Enhancement of dissolution rate of poorly-soluble active ingredients by Supercritical Fluid processes. Part II: Preparation of composite particles

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Formulation processes:

Different SCF processes [1-3] are being developed to design ***composite*** particles with several purposes among which bio-availability enhancement of poorly-soluble compounds can be obtained by incorporating the active in a fast-dissolving hydrophilic excipient [4-9].
For example, on figure 1, is presented a picture of micro-spheres of a drug co-precipitated with PEG from a CO_2-saturated suspension according to the Fluid-Assisted Micro-Encapsulation process derived from the PGSS concept.

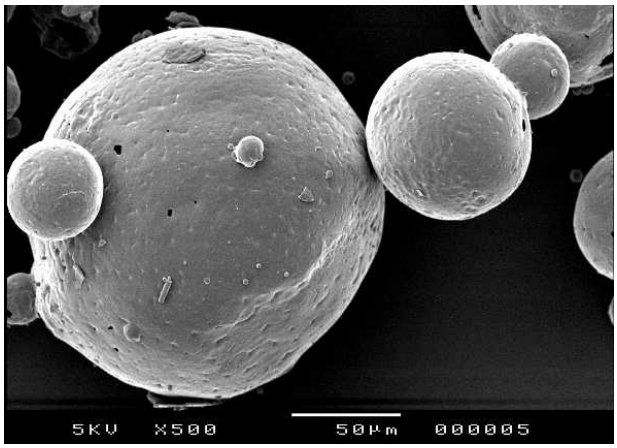

Figure 1: Micro-spheres of drug-PEG composite (bar: 50 µm). (Courtesy of SEPAREX)

This also concerns many works focused on the preparation of particles consisting in a complex of the active drug inserted in a cyclodextrin-type molecule [10-19].

1. **Dissolution of SCF formulated drugs embedded into hydrophilic carriers:**

- ***Carbamazepine*** was micronized to neat particles as said earlier, but also co-precipitated with PEG 4000 using the supercritical anti-solvent process [6,7]. In all cases, the dissolution rates of these SCF-processed composite particles was much higher than those of the neat particles (original and SCF-micronized), and increased with the ratio polymer/drug. Moreover, the SCF-processed composite particles appeared very different from the particles obtained by the classical rotary evaporation and exhibited a much faster dissolution rate in pure water: for 11/1 polymer/drug ratio, 90% of the first ones were dissolved in only 6.5 min in comparison with 60 min for the second ones.
- ***Nifedipine*** was co-precipitated with poloxamer 188 (Lutrol® from BASF) by RESS with dimethyl ether as solvent of the mixture. Figure 2 clearly shows the considerable

improvement of dissolution rate in simulated pepsin-free gastric juice (pH 1.2) of the SCF-processed composite lutrol/nifedipine (92/8 w/w) particles in comparison with the non-processed nifedipine, then SCF atomized nifedipine and the lutrol/nifedipine (92/8 w/w) physical mixture.

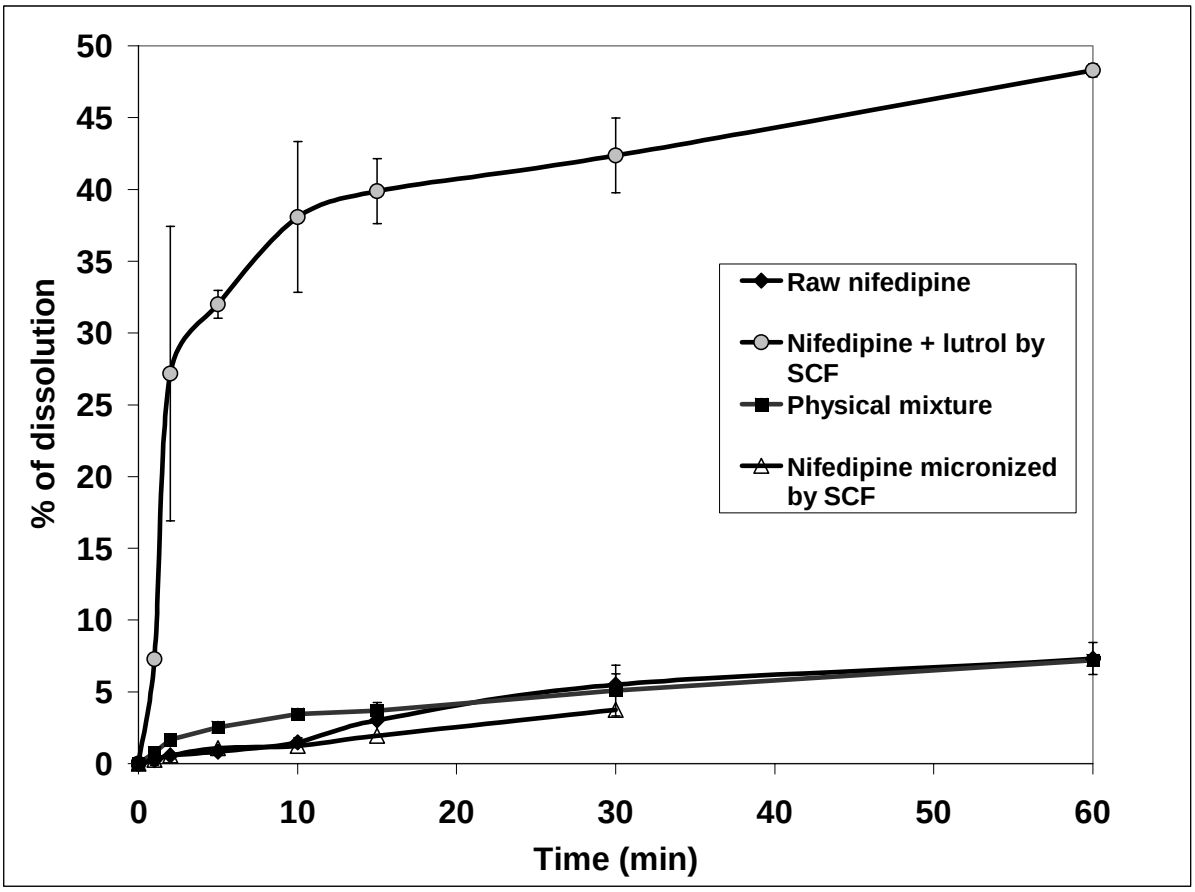

Figure 2: Dissolution curves of nifedipine, lutrol/nifedipine(92/8) physical mixture and lutrol/nifedipine (92/8)composites in simulated pepsin-free gastric juice (pH1.2).

- ***Felodipine*** co-precipitation with PEG 4000 led to a similar dissolution enhancement with a concentration of 3.5 mg/l after one hour in comparison with the 0.26 and 0.29 mg/l observed with the original and SCF-micronized particles [6].
- ***Cefuroxime axetil*** (antibiotic drug) in amorphous form is known to exhibit a higher absorption along the gastrointestinal tract than crystalline form, and adequate stability upon storage. Amorphous form was obtained by embedding this compound into various classical carriers (PVP, HPMC, PEG) using acetone, methanol or methylene choride as organic solvent and CO_2 as anti-solvent. DSC thermograms and XRD diffractograms demonstrated that the polymers inhibited crystal formation during precipitation [9]. Dissolution in pH 1.2 simulated (pepsin-free) gastric juice was evaluated at 24 hours: the three processed composite particles had a similar concentration, slightly higher than the commercial product (*Zinnat*®) one, but 5 times higher than the original crystalline compound one.
- ***Lidocaine*** was co-precipitated with poloxamer 188 (Lutrol® from BASF) by RESS with dimethyl ether as solvent of the mixture as done for nifedipine. On figure 3, appears a complete dissolution of the SCF-processed composite lutrol/lidocaine (92/8 w/w) particles in about 5 min in comparison with the non-processed lidocaine, and the

lutrol/lidocaine (92/8 w/w) physical mixture that are completely dissolved after 40 and 60 min respectively.

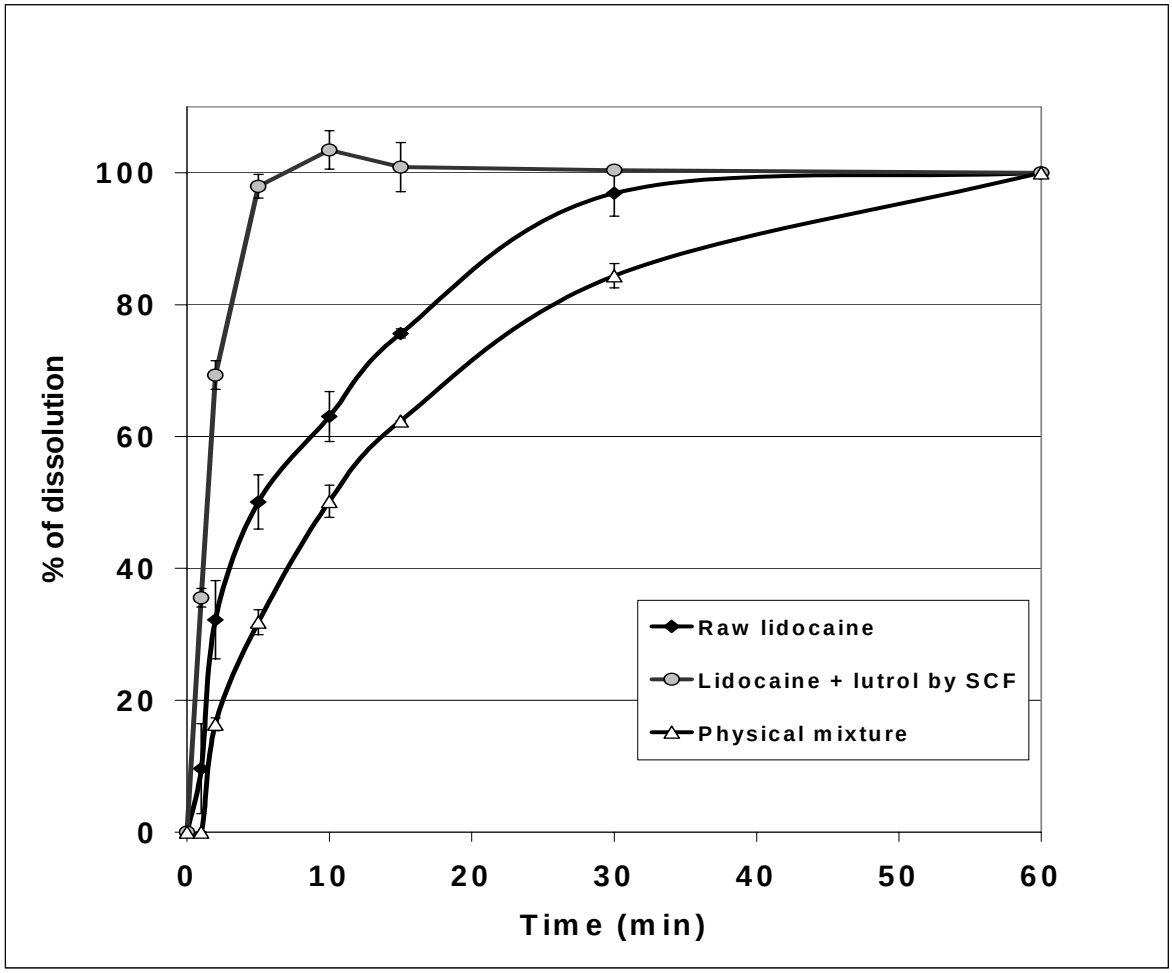

Figure 3: Dissolution curves of lidocaine, lutrol/lidocaine(92/8 w/w) physical mixture and lutrol/lidocaine (92/8 w/w) composites in simulated pepsin-free gastric juice (pH1.2).

- ***Sulfathiazole*** was also co-precipitated with poloxamer 188 (Lutrol® from BASF) by RESS with dimethyl ether as solvent of the mixture as done for nifedipine and lidocaine. On figure 4, no major difference can be found between the SCF-processed composite lutrol/sulfathiazole (92/8 w/w) particles and the lutrol/ sulfathiazole (92/8 w/w) physical mixture that are completely dissolved after 5min meanwhile the non-processed sulfathiazole is completely dissolved after 15 min. Obviously, the dissolution rate improvement is much less significant with this rapidly-dissolving compound than with slowly-dissolving ones like nifedipine, with the intermediate case of lidocaine.

2. Dissolution of drugs complexed in CDs:

- ***Ibuprofen*** micronization by RESS-CO_2 leading to unexpected results as said in the precedent article (Part I); but the authors [10] obtained an important enhancement of the dissolution rate in a phosphate buffer solution (pH 7.2) at 37°C, by addition of β–cyclodextrin, probably due to a partial complexation of the molecule inside the CD cage, meanwhile no improvement was found by addition of lactose.

- ***Eflucimibe*** was also co-precipitated with γ-cyclodextrin by supercritical anti-solvent, using DMSO as solvent and carbon dioxide as anti-solvent [15,16]. The authors stressed on the fact that the degree of complexation, evaluated as the concentration of non-crystalline material, is significantly increased by a static "maturation" step following the atomising step. The dissolution rate in an aqueous solution of SDS (5% m/v) surfactant at 37°C reached up to 7 times more than the non-processed material one, depending on the degree of complexation. It is interesting to note that these results, obtained on a pilot plant, were confirmed on a semi-commercial GMP plant [17].

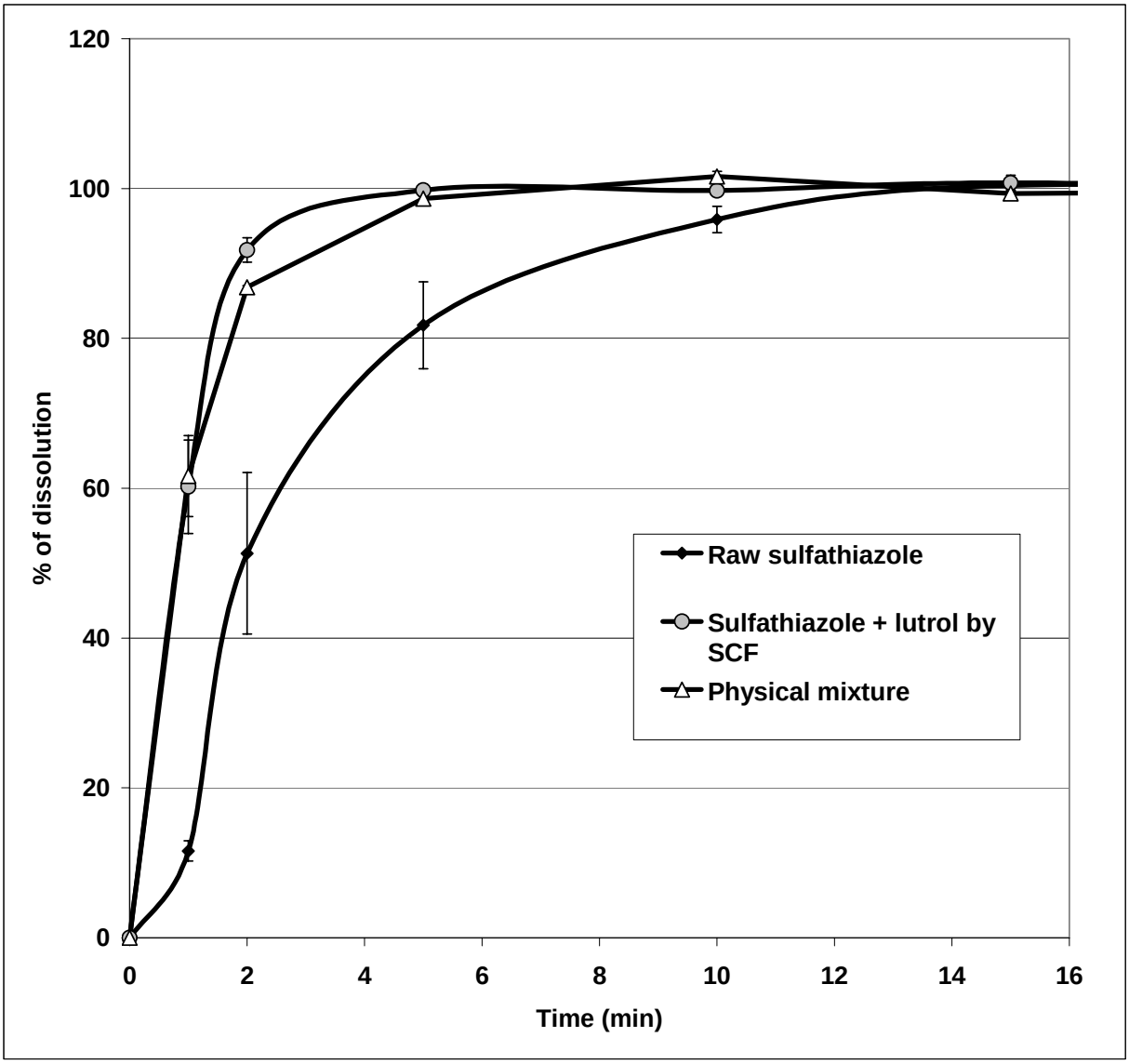

Figure 4: Dissolution curves of sulfathiazole, lutrol/sulfathiazole (92/8 w/w) physical mixture and lutrol/sulfathiazole (92/8 w/w)composites in simulated pepsin-free gastric juice (pH1.2)

- ***Naproxen*** (non-steroidal anti-inflammatory drug), known to have a poor gastro-intestinal absorption, was co-precipitated with cyclodextrins by supercritical anti-solvent process, using ethanol, or DMSO-Ethanol or DMSO-Acetone mixtures as solvent and carbon dioxide as anti-solvent [18]. The resulting particles were mainly

constituted by naproxen-CD complex (as shown by DSC curves) exhibiting a very fast dissolution profile in water at 37°C, in comparison with a physical mixture or a co-evaporated mixture of both compounds.

- ***Celecoxib*** was complexed with hydroxypropyl- and methyl-β-cyclodextrin in acetone at a molar drug/CD ratio of 1/2 and atomized in SCF CO_2 as described in our patent [13], leading to a free-flowing powder consisting in agglomerates of very fine submicronic elementary particles. This powder readily dissolved in pure water reaching 23-26 µg/ml after 15 min and 33-36 µg/ml after 30 min in comparison with less than 0.8 µg/ml after 30 min for the neat celecoxib particles; however, a similar result was found with a physical mixture of same composition, showing that the particle size does not look to play a major role. As made with the neat particles, this powder was formulated with the commercially-used excipients and dissolved into simulated intestinal juice (pH 5 with 1% wt. SLS): it is rather surprising to see that the CD-complex behaved exactly like the commercial formula as shown on figure 6. Might it be the proof that the commercial formulation is perfectly adapted for the chosen dissolution medium, and that it is quasi impossible to do better ?

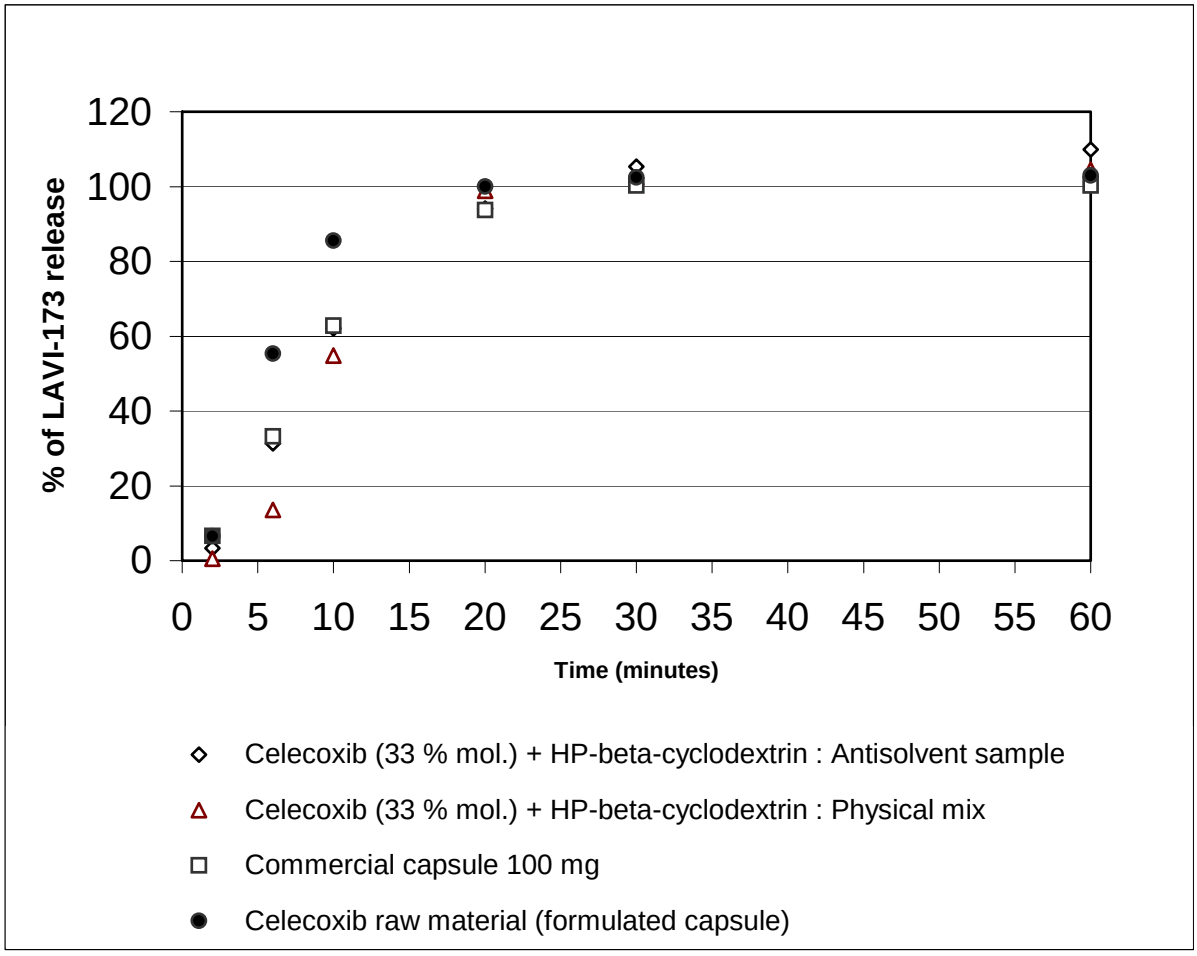

Figure 5 : Dissolution of formulated Celecoxib in a sodium phosphate buffer (pH 5) with 1% SLS.

Discussion:

Composite particle generation by SCF processes looks as a very promising solution to enhance the dissolution of poorly-soluble compounds, although results may deeply vary for one case to the other as shown by the brief review presented here. At present time, most works were conducted with hydrophilic polymers and CDs leading to size-controlled particles that rapidly release the active compound in the aqueous media.
Notwithstanding these attractive results, it is certainly not wise to deduct that dissolution rate enhancement of these SCF-processed materials signifies a comparative enhancement of the *bio-availability* of the final drug, especially when dissolution tests were performed in pure water instead of "representative" artificial media. And finally, only animal or human tests could quantify the improvement, case-by-case.
Moreover, we strongly believe that amphiphilic carriers could supply valuable alternatives as the hydrophobic moiety will permit a labile association of the excipient with the active compound by formation of a sort of cluster around each active molecule (or nano-aggregate of molecules), meanwhile the hydrophilic moiety will induce a rapid dispersion at the molecular scale in the aqueous media, inducing a micellar-like solubilization that may lead to a high bio-availability of the active molecule associated with this amphiphilic excipient.

References:

[1] Jung J., Perrut M., *Particle design using supercritical fluids: Literature and patent survey.* J. of supercritical fluids, 20, **2001**, pp 179-219.

[2] Perrut M., *Supercritical fluids applications in the pharmaceutical industry.* STP Pharma Sci., 13(2), **2003**, pp 83-91.

[3] Perrut M., Clavier J.Y., *Supercritical fluid formulation : Process choice and scale-up*. Ind. Eng. Chem. Res. 42, **2003**, pp 6375-6383.

[4] Jung J., Leboeuf F., Perrut M., *Supercritical Fluid Micro-encapsulation*, Proceedings of the 8th Meeting on Supercritical Fluids, Bordeaux (France), Besnard M. & Cansell F. (Edts), **2002**, pp 805-812.

[5] Knez Z., *Micronization of pharmaceuticals using supercritical fluids.* Proceedings of the 7th Meeting on Supercritical Fluids, Perrut M., Reverchon E., Edts., **2000**, Tome 1, pp 1-26.

[6] Kikic I., Moneghini M., Perissutti B., Voinovich D., *Improvement of carbamazepine dissolution characteristics using supercritical carbon dioxide.* Proceedings of the 7th Meeting on Supercritical Fluids, Perrut M., Reverchon E., Edts., **2000**, Tome 1, pp 95-100.

[7] Kikic I., Alessi P., Cortesi A., Eva F., Fogar A., Moneghini M., Perissutti B., Voinovich D., *Supercritical anti-solvent precipitation processes : Different ways for improving the performances of drugs*. In: Chemical Engineering Transactions, Bertucco A. Edt., AIDIC (Milano), **2002**, Vol. 2, pp 821-826.

[8] Nam K.-W., Lee S., Hwang S.-J., Woo J.S., *Enhancing water-solubility of poorly soluble drug, itraconazole with water-soluble polymer using supercritical fluid processing*. In Controlled Release Society 29th Annual Meeting Proceedings 2002.

[9] Jo G.H., Yu J.H., Yun J.H., Hwang S.-J., Woo J.S., *Preparation of amorphous form of cefuroxime axetil using supercritical fluid processing*. Controlled Release Society, **2002**, paper 057.

[10] Cristini F., Delalonde M., Joussot-Dubien C., Bataille B., *Elaboration of ibuprofen microcomposites in supercritical CO_2.* Proceedings of the 6th International Symposium on Supercritical Fluids, Brunner G., Kikic I., Perrut M., Edts., **2003**, pp 1917-1922.

[11] Kamihira M., Asai T., Yamagata Y., Taniguchi M., Kobayashi T., *Formation of inclusion complexes between cyclodextrins and aromatic compounds under pressurized carbon dioxide.* J. Fermentation Bioeng., 69(6), **1990**, pp 350-353.

[12] Van Hees T., Piel G., Evrard B., Otte X., Thunus L., Delattre L., *Application of Supercritical carbon dioxide for the preparation of a piroxicam-β-cyclodextrin inclusion compound.* Pharmaceut. Res., 16(12), **1999**, pp 1864-1870.

[13] Fabing I., Leboeuf F., Jung J., Perrut M., *A method and apparatus for making very fine particles containing a complex of an active principle and a cyclodextrin.* World patent WO02/32462, European patent EP 1 330 266, **2002**.

[14] Freiss B., Marciacq F., Fages J., Sauceau M., Lochard H., Letourneau J.J., Joussot-Dubien C. *Procédé de préparation d'un composé d'interaction de substances actives avec un support poreux par fluide supercritique.* World patent WO 03/043604, **2003**.

[15] Freiss B., Marciacq F., Fages J., Sauceau M., Lochard H., Letourneau J.J., Joussot-Dubien C. *Procédé de préparation d'un composé d'interaction d'un dérivé d'anilide avec un support poreux par fluide supercritique.* World patent WO 03/030867, **2003**.

[16] Lochard H., Rodier E., Sauceau M., Letourneau J.J., Freiss B., Joussot-Dubien C., Fages J., *A three-step supercritical process to improve the dissolution rate of eflucimibe.* Proceedings of the 6th International Symposium on Supercritical Fluids, Brunner G., Kikic I., Perrut M., Edts., **2003**, pp 1659-1664.

[17] Papet S., Marciacq F., Lochard H., Sauceau M., Freiss B., Joussot-Dubien C., Sarrade S., *Supercritical CO_2 anti-solvent process for drug precipitation : From lab-scale to cGMP-compliant pilot scale.* Proceedings of the 6th International Symposium on Supercritical Fluids, Brunner G., Kikic I., Perrut M., Edts., **2003**, pp 1689-1694.

[18] Foster N.R., Mammucari R., Dehghani F., *Co-precipitation of pharmaceuticals using gas anti-solvent technique.* Proceedings of the 8th Meeting on Supercritical Fluids, Besnard M., Cansell F., Edts., **2002**, Tome 1, pp 321-326.

[19] Thompson D.O., *Cyclodextrins-enabling excipients: Their present and future use in pharmaceuticals.* Crit. Rev. in Therapeutic Drug Carrier Systems, 14(1), **1997**, pp 1-104.

[20] Majewski W., Perrut M., *On-line direct impregnation of natural extracts.* Proceedings of the 7th Meeting on Supercritical Fluids, Perrut M., Reverchon E., Edts., **2000**, Tome 2, pp 779-780.

[21] Weidner E., *Powderous composites by high pressure spray processes.* Proceedings of the 6th International Symposium on Supercritical Fluids, Brunner G., Kikic I., Perrut M., Edts., **2003**, pp 1483-1495.