

# Pharmaceutical Cocrystals and Nanococrystals

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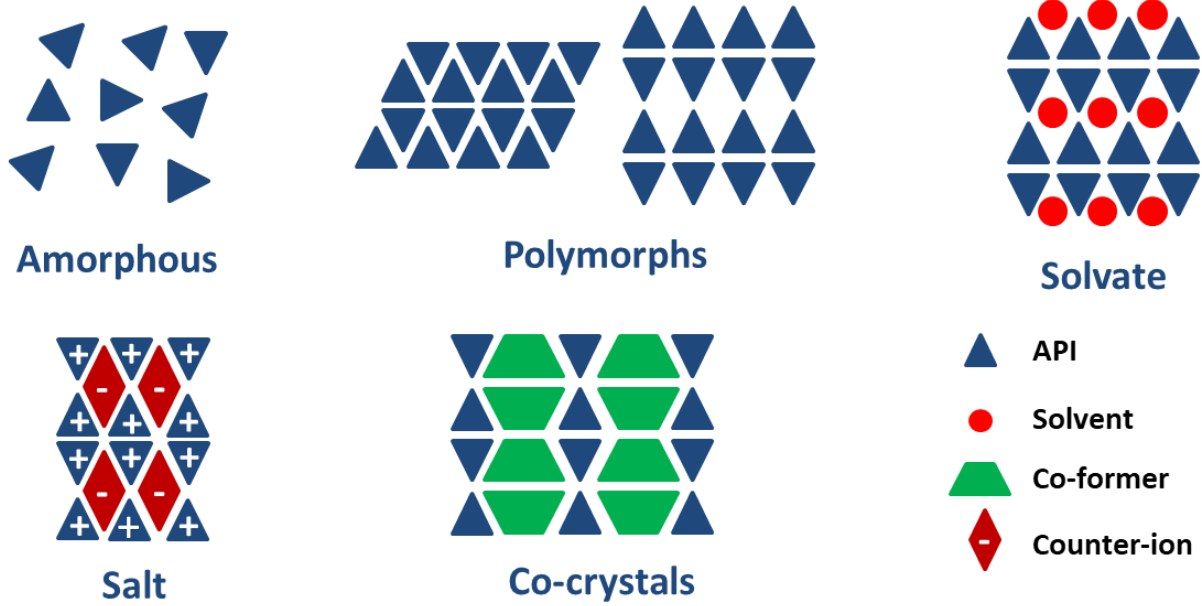
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# Pharmaceutical Co-crystals

- Use of different solid state forms of active pharmaceutical ingredients (API) in medicinal products, for either human or veterinary use



Adapted from: N. Schultheiss, Cryst. Growth Des. 9 (2009) 2950-2967

FDA approval	Commercial name	Pharmaceutical company	Cocrystal	Indication
2021	Seglentis®	Esteve	tramadol hydrochloride ... celecoxib	Acute pain
2017	Steglatro®	Merck Sharp & Dohme	ertugliflozin ... L-pyroglutamic acid	Diabetes
2015	Odomzo®	Novartis	sonidegib monophosphate ... phosphoric acid	Basal cell carcinoma
2015	Entresto®	Novartis	Sacubitril sodium ... valsartan sodium	Heart failure
2014	Suglat®	Astellas Pharma	ipragliflozin ... L-proline	Diabetes
2002	Lexapro®	Forest Laboratories	escitalopram oxalate ... oxalic acid	Depression
1999	Cafcit®	Bristol-Myers Squibb	caffeine ... citrate	Infantile apnea
1983	Depakote®	Abbott Laboratories	sodiumvalproate ... valproic acid	Epilepsy
1963	Beta-Chlor®	Mead Johnson	chloral hydrate ... betaine	Sedation

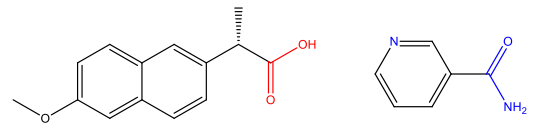
### Patents

- Pharmaceutical Cocrystal 12 200
- Pigments Cocrystal 1 710
- Flavour Cocrystal 1 310
- Explosive Cocrystal 568
- Agrochemical Cocrystal 526
- Nutraceutical Cocrystal 441

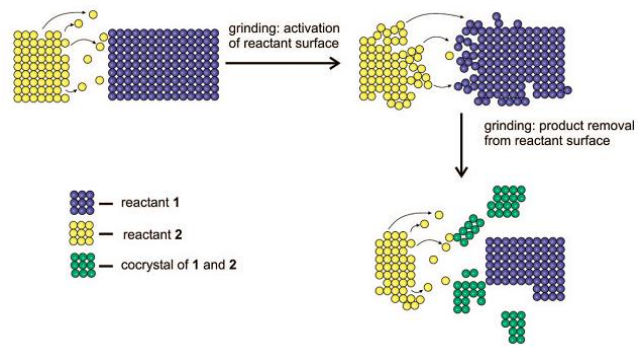
# Pharmaceutical nanococrystal synthesis: a novel grinding approach

- Drugs belonging to class II of the biopharmaceutical classification system
- (S)-naproxen–nicotinamide (2 : 1) as a cocrystal model
- Conjunction of the advantages of cocrystal formation and particle size reduction

	High Solubility	Low Solubility
High Permeability	<b>Class I</b> High Solubility High Permeability	<b>Class II</b> Low Solubility High Permeability
Low Permeability	<b>Class III</b> High Solubility Low Permeability	<b>Class IV</b> Low Solubility Low Permeability



## Mechanochemistry



Tomislav Friscic and William Jones *Cryst. Growth Des.* 9 (2009)

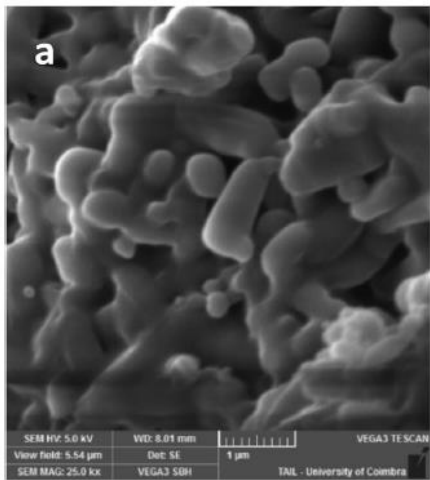
- Neat Grinding (NG)
- Liquid Assisted Grinding (LAG)
- Surfactant Assisted Grinding (SAG)
- Wet Milling (WM)
- Wet Milling with Surfactant (SWM)

10 mL stainless steel grinding jar with two 7 mm, diameter stainless steel balls ; 10 mL zirconium oxide grinding jar with eighteen 5 mm diameter zirconium oxide balls; Total of 70 mg of compound mass; LAG - 10 μL ethanol; SAG - 10 μL ethanol mixed with surfactant; Frequency of 30 Hz during 30 min; Wet milling - 10 mL zirconium oxide grinding jar and eighteen 5 mm diameter zirconium oxide balls per jar

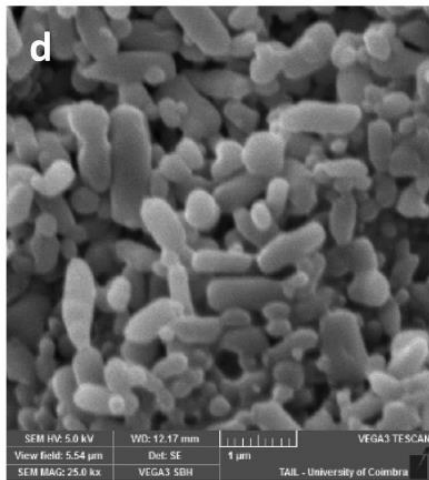
- Solid forms were characterized by attenuated total reflectance-infrared spectroscopy, differential scanning calorimetry and X-ray powder diffraction
- Particle size was determined by scanning electron microscopy and laser diffraction

# Pharmaceutical nanococrystal synthesis: a novel grinding approach

## LAG



## SAG



## Wet Milling



This technique leads to the formation of a nanodispersion instead of the dry nanopowder

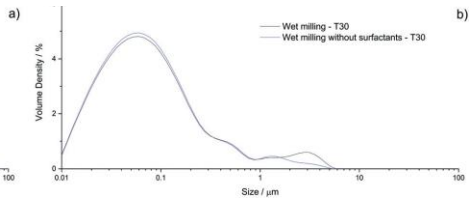
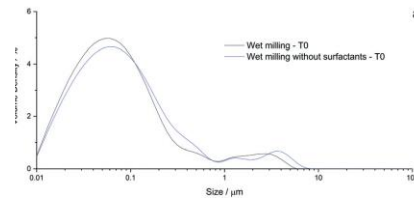
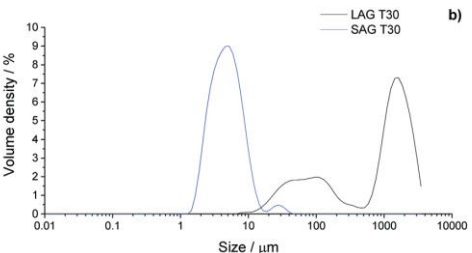
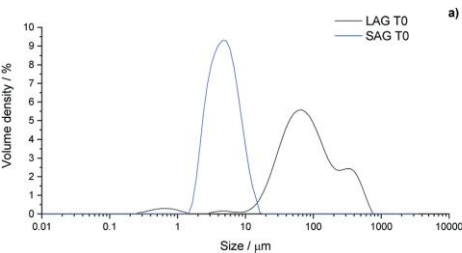
Wet milling is clearly better when it comes to particle size reduction

Percentiles of 10%, 50% and 90% of the total volume obtained from LD measurements regarding the sizes of the obtained (2 : 1) (S)NPX–NIC nanocrystals prepared by SAG with the assistance of an ethanolic mixture of surfactants (37.5% Span® 85 + 25% Tween® 85) and by LAG, assisted only by ethanol (T0). Comparison with the sizes of the same samples after a thirty day storage period at room temperature

Percentiles	LAG T0	SAG T0	LAG T30	SAG T30
DV (10)	21 ± 2 µm	2,3 ± 0,1 µm	47 ± 5 µm	2,3 ± 0,3 µm
DV (50)	68 ± 4 µm	4,3 ± 0,1 µm	917 ± 171 µm	4,3 ± 0,1 µm
DV (90)	253 ± 72 µm	8,4 ± 0,4 µm	2192 ± 138 µm	8,8 ± 0,8 µm

Percentiles of 10%, 50% and 90% of the total volume obtained from LD measurements, regarding the particle sizes of the obtained (2 : 1) (S) NPX–NIC nanocrystals prepared by wet milling assisted by a mixture of Span® 85 and Tween® 85, as described in the text, and by wet milling without any surfactant. Comparison with sizes of the same samples after a thirty day storage period

Percentiles	WM T0	SWM T0	WM T30	SWM T30
DV (10)	22 ± 0 nm	21 ± 0 nm	21 ± 0 nm	21 ± 0 nm
DV (50)	76 ± 1 nm	68 ± 0 nm	69 ± 1 nm	71 ± 0 nm
DV (90)	463 ± 22 nm	372 ± 4 nm	339 ± 13 nm	450 ± 7 nm



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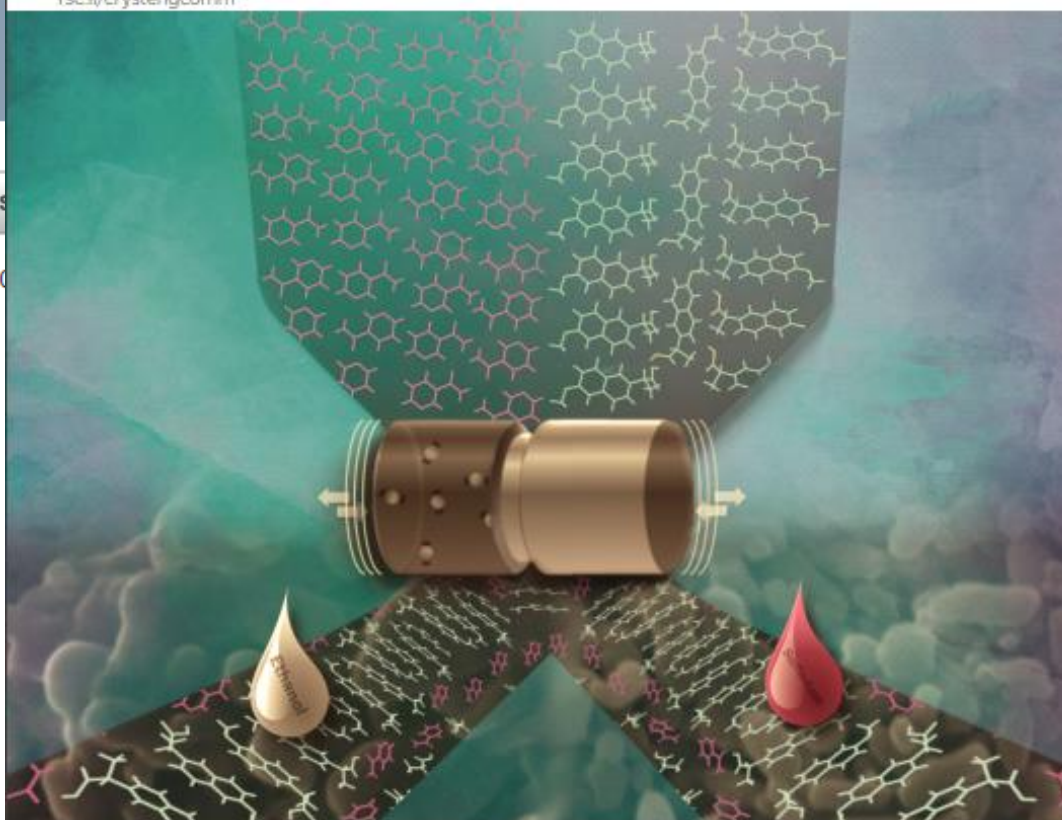
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PAPER

Ricardo A. E. Castro, M. Ermelinda S. Eusébio et al.  
Pharmaceutical nanocrystal synthesis: a novel  
grinding approach

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Pharmaceutical nanocrystal synthesis: a novel grinding approach

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Improving the oral bioavailability of drugs with the conjunction of the grinding process regarding the investigation of pharmaceutical nanocrystal synthesis. The synthesis of nanocrystals of nicotinamide as a cocrystal with hydrophilic ionic surfactants or by PEG assisted grinding method were also carried out. The nanocrystals and nanodispersions, the choice of grinding method and forms were characterized by dynamic light scattering, laser diffraction, gravimetry and X-ray powder diffraction, proving the efficiency of the method and a nanodispersion (wet grinding) for the synthesis of nanocrystals, paving the way for an

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