Improvement of the Bioavailability of Poorly Soluble Drugs via Wet Bead Milling and Fluid Bed Processing - Scale Up

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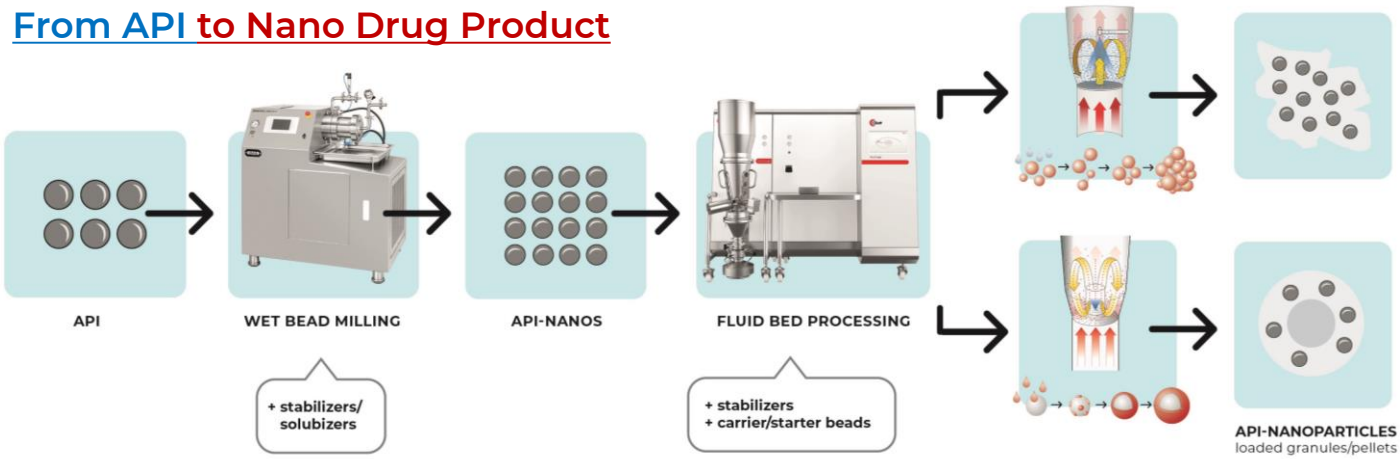
INTRODUCTION

- The **bioavailability** of many drugs is limited by the **poor solubility** of the active ingredient [1]. Over time, various formulation strategies have been investigated to enhance drug solubility and bioavailability [2].
- Among these, **reducing API particle size to the nanometer scale** – resulting in API nanoparticle formulations – has demonstrated significant potential as it increases surface area, and thereby enhances dissolution rate, apparent saturation solubility, and membrane adhesiveness, improving the bioavailability [3].
- **Fluid bed processing**, including drug layering and granulation after **wet bead milling,** provides an effective method for solidifying formulations to create oral dosage forms, and is also applicable to API nanoparticle formulations [4,5].
- In this study the combination of wet bead milling with fluid bed techniques was investigated. Specifically, granulation and drug layering, as methods for converting API nanoparticles into stable oral dosage forms, were **scaled up from the Mini-Glatt® scale (~20 – 50 g) to the Glatt MultiLab® scale (~1200 g)**.

From API to Nano Drug Product



- API: BCS II, Log P > 3,water solubility 16 mg/L, particle size (X_{50}) = 11 µm
- Stabilizers: Kollidon® VA 64 (BASF)
- Solubilizers: sodium dodecyl sulfate

Figure 1. Schematic overview of the manufacturing and analytic procedures

RESULTS AND DISCUSSION

Granules and pellets characterization (Figure 2-3):

- Particle size distribution analysis (sieve analysis and Eyecon2™) and scanning electron microscopy revealed compact structures with uniform particle sizes, demonstrating high product quality of granules and pellets.
- A drug load of 10% API in nanoparticle formulation was successfully achieved, while higher loads (30–40%) are feasible if required.
- Bulk density varied between granules and pellets (GRA: 0.4 g/cm³, PEL: 0.8 g/cm³).
- The water content of all products was maintained below 2% through efficient drying in the fluid-bed process.
- All process yields exceeded 90%, indicating highly efficient fluid-bed manufacturing for both granulation and drug layering.

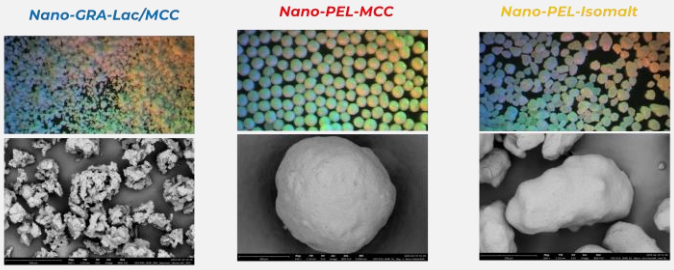


Figure 2. API nanoparticle-loaded granules and pellets

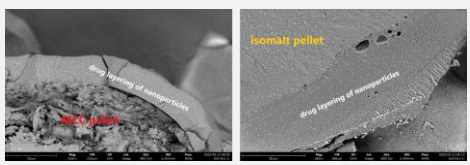


Figure 3. Cross-sectional nanoparticle-loaded drug-layered MCC and isomalt pellets.

Redispersibility (Figure 4):

- The redispersed nanoparticles from pellets and granules maintained similar sizes (<16 nm) to the original nanosuspensions, with low polydispersity index (PDI) values (< 0.12) and remained stable during 6 months of storage at 25 °C/60% RH.

In vitro dissolution (Figure 4):

- The study demonstrated a significant improvement of dissolution rates of both processed granules and pellets compared to the unmilled raw API.

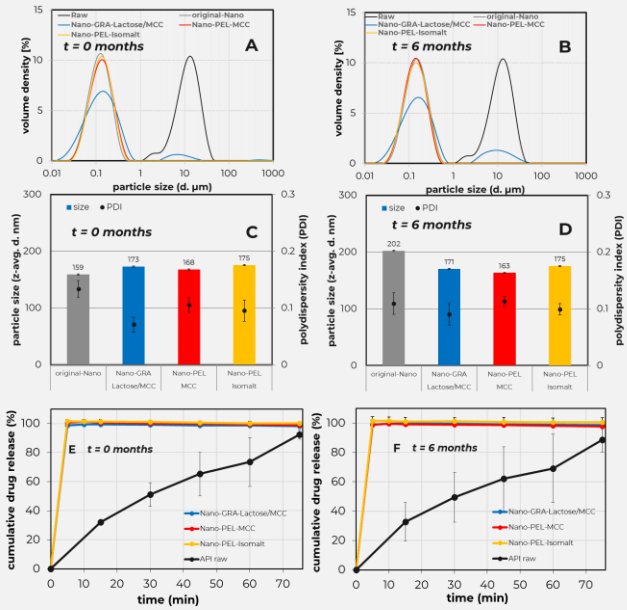


Figure 4. Characterization of API nanoparticle-loaded products. (A-D) Redispersibility, (E-F) *in vitro* Dissolution

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ACKNOWLEDGEMENT:

We gratefully acknowledge the supply of MCC pellets (CELLETS® 500) from IPC Process-Center GmbH & Co. KG (Dresden, Germany) and isomalt pellets (galenIQ™ 960) from BENEO GmbH (Mannheim, Germany). We also sincerely thank Dr. Jan Henrik Finke and Prof. Dr. Heike Bunjes (TU Braunschweig, Germany) for their insightful discussions on the formulation of nanosuspensions.