A NEW TOOL FOR NANO-MILLING POORLY WATER-SOLUBLE API USING THE PRECELLYS® + CRYOLYS

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/ CONTEXT

The majority of approved drugs have poor solubility and permeability. Reducing the particle size and surface area of the API (Active Pharmaceutical Ingredient) increases drug performance and bioavailability. The Precellys®24 with Cryolys was validated for drug nano-sizing using different milling protocols.

/ MATERIALS

- Precellys®24 Homogenizer + Cryolys
- Precellys lysing kits: different bead sizes, material, and concentration were tested in 2mL reinforced tubes
- Samples: 5 mg/mL of Indomethacin, Ibuprofen, and Itraconazole were used as models of poorly water-soluble API
- Aqueous vehicles: 0.5% Pluronic® F68 and 0.5% HPC (low viscosity) dissolved in 1mL of ultrapure water
- Oily-based vehicles: 1mL each of soybean and peanut oils (Olvea), glycerol monocaprylocaprate (Capmul® MCM) and triglycerides (Miglyol® 812N and 840)

/ PROTOCOL

Precellys® 24: 5500 rpm, 24 cycles x 30s, 5s pause

Cryolys cooling unit: Maintained a sample chamber temperature between 2-4°C

Nano-milling efficiency was studied using different parameters: bead diameter (0.5-2.8 mm), bead concentration (1-4 g/ml) and material (yytrium stabilized zirconia, zirconium oxide, VHD zirconium oxide and stainless steel). Particle size after nano-milling was measured by a Malvern Zetasizer (dynamic light scattering).

/ RESULTS

The particle size distribution of indomethacin (IN), ibuprofen (IB), and itraconazole (IT) was determined using microscopy. The average particle diameter (D50) was calculated as 27 µm (IN), 144 µm (IB) and 14 µm (IT), respectively. When using aqueous vehicles, the smallest particle sizes were obtained using 0.6-0.8mm yytrium stabilized zirconia at a bead concentration of 2 grams/mL (Figure 1A, highlighted in yellow). The use of Capmul MCM® yielded the smallest particle sizes for all three drug compounds tested (Figure 1B, highlighted in green).

API	IN	IB	IT	IN	IB	IT	IN	IB	IT
Aqueous vehicle (1mL)	0.5% Pluronic F68 and 0.5% HPC								
Bead Concentration and Type	2 g/mL of 0.5mm VHD ZrO			2 g/mL of 0.6-0.8mm yytrium stabilized zirconia			2 g/mL of 1-1.2mm ZrO2		
D_{50} (nm)	380.6	677.1	1426	326.8	464.3	719.2	348	601	700

Figure 1A. Poorly water soluble API were reduced to nano-size using small zirconia beads in aqueous stabilizers. The best results were obtained with bead sizes ranging between 0.5 – 1.2mm at a bead concentration of 2 grams/mL.

IN=Indomethacin; IB=Ibuprofen; IT=Itraconazole. Particle size in red indicates a non-homogeneous mixture.

Oily vehicle (1mL)	Soybean oil			Peanut oil			Capmul® MCM			Miglyol® 812N			Miglyol® 840		
API	IN	IB	IT	IN	IB	IT	IN	IB	IT	IN	IB	IT	IN	IB	IT
D_{50} (nm)	95 + (2957 – 38%*)	456	497	500	433	815 + (5172 – 1%*)	150 + (4737 – 11%*)	275	373	489	469	1024	633	534	1767 + (5412 – 2%*)

Figure 1B. Poorly water soluble API were reduced to nano-size using 0.6-0.8mm yytrium stabilized zirconia at a bead concentration of 2 grams/mL in 5 different oily-based vehicles. *represents the % intensity of larger particle sizes in the sample when 2 peaks are observed.

/ CONCLUSION

Nano-milling of poorly water-soluble drugs can be easily performed using the Precellys® + Cryolys in both aqueous and oily based vehicles, while limiting API consumption. Amongst the different dispersing media tested, Capmul® MCM yielded the smallest particle size, and reduced indomethacin to 150 nm. The Precellys® + Cryolys represents a new technology for drug nano-milling that can be utilized in early discovery and preclinical research.

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