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FROM SCREENING TO UPSCALING - SOLUTIONS FOR CO-GRINDING

Different crystalline forms of a drug, known as polymorphs play a crucial role in the pharmaceutical industry, as they can significantly impact the physical and chemical properties of a drug, such as solubility, stability, and bioavailability, These polymorphs can exhibit varying characteristics, which can influence the drug's performance and effectiveness. Polymorph screening is an essential process in drug development, as it helps identify stable forms of a drug with desirable properties, ultimately improving drug formulation and performance.

In the context of pharmaceutical manufacturing, polymorphs are often explored through techniques such as co-grinding and cocrystal formation. These methods involve the simultaneous grinding of an active pharmaceutical ingredient (API) with excipients or coformers to enhance the drug's solubility, stability, and bioavailability. The use of ball mills and other specialized equipment can aid in the production of pharmaceutical cocrystals, which can improve drug properties without altering the molecular structure of the API. Overall, understanding and utilizing polymorphs in pharmaceutical research and development is vital for creating effective and stable drug formulations that meet the desired therapeutic outcomes.

Cocrystals and Co-grinding

Planetary Ball Mill PM 400

1) Cocrystals consist of two or more crystalline components, typically an active pharmaceutical ingredient (API) and a coformer, in a definite stoichiometric ratio, held together by non-covalent bonds. Ball mills are used to produce pharmaceutical cocrystals, which can improve drug solubility, stability, and bioavailability without altering the molecular structure of the API.
2) Co-grinding often refers to simultaneous grinding of an API and a (amorphous) excipients. Co-grinding can improve the solubility, stability, and bioavailability of drugs by creating fine and uniform particles and improved fluidity. The excipient can be another API, an amino acid or a polymer like cellulose or starch. Excipients as binders help hold the ingredients of a tablet together. Common fillers include lactose, mannitol, and dibasic calcium phosphate. Other excipients act as lubricants, preservatives, colouring or flavouring agents.

Screening of Cocrystals in Retsch Planetary Ball Mills

Planetary Ball Mill PM 300

To find the optimal coformer or excipient for an API and a specific purpose, a screening approach is typically required. Different ratios of the API and the other substance need to be investigated, resulting in numerous combination options. Since substances can be very expensive, the screening is usually performed on a small scale.

Screening adapter for 24 x 2 ml GC glass vials

The special screening adapter for planetary ball mills can significantly support this process by using disposable vials, such as 2 ml gas chromatography glass vials. The adapter features 24 positions arranged in an outer ring with 16 positions and an inner ring with 8 positions. In total, 96 samples can be screened in one batch if a PM 400 is used, capable of clamping 4 adapters simultaneously. There are already scientific publications [1] describing to start the screening with 2 or 3 grinding balls made of stainless steel, each with a size of of 3 mm. About 20 µl substance,(the AP) are required per vial. Depending on the different stoichiometries (like 1:1, 1:2, 2:1, ...), also a very small amount of the second substance, the conformer or excipient, is added. It is very important to add a few µl liquid to allow the co-crystallisation effects.

For cocrystallization effects, only medium speed and energy input are necessary. This is why steel balls can be used in a small glass vial without causing damage. The Planetary Ball Mills from Retsch have different sun wheel diameters, resulting in three distinct speed limits for safe operation: PM 100 at 550 rpm, PM 300 at 500 rpm and PM 400 at 400 rpm. Generally, a speed range of 200 - 400 rpm is sufficient. Typical process times of cocrystallization experiments lie between 30 minutes and several hours.

After the first screening trials, there might be some substance combination which promise good results – and thus more material might be required. For this purpose, Retsch offers another adapter for Planetary Ball Mills, which keeps 7 x 20 ml gas chromatography glass vials. Here the best filling for starting experiments is about 5 ml of 3 mm steel balls, API and coformer (or excipient) and liquid added up to about 10 ml filling level in each vial. Here, a viscosity similar to ketchup should be achieved. The maximum speed levels for the three suitable mills PM 100, PM 300 and PM 400 are 350 rpm, 300 rpm and 240 rpm. Again, process times of 30 min to several hours are required

Screening adapter for 7 x 20 ml GC glass vials

Upscaling options by Retsch – Planetary Ball Mills and Drum Mill TM 300

Drum Mill TM 300

The next level of upscaling trials can be conducted using the steel or zirconium oxide jars of the Planetary Ball Mills, which offer volumes from 12 to 500 ml. In a PM 400, the maximum volume is approximately 200 ml of te API-coformer mixture in a 500 ml jar, allowing for four different approaches to be tested simultaneously.

Grinding jars for Retsch Planetary Ball Mills

Last but not least, upscaling the cocrystal formation to a kg-scale is the next step. For that, Retsch offers systems such as the Drum Mill TM 300. This mill meets the demands of modern pharmaceutical manufacturing, as demonstrated by he mechanochemical synthesis of rac-Ibuprofen: Nicotinamide co-crystals [2]. In just 90 minutes, 3.2 kg of co-crystals were produced with a 99% yield, using minimal amounts of ethanol in the LAG (Liquid assisted grinding) process, see figure 1. Notably, the metal abrasion was minimal, with measured values well below concerning levels, see table 1.

Sample	Al [ppm]	Cr [ppm]	Co[ppm]	FE [ppm]	Ni [ppm]
Raw Material IBU	11.3	39.0	25.7	71.9	34.9
Raw Material Nicotinamid	8.9	33.3	26.7	40.0	33.3
Co-crystals after 30 min	10.8	35.9	30.8	51.3	38.5
After 60 min	11.0	37.0	31.7	63.4	39.6
After 90 min	17.2	43.8	35.9	65.6	45.3

Results presented by the research group of Michael Felderhoff

Table 1: Measurement of different elements in the raw materials and the co- crystal at different grinding times

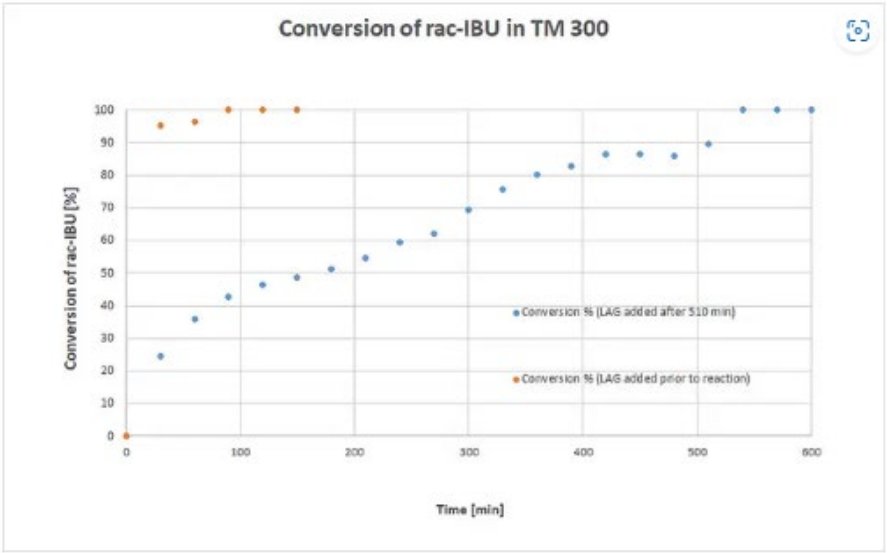

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Figure 1: The diagram shows a conversion of rac-IBU.
Blue plot: neat grinding approach with addition of 10 kg of balls (d = 10 mm) after 270 min and 10 kg of balls (d = 30 mm) after 360 min; addition of LAG additive EtOH after 510 min.
Orange plot: LAG-assisted approach with EtOH added prior to the reaction and 20 kg balls 10 mm

References

[1] Stephen R. Bysouth, Joanna A. Bis, David Igo; Cocrystallization via planetary milling: Enhancing throughput of solid-state screening methods; 2011, DOI: 10.1016/j.ijpharm.2011.03.03

[2] Jan-Hendrik Schöbel, Frederik Winkelmann, Joel Bicker, and Michael Felderhoff; Mechanochemical kilogram-scale synthesis of rac:ibuprofen:nicotinamide co-crystals using a drum mill; RSC Mechanochemistry, 2025, DOI: 10.1039/D4MR00096J