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Effect of dry ball milling process on curcumin crystals and its impact on physico-chemical and biopharmaceutical properties

Marine Dandignac, Suenia de Paiva Lacerda, Alain Chamayou, Laurence Galet

► To cite this version:

Marine Dandignac, Suenia de Paiva Lacerda, Alain Chamayou, Laurence Galet. Effect of dry ball milling process on curcumin crystals and its impact on physico-chemical and biopharmaceutical properties. PBP 2021 - 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, May 2021, Online, France. <hal-05068846>

HAL Id: hal-05068846

<https://hal.science/hal-05068846v1>

Submitted on 15 May 2025

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CONTEXT AND OBJECTIVE

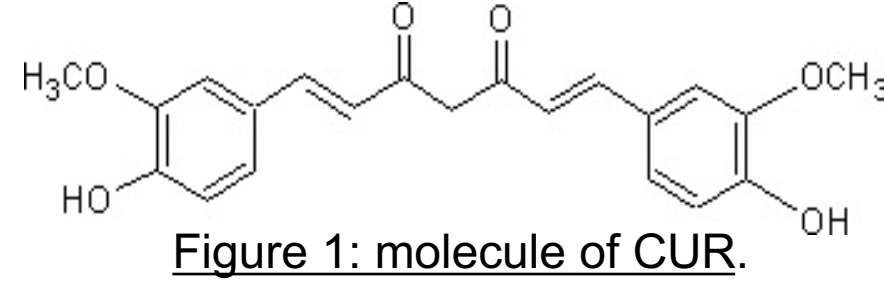
90% of the drugs available on the market present low solubility, low permeability or both. These properties limit their bioavailability, restricting drug delivery technologies [1]. The bioavailability improvement is directly related to solubility or dissolution kinetics of drugs. According to Equation 1 (Noyes-Whitney) the improvement of dissolution rate can be linked to the increase of drug surface area, increase of equilibrium concentration and the increase of constant diffusion. These properties can be improved through the use of several methods. The strategy adopted in this study is to reduce the particle size using dry milling to avoid the use of organic solvent and evaluate the physicochemical and biopharmaceutical properties of curcumin (CUR) milled powders

$$\frac{dC_b}{dt} = kA(C_s - C_b) \quad \text{Equation 1.}$$

dC_b/dt : Drug dissolution rate (kg.s⁻¹)
 k : Diffusion constant (m.s⁻¹)
 C_s : Saturation solubility of the drug (kg.m⁻³)
 C_b : Concentration of the drug in the bulk medium (kg.m⁻³)
 A : Surface Area (m²)

MATERIALS AND METHODS

Natural compound Curcumin (CUR)



Milling Process Parameters

Mass of raw material	1, 2 and 3 g
Amplitude	1.8 mm
Milling time	20 min
Cryostat temperature	24°C

Table 1: Process parameters.

Dry milling process was performed with Pulverisette 00® (Fritsch Company, Germany) Stainless-steel ball of 500 g and 5 cm in a stainless-steel jar

Solid Characterization

1. Morphology and Particle size

Determined by laser diffraction Mastersizer 3000 (Malvern instrument Ltd., UK)

- Samples were dispersed in water

Observed by tabletop scanning electron microscopy (SEM) (TM30 Plus Mini SEM, Hitachi, Tokyo, Japan)

- Analyzed in SE signal
- 1500 Volt
- Magnification : x400

2. Crystallin state

Determined by X-ray powder DRX X' PERT PRO MDP, Philips PANalytical

- 5 to 50 ° scanning
- Scanning rate : 1.228 min⁻¹
- Measurement step : 0.017°
- 45 kV at 40 mA

Determined by DSC Q200 with the base module (TA instruments, USA)

- From 20 to 200 °C
- Heating rate : 10°C/min

$$\chi_c(\%) = \frac{\Delta H_m(\text{grinded sample})}{\Delta H_m(100\% \text{ crystallin})} \times 100$$

Equation 2. Relative crystallinity

3. Solubility and dissolution rate analysis

Determined by a drug excess in phosphate buffer pH 7.2 up to 48h

- Times points (h): 2, 4, 24 and 48
- Bath Temperature: 37 ± 0.5 °C
- n = 2

$$R.S(\%) = \frac{\text{Solubility value}_{\text{sample}}}{\text{Solubility value}_{\text{raw API}}} \times 100$$

Equation 3. Relative solubility (%)

Determined by paddle apparatus USP II (AT Xtend, SOTAX, Switzerland)

- 500 mL pH phosphate buffer 7.2
- 37 ± 0.5 °C ; 100 rpm
- 9.24 mg CUR ; n = 3
- Sampling time (min): 5, 10, 15, 30, 45, 60

RESULTS AND DISCUSSION

Particle size distribution (PSD) and milled powder morphology

Table 2 reveals a slight PSD decrease in volume D[4;3], with a PSD decrease of 50% in number D[3;2]. This phenomenon may be related to an agglomeration effect, as shown on SEM analysis of milled powders.

Samples	Span	D[4;3] (µm)	D[3;2] (µm)
Raw CUR	1.81	194.33	101.23
1g milled	2.18	191.50	67.90
2g milled	2.52	180.00	57.97
3g milled	1.83	223.00	60.55

Table 2: CUR particle size distribution

Crystallin state analysis: Evaluation through two different scales : surface (DRX) and volume (DSC)

- DRX : crystallinity maintained; Bragg's pattern decrease which can indicate default surface → could be related to local surface amorphization [3].
- DSC : No polymorphs (same T_m) ; relative crystallinity between 94% to 98% [4].

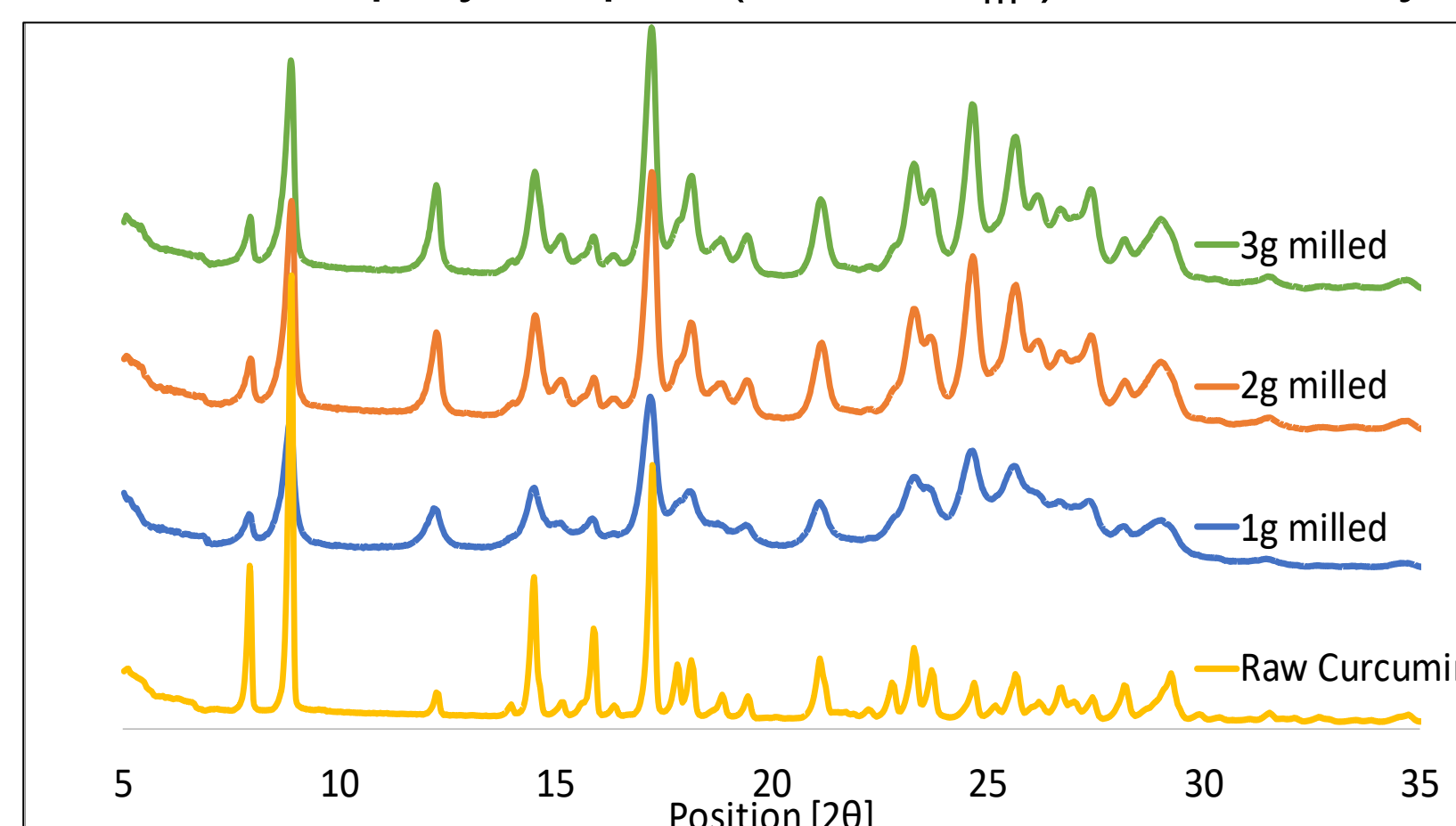


Figure 4: XRPD of raw and milled CUR.

Sample	Raw CUR	1g milled	2g milled	3g milled
T _{onset} (°C)	181.82	179.25	180.54	181.57
T _{melting} (°C)	183.33	181.55	182.41	182.94
ΔH _m (J.g ⁻¹)	132.9	124.75	127.16	129.9
χ _c (%)	100	94	96	98

Table 3: CUR DSC data.

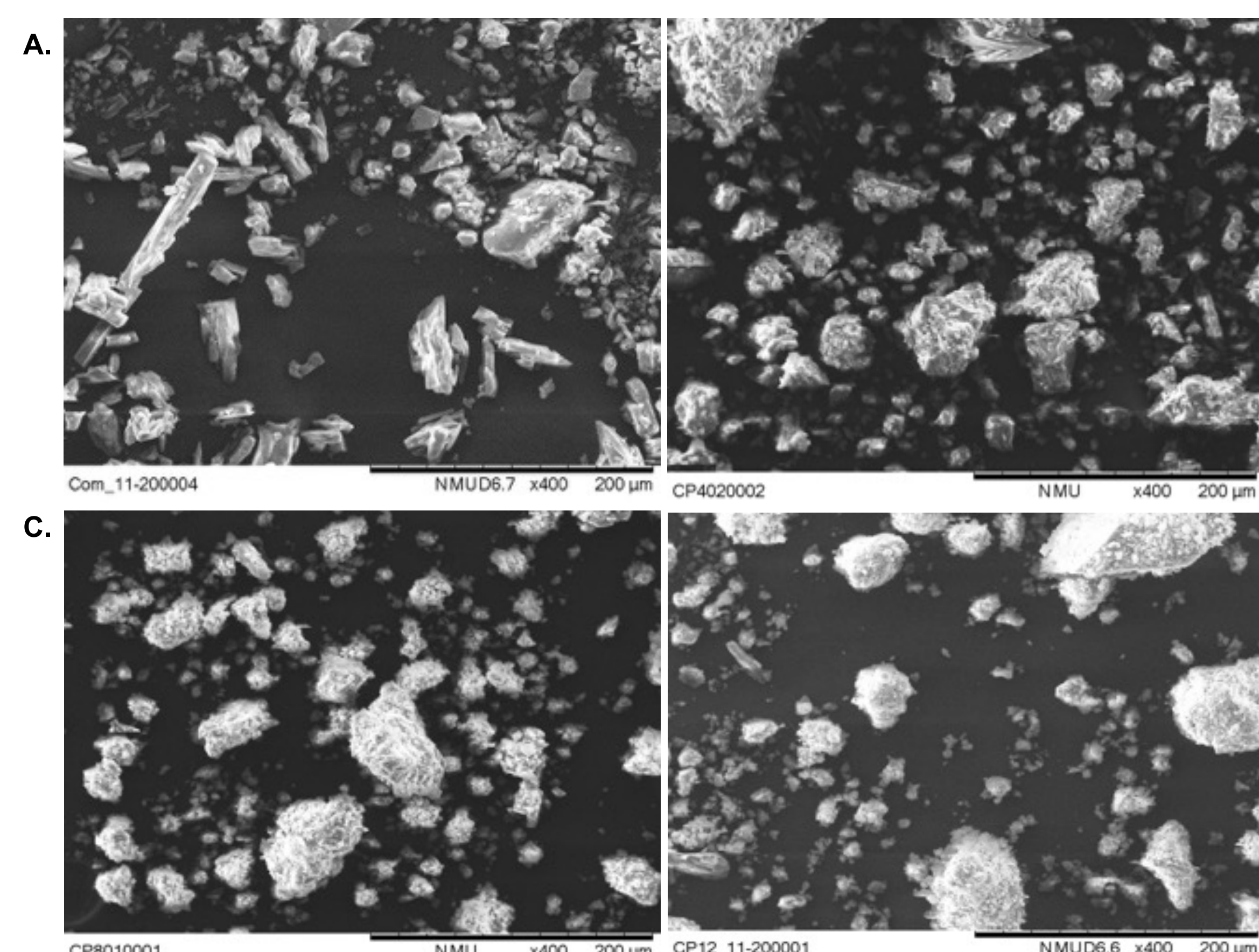


Figure 3: SEM images. A. Raw Curcumin B. 1g Milled C. 2g Milled D. 3g Milled

Solubility and kinetic dissolution evaluation :

Figure 5 (A) shows a relative solubility improvement between 18 - 38 %. Moreover, it is observed a stability of the milled CUR in solution up to 48h.

Figure 5 (B) shows a 3-4-fold increase in the dissolution kinetics over 1h of the milled CUR. The Table 4 presents the cumulative CUR release at 10 and 45 minutes.

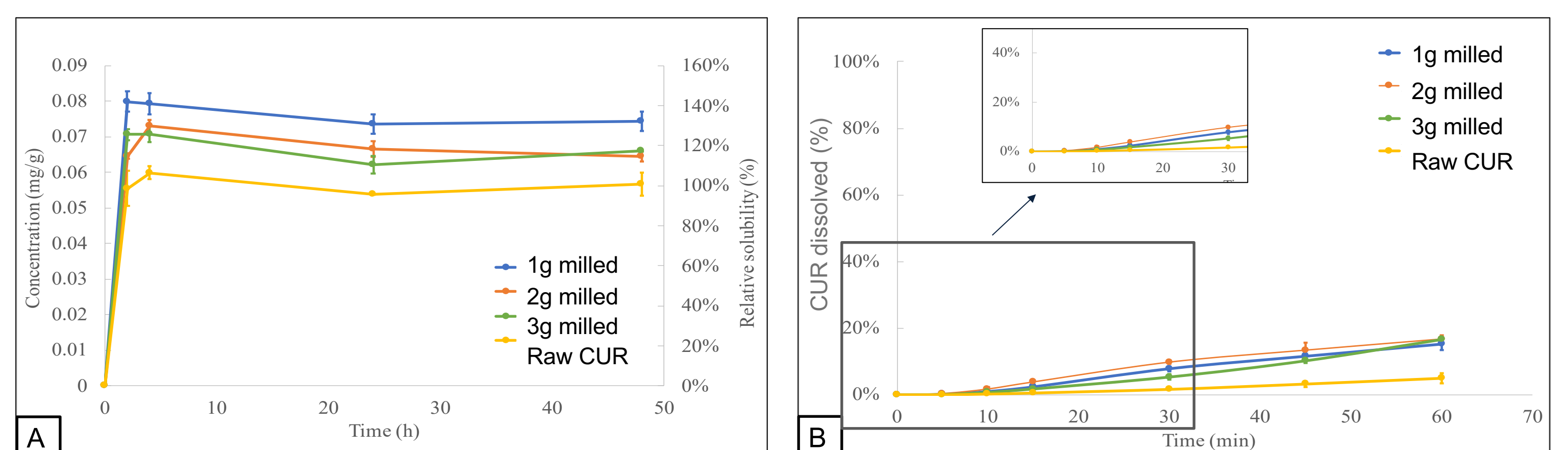


Figure 5: Solubility (A) and Dissolution kinetics (B) results of CUR.

Time (min)	Raw CUR	1g milled	2g milled	3g milled
10	0.22 ± 0.03	1.00 ± 0.68	1.63 ± 0.68	0.74 ± 0.41
45	3.23 ± 0.86	11.48 ± 0.83	13.35 ± 2.32	10.23 ± 0.70

Table 4: % CUR release at 10 and 45 min.

CONCLUSION AND PERSPECTIVES

CONCLUSION

- Improvement of solubility and dissolution kinetics for milled CUR more related to the presence of surface defaults than to particle size reduction.
- Dry milling appears like a promising tool to improve solubility and dissolution kinetics of CUR.

PERSPECTIVES

- Application of the dry milling process with additives.
- Evaluation of co-milling on the physico-chemical properties of CUR.