



Minitablet (Granule) Development and Manufacturing Considerations

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*MCERSI: Shaping the Future of Pediatric
Formulation Development*

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Minitablet Manufacturing Challenges

Agenda

Composition Development

- ✓ *Aligning early-stage formulation to support manufacturing and dosing*

Lab-scale Development

- ✓ *Unique considerations posed by minitablet processing*

Scale-up and Manufacturing

- ✓ *Robust tooling design*
- ✓ *Press set-up specifics*
- ✓ *In-process control of MTs*

Summary and Conclusions

Acknowledgements

Introduction to Minitablets

- *Varied definition: <4 mm, <2.5 mm (bead labeled as sprinkle)*
- *Intended for oral delivery*
- *Suitable for many pediatric populations*



Advantages:

- Flexible dosing with a single image
- May be swallowed or dispersed in food or liquid
- Frequently better stability and simpler supply chain access than liquid formulations

Considerations:

- Palatability (taste, mouthfeel)
- Caregiver/patient experience with preparation of dose
- Specialized tablet tooling design
- Drug load and minitablen count impact on packaging

Minitablet Composition Development: Drug Load and Dose Count

- Dose flexibility with a single image is a great advantage but requires careful planning
- Drug load needs to account for minitablet (MT) count across the intended dosage range
 - Low fill counts are more susceptible to dosing error if there is a miscount in packaging or handling
 - High fill counts increase dispersion time and patient acceptability challenges

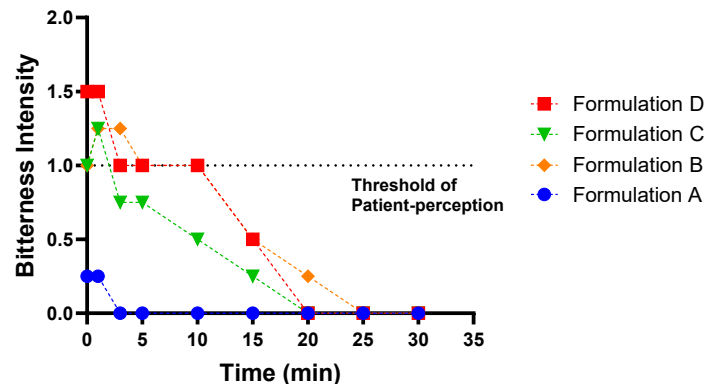
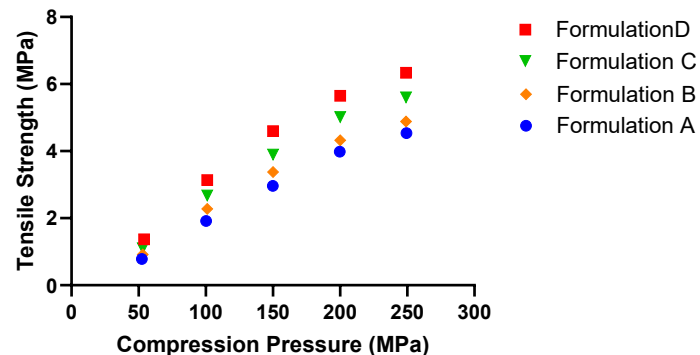
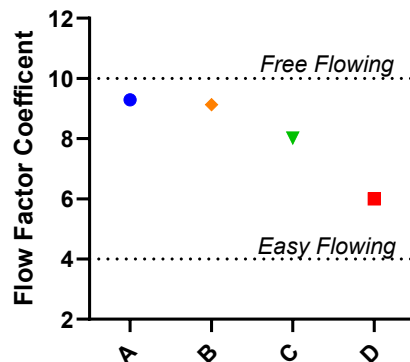
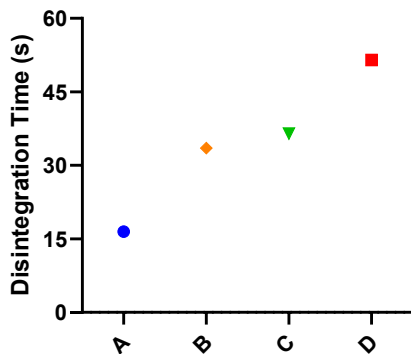
		# Mini-tablets		
Drug Load		30%	20%	10%
Dose Level	Low	8	12	25
	Medium	16	24	50
	High	32	50	100

- Drug load will also impact powder handling properties, tabletability, dissolution, disintegration, uniformity, and other CQAs

Minitablet Composition Development: Excipient Selection

➤ Excipient selection optimizes MT attributes with consideration to the small image size as well as patient experience

- Fillers (lactose, microcrystalline cellulose, mannitol, etc.): contribute to flow, mechanical strength, dose level, taste, mouthfeel, and speed of disintegration
- Disintegrant: ensure rapid dispersion in dosing vehicle
- Wetting agent: improve disintegration into dispersion
- Flow aid or glidant: consider small die opening and scale-up
- Flavor or sweetener: taste-masking for patient experience
- Lubricant: high surface area to volume ratio drives up ejection forces



Minitablet: Lab-scale Manufacturing Scale-Up Considerations

➤ **Material sparing approaches during development present unique challenges with MTs**

- Hand-filling or use of single-station presses with small diameter dies is difficult and impractical; rotary press may be preferred for studies

➤ **Small diameter die requires smaller particle ranges**

- Particle size in relation to die diameter will impact die fill uniformity
- Granulation process steps may require secondary milling to meet particle size needs

➤ **High surface area to volume ratio of tablet impacts compression**

- Lower compression forces may be required due to higher surface area
- Higher ejection forces due to high surface area can impact tooling integrity

Minitablet Manufacturing Challenge: Robust Tooling Design



Precise die-punch clearance is important with ratio of tablet diameter

- Too wide and powder will leak as lower punch pulls down
- Too tight can lead to high ejection forces and damage



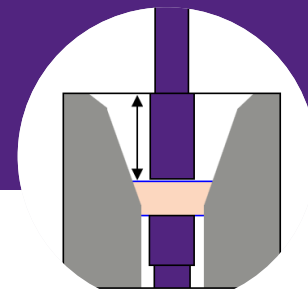
Multi-tip tooling tip layout impact beyond compression pressure

- Tight spacing can lead to buildup
- Number and layout of tips can impact die fill uniformity



Recessed dies can improve tooling lifespan

- Less friction along the lower punch tips
- Design to ensure the fill depth will not exceed recess



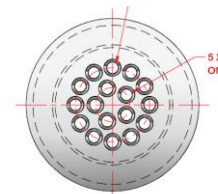
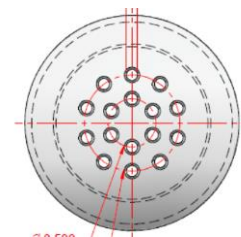
Die taper and chamfer geometry can impact defects and die fill

- Can impact ejection stresses and defects
- Can impact fill and “splashing” of powder on upper punch contact

Minitablet Manufacturing: Tooling and Press Considerations

- *Increased number of tips decreases run time and improve manufacturing efficiency*
 - Paddle speeds, fill depths, compression force will need optimization for number of tips
 - D-press vs. B-press dies with same tip count require different spacing
 - Die hole position and layout influences MT weight

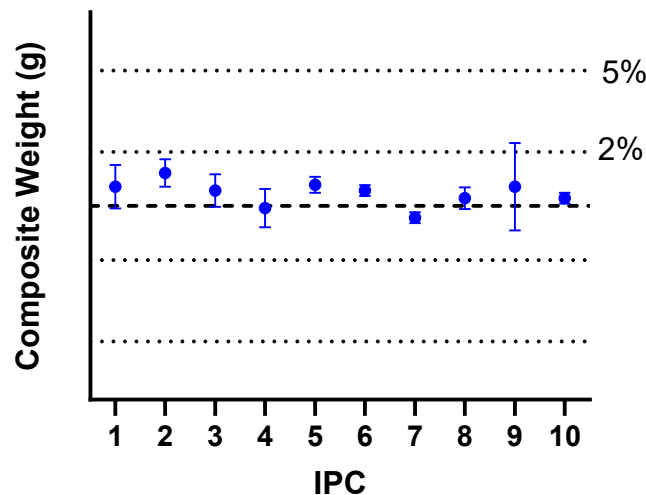
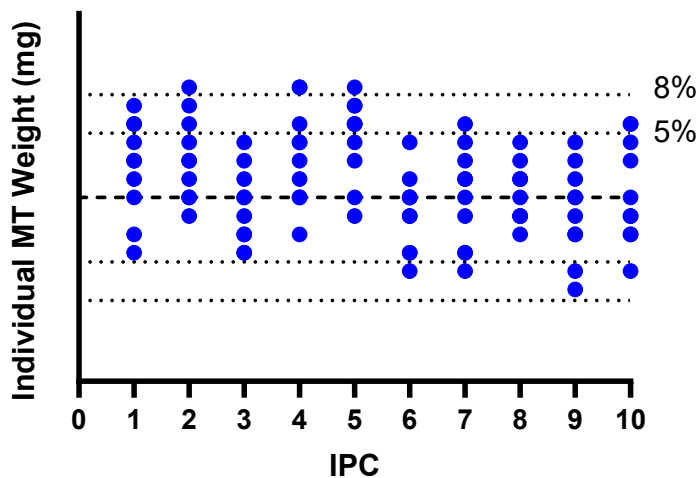
- *Careful set up and attention to install of tooling and moveable parts is needed*
 - Tooling tip position during ejection will need adjustment for minitab tooling
 - Tooling tips are fragile and can be easily damaged- consider special training
 - Uneven die filling can cause unequal compression force distribution across tips; uneven tooling degradation
 - Targeting compression pressures below recommended limits takes force distribution into consideration



Minitablet: Manufacturing In-Process Control Strategy Considerations

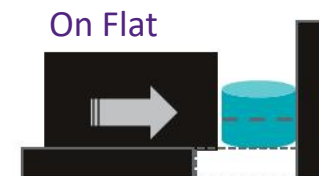
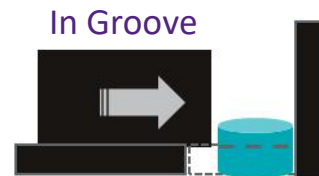
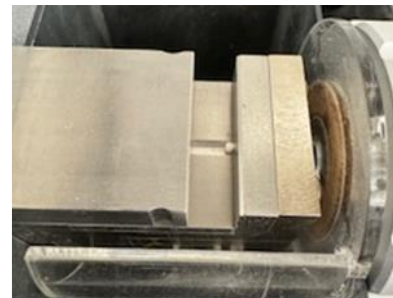
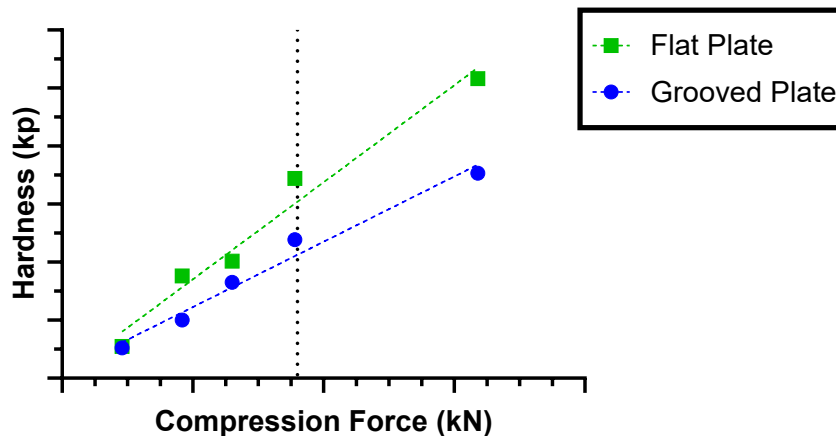
Composite weight measurement as an in-process control

- Larger tablet images are weighed individually, may not be feasible for MTs
- Smaller image means minor weight variations are a larger percentage of target weight
- Composite weight allows for rapid reaction and adjustment
- MTs are dosed as a population; composite weight (lowest dosage count) demonstrates dose-level control



Minitablet Hardness Testing Considerations

- MTs placed in the alignment groove will break across a plane closer to the top of the tablet
- Impact worsens with thinner, higher hardness tablets
- Can lead to discrepancies during personnel or site transfers
- Add instruction in batch records to ensure consistent placement



Conclusions and Summary

- ✓ Minitablets are a useful option for pediatric dosing, with the advantages of flexible dosing and ease of administration
- ✓ A view toward manufacturing should be considered starting with composition development
- ✓ Minitablet manufacturing poses new and different considerations as compared to traditional images
 - Smaller die openings and multi-tip tooling need careful design
 - Minor differences in press or tooling set-up can lead to damage or defects
 - Unique in process controls and testing considerations



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