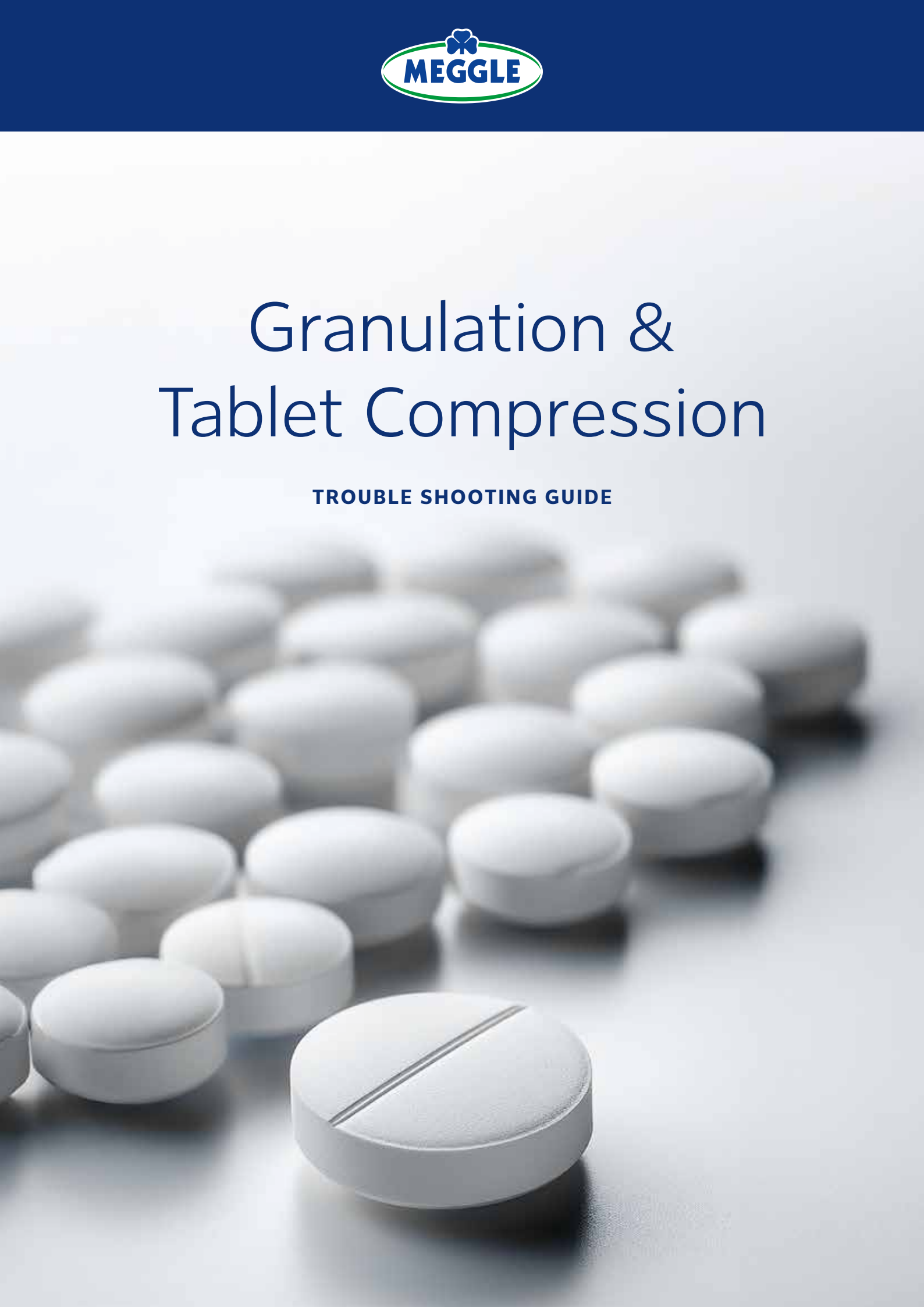
MEGGLE

Granulation & Tablet Compression

TROUBLE SHOOTING GUIDE



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Abstract

This troubleshooting guide provides a structured approach for resolving common issues encountered in pharmaceutical granulation and tablet compression. It is intended for R&D, MS&T, and production teams across product development, scale-up, and commercial manufacturing.

The guide outlines critical process parameters (CPPs) and critical quality attributes (CQAs) for wet granulation, dry granulation, direct compression, and tablet compression. For each step, typical issues are linked to likely root causes, with recommended corrective actions categorized into process adjustments, formulation modifications (Level 1: excipient grade or supplier changes), and reformulation strategies (Level 2).

Special focus is given to challenges with low-dose and high-dose APIs, segregation risks, and chemical stability considerations. Recommendations for MEGGLE excipients are provided throughout, highlighting their functional advantages in different processes.

The guide aims to support systematic problem-solving, improve robustness in manufacturing, and facilitate life-cycle management of solid oral dosage forms.

1. Abbreviations

Table 1: Abbreviations

API	Active pharmaceutical ingredient	**LOD**	Loss on Drying
BU	Blend Uniformity	**MCC**	Microcrystalline Cellulose
CDC	Continuous Direct Compression	**MS&T**	Manufacturing science and technology
CPE	Co-processed excipients	**NIR**	Near-Infrared Spectroscopy
CPP	Critical process parameter	**PAT**	Process analytical technology
CQA	Critical quality attributes	**PSD**	Particle size distribution
CU	Content Uniformity	**PVP**	Polyvinylpyrrolidon
DC	Direct Compression	**RSD**	Relative Standard Deviation
FBG	Fluid bed granulator	**R&D**	Research and Development
HPMC	Hydroxypropylmethylcellulose	**SSF**	Sodium stearyl fumarate
HSG	High-shear granulator	**TSG**	Twin-screw granulator

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2. Purpose & Scope

This troubleshooting guide provides a step-by-step trouble-shooting and decision-support procedure for common granulation and tablet manufacturing issues. It is designed for R&D, MS&T, and production teams during development, scale-up, commercial manufacturing and life-cycle management of products (e.g., new API manufacturer, site/equipment transfer).

This guide provides structured guidance for diagnosing issues, identifying likely causes, and applying corrective actions. Corrective actions are classified into:

- Process-related adjustments
- Formulation-related adjustments (Level 1: excipient grade / supplier changes)
- Formulation-related adjustments (Level 2: e.g., new excipient or reformulation)

The classification does not directly correspond to the regulatory variation classification, as this depends on various factors, such as the country or region, the specific registration dossier submitted, the type of product, and its criticality.

3. Wet Granulation

3.1 Process

The granulation process typically begins with the addition of water or a binder solution to powders. This can be performed in a high-shear granulator (HSG), a fluid bed granulator (FBG), or continuously in a twin-screw granulator (TSG).
Following wet massing, the granules are dried – most commonly in a (continuous) fluid bed dryer. wet and / or dry sieving is applied to achieve the desired particle size distribution.
The extra-granular phase (e.g., lubricant or additional disintegrant) is incorporated during final blending, usually in a bin blender to ensure gentle mixing. Potential issues related to final blending and lubrication are discussed in chapter 5.

Wet Granulation Technologies:

- High-Shear Granulation (HSG):
  - Provides intense mixing and rapid binder distribution.
  - Requires less liquid.
  - Produces denser, coarser granules with higher mechanical strength.
- Fluid Bed Granulation (FBG):
  - Requires larger binder solution volumes to achieve agglomeration.
  - Produces more porous, friable granules.
  - Enhanced drying efficiency due to simultaneous granulation / drying.
- Continuous Granulation – Twin-Screw Granulation (TSG):
  - Uses kneading elements to achieve granule growth.
  - Typically requires significantly less liquid than FBG.
  - Powder transport behaviour strongly influenced by screw design and feeding consistency.

3.1.1 Critical Process Parameters (CPPs)

- High-Shear Granulation (HSG):
  - Wet massing time and intensity (impeller / chopper speed)
  - Liquid addition rate and distribution
  - Kneading time
  - Endpoint detection (torque, power, PAT sensors)
  - Binder solution preparation
- Fluid Bed Granulation (FBG):
  - Inlet air temperature and volume
  - Spray rate and atomization pressure
  - Fluidization
  - Binder solution preparation
- Twin-Screw Granulation (TSG):
  - Screw configuration (kneading vs conveying elements)
  - Residence time and screw speed
  - Temperature (if heated barrel zones)
  - Consistent powder feeding
  - Binder solution preparation

3.1.2 Critical Quality Attributes (CQAs)

- Moisture content (Loss on Drying, LOD)
- Particle size distribution (PSD)
- Bulk and tapped density
- Flowability indices (Compressibility Index, Hausner Ratio)
- Granule strength and friability (relevant for compression)

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3.2 Issues, Potential Causes and Mitigations

Table 2: Issues, potential causes and mitigations of wet granulation

Issue / Cause	Mitigation – Process	Mitigation – Formulation (Level 1)	Mitigation – Formulation (Level 2)
Excess fines / poor flow – insufficient granule growth	Increase impeller speed or wet massing time (HSM) or kneading intensity / kneading element (TSG); adjust spray rate or air temperature (FBG).	Increase amount of binder solution added or increase binder concentration (higher viscosity).	Switch binder grade (higher viscosity).
Excess fines / poor flow – insufficient granule strength	Avoid overdrying; reduce drying time / inlet temperature. Increase screen size for sieving.	Dissolve part of lactose (e.g. GranuLac®) in binder solution. Select lactose grade with better binding properties (e.g. finer GranuLac® like GranuLac® 230).	Reformulate with alternative binder system (PVP, HPMC) .
Large lumps – overwetting	Add water / binder solution in smaller increments (HGS, TSG). Reduce spray rate or increase atomization pressure or increase inlet air temperature / flow (FBG). Determine the suitable granulation endpoint.	Reduce amount of binder solution added, eventually also reduce binder concentration (lower viscosity).	Note: Lactose typically requires significantly less water than MCC for granulation (less energy for drying).
Blinding of screens	Tighten LOD target, cool granules before milling to avoid sticking.		Consider anti-tacking agent like colloidal silica.
Variability of granules	Standardize / improve endpoint control (torque/ power, PAT like NIR).	Select excipient supplier with low variability like e.g. MEGGLE.	Use excipients with low variability, like GranuLac®. Note: for MCC water uptake may differ significantly between lots (pulp source).
Too low assay – API losses	Avoid API losses during processing / sieving. Fluid Bed: reduce air volume (API in filter). Using fluidized bed filter bags with lower air permeability.	Rinse API container and sieves used for API with excipient (e.g. GranuLac®) to avoid losses. Pre-blend API with lactose.	Use pre-mix (trituration) with GranuLac®.
Blend Uniformity (BU) issues	Desagglomeration by sieving of fine materials (API) before addition. Load API in layers (e.g. double-sandwich). HSG: optimum dry mixing time and impeller speed. TSG: Inconsistent feeding or flow differences or between API and excipients might cause variability.	Pre-Blend API with part of the GranuLac® (trituration). GranuLac® grade with higher dilution potential helps in adsorption of more API particle e.g. SorboLac® 400, GranuLac® 230. Adjust GranuLac® grade to adjust flow / feeding in conti manufacturing; coarser grades like GranuLac® 70, 80 or 140 have a better flowability. FlowLac® might be another option to achieve granules with more consistent flow and better CU (low dose granulation).	Dissolve API in binder solution. Refer to chapter 6.1.

Tablet properties can also be influenced by granules by

- Too much fines: flowability / weight variation issues
- Too large granules: die filling issues, especially for small tablets
- Overdried granules: less bonding / tablet defects
- Type of GranuLac®: tablet hardness and disintegration can be "designed" by choosing appropriate GranuLac® grade.

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3.3 Recommended MEGGLE Excipients

Recommended MEGGLE excipients for wet granulation: GranuLac® grades, milled lactose monohydrate, are ideally suited for wet granulation. Different available particle size ranges, can be used to match to API properties, flow properties in feeder (conti) and even tablet properties like tablet hardness and disintegration.

If granules are intended for sachet or capsule filing sieved lactose monohydrate grades, like SacheLac® or CapsuLac®, are also a good option.

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4. Dry Granulation (Roller Compaction)

4.1 Process

The dry granulation process begins by blending the API with excipients (often including a dry binder). The blend is then fed into a roller compactor, where ribbons are formed under controlled pressure. These ribbons are gently milled into granules, which are subsequently blended with the outer phase (e.g., lubricant, disintegrant).

4.1.1 Critical Process Parameters (CPPs)

- Roll pressure & gap width: Determine ribbon density and granule size.
- Feeding system (screw type, speed): Critical for achieving consistent ribbon density and avoiding segregation.
- Roll speed: Influences dwell time and compaction uniformity.
- Roll surface type (smooth, knurled, textured): Affects throughput and tendency for sticking.
- Mill screen size and impeller speed: important for particle size distribution.

4.1.2 Critical Quality Attributes (CQAs)

- Ribbon density and uniformity
- Particle size distribution (PSD)
- Bulk and tapped density
- Flowability indices (Compressibility Index, Hausner Ratio)
- Recompactibility (tabletability)

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4.2 Issues, Potential Causes and Mitigations

Table 3: Issues, potential causes and mitigations of dry granulation

Issue / Cause	Mitigation – Process	Mitigation – Formulation (Level 1)	Mitigation – Formulation (Level 2)
Too soft ribbons – too many fines	Increase compaction pressure / reduce gap width. Optimise throughfall of fines or sieving.	Use finer GranuLac® grade or preferably DuraLac® H for better compactibility.	Add dry binder or adjust binder concentration. Use of CPE like MicroceLac® 100 or CombiLac® (Lactose-MCC synergy regarding deformation).
Too hard ribbons – re-compactibility issues (tablets)	Decrease compaction pressure (feeding rate), increase gap width.	Use DuraLac® H (anhydrous lactose), as it has superior (re-)compactibility. Spray dried Lactose leads to hard ribbons, but if intended for tableting recompaction reduced.	Some substances like croscarmellose sodium improve re-compactibility.
Sticking on roller surface	Use cooled rollers or change roller surface type (smooth, knurled, textured).	Use coarser GranuLac® grade (less fines).	Add lubricant; avoid materials with low Tg / melting point.
Variability – feeding issues	Adapt screw speed and if needed reduce roller speed. Change screw type to improve powder transport.	Use coarser GranuLac® grade (better flowability) like GranuLac® 70, 80 or 140. DuraLac® H (anhydrous lactose – good flowability under shear) eventually also other DC grades like Tablettose® or FlowLac® for excellent flowability.	Add flow aid (e.g. colloidal silicon dioxide). Consider CPE like MicroceLac® 100 or CombiLac® 100.

4.3 Recommended MEGGLE Excipients

Recommended MEGGLE excipients for dry granulation: DuraLac® H, GranuLac® Grades, also FlowLac®, Tablettose®, MicroceLac® 100 or CombiLac® could be used.

DuraLac® (anhydrous lactose) is ideally suited for roller compaction due to its superior re-compactibility and good flowability.

GranuLac®, preferably in combination with a dry binder, is also well suited for roller compaction. Also MicroceLac® 100, lactose combined with 25 % microcrystalline cellulose (MCC), might be an interesting option – combining brittle deformation of lactose with plastic deformation of MCC. CombiLac®, including lactose, microcrystalline cellulose and starch, could be also an option – especially if fast disintegration is required.

Excipients with predominantly plastic deformation behaviour often produce very good ribbons and granules (e.g. for capsule filling). However, they are often less suitable for tablet compression (reduced re-compactibility).

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5. Blending (Direct Compression / Final Blend)

5.1 Process

In direct compression (DC) and continuous direct compression (CDC), APIs and excipients are directly blended before compression. Ingredients are often sieved before blending to break up agglomerates. In CDC, feeders dose components directly into continuous blenders. The lubricant is typically added at the final stage and mixed briefly to prevent over-lubrication.

5.1.1 Critical Process Parameters (CPPs)

- Order of addition: Impacts API distribution, particularly at low doses.
- Blending time and intensity: Critical for uniformity, but overblending can reduce tabletability.
- Blender fill volume and geometry: Affect powder movement and mixing efficiency.
- Lubrication: time and intensity
- Continuous blending processes: feeding accuracy and consistency are most important factors, also residence time needs to be considered.

5.1.2 Critical Quality Attributes (CQAs)

- Blend uniformity (RSD ≤ 5 %; more preferably ≤ 3 %;)
- Particle size distribution (PSD)
- Bulk and tapped density
- Flowability indices (Compressibility Index, Hausner Ratio)
- Segregation risk during transfer or storage

5.2 Issues, Potential Causes and Mitigation

Table 4: Issues, potential causes and mitigations of blending

Issue / Cause	Mitigation – Process	Mitigation – Formulation (Level 1)	Mitigation – Formulation (Level 2)
Blend Uniformity (BU) failure	Optimize blending time or reduce blender load (around 60 % fill volume for free fall / tumble blender) or blender type. In continuous processes, improve feeding accuracy / consistency. Consider pre-blending of some ingredients.	Use agglomerated lactose (Tablettose®) or CPE (e.g. MicroceLac® or Cellactose®) for better API adhesion. Consider pre-blending of some ingredients.	Refer to special Low / High Dose consideration chapter 6.2 and 6.3.
Overblending (particle attrition, agglomeration of micronized API)	Reduce blending time / intensity. For micronized APIs consider additional sieving step after blending.	Replace Tablettose® 80 with Tablettose® 100 or use spray dried lactose (FlowLac® grades) our CPEs like MicroceLac® (not shear sensitive).	Reformulate excipient system to reduce shear sensitivity.
Overlubricating	Reduce lubrication time / intensity.	Lactose is typically not prone to overlubricating, in contrast to MCC. Also CPEs like CombiLac® are not lubricant sensitive.	Reduce Mg stearate level (0.25 – 0.5 % w/w). Change lubricant type (e.g. SSF).
Segregation during handling (for more details refer to chapter 6)	Minimize gravity transfer and vibration; use controlled transfer methods.	Match API and excipient PSD / density. Low dose: triturations with GranuLac® reduces segregation risk.	Introduce agglomerated lactose or CPE, like MicroceLac® or Cellactose®, to stabilize blend.

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5.3 Recommended MEGGLE Excipients

Recommended MEGGLE excipients:
- for Granulation typically GranuLac® grades
- for direct compression DC lactose grade (Tablettose® grades, FlowLac® grades, DuraLac® or CPEs like Cellactose®, MicroceLac® and CombiLac®.

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6. Tablet Compression

6.1 Process

During compression, the blended or granulated material is fed into a tablet press, where it is metered into dies and compacted between punches. The process must achieve consistent tablet weight, hardness, friability, disintegration, and dissolution, while avoiding tablet defects.

6.1.1 Critical Process Parameters (CPPs)

- Feeding system (paddle speed, paddle geometry): Controls die fill uniformity.
- Pre-compression: Reduces air entrapment and prevents capping / lamination.
- Main compression force: Determines hardness, porosity, friability.
- Turret speed: Influences dwell time and throughput.
- Tooling (die design, punch coatings): Impacts sticking, ejection force, and tablet quality.

6.1.2 Critical Quality Attributes (CQAs)

- Dose uniformity (pharmacopoeia compliance, mass / content uniformity)
- Tablet appearance (capping, lamination, sticking, picking)
- Tablet hardness (resistance to crushing Ph. Eur. / breaking force USP-NF); as tablet size independent measure tensile strength is used
- Friability (≤ 1.0 %)
- Disintegration time (typically not more than 15 min for uncoated or 30 min for film-coated immediate release tablets, unless specified otherwise)
- Dissolution profile (bioequivalence and release testing)

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6.2 Issues, Potential Causes and Mitigations

Table 5: Issues, potential causes and mitigations of tablet compression

Issue / Cause	Mitigation – Process	Mitigation – Formulation (Level 1)	Mitigation – Formulation (Level 2)
Weight variability – poor or erratic flow	Optimize paddle speed / geometry (automatic feeder) and turret speed. Adjust feeding type / bin type or hopper level.	Use DC grade lactose based on formulation needs – spray dried lactose (FlowLac® grades) for excellent flow or agglomerated lactose (Tablettose® grade) for good flow and adherence. DuraLac® H has also a good flowability under shear feeding (shear thinning).	Add flow aid (e.g. colloidal silica) or reformulate with good flowing CPE (e.g. CombiLac® or MicroceLac® 100).
Weight variability – irregular die filling	Optimize particle size uniformity or reduce particle size of granules based on tablet size.	Select appropriate grade based on PSD (e.g. FlowLac® 90).	Switch to CPE like e.g. MicroceLac® Plus.
CU issues	Avoid segregation during transport and filling of tablet press feed frame (refer to segregation section). Optimize tablet press speed and paddle speed / geometry.	Match API and lactose type (density / particle size) to reduce segregation risk. Low Dose: a) Active blends with agglomerated lactose (Tablettose® 100) b) Prepare trituration with fine milled lactose (GranuLac® 230) refer to low dose section	Use CPE with high adherence (rough surface) e.g. Cellactose® or MicroceLac®. Add flow aid (e.g. colloidal silica). Use dry or wet granulation instead DC.
Capping / lamination – insufficient bonding	Increase pre-compression, reduce turret speed; use tapered dies for deaeration.	Optimize granule moisture and reduce particle size to improve bonding. Change from FlowLac® 100 to FlowLac® 90 (higher amorphous content).	Reformulate to balance brittle and plastic excipients e.g. MicroceLac®. Change type of dry binder.
Sticking (high ejection force) – hygroscopic or low Tg API	Use coated punches / dies; optimize LOD of granules. Reduce mixing time with magnesium stearate.	Use coarser lactose grades (better flow, less fines). Lactose monohydrate is non-hygroscopic.	Increase lubricant or add glidant (e.g. colloidal silicon). Reformulate with CPE e.g. MicroceLac® or CombiLac® (starch / MCC absorb moisture as scavenger for API).
Low hardness / high friability	Increase compression force, adjust speed / dwell time. Avoid overlubrication (refers to blends).	Select finer lactose grade (GranuLac®) for granulation or anhydrous lactose (DuraLac®) for dry granulation. For DC, change type of spray-dried lactose (e.g. FlowLac® 90 / higher amorphous content).	Reformulate with CPE. For superior tabletability select MicroceLac® Plus.
Disintegration Time too long	Reduce compression pressure (tablet hardness). Typically tensile strength of 1.5 to 2.0 MPa is sufficient to assure friability below 1 %. Avoid overlubrication with hydrophobic lubricant (refer to blends).	Granulation: use finer GranuLac® type, e.g. GranuLac® 230, to increase disintegration of granules. Direct compression: FlowLac® and Tablettose® have a fast disintegration, but dependent on tablet hardness; for DuraLac® H disintegration almost independent of tablet hardness.	Reformulate with CPE: StarLac® or CombiLac®, they have a very fast and tablet hardness independent disintegration. Add/ increase superdisintegrant amount. For granulation it might be added to inner and outer phase for maximum effect. To improve dissolution of API: micronization of API or addition of solubilizer (e.g. sodium lauryl sulphate).

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6.3 Recommended MEGGLE Excipients

Recommended MEGGLE excipients for direct compression (DC):

- DC Lactose grades: Tablettose® grades (agglomerated lactose), FlowLac® grades (spray dried lactose) or DuraLac® H (anhydrous lactose).
- CPEs specially designed for DC and also ideally suited for CDC:
  - Combination with powdered Cellulose: Cellactose®
  - Combination with microcrystalline Cellulose (MCC): MicroceLac® 100, MicroceLac® Plus
  - Combination with Starch: StarLac®
  - Triple Combination (lactose with MCC and corn starch): CombiLac®
- Granulation: GranuLac® grades

7. Special Considerations

7.1 Segregation (from Blending to Compression)

Segregation is a frequent hidden cause of blend uniformity (BU) and content uniformity (CU) failures. Understanding the mechanism is critical for selecting effective mitigation strategies.

The main types of segregation and their countermeasures are listed below:

Table 6: The main types of segregation

Segregation Mechanism	Description	Mitigation Strategies
Sifting (Percolation)	Fine particles migrate downward through voids between coarse particles. Vibration induced (e.g. vibration of machines).	Narrow PSD; granulation to reduce fines; match density of API and excipients. Use continuous manufacturing (lower risk for this type of segregation) or consider granulation.
Fluidization	Fine particles are carried upward by air currents, common in discharge or pneumatic conveying.	Minimize air entrainment; avoid pneumatic transport. For formulations with fine API consider granulation.
Rolling	Coarse particles roll to periphery during gravimetric flow e.g. hopper discharge.	Use blends with higher API adhesion like active blends or trituration. Narrower particle size distribution. Apply rough surface, less spherical particles. Reduce gravimetric-fall distance.
Funnel Flow and Rat-holing	Only a channel of material above the outlet moves while powder near the vessel walls remains stagnant. Fines and lighter particles may preferentially flow through the central channel, while coarse or denser particles accumulate at the periphery. Very critical for CU (erratic flow).	Use mass-flow hoppers (steeper wall angles, smooth surface). Improve flowability of blend: coarser particles or reduction of fines or adding flow aids (e.g. colloidal silica, magnesium stearate at low level). Humidity control, for hygroscopic APIs. Consider granulation to improve flowability / segregation risk. Use aeration, vibrators or mechanical agitators to break up stagnant zones.

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7.2 Low-Dose APIs (< 5 % w/w)

Challenges: Poor blend uniformity, content uniformity failures, API losses (low assay).

Mitigation Strategies

Table 7: Mitigation strategies with regard to challenges by using low-dose APIs

Step	Process Adjustments	Formulation (Level 1)	Formulation (Level 2)
Granulation	Minimize losses during processing / rinsing with lactose.	Prepare pre-mix (trituration) with fine GranuLac® grade (e.g. GranuLac® 230, SorboLac® 400).	Dissolve API in binder solution to assure homogenous distribution and reduce powder losses.
DC	For API addition use layering ("multi-sandwich") technique.	Use active blends with agglomerated carriers (e.g. Tablettose® 100) or CPEs (like MicroceLac® 100 or Plus) with good adherence.	Use pre-mix (triturate API with GranuLac®), increase blending time cautiously.

7.3 High-Dose APIs (> 40 % w/w)

Challenges: Poor tabletability, high friability, sticking, poor disintegration – only limited influence of excipients as API is major component and dominates blend behaviour.

Mitigation Strategies

Table 8: Mitigation strategies with regard to challenges by using high-dose APIs

Step	Process Adjustments	Formulation (Level 1)	Formulation (Level 2)
Granulation	Optimize liquid addition and endpoint to assure proper granulation	Use finer GranuLac® grade, e.g. GranuLac® 230, for better binding. For dry granulation use DuraLac® H.	Use high-performance binders as solution / and eventually intragranular (e.g. PVP, HPMC).
DC	Ensure adequate mixing despite high API content.	Use FlowLac® 90 for better recompactibility. Use high-functionality excipients (CPEs), for highest performance choose MicroceLac® Plus.	Add flow aid like colloidal silicon or aluminium metasilicate to improve flow & compression. Consider dry or wet granulation.

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7.4 Life Cycle Management

Ideally lactose is registered simply as “lactose monohydrate”, specification according pharmacopeia (Ph. Eur./USP-NF/JP, harmonized). This allows easier adaption of lactose grade based on changing needs.

Depending on the actual filed registration documents, type of product and especially the countries, the actual variation classification and requirements may vary.

Example: API supplier change

→ As a result compaction profile differs and tablet hardness can no longer be reached

Possible mitigation

a) Wet Granulation: change from GranuLac® 70 to GranuLac® 140 (grade with lower particle size)
b) DC: change form Tablettose® 80 to Tablettose® 100 or from FlowLac® 100 to FlowLac® 90 (aluminium-liner).

In case of spray dried lactose, packaging and storage after opening has to be considered.
Spray dried lactose contains amorphous lactose. Humidity can cause recrystallisation of amorphous lactose. If the spray dried lactose is recrystallised before tablet compression, the achievable tablet hardness and disintegration time might be impacted.

7.5 Stability Topics

The stability of an API in solid oral dosage forms can be significantly influenced by the choice of excipients and the manufacturing process.
In solid-state reactions, conversion rates are typically much lower compared to those in the liquid state. For most degradation reactions, the availability of water is a critical factor. Additionally, molecular mobility and pH can play important roles in the reaction mechanisms.

Alpha-Lactose Monohydrate (e.g., GranuLac®):

- This is the thermodynamically most stable form of lactose and is non-hygroscopic.
- The crystal water is chemically bound to the lactose molecule and is not available for reactions.
- Dehydration (loss of crystal water) occurs at approximately 150 °C.

Anhydrous Lactose (e.g., DuraLac®):

- Consists of a mixture of beta- and alpha-anhydrous lactose.
- It does not contain crystal water but is slightly more hygroscopic than alpha-lactose monohydrate.

Spray-Dried Lactose (e.g., FlowLac®):

- Contains some amorphous lactose.
- The amorphous portions are more sensitive to water and may recrystallize upon exposure to humidity.

The reactivity of the excipient in the dry powder state can also be influenced by factors such as surface area (particle size), surface energy, and composition.

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Table 9: Stability topics

Step	Process Adjustments	Formulation (Level 1)	Formulation (Level 2)
Nitrosamine	Avoid water, excessive heat / air during drying. Direct compression or dry granulation preferred.	Switch to low nitrite grades e.g. GranuLac® 200 LN, Tablettose® 100 LN or FlowLac® 90 LN Use protective packaging with low water vapor permeability.	Reformulate from wet granulation to DC or dry granulation. Use agglomerated lactose for DC (e.g., Tablettose® 100 LN). Add scavengers.
API Hydrolysis	Favor DC or dry granulation (avoid aqueous processing).	Lactose monohydrate is non hygroscopic. If API is very hygroscopic add moisture scavenger excipients .e.g. CombiLac® with MCC and starch or MicroceLac® Plus with MCC. Use protective (high-barrier) packaging.	Add pH modifiers to stabilize API (depending on optimum stability range e.g. lactose slightly acidic). Reformulate process if needed.
Maillard Reaction*	Prefer DC or dry granulation (wet granulation increases risk).	Select lactose grades with low reactivity. DC: agglomerated lactose e.g. Tablettose® instead of anhydrous lactose or spray-dried lactose. Other processes: sieved < milled < micronized (highest reactivity). Use protective packaging with low water vapor permeability.	Reformulate excipient system if needed. Note: in some cases Maillard reaction serves as protective mechanism for further API degradation (e.g. Gabapentin)

* The Maillard reaction is a chemical process that can occur between reducing sugars and amines at favorable conditions (e.g. high temperature). This reaction may lead to the formation of API-sugar conjugates and melanoidins. It is also responsible for the browning and flavor development in foods. Lactose, as a disaccharide, is significantly less reactive compared to monosaccharides like fructose or glucose, which may also be present in other excipients. Mainly primary amines are affected in this reaction, whereas secondary amines are often successfully formulated with lactose.

Appendix – Typical Formulation / Starting Range

Table 10: Appendix

Function	Material	Typical Range
API	Active pharmaceutical ingredient	
Filler / Binder	Lactose often combined with MCC (e.g. 75 % Lactose / 25 % MCC)	60 – 90 %
Binder	e.g. Povidone, Hypromellose, Isomalt	2 – 6 %
Disintegrant	e.g. Croscarmellose, Crospovidone, Carboxymethylcellulose	2.5 – 5 %
Lubricant	e.g. Magnesium Stearate, Sodium Stearyl Fumarate	0.25 – 1 %
Glidant	e.g. Colloidal Silicium Dioxide, Aluminium Metasilicate	0.1 – 0.5 %

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