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Commentary

Enhancement of dissolution rate of poorly soluble active ingredients by supercritical fluid processes Part II: Preparation of composite particles

M. Perrut*, J. Jung, F. Leboeuf

SEPAREX, 5 Rue Jacques Monod, F-54250 Champigneulles, France

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Abstract

In this second of two articles, we show that several supercritical processes have been developed to prepare composite particles of poorly soluble active ingredients. Microencapsulation, cyclodextrin inclusion and impregnation allow to incorporate poorly soluble materials in fast-dissolving hydrophilic excipients, leading to promising results in terms of dissolution rate enhancement.
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Keywords: Particle design; Supercritical fluid; Dissolution enhancement; Micronization; Nanoparticles; Microspheres

1. Introduction

Different supercritical fluid processes (Jung and Perrut, 2001; Perrut, 2003a; Perrut and Clavier, 2003b) are being developed to design composite particles with several purposes including the preparation of sustained-release drugs by incorporating the active in a slow-dissolving (bio-degradable or bio-erodable) matrix (Jung et al., 2002), stabilization of fragile molecules (mainly bio-molecules) in the solid form, and bio-availability enhancement of poorly soluble compounds by incorporating the active in a fast-dissolving hydrophilic excipient (Kikic et al., 2000; Knez, 2000; Jo et al., 2002; Nam et al., 2002). For this latter purpose, many papers are focused on the preparation of particles consisting of a complex of the active drug inserted in a cyclodextrin-type molecule (Kamihira et al., 1990; Van Hees et al., 1999; Fabing et al., 2002; Foster et al., 2002; Cristini et al., 2003; Freiss et al., 2003a, 2003b; Lochard et al., 2003; Papet et al., 2003). The cyclodextrin "cage" presents a hydrophilic character on its outside, leading to a very fast dissolution in aqueous media, but a hydrophobic character on its inside, permitting a stable inclusion of poorly soluble molecules of an adapted size. This explains why these inclusion compounds are widely

* Corresponding author. Tel.: +33 3 83 31 24 24; fax: +33 3 83 31 24 83.
E-mail address: mperrut@separex.fr (M. Perrut).

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Table 1
Formation of composite microparticles for dissolution enhancement (from Perrut, 2003a)

Substrate solubility in SCF	Matrix solubility in SCF	Available process	Type of particles produced	Remarks
Yes	Yes	RESS	Microspheres	–Few substrates/coatings both soluble in SCF CO_2 –Possible use of polar SCFs
Yes	No	SCF impregnation	Active adsorbed onto a porous carrier	–Carrier impregnation by extracted active –Easy scale-up –Rarely used for dissolution enhancement
No	No	Supercritical anti-solvent	Microspheres and microcapsules CD complexes	–Difficult solvent/fluid separation and scale-up
		Fluid-assisted micro-encapsulation	Micro-spheres/capsules	–Very low CO_2 consumption –Easy scale-up
		CPF impregnation	Liquid active adsorbed onto a porous carrier	–Continuous process –Easy scale-up –Rarely used for dissolution enhancement

considered for designing delivery systems adapted to poorly soluble drugs (Thompson, 1997). Moreover, impregnation of hydrophilic porous carriers can be operated using a supercritical fluid as vector of the active ingredient (Majewski and Perrut, 2000; Weidner, 2003).

The choice of the carrier and the choice of the process are correlated, as summarized in Table 1 (Perrut, 2004). One might be surprised that we do not list other SCF processes applicable when the active compound is not soluble in the fluid and the carrier is soluble, such as SCF deposition, but these processes are generally used for production of sustained-release microcapsules.

For example, in Fig. 1, is presented a picture of microspheres 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 (particle from gas-saturated solutions) concept.

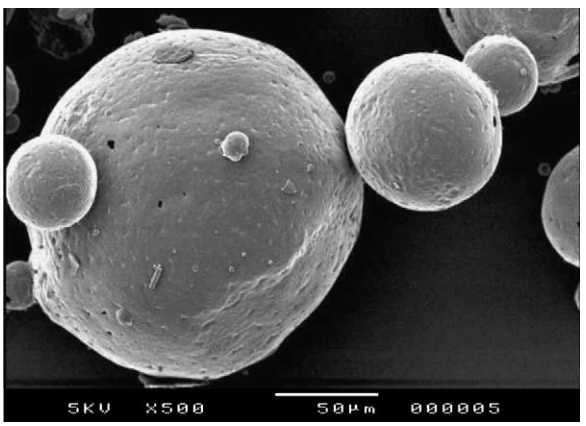

Fig. 1. Micro-spheres of drug-PEG composite (bar: 50 μm) (courtesy of SEPAREX).

2. Dissolution of SCF formulated microspheres and microcapsules

- *Carbamazepine* has been micronized to neat particles as discussed in the preceding article (Perrut, 2005), but also co-precipitated with PEG 4000 using the supercritical anti-solvent process (Kikic et al., 2000, 2002). In all cases, the dissolution rates of these SCF-processed composite particles were 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 classical rotary evaporation and they exhibited a much faster dissolution rate in pure water: for a 11/1 polymer/drug ratio, 90% of the SCF-processed particles were dissolved in only 6.5 min in comparison with 60 min for the particles obtained from evaporation.

- *Felodipine* co-precipitation with PEG 4000 leads to a similar dissolution enhancement with a concentration of 3.5 mg/l after 1h in comparison with the 0.26 and 0.29 mg/l observed with the original and SCF-micronized particles (Kikic et al., 2002).
- *Cefuroxime axetil* in amorphous form is known to exhibit a higher absorption along the gastrointestinal tract than crystalline form, and adequate stability upon storage. An 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 (Jo et al., 2002). Dissolution in pH 1.2 simulated (pepsin-free) gastric juice was evaluated at 24 h: the three processed composite particles had a similar active content, but a dissolution rate slightly higher than the commercial product (*Zinnat*®) one and 5 times higher than the original crystalline compound one.

Composite microparticles were produced by our team at SEPAREX in order to study their dissolution rates.

- *Nifedipine* has been co-precipitated with poloxamer 188 (Lutrol®, BASF) by RESS with dimethyl ether as solvent of the mixture. Fig. 2 clearly shows the considerable improvement in 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, the SCF atomized nifedipine and the Lutrol®/nifedipine (92/8, w/w) physical mixture.
- *Lidocaine* was co-precipitated with poloxamer 188 (Lutrol®, BASF) by RESS with dimethyl ether as solvent of the mixture as done for nifedipine. In Fig. 3, the complete dissolution of the SCF-processed composite Lutrol®/lidocaine (92/8, w/w) particles is seen 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.
- *Sulfathiazole* was also co-precipitated with poloxamer 188 (Lutrol®, BASF) by RESS with dimethyl

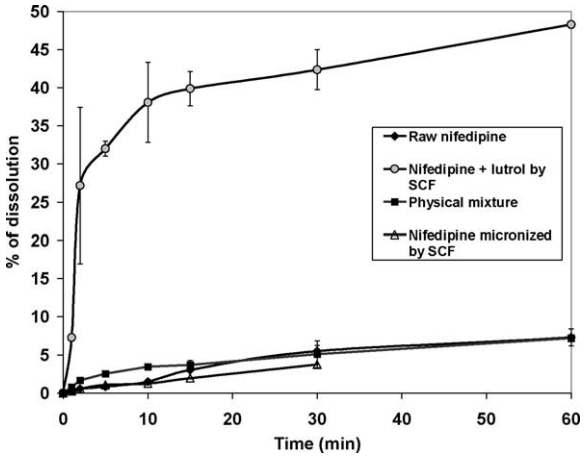

Fig. 2. Dissolution curves of nifedipine, Lutrol®/nifedipine(92:8, w/w) physical mixture and Lutrol®/nifedipine (92:8, w/w) composites in simulated pepsin-free gastric juice (pH 1.2) (*source*: this work).

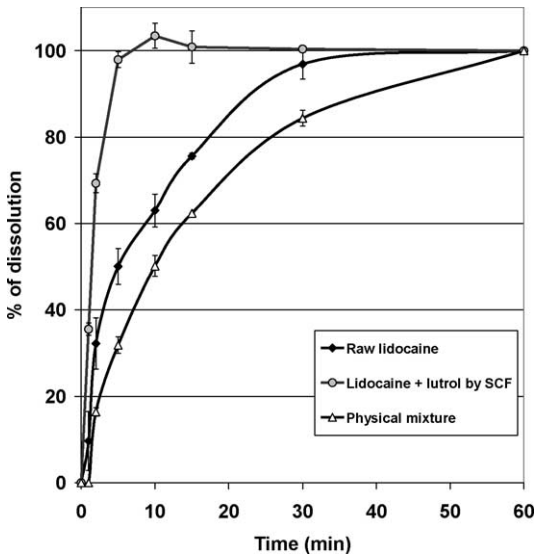

Fig. 3. Dissolution curves of lidocaine, Lutrol®/lidocaine(92:8, w/w) physical mixture and Lutrol®/lidocaine (92:8, w/w) composites in simulated pepsin-free gastric juice (pH 1.2) (*source*: this work).

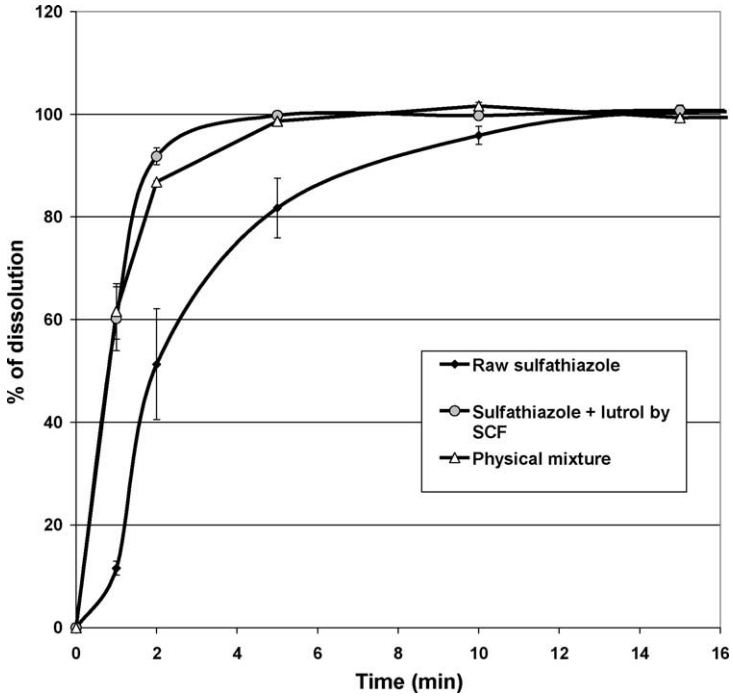

Fig. 4. Dissolution curves of sulfathiazole, Lutrol®/sulfathiazole (92:8, w/w) physical mixture and Lutrol®/sulfathiazole (92:8, w/w) composites in simulated pepsin-free gastric juice (pH 1.2) (*source*: this work).

ether as solvent of the mixture as done for nifedipine and lidocaine. In Fig. 4, no major differences can be seen between the SCF-processed composite Lutrol®/sulfathiazole (92/8, w/w) particles and the Lutrol®/sulfathiazole (92/8, w/w) physical mixture, which are completely dissolved after 5 min. The non-processed sulfathiazole dissolves 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.

3. Dissolution of SCF formulated CD-complex

- *Ibuprofen* micronization by RESS–CO_2 leads to unexpected results as stated in the preceding article (Perrut et al., 2005); but the authors (Cristini et al., 2003) 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* has been co-precipitated with γ-cyclodextrin using a supercritical anti-solvent technique, with DMSO as solvent and carbon dioxide as anti-solvent (Freiss et al., 2003; Lochard et al., 2003). The authors stressed 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 7 times more than the unprocessed 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 (Papet et al., 2003).
- *Naproxen*, known to have poor gastro-intestinal absorption characteristics, was co-precipitated with cyclodextrins by supercritical anti-solvent process, using ethanol, or DMSO–ethanol or DMSO–acetone

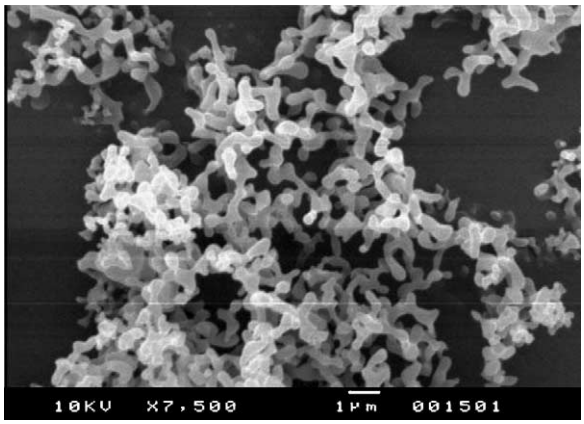

Fig. 5. Celecoxib/methyl-β-cyclodextrin complex particles (courtesy of SEPAREX).

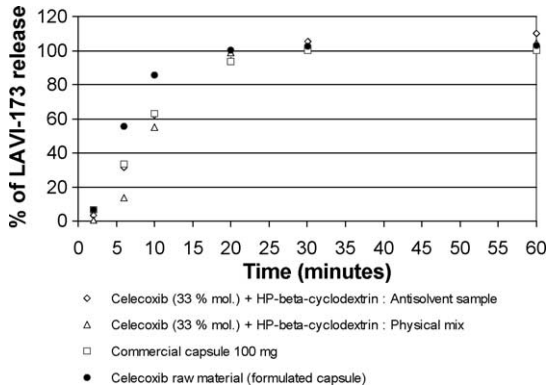

Fig. 6. Dissolution of formulated Celecoxib in a sodium phosphate buffer (pH 5) with 1% SLS (*source*: this work).

mixtures as solvent and carbon dioxide as anti-solvent (Foster et al., 2002). The resulting particles were mainly composed of the 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.

- At SEPAREX, *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 (Fabing et al., 2002), leading to a free-flowing powder consisting in agglomerates of very fine submicronic elementary particles (Fig. 5). This powder readily dissolves in pure water reaching 23–26 μg/ml after 15 min and 33–36 μg/ml after 30 min (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 always play the major role. As made with the native particles, this powder was formulated with commercially used excipients and dissolved in simulated intestinal juice (pH 5 with 1% wt. SLS). It is rather surprising to see that the CD-complex behaved exactly like the commercial formulation as shown on Fig. 6. Might it be the proof that the commercial formulation is perfectly adapted for the chosen dissolution medium, and that it is nearly impossible to do better?

4. Discussion

Composite particle generation by SCF processes looks to be a very promising approach to enhance the dissolution of poorly soluble compounds, although results may vary from one case to the other as shown by the brief review presented here. At present time, most works has been conducted with hydrophilic polymers and cyclodextrins leading to size-controlled particles that rapidly release the active compound in aqueous media.

Notwithstanding these promising results, it is certainly not wise to deduce 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 are performed in pure water instead of “representative” artificial media. Only animal or human tests can quantify the improvement, case-by-case.

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