

TESTING AND RELEASE STRATEGIES FOR MINITABLETS



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What is a Minitablet?



Minitables with (from top to bottom) four, three, and two millimeter diameters, pictured with a U.S. penny to illustrate their sizes

Rumondor, Alfred et al. "Minitables: Manufacturing, Characterization Methods, and Future Opportunities". *American Pharmaceutical Review*. July 30, 2016

The term "*minitables*" commonly refers to compressed tablets with size smaller than typical tablets.

"Granules, Oral Granules, Sprinkles, Micro tablets"

- No regulatory guidelines that define minitables, the term has been used to describe tablets with diameters between one to four millimeters (mm).
- Oral dosage forms smaller than 2.5 mm → oral granules
 - Many minitabulet products are focused at this size range, to take advantage of the potential flexibility in dosage form administration (e.g. mixed with soft foods).

Few Examples of Minitablet Products

Product	Company	Molecule	Indication	Product presentation
Kalydeco®	Vertex	Ivacaflor	Cystic fibrosis	~2 mm mini-tablets in stick pack
Lamisil®	Novartis	Terbinafine	Antifungal	~2 mm mini-tablets in stick pack
Orifil Long®	Desitin	Valproate	Epilepsy	~2 mm mini-tablets in capsules and stick pack
Levetiracetam Desitin®	Desitin	Levetiracetam	Epilepsy	~2 mm mini-tablets in stick pack
Pancrease® MT10/MT20	McNEIL	Pancrelipase	Pancreatitis, cystic fibrosis	~2 mm mini-tablets in capsules



Opportunities Offered by Minitablets

Compliance

- Accurate and flexible dosing -> Reduce discards!
- Reduce user errors
- Less complicated human factor studies

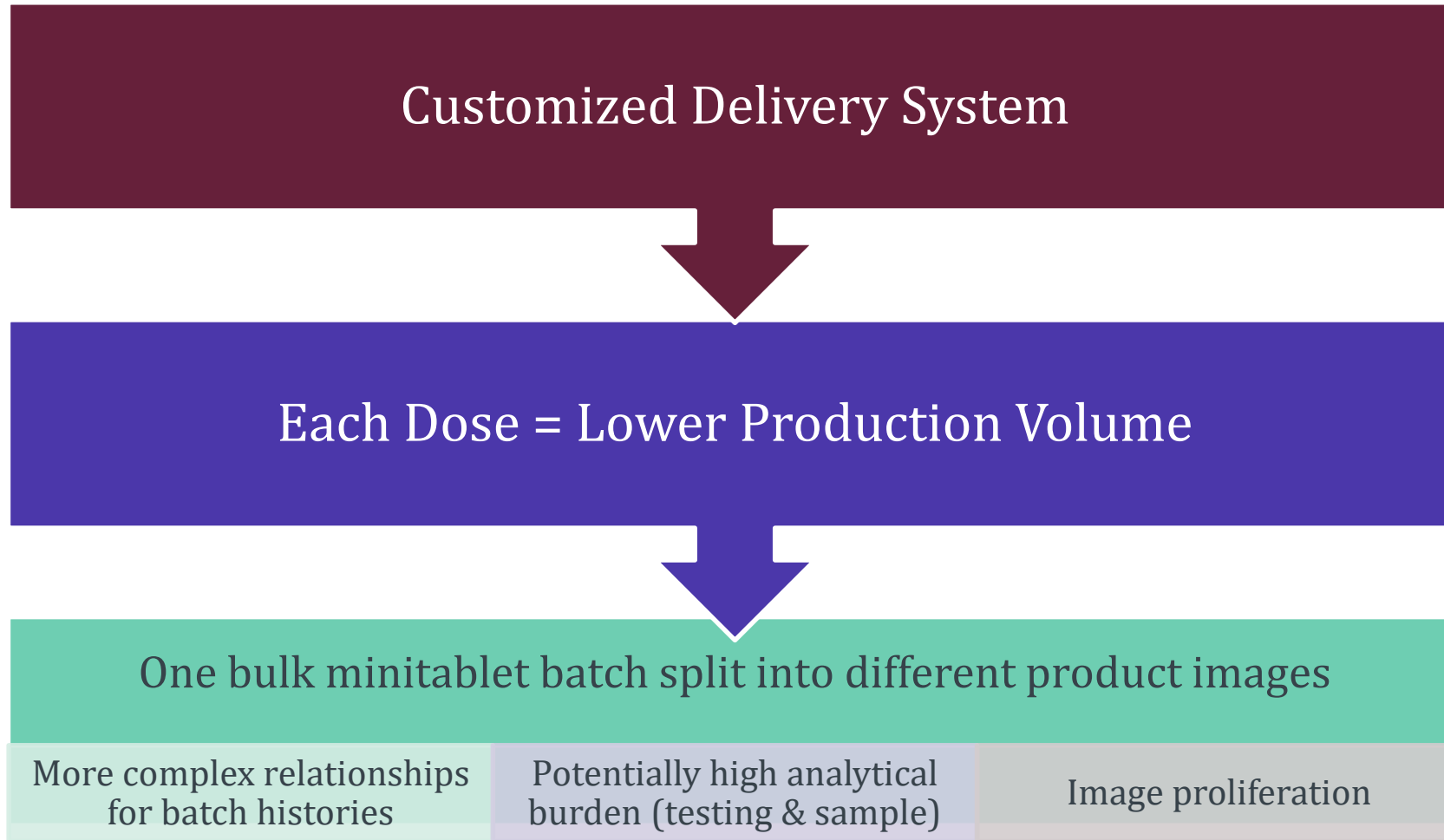
Patient Friendly and Personalized Medicine

- Palatability (Easy to swallow and enhance palatability when mixed with food and drink)
- Dose flexibility, unit dose options
- Multiple dose unit options which can combine different release kinetics/API

Production & Stability

- Utilize standard tablet presses/multiple-tip tooling , Coated or uncoated minitables
- Ability to separate API interactions and increase palatability
- Various product presentations: Ease of capsule or sachet filling or desiccated bottles

Challenges Offered by Minitablets



Traditional vs Minitablet Batches?



One/two final product image



Bulk Minitablet lot

10 minitables



Dose 1

50 minitables



Dose 2

100 minitables



Dose 3

Why Not Traditional Testing?

Goal is to demonstrate product quality

Traditional testing = Repeat testing

- Repeat testing (e.g same granule batch in different capsule batches)
- Analytical testing and quality release burden on several small scale batches (significantly higher numbers of tests)
- Utilizing a significant portion of the batch just for analytical testing

Increased supply chain flexibility- Lower volumes, Personalized medicine

- Make-to-order for final step:
 - Faster turnaround from demand to delivery
 - Unclear forecasts
 - Image proliferation

**Bulk
minitablets
can be
counted!**

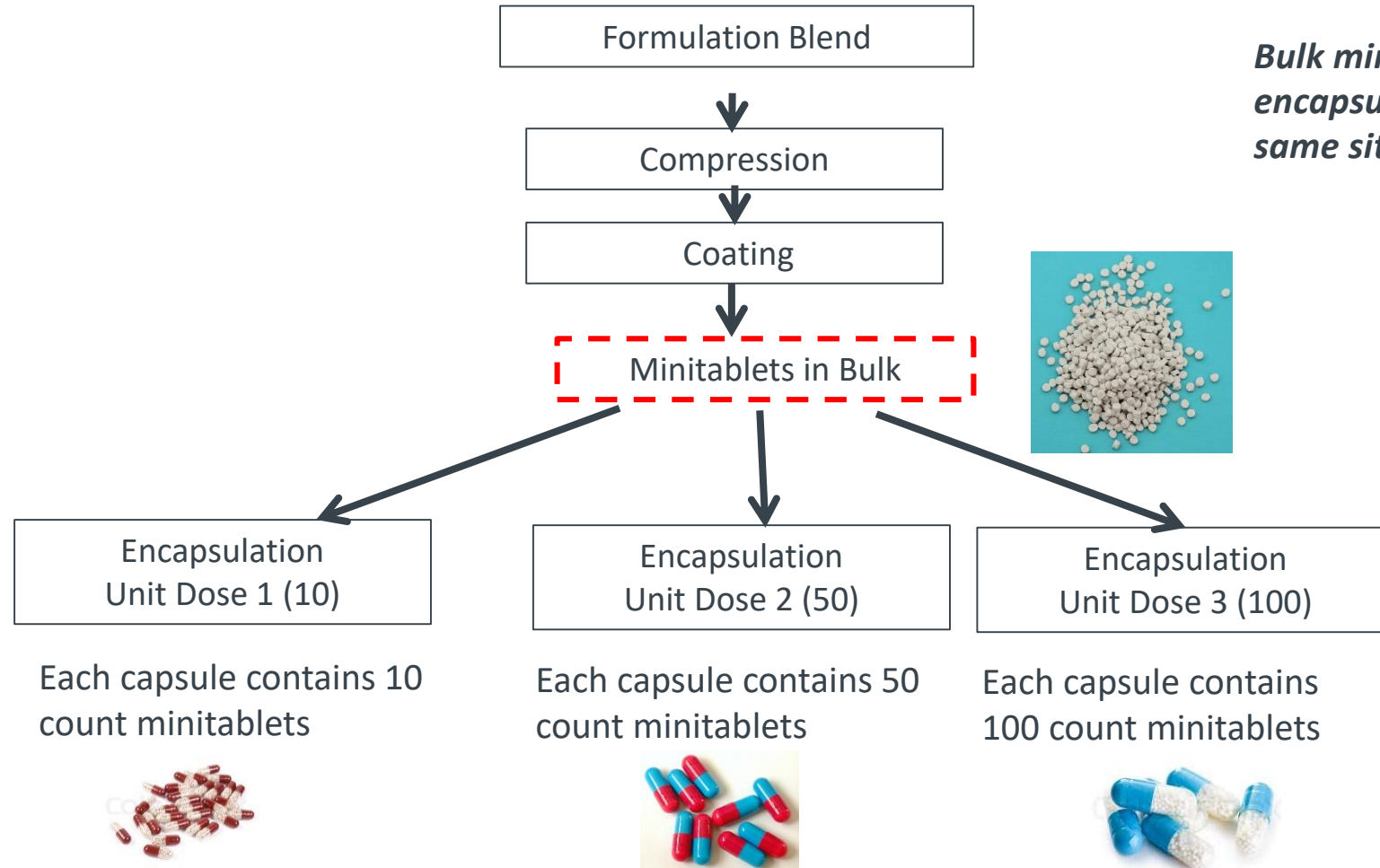
Many CQAs determined by the compression/coating steps

Collect
industry/regulatory
input on efficient product
release for
minitablets/granules by
conducting testing at the
right stage to ensure
product quality

CASE STUDY

- ❑ **Product:** IR oral granule –Single entity product
- ❑ **Dosage form:** Capsules intended for sprinkling(could be stick packs/sachets too)
- ❑ **Quality attributes:** Identity, Content uniformity, Assay and Degradation products, Dissolution, Water activity, Microbial limits
- ❑ **Terminology used here:**
 - ❑ Oral granules = minitablets
 - ❑ Bulk minitablets = coated/uncoated minitablets prior to encapsulation
 - ❑ Unit dose = minitablets in capsules with varying counts based on the dose.
 - Lowest dose = 10 count
 - Highest dose = 100 count

Example Manufacturing Steps



RELEASE & SPECIFICATION



3 Possible Approaches

1. Conduct release testing only after encapsulation- no testing of bulk minitablets
2. Conduct testing at bulk minitablelet step
AND for each unit dose after encapsulation
3. Hybrid approach:
 - a) Conduct tests on bulk minitablets for CQAs that are not impacted by encapsulation step.
 - b) Limited tests at minitablets in capsules

THANK YOU

MERCK

