Testing and Release Strategies for Minitablets

Jun2019

CASE STUDY

- **Product:** IR oral granule –Single entity product with multiple strengths
- **Dosage form** (could be stick packs/sachets too)
- **:** Capsules intended for sprinkling **Quality attributes:** Identity, Content uniformity, Assay and Degradation products, Dissolution, Water activity, Microbial limits

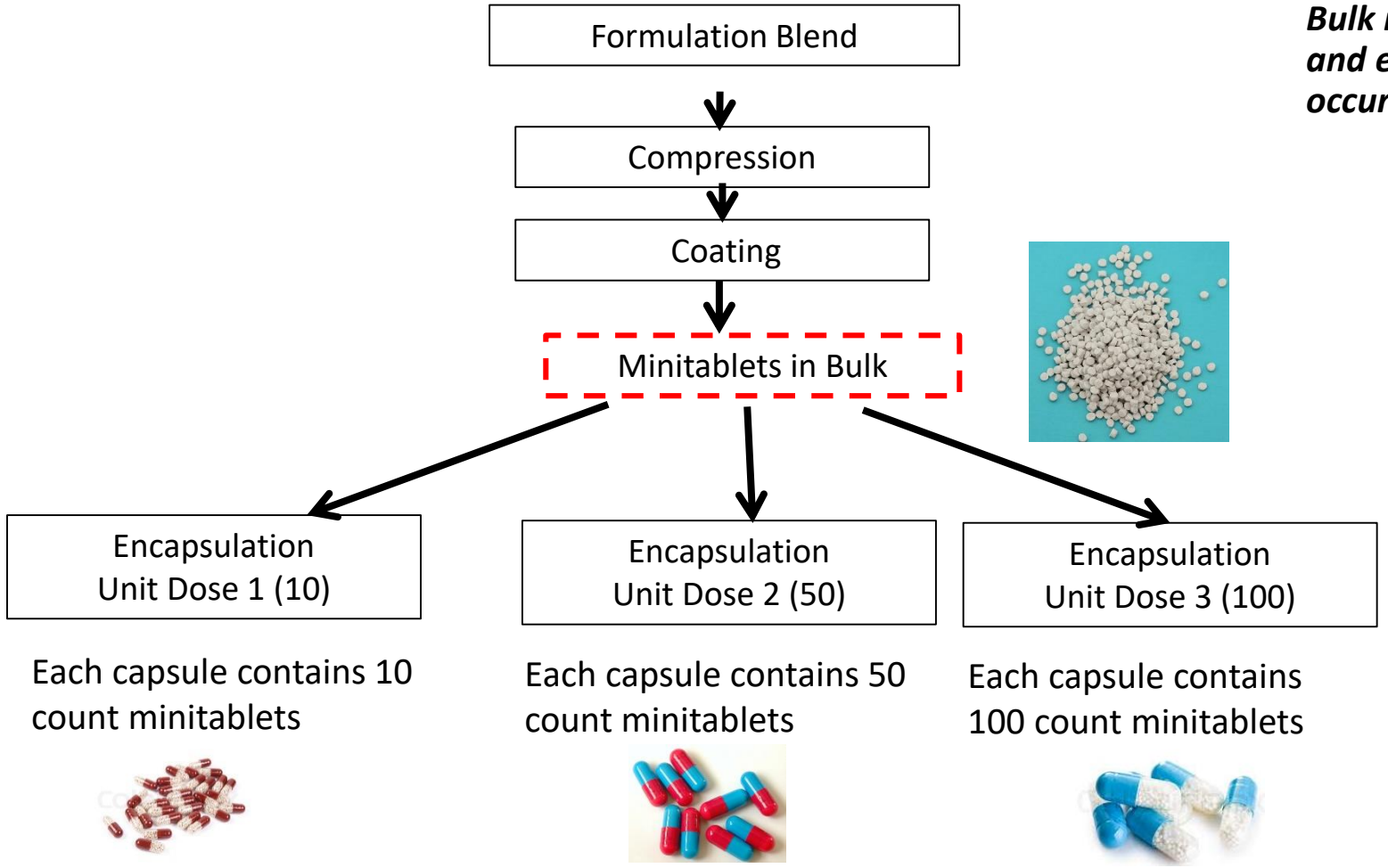
- Terminology used here:
  - Oral granules = minitablets
  - Bulk minitablets = coated/uncoated minitablets prior to encapsulation
  - Unit dose = minitablets in capsules with varying counts based on the dose.
    - E.g. Lowest dose = 10 count
    - Highest dose = 100 count

RELEASE & SPECIFICATION

3 Possible Approaches

1. Conduct release testing only after encapsulation- no testing of bulk minitablets
2. Conduct testing at bulk minitablet 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

Example Manufacturing Steps



Bulk minitablet manufacture and encapsulation are occurring at the same site

Approach 1:

Conduct release testing only after encapsulation- no testing of bulk minitablets

- Minitablets are considered an intermediate, hence no testing is conducted at the bulk minitablet stage.
- Test all CQAs for capsules per unit dose

Questions

Q1. What are the Pros and Cons of this approach?

Q2. What is the desired approach for unit dose testing and specifications?

- E.g Test each unit dose for all the CQAs?
- Test only the lowest count or the highest count as the “worst case” for testing ?
- OR use bracketing approach i.e. test the lowest and the highest count unit doses for all CQAs to bracket everything in between.

Q3. What is your experience on this approach?

Q4. Would this approach be acceptable for a combination product?

Approach 2:

Conduct testing at bulk minitablet step and REPEAT testing for each unit dose after encapsulation

Questions

Q1. Do we need to test at both stages if the manufacturing and encapsulation occurring at the same facility?

Q3: If the manufacture and encapsulation sites are different, how do you quality release bulk minitablets and then unit dose after encapsulation step?

Q3: Do you have any experience with this approach?

What are the Pros and Cons of this approach?

Approach 3:

Hybrid Approach: Test CQAs that are not impacted by the encapsulation step at Bulk minitablet stage and limited tests such as ID at the unit dose step

- E.g. bulk minitablets: Assay/Deg, CU, Dissolution
- Unit dose: ID, microbial Quality, Water Activity

Questions

Q1. How do we decide which tests are conducted at which step?

- Conduct a Risk assessment?

Q2: Do you have any experience with this approach? What are the Pros and Cons of this approach?

Q3: For sprinkle only capsules, do we need dissolution testing in capsules?

Q4. Do you have experience with IPC testing (stratified CU testing of minitablets) and full testing on dosage units?

- If yes, do you have experience with using weight variation of dosage units to fulfill the UDU requirements?
- For weight variation what's your experience with weighing filled content versus gross weight of the dosage unit?

Specifications

- Most common approach is to set specifications based on dose unit.
  - Test dose unit and apply specifications to the dose unit

Test	Typical number of dose units	Specification Application
Assay/deg	5/10 dose units	Average of 5 or 10 dose units
CU	10 Individual dose units	compendial
Dissolution	Stage testing: 6 individual dose units for stage 1, etc..	Product specific

Q1: Do you have experience with applying specifications for a single minitablet vs dose unit either during clinical release or commercial release?