Enhancement of dissolution rate of poorly-soluble active ingredients by Supercritical Fluid processes. Part I: Micronization of neat particles

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Dissolution rate of SCF-micronized particles:

Among the hundreds of articles dealing with SCF particle design [3-5], it is rather surprising that very few ones disclosed interesting results on dissolution-rate comparison between the unprocessed material and the SCF micronized solid, as detailed below ; moreover, in most publications, data are not complete and physical properties of the solid material are lacking. Perhaps this is to be related to the difficulty to reach reliable results as mentioned before !
We would honestly confess that our team did experience such difficulty and prefer not to disclose some uncertain results, while other ones were covered by trade secrets; however, in spite of these reservations, our results on lovastatin and celecoxib micronization are presented below.

- ***Phenacetin*** was micronized by RESS with CO_2 and CHF_3 as solvents, and the samples compared with the milled material [7]: No polymorphic modification was observed but large differences appeared in particle shapes, sizes and specific surface areas. However, despite considerable differences in specific surface area ***a*** (from 23,800 to 34,100 cm^{-1} for the RESS-material in comparison with 14,500 cm^{-1} for the milled material), the dissolution rates in pure water remained of the same order of magnitude, due to agglomeration and wetting problems; this was confirmed by the very significant increase in dissolution rates after addition of a hydrophilic solubilising agent (Aerosil R 972) or a mixture of it with mannitol.
- ***Nifedipine*** (anti-hypertension agent) was processed by RESS-CO_2, leading to particles of a very uniform size (1-3 µm) that were later incorporated at a concentration of 20% into fast-disintegrating tablets for dissolution release in pepsin-free artificial gastric juice, in comparison with tablets containing milled material [8]: The micronized compound was released faster, (50% in 38 min and 54 min respectively) but not as much as expected from the particle size difference, due to re-agglomeration and poor wettability of the micronized particles. This compound was also processed by PGSS-CO_2 (atomization of the melted compound saturated in high-pressure gas) [9,10]. Particles of 15-30 µm-size were obtained in comparison with the 50 µm-size unprocessed material. Depending on the processing conditions, the resulting dissolution rate in pure water was significantly increased: about twice after 15 to 60 min [9] up to 7 times at 60 min [10].
  We micronized nifedipine by RESS using dimethyl ether as solvent and obtained micro-particles that did not exhibit a better dissolution rate in simulated pepsin-free gastric juice (pH 1.2) than the original material as shown on figure 2.

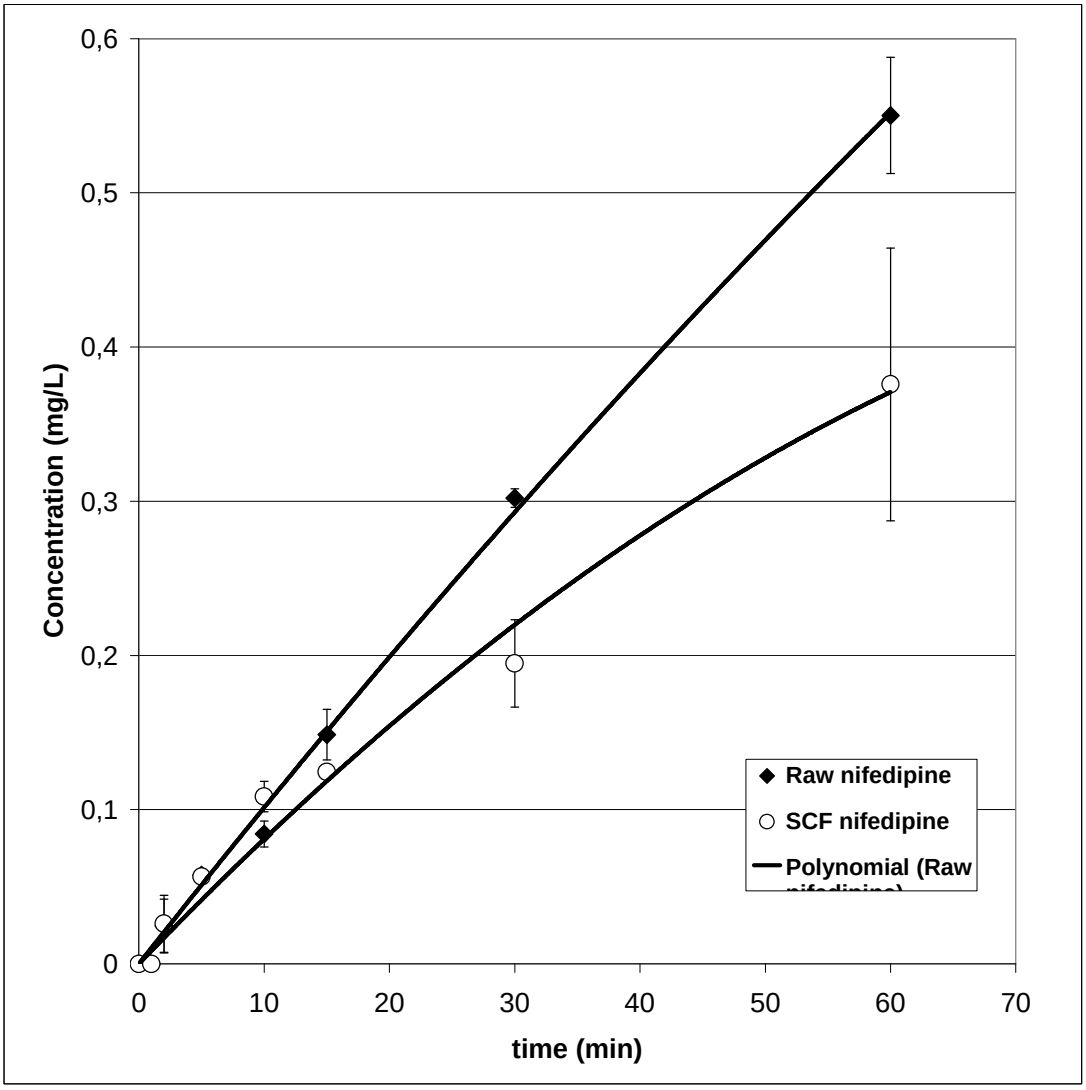


Figure 2: Dissolution curves of nifedipine in simulated pepsin-free gastric juice (pH1.2)

- ***Felodipine*** (anti-hypertension agent) was processed by PGSS-CO_2 similarly to nifedipine [10]. Particles of 45 µm average diameter were obtained with a BET specific surface area of 1.33 m^2/g in comparison with the unprocessed particles of 60 µm average diameter and 0.33 m^2/g area. However, both the unprocessed and micronized particles exhibit a similar very low dissolution rate in pure water of 0.26 mg/l and 0.29 mg/l after 1 hour, once again due to the very low wettability of the compound.
- ***Griseofulvin*** (anti-fungal drug) particles were prepared by RESS-CO_2 [11,12]. The dissolution rates into artificial gut fluid (pH 4.7) of the unprocessed crystalline compound (~1 µm particles adsorbed onto larger particles up to 200 µm), the micronized compound (~1 µm particles) and the RESS-processed ones (agglomerates of ~200 nm particles) were compared; the excellent fit with the Hixson-Crowell cube root law (equation (4)) led to dissolution rate constants ***K*** of 0.0024, 0.0043 and 0.0069 respectively, demonstrating the interest to use RESS for processing such hydrophobic compound known for its poor absorption along the gastro-intestinal tract.

- ***Carbamazepine*** (anti-convulsant drug) was micronized by supercritical anti-solvent process, using acetone as solvent and carbon dioxide as anti-solvent [13,14]. A 90% dissolution of the drug in pure water was obtained in ~15 min for the SCF-processed powder meanwhile ~140 min were required for the unprocessed material. Unfortunately, no details on the solid morphology and particle size were disclosed.
- ***Lidocaine*** (local anesthetic) was micronized using RESS-CO_2 [15], leading to spherical nano-particles (size estimated ~100 nm) with similar DSC analysis as the starting material; the dissolution rates of these very fine particles in pure water at 37°C were found substantially higher than the dissolution rate of the non-processed compound (size estimated 5-7 µm): At one hour, the dissolution reaches 75% and 60% respectively. However, this difference is much lower than it should be expected from the considerable difference in specific surface area of the two powders.
- ***Ibuprofen*** (non-steroidal anti-inflammatory drug) is generally found as racemic. As it exhibits a significant solubility in supercritical carbon dioxide, several authors reported micronization by RESS. Among these works, Foster et al [16,17] obtained particles of around 2 µm size that were dissolved in phosphate buffer (pH 6.3) at 37°C: the dissolution rate coefficient (defined in [16]) was 5 times higher than the original material (size ~ 250 µm) one (figure 2); as they observed re-agglomeration of the micronized particles that may explain this relatively limited gain in dissolution rate, they investigated the effect of surfactant addition in the dissolution medium: The dissolution rate constant of the RESS-micronized powder was significantly increased (~3 times), due to an improvement of the solid wettability; the same dissolution enhancement was also seen for the original material that, surprisingly, dissolves as quickly as the micronized material in such surfactant-added medium!
  Ibuprofen was also used as model molecule for RESS-CO_2 demonstration by other authors[18]. Surprisingly, the unprocessed material with large crystals (100-200 µm) dissolved significantly faster in a phosphate buffer solution (pH 7.2) at 37°C, than the micronized one (1-3 µm), leading the authors to incorporate the drug into other components as described in the following chapter.
- ***Mefenamic acid*** (non-steroidal anti-inflammatory drug) was precipitated from solutions in methanol, ethanol and acetone by pulverization into supercritical CO_2 (anti-solvent), leading to 10-50 µm platelets [19]. The dissolution rate in water of these particles was similar to the micronized commercial product (several to 20 µm) one, and much higher than the original material (irregular-shape 150 µm crystals) one: The authors concluded that this enhancement is founded on the surface area increase.
- ***Copper-Indomethacin*** (non-steroidal anti-inflammatory drug) being insoluble in CO_2 was precipitated from a dimethylformamide solution by supercritical CO_2 anti-solvent [17,20]: the resulting micro-particles were spherical with 90% of a diameter below 10 µm, well adequate to be used as suspensions for injections or for ophthalmic applications; the micronization was demonstrated to lead to an 8-fold increase in dissolution rate in water compared with the original form of the compound.
- ***Phytosterol*** (blood cholesterol lowering agent) was micronized by RESS-CO_2 [21], leading to particles of size varying between 1 and 20 µm according to the processing conditions, that presented a dissolution rate in water at 35°C, much higher than the unprocessed material: 100% dissolution in 90 min instead of 240 min.
- ***Lovastatin*** (anti-cholesterol drug), available as coarse crystals shown on figure 3, was micronized by RESS-CO_2 on a wide range of process parameters, with particles characterization by SEM and dissolution rate into pure water at room temperature. Agglomerates (5 - 20 µm) of very fine particles (< 1 µm) were obtained as shown on a few examples (figure 4). In most cases, the dissolution rates were found higher than

the original material one. However, the size reduction also induced drastic electrostatic phenomena and the particles wetting became problematic, leading to non-reproducible dissolution rates. Comparison of the SEM pictures and dissolution curves (some are presented on figure 5) is rather surprising as the fastest dissolution rates correspond to samples that look "unsatisfactory" in terms of particle size (sample 4) meanwhile other ones looking "satisfactory" led to the same rate as the unprocessed material (sample 8) or even a lower one (sample 10). This may be attributed to a strong particle agglomeration, leading to a low "available" specific surface area.

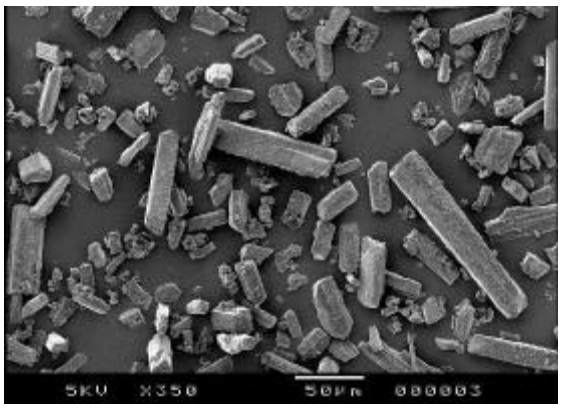
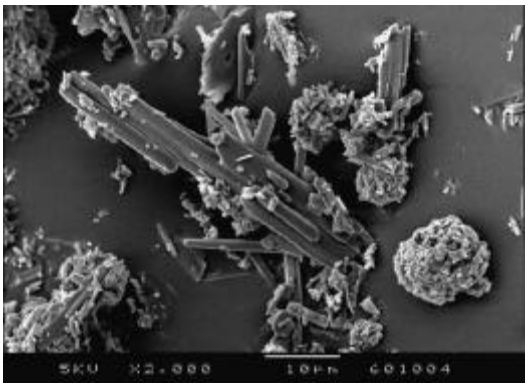
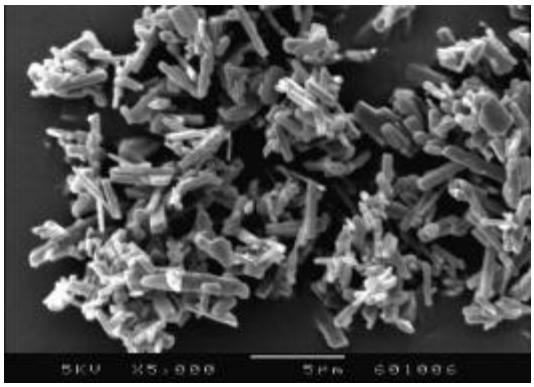


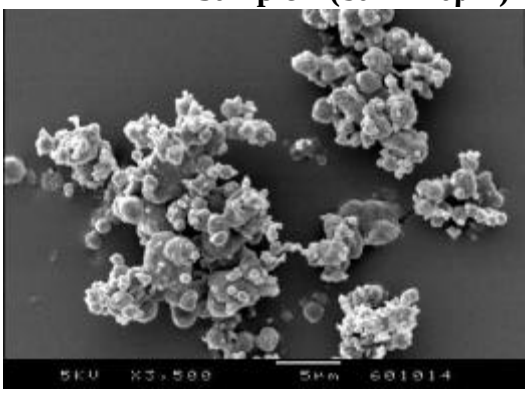
Figure 3: Lovastatin unprocessed material (Courtesy of SEPAREX) (bar = 50 µm)



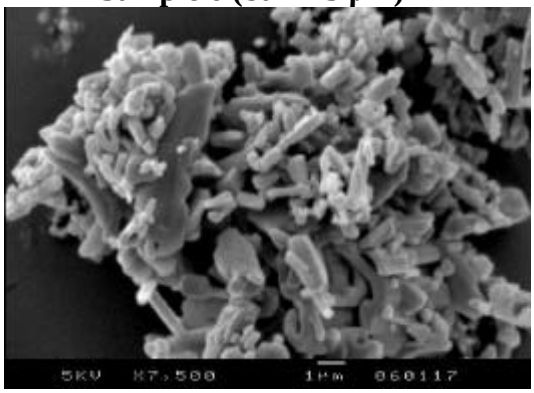
Sample 4 (bar = 10µm)



Sample 6 (bar = 5 µm)



Sample 8 (bar = 5 µm)



Sample 10 (bar = 1 µm)

Figure 4: SEM pictures of RESS-CO_2 processed Lovastatin. (Courtesy of SEPAREX)

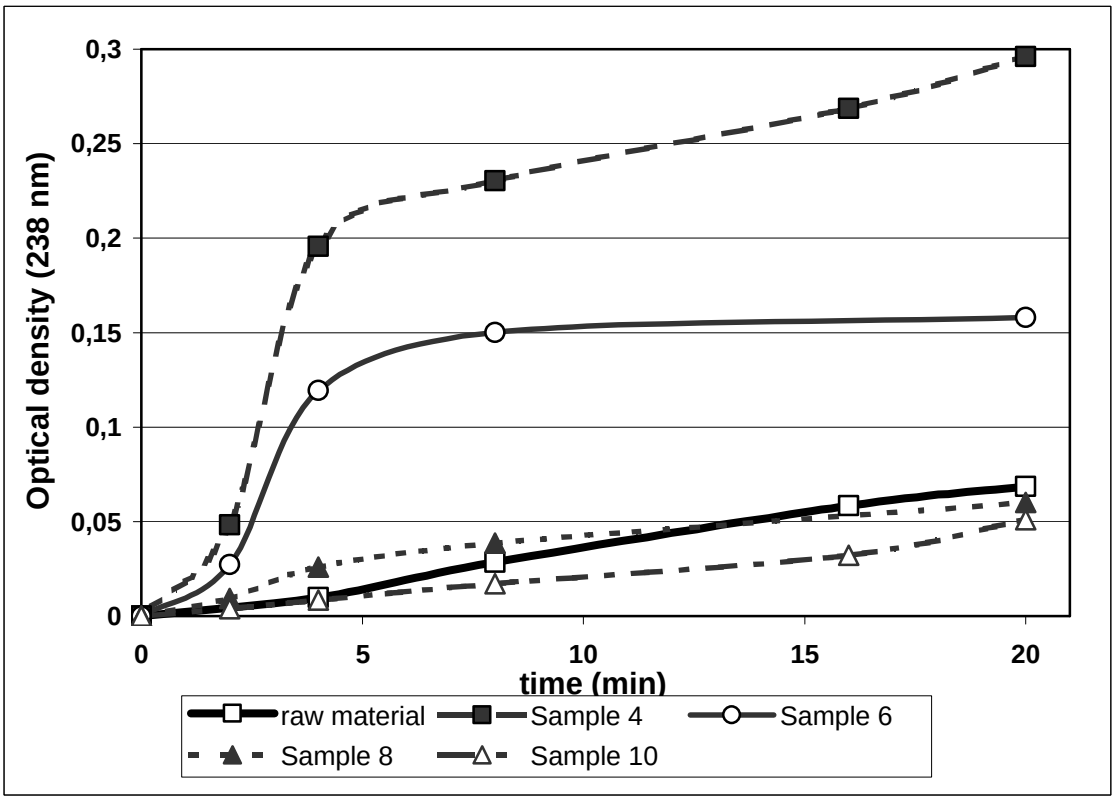


Figure 5 : RESS-CO_2 Lovastatin dissolution curves

- ***Celecoxib*** and ***Rofecoxib*** (anti-arthritis agents) particles (figure 6) were generated by RESS with CO_2 (solubility is very low) and dimethyl ether (higher solubility), exhibiting different solid morphologies, either amorphous or crystalline [22]. The dissolution rate of these particles in pure water was found only slightly higher than the unprocessed material (large flakes) one, in spite of very different particle sizes and specific areas. More surprisingly, after formulation with the commercially-used excipients, the micronized amorphous material dissolves slower into simulated intestinal juice (pH 5 with 1% SLS) than the crystalline original one - that behaves exactly like the commercial formula - probably due to poor wetting and difficult penetration of the aqueous medium inside the micro-particles agglomerates.

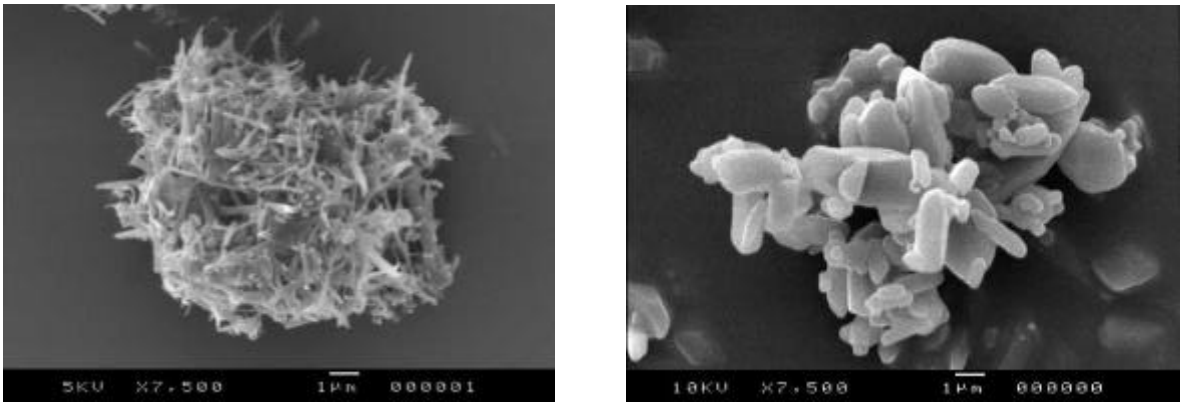


Figure 6: Celecoxib particles by RESS-Dimethyl ether (left picture) and Rofecoxib particles by RESS-Carbon dioxide (right picture). Bars = 1 µm. (Courtesy of SEPAREX)

Discussion:

These results demonstrate that the dissolution rate of poorly-soluble compounds depend on many factors apart from the particle size, among which the most important one is ***wettability***. This means that an optimized formulation is required to take profit of the important specific surface area increase obtained by SCF-micronization.

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