Granulation and Direct-Compression Technology for VitaSphere™B12

1. Formulation challenge

Vitamin B12 is used in tablets in microgram amounts, which makes distribution, flowability and tablet strength major formulation issues. Factors influencing the stability of B12 may include temperature, pH, illumination and interactions with other components. This paper reviews granulation, direct compression and key quality factors for developing tablets containing encapsulated VitaSphere™B12.

2. Granulation and direct-compression methods

Granulation improves powder flow, reduces segregation and supports tablet formation. It can improve low-dose ingredient distribution, while direct compression skips granulation but requires good flow and compression properties.

The paper discusses five manufacturing approaches:

Method	Advantages	Limitations
High-shear wet granulation	Produces dense, relatively uniform granules; improves powder handling.	Moisture, drying heat and possible active migration.
Fluid-bed granulation	Combines granulation and drying in one unit.	Granule properties, fines and attrition depend on process conditions.
Melt granulation	Avoids water and organic solvents.	Processing temperature must be compatible with the active and coating.
Roller compaction (dry granulation)	Avoids liquid and drying heat.	Mechanical stress, coating damage, fines and reduced tabletability may occur.
Direct compression	Simple process with fewer steps; avoids granulation moisture and heat.	Requires good powder flow and control of segregation and content uniformity.

Each formulation should be evaluated according to its own requirements and complexities. The stability of vitamin B12, the characteristics of the encapsulated ingredients, the compatibility of excipients and the required tablet quality should determine the process to be used.

3. Powder flow and its measurement

The issue with powder flow is that inconsistent die filling will produce tablets with varying weights, which may contribute to dose variation. This paper describes common methods used to screen powder flow.

Parameter	Formula / Measurement	Interpretation
Bulk Density	Mass / Bulk volume	Density of loosely filled powder.
Tapped Density	Mass / Tapped volume	Density after a defined tapping procedure.
Carr Index (CI, %)	[(Tapped density − Bulk density) / Tapped density] × 100	Indicates powder compressibility and flow behaviour.
Hausner Ratio (HR)	Tapped density / Bulk density	Indicates powder packing and flow behaviour.
Angle of Repose	$tan\ \theta$ = Height / Radius	Estimates flow based on the angle of a powder cone.
Shear-cell / Powder Rheometer	Testing under applied stress	Provides additional flow information for borderline or inconsistent powders.

4. Powder compression and tablet strength

Parameter	Definition / Formula	Importance
Compressibility	Change in solid fraction with compaction pressure.	Indicates powder densification.
Tabletability	Relationship between compaction pressure and tablet tensile strength.	Evaluates tablet strength during compression.
Compactibility	Relationship between tablet tensile strength and solid fraction.	Helps compare formulations and support scale-up.
Tensile Strength	$\sigma_t = 2F / (\pi dt)$	For flat-faced round tablets; F = breaking force, d = diameter, t = thickness.
Heckel Equation	$\ln [1 / (1 - D)] = KP + A$	Evaluates powder deformation behaviour; mean yield pressure = $1/K$.

5. Content uniformity, segregation and coating protection

Parameter	Description	Key Point
Content Uniformity	Low-dose ingredients may show high variability. RSD (%) ≈ 100/√N, where N is the mean number of active-bearing particles per tablet.	10,000 particles ≈ 1% RSD; 100 particles ≈ 10% RSD. Theoretical estimates, not experimental VitaSphere™B12 results.
Segregation Control	Differences in particle size, density, transfer, sieving and fluidisation may cause segregation.	Matching particle properties and minimising free fall may reduce segregation risk.
Coating Integrity	Compression may damage encapsulated particles.	Core strength, coating flexibility and thickness, and cushioning excipients can affect particle survival. Findings from other coated-pellet systems require validation for VitaSphere™B12.

6. Quality evaluation and conclusion

Quality evaluation

- **Powder Flow:** Bulk/tapped density and shear testing assess powder flow.
- **Tablet Strength:** Compaction studies, tensile strength and breaking force evaluate mechanical properties.
- **Friability:** Measures tablet mass loss due to abrasion.
- **Disintegration:** Evaluates tablet breakdown under specified conditions.
- **Content Uniformity:** Measures active ingredient content in individual dosage units.
- **Coating Integrity:** Compares coating condition or release performance before and after compression.

Conclusion

Tableting performance depends on powder flow, particle size distribution, compression properties and coating quality. The suitability of each VitaSphere™B12 grade must be verified using the manufacturer's data as well as formulation tests related to content uniformity, tablet strength and coating performance after compression.