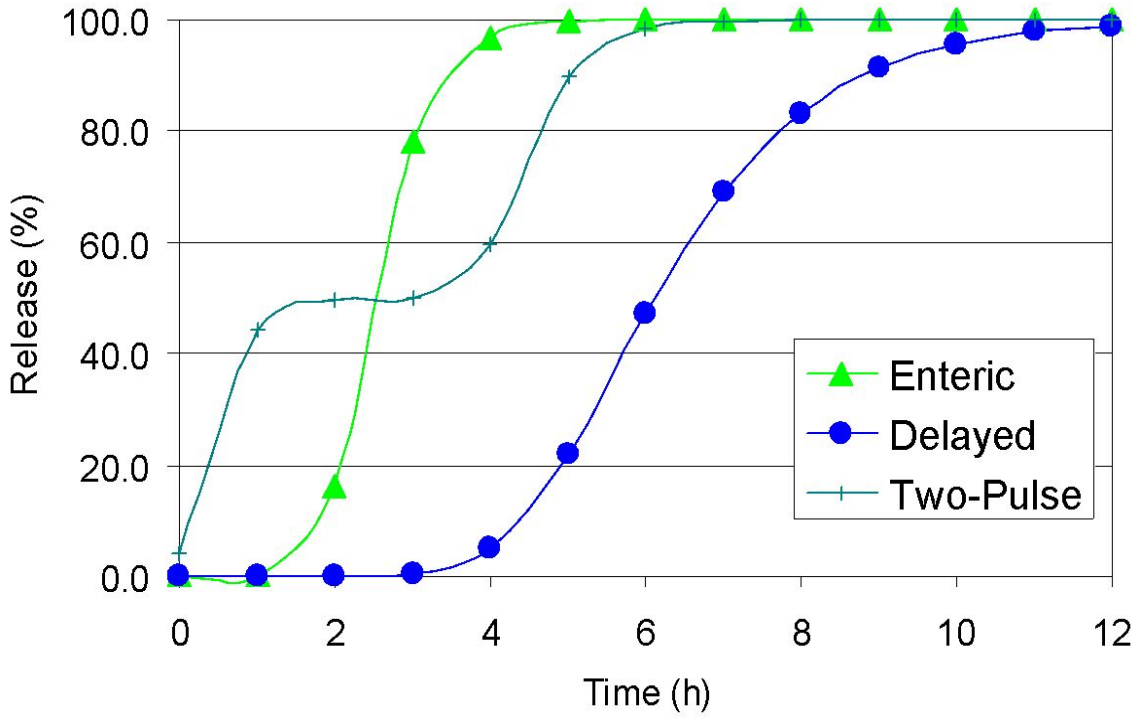
pH Independent Sustained Release

- Diffusion Controlled Release
  - Insoluble, permeable coating films surround the drug layered core
  - Pores dissolve allowing drug to diffuse out of the coating
  - Lag time / delay release while the water penetrates and creates pores



Various Modified Release Dissolution Profiles





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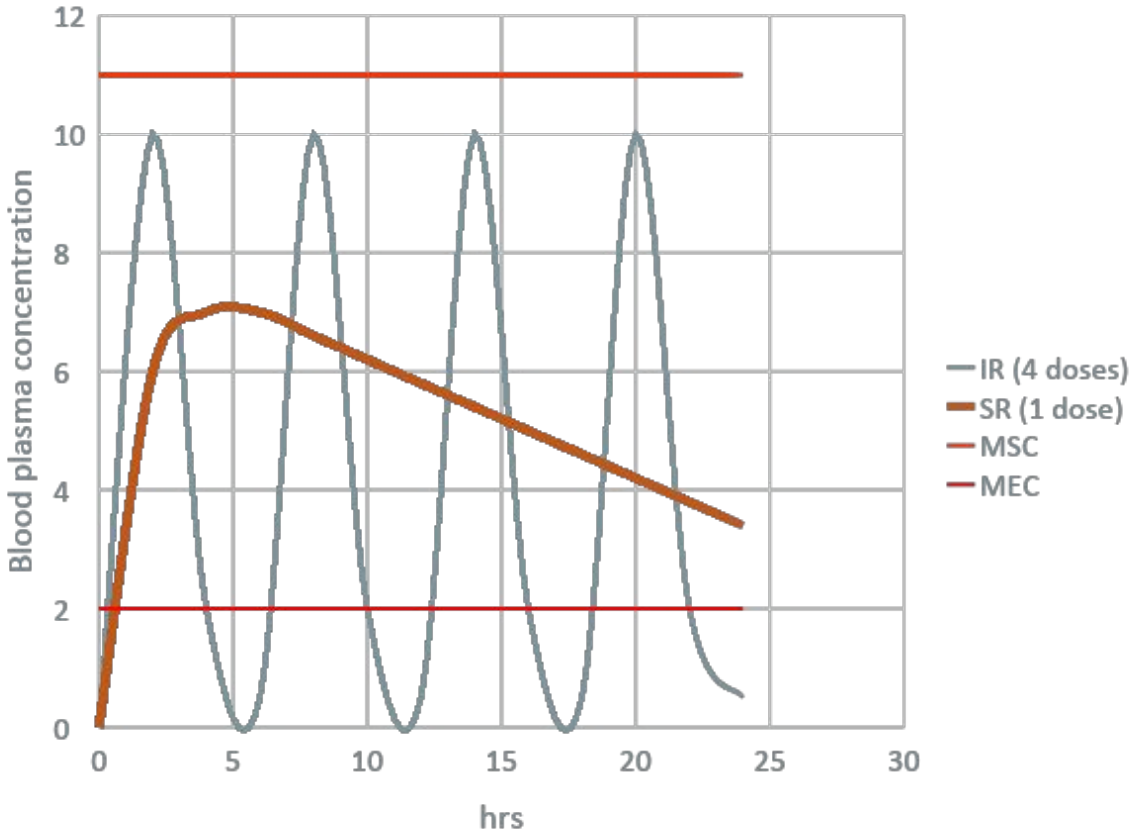
Sustained Release PK profile

- Once/day dosing vs 4 times/day (improved patient compliance)
- Lower overall API dosed (400mg IR vs 300mg SR)
- Lower Cmax / lower side effects
- No troughs below MEC



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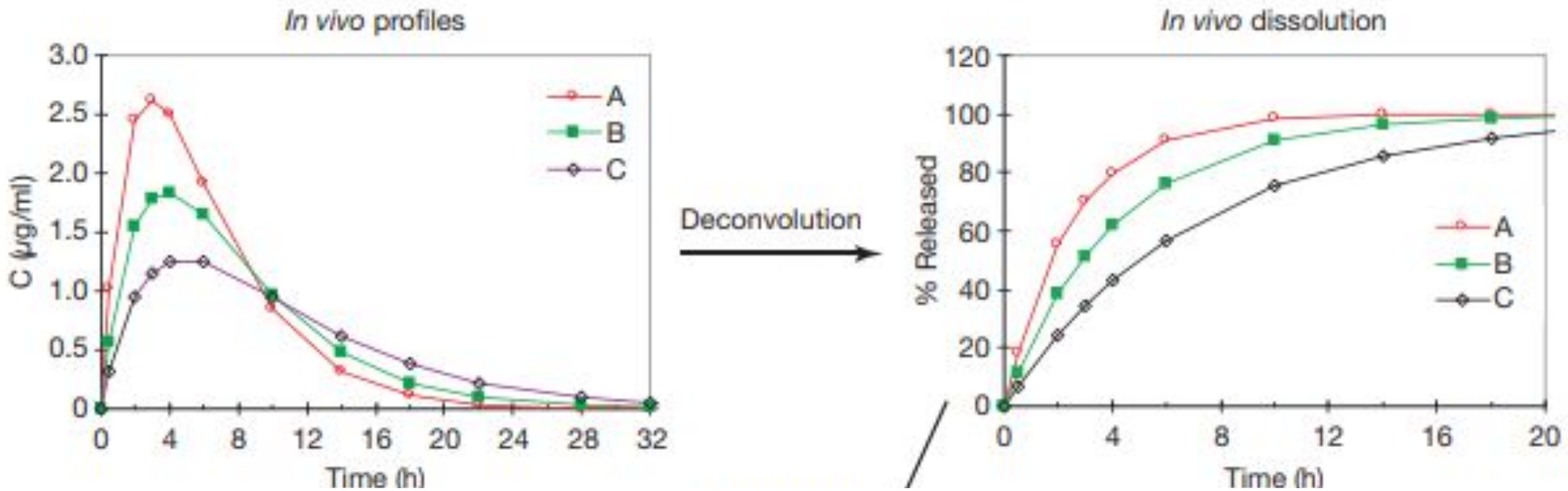
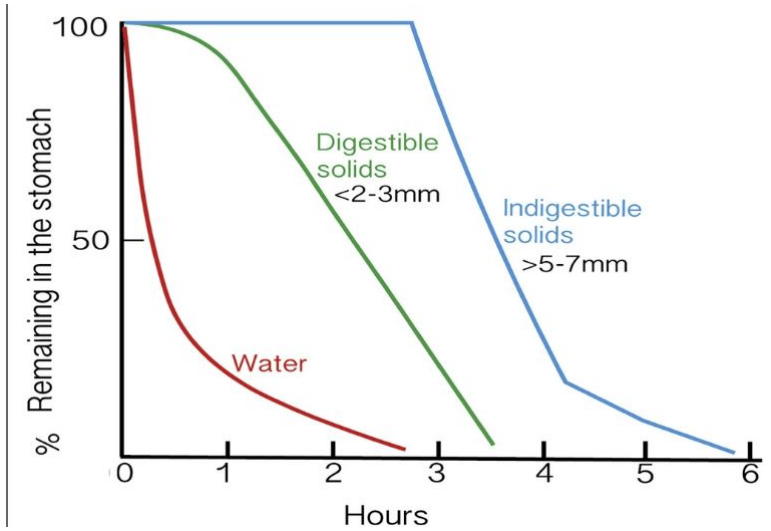
Deconvolution of PK data to dissolution data



Reference: Understanding Biopharmaceutics Properties for Pharmaceutical Product Development and Manufacturing II—Dissolution and In Vitro- In Vivo Correlation}, author={Deliang Zhou and Yihong Qiu}, Journal of Validation Technologies 2010

Multiparticulates – High Flexibility

- Advantages over SR matrix or coated tablets
  - Consistent gastric emptying and less food effect
  - Lower potential for dose dumping
  - Lower potential for gastric irritation
  - Dose can be changed without re-formulation



Reference: Advances in the physiology of gastric emptying. Goyal et al. Neurogastroenterology & motility, V31/4, 2019

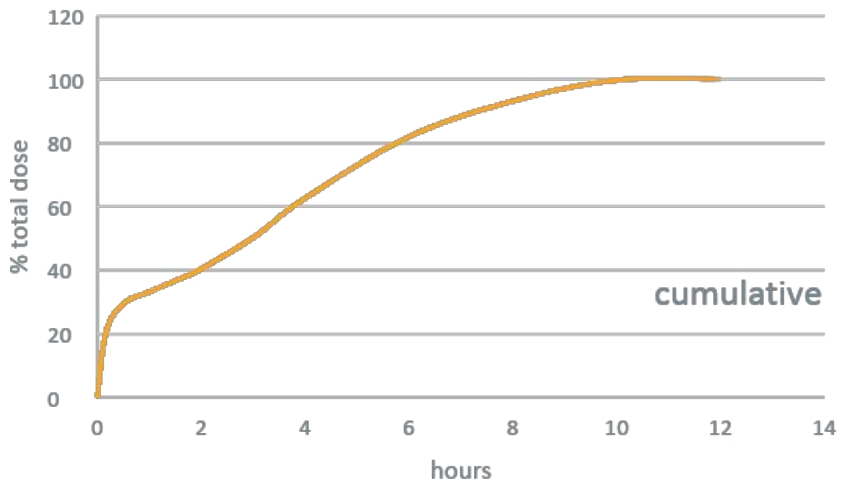
Multiparticulates- Highly Flexible

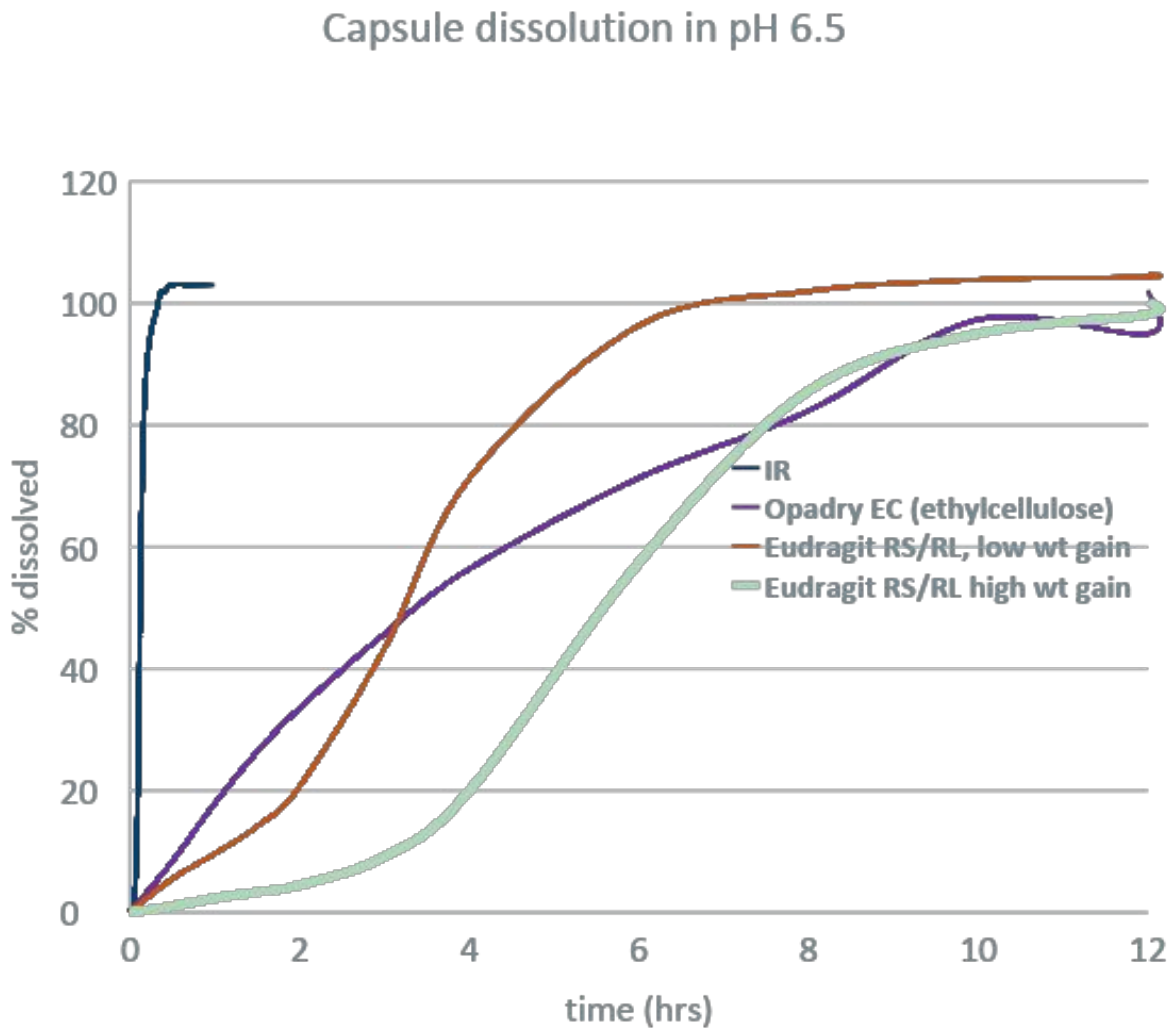
- During development of an SR product, often the exact target dissolution profile and the exact dose are not known. Multiparticulates allow for the development of several related bead populations with different dissolution profiles, and simple tailoring of the dose and dissolution profile by changing the ratio of each population

- Example:
  - Develop & manufacture a batch of IR beads, 25% drug load
  - Coat a portion of the IR beads with SR 1 (full dissolution in 8 hrs)
  - Coat a second portion of the IR beads with SR 2 (full dissolution in 16 hours)
  - Dose all 3 populations separately to get the pk profiles of each; conduct pk modeling to determine the ratio of IR: SR1: SR2 to reach the desired pk profile and dose
  - Final product = the identified ratio and dose of each of the 3 developed components

Case Study

- Water soluble compound
- Goal to have full release within 12 hrs
- Requires loading dose (IR) and high blood levels throughout the 12 hrs
- Methacrylate mixture with 10% RL (highly permeable) and 90% RS coated to different levels provided a delay, then SR
- Ethylcellulose provided steady SR release





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Conclusions

- Multiparticulates are a great choice for certain target product profiles
- There are several ways to manufacture multiparticulates, with bottom spray coating being the most common
  - Not particularly difficult to make, and been around since the 1950's
- Multiparticulates are highly flexible, allowing for multiple drugs in a product and/or multiple, complex drug release profiles, and simple pediatric formulations

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Contract Development and Manufacturing Organization

- 3 sites
  - Gainesville, GA; formerly Elan/Alkermes/Recro site
    - First FDA approval for a multiparticulate CR capsule in 1990 (Elan)
    - Capable of Phase I through commercial for oral solid dosages
  - Gainesville, GA (east) – opened in 2018 for early development and potent compounds
  - San Diego, CA; Formerly Irisys Pharma
    - CDMO started in 1996, specializing in sterile products (liquids and lyophilization)

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Big thanks to Richard Sidwell (CSO)

Thank you for your attention!

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