Characterization and Evaluation of Immediate Release Tablets by Wet Granulation: A Comprehensive Review

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Abstract: Immediate Release (IR) tablets remain the most widely prescribed oral dosage form due to their cost-effectiveness, stability, and patient compliance. While Direct Compression (DC) is popular for its simplicity, Wet Granulation (WG) remains the gold standard for Active Pharmaceutical Ingredients (APIs) with poor flowability and compressibility. This review critically examines the wet granulation process, the pre-compression characterization of granules (micromeritics), and the post-compression quality control of the finished dosage form to ensure therapeutic efficacy.

1. Introduction

Oral Solid Dosage (OSD) forms constitute approximately 70% of all pharmaceutical preparations, with tablets being the dominant format (Aulton & Taylor, 2013). An Immediate Release (IR) tablet is designed to disintegrate and release the drug with no special rate-controlling features, such as enteric coatings or sustained-release matrices.

However, many modern APIs possess poor physicochemical properties—low bulk density, poor flow, and insufficient compressibility—making them unsuitable for direct compression. Wet Granulation is the size enlargement process that converts fine powder particles into larger, physically strong agglomerates (granules) using a liquid binder (Lachman et al., 1986). This process improves:

1. **Flowability:** Ensuring uniform die filling and weight consistency.
2. **Compressibility:** enhancing the bonding properties of the tablet.
3. **Content Uniformity:** Preventing segregation of low-dose drugs.

2. The Wet Granulation Mechanism

The wet granulation process involves the formation of liquid bridges between particles, which solidify into solid bridges upon drying.

2.1 The Unit Operations

The conventional wet granulation workflow follows a sequential path:

1. Dry Mixing: Blending API with diluents (e.g., Lactose, Microcrystalline Cellulose) and disintegrants.
2. Wet Massing: Addition of a binder solution (e.g., Starch paste, PVP K30) to form a damp mass.
3. Wet Screening: Passing the mass through a sieve (usually #8 or #10 mesh) to form pellets.
4. Drying: Removal of solvent in a Tray Dryer or Fluidized Bed Dryer (FBD) to reach a target moisture content (usually 1-3%).
5. Dry Screening: Sizing the dried granules (usually #20 or #24 mesh).
6. Lubrication: Blending with lubricants (Magnesium Stearate) and glidants (Talc).

2.2 Critical Process Parameters (CPPs)

- Binder Concentration: Insufficient binder leads to friable granules; excess binder leads to "hard" granules that retard dissolution.
- Kneading Time: Over-kneading can result in a dense mass that fails to disintegrate.
- Drying Temperature: High temperatures can degrade thermolabile drugs or cause "case hardening" (trapping moisture inside the granule).

3. Pre-Compression Characterization: Evaluating the Granules

Before compression, the granules must be characterized to predict their behavior during the high-speed tableting process. This science is known as Micromeritics.

3.1 Flow Properties

Poor flow leads to "rat-holing" in the hopper and weight variation in the tablets.

- **Angle of Repose**:

This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is calculated using the funnel method:

- **Bulk and Tapped Density:**
  - *Bulk Density:* Mass of powder divided by bulk volume.
  - *Tapped Density:* Mass divided by volume after mechanical tapping (100 or 500 taps).
- Compressibility Index (Carr's Index) & Hausner Ratio:

These are derived from density measurements and indicate the propensity of the powder to compress.

A Carr's Index of <15% indicates good flow properties (Wells, 2002).

3.2 Moisture Content (Loss on Drying - LOD)

Determined using a halogen moisture analyzer or IR balance.

- **Significance:** If granules are too dry, they will not bond (capping/lamination). If too wet, they will stick to the punch faces (sticking/picking). The ideal range is typically 1.5% to 3.0% w/w.

4. Post-Compression Evaluation: Quality Control of Tablets

Once compressed, the tablets undergo rigorous evaluation to ensure they meet pharmacopeial standards (USP, BP, IP).

4.1 Organoleptic and Physical Evaluation

- **Appearance:** Visual inspection for capping, lamination, or mottling (unequal color distribution).
- **Dimensions:** Thickness and diameter are measured using a vernier caliper. Thickness should be within $\pm 5\%$ of the standard value.

4.2 Mechanical Strength

- Hardness (Crushing Strength):

The force required to break a tablet across its diameter. Measured using Monsanto or Pfizer hardness testers.

  - *Target:* 4–8 kg/cm² for standard IR tablets.
- Friability:

Evaluates the ability of the tablet to withstand abrasion during packaging and transport. Tested using a Roche Friabilator (25 rpm for 4 minutes).

4.3 Performance Evaluation (Bio-relevant Properties)

- Disintegration Test:

For an IR tablet to work, it must first break down into granules.

  - *Apparatus:* Basket-rack assembly moving in immersion fluid.
  - *Limit:* Uncoated IR tablets must disintegrate within 15 minutes.

- Dissolution Test:

This is the most critical parameter linking in-vitro quality to in-vivo efficacy. It measures the rate and extent of drug release.

  - *Apparatus:* USP Type I (Basket) or Type II (Paddle).
  - *Medium:* Simulated Gastric Fluid (0.1N HCl) or Phosphate Buffer pH 6.8.
  - *Criteria:* typically, (amount dissolved)

- Content Uniformity:

Ensures that every tablet contains the intended amount of drug.

  - *Method:* 10 tablets are assayed individually.
  - *Limit:* The acceptance value (AV)

5. Advanced Characterization Techniques

In modern pharmaceutical development, simple physical testing is often supplemented by instrumental analysis to ensure stability.

1. Fourier Transform Infrared Spectroscopy (FTIR):

Used to check for Drug-Excipient Compatibility. Wet granulation involves moisture and heat, which can trigger chemical reactions (e.g., Maillard reaction between amine drugs and lactose). FTIR confirms no new chemical bonds are formed.

2. Differential Scanning Calorimetry (DSC):

Analyzes the melting point and thermal behavior. A shift in the melting peak of the drug after granulation might indicate a change in crystallinity (polymorphism) or amorphization, which affects stability.

3. Scanning Electron Microscopy (SEM):

Used to visualize the surface topography of the granules. It helps in understanding the mechanism of bonding—whether it is solid bridges or interlocking mechanisms.

6. Conclusion

The characterization and evaluation of immediate-release tablets via wet granulation is a multi-disciplinary effort. It begins with the engineering of the granule—optimizing flow and moisture—and ends with the rigorous quality control of the finished tablet.

While newer technologies like hot-melt extrusion and direct compression continue to rise, wet granulation remains indispensable for high-dose, poor-flow APIs. Mastery of the evaluation parameters discussed (Carr's

Index, Dissolution, Friability) is essential for any formulation scientist to ensure the delivery of a safe, effective, and stable drug product.

7. References

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