Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 288 (2005) 3–10
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Commentary

Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes Part I: Micronization of neat particles

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

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

Received 9 March 2004; received in revised form 28 August 2004; accepted 5 September 2004
Available online 13 November 2004

Abstract

In this first of two articles, we discuss some issues surrounding the dissolution rate enhancement of poorly-soluble active ingredients micronized into nano-particles using several supercritical fluid particle design processes including rapid expansion of supercritical solutions (RESS), supercritical anti-solvent (SAS) and particles from gas-saturated solutions/suspensions (PGSS). Experimental results confirm that dissolution rates do not only depend on the surface area and particle size of the processed powder, but are greatly affected by other physico-chemical characteristics such as crystal morphology and wettability that may reduce the benefit of micronization.

Keywords: Particle design; Supercritical fluid; Dissolution enhancement; Micronization; Nanoparticles; Microspheres

1. Introduction

As a growing number of new active compounds exhibit a very low solubility in biological media, the pharmaceutical industry is facing a major challenge to find means to formulate such compounds in order to reach an "acceptable" bio-availability (Liu, 2000). More than one-third of the drugs listed in the US Pharmacopoeia are considered to be "poorly-soluble", and a recent study stated that 41% of failures in new drug development in seven UK-owned companies have been attributed to poor biopharmaceutical properties, including water insolubility (Prentis et al., 1999).

In fact, it has been shown that, for most orally administered poorly-soluble compounds, the bio-absorption process is rate-limited by dissolution in gastro-intestinal fluids; in the case of parenteral administration, the effective bio-availability of compounds is also limited by solubility issues (risk of precipitation at the injection point, slow dissolution in serum, . . .). Many

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

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.09.007

parameters related to solid morphology influence the dissolution rate of a compound, among which the particle size and the crystal habit and crystal pattern have a key-role.

Here we review literature and present some of our own results on the dissolution rate enhancement of poorly-soluble active ingredients by using supercritical fluid (SCF) processes (Jung and Perrut, 2001; Perrut, 2003a; Perrut and Clavier, 2003b) in order to micronize these compounds into neat nano-/micro-particles (Part I), or to formulate them by microencapsulation, cyclodextrin (CD) inclusion and impregnation (Part II, Perrut et al., 2005).

For the purpose of dissolution enhancement, several supercritical fluid particle design processes can be used, classified according to the four main basic concepts (see details in Jung and Perrut, 2001), with the possibility to micronize neat particles with the first two processes and to prepare composite particles by the all four:

- *Rapid expansion of supercritical solutions* (*RESS*): A solution of the compound(s) in a supercritical fluid is rapidly depressurised through a nozzle, causing a rapid nucleation of fine particles (neat or composite) (Jung and Perrut, 2001).
- *Supercritical anti-solvent* (*SAS*): A solution of the compound(s) in an organic solvent is contacted with a supercritical solvent that causes solid precipitation by anti-solvent effect, the organic solvent being eventually entrained by the supercritical fluid; either neat particles of a unique compound, or microspheres of an ingredient embedded in an excipient, or CD-complex particles may be generated (Jung and Perrut, 2001).
- *Particles from gas-saturated solutions* (*PGSS*): The compound(s) are melted in presence of a compressed gas that dissolves in the liquid phase which is pulverized towards a low-pressure vessel, leading to precipitation of solid particles of compound(s); when a suspension of fine particles of an ingredient dispersed in a liquid excipient is processed, composite microcapsules are generated (Jung and Perrut, 2001).
- *Impregnation*: The compound is dissolved in a supercritical fluid that is then depressurized into a vessel containing a porous excipient on which the compound is adsorbed. In another concept called concentrated powder formulation (CFP), applicable to liquid compounds, the liquid viscosity is decreased by saturation with high-pressure CO_2, and the liquid penetrates the carrier pores where it is adsorbed during the co-pulverization of the solid and liquid phases (Jung and Perrut, 2001).

We will not enter into the solubility theory and solubility prediction as the reader can find comprehensive accounts in Liu (2000) but here we simply recall some fundamental aspects.

2. Fundamentals (Liu, 2000)

Applying the Fick's law, it is easy to demonstrate that the mass transfer rate of a particulate solid of mass M (composed of particles with an average volume V_p) into a liquid of volume V_L is proportional to the solid surface S:

$$\frac{\delta m}{\delta t} = -hS(C_S - C_b) \tag{1}$$

where h is the mass transfer coefficient (generally estimated by $h = D/e$ where D is the diffusion coefficient of the compound in the liquid and e is the thickness of the diffusion layer), C_S the solid solubility and C_b is the solute bulk concentration. This leads to the Noyes–Whitney equation giving the dissolution rate R (defined as the concentration change $R = \delta M/\delta t/V_L$):

$$R = DS\frac{C_S - C_b}{eV_L} \tag{2}$$

Supposing that C_b remains very small in comparison with the saturation solubility C_S, and as the solid surface area S_p is the proportional to $V_p^{2/3}$, Eq. (1), into:

$$M^{1/3}(0) - M^{1/3}(t) = Kt \tag{3}$$

known as the Hixson–Crowell cube root law.

On the contrary, when the initial amount of solid approaches the amount needed for reaching a saturated solution, the following equation is obtained, known as the negative two-thirds law:

$$M^{-2/3}(t) - M^{-2/3}(0) = K't \tag{4}$$

Eqs. (3) and (4) can be expressed in the case of spherical mono-dispersed particles, showing the dependence of the dissolution rate with the particle diameter. But,

as powders are never mono-disperse and rarely spherical, this is of little help. The knowledge of the particle size distribution may also mislead: a powder sample with a small mean diameter and large size distribution may have a deceptively low dissolution rate due to the presence of large particles at the end of the distribution. It is always better to consider the specific area *a* rather than the particle size, the more so because the particle size information may hide particle re-agglomeration that considerably reduces the specific area.

Moreover, it is to be noted that the solubility C_S of solid particles also depends on the particle size, increasing for colloidal suspensions. Particles with diameter below 1 μm possess significantly greater solubility than larger ones (Higuchi, 1985); this difference may be attributed to a greater specific surface area and higher surface free energy for fine particles in comparison with their larger counterparts. It was widely observed that very fine particles have a tendency to dissolve and recrystallize onto larger ones, producing a shift in particle size distribution until an equilibrium solubility is reached ("Ostwald ripening").

3. Experimental issues

It must be emphasized that solid dissolution is a complex operation influenced by a great number of factors, not only the particle size. This can be illustrated in Fig. 1 (Crison, 2000) showing the dissolution curves of a poorly soluble compound as bulk or micronized, compared with the theoretical curve of the micronized form, according to the Hixson–Crowell cube-root equation (Eq. (3)). Further observations using a light microscope showed a high degree of re-agglomeration of the micronized particles.

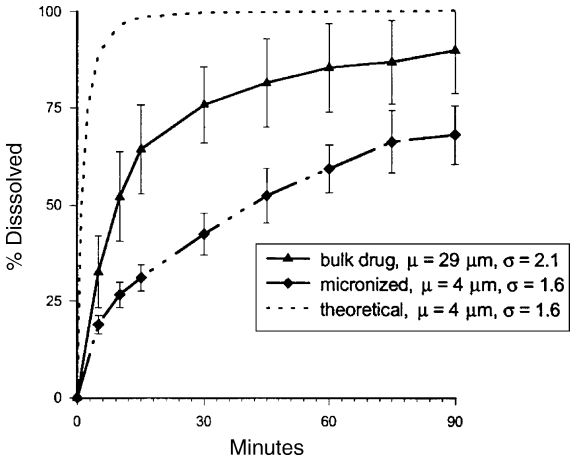

Fig. 1. Dissolution curves of a poorly-soluble compound (Crison, 2000).

As a matter of fact, micronization—whatever the process—may alter the solid morphology to a greater or lesser extent. This is of major importance when the solid exhibits polymorphism and when an amorphous phase is formed, creating unexpected behavior and/or unstable properties. On the other hand, the particle or particle aggregate tends to adsorb air and becomes extremely difficult to disperse into an aqueous media. The micronized powder then is not wetted by the liquid, floating on the surface instead of dispersing in the liquid bulk, except when a surface-active agent is present in the medium.

So, experimental dissolution curves are often altered by artefacts or lead to unreliable results when a robust method of particle processing and dissolution evaluation is not utilized. Of course, subsequent formulation may also dramatically affect the dissolution rate that is then very different from what is observed with the non-formulated particles.

4. Dissolution rate of SCF-micronized particles

Among the hundreds of articles dealing with SCF particle design (Jung and Perrut, 2001; Perrut, 2003a; Perrut and Clavier, 2003b), it is rather surprising that very few disclose results on the difference in dissolution rate between unprocessed material and SCF micronized solid, as detailed below. Moreover, in many publications, data are not complete and the physical properties of the solid material are lacking. We have experienced difficulties in obtaining such comparisons, but some of our own micronization results are presented below among literature results.

4.1. RESS process

- *Phenacetin* was micronized by RESS with CO_2 and CHF_3 as solvents, and the samples compared with the milled material (Loth and Hemgesberg, 1986). 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 free-flow aid agent (Aerosil R 972) and yet much more when mixed with mannitol (1:1).

- *Nifedipine* 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 (Gerard and Quirin, 1986): the micronized compound was released faster (50% in 38 and 54 min, respectively) but not as much as expected from the particle size difference. Again this is likely to be due to re-agglomeration and poor wettability of the micronized particles.
- *Griseofulvin* particles were prepared by RESS-CO_2 (Martin et al., 2000; Turk et al., 2002). 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 (Eq. (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 a hydrophobic compound known for its poor absorption from the gastro-intestinal tract.
- *Lidocaine* was micronized using RESS-CO_2 (Frank and Ye, 2000), leading to spherical nanoparticles (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 1 h, 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* is generally found as racemic. As it exhibits a significant solubility in supercritical carbon dioxide, several authors have reported micronization by RESS. Among these, Charoenchaitrakool et al. (2000) and Foster et al. (2003) 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 Foster et al. (2003), was five times higher for RESS-processed material than the original material (size ∼250 μm); as they observed re-agglomeration of the micronized particles, this 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 more than in surfactant-free medium), due to an improvement in the wettability of the solid; 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 in other studies of the RESS-CO_2 process (Cristini et al., 2003). 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 sample (1–3 μm), leading the authors to incorporate the micronized drug into excipient as described in part II (Perrut et al., 2005).
- *Phytosterol* was micronized by RESS-CO_2 (Jiang et al., 2003), 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.

Separex used the RESS process to prepare microparticles and compared the dissolution rate of processed and unprocessed particles.

- We micronized *Nifedipine* by RESS using dimethyl ether as solvent and obtained microparticles that did not exhibit an improved dissolution rate in simulated pepsin-free gastric juice (pH 1.2) as shown in Fig. 2.
- *Lovastatin*, available as coarse crystals shown in Fig. 3, was micronized by RESS-CO_2 with a wide range of process parameters. Particle characterization was operated by SEM and the dissolution rate

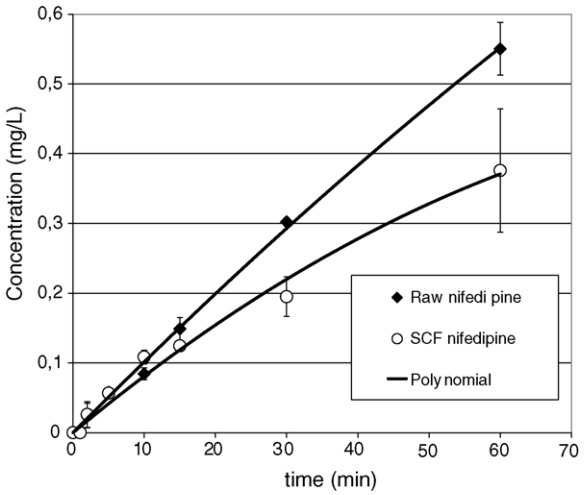

Fig. 2. Dissolution curves of nifedipine in simulated pepsin-free gastric juice (pH 1.2) (Courtesy of SEPAREX).

into pure water was measured at room temperature. Agglomerates (5–20 μm) of very fine particles (<1 μm) were obtained as shown in a few examples (Fig. 4). In most cases, higher dissolution rates were found. However, the size reduction also induced drastic electrostatic phenomena and particle wetting became problematic, leading to non-reproducible dissolution rates. Comparison of the SEM pictures and dissolution curves (some are presented in Fig. 5) is rather surprising as the fastest dissolution rates correspond to samples that look "unsatisfactory" in terms of particle size (samples 4 and 6) while material appearing "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.

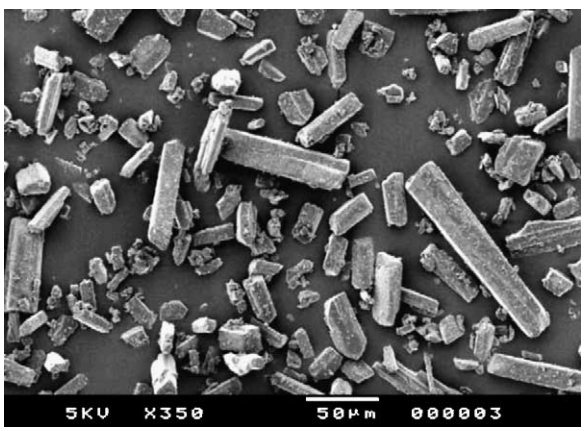

Fig. 3. Lovastatin unprocessed material (bar = 50 μm) (Courtesy of SEPAREX).

- *Celecoxib* and *Rofecoxib* particles (Fig. 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 (Perrut et al., 2002). 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 more slowly into simulated intestinal juice (pH 5 with 1% SLS) than the original crystalline material which behaves exactly like the commercial formulation—probably due to poor wetting and difficult penetration of the aqueous medium inside the micro-particles agglomerates.

4.2. Anti-solvent process

- *Carbamazepine* has been micronized by supercritical anti-solvent process, using acetone as solvent and carbon dioxide as anti-solvent (Kikic et al., 2000, 2002). Ninety percent dissolution of the drug in pure water was obtained in ∼15 min for the SCF-processed powder, while ∼140 min were required for the unprocessed material. Unfortunately, no details on the solid morphology and particle size were disclosed by the authors.
- *Mefenamic acid* has been precipitated from solutions in methanol, ethanol and acetone by pulverization into supercritical CO_2 (anti-solvent), leading to 10–50 μm platelets (Foster et al., 2000). 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* being insoluble in CO_2 was precipitated from a dimethylformamide solution by supercritical CO_2 anti-solvent: work by Warwick et al. (2002) and Foster et al. (2003). The resulting

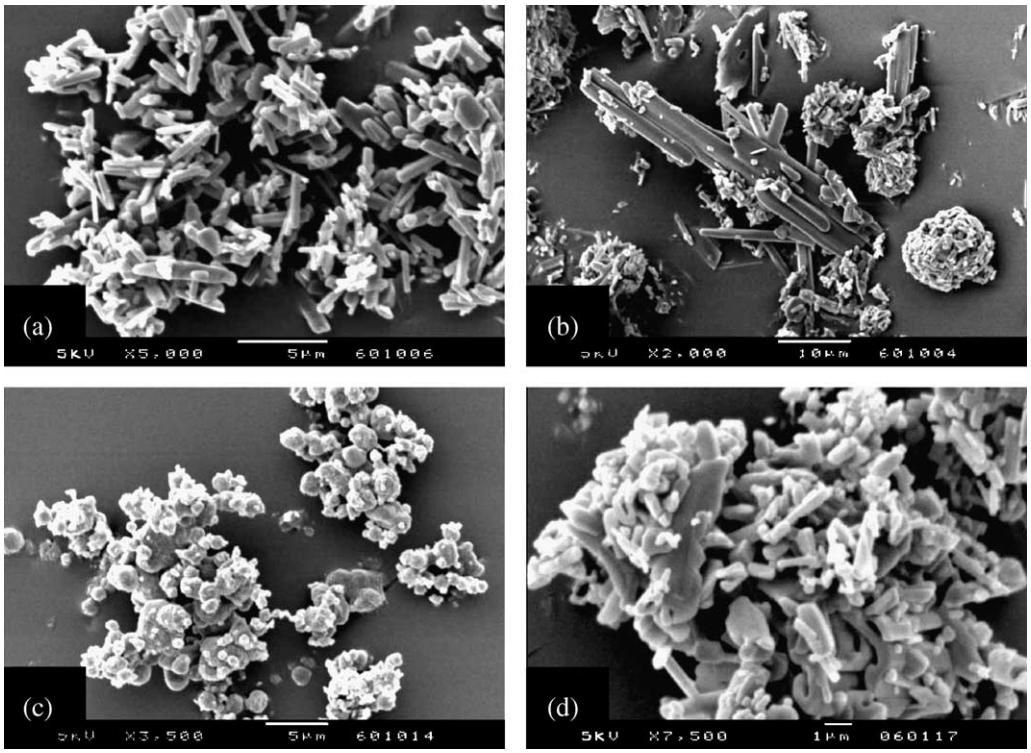

Fig. 4. SEM pictures of RESS-CO_2 processed Lovastatin (Courtesy of SEPAREX). (a) Sample 4 (bar = 10 μm); (b) sample 6 (bar = 5 μm); (c) sample 8 (bar = 5 μm); (d) sample 10 (bar = 1 μm).

microparticles were spherical with 90% of the particles with diameters below 10 μm, adequate to be used as suspensions for injections or for ophthalmic applications. Micronization was demonstrated to lead to an eight-fold increase in dissolution rate in water compared with the original form of the compound.

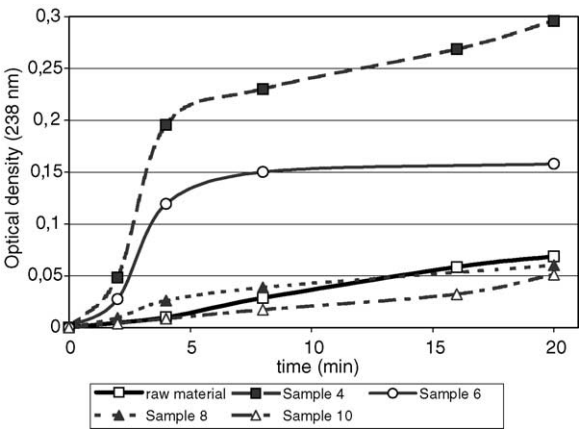

Fig. 5. RESS-CO_2 lovastatin dissolution curves (Courtesy of SEPAREX).

4.3. The PGSS process

- *Nifedipine* has also been processed by PGSS-CO_2 (atomization of the melted compound saturated in high-pressure gas) (Weidner et al., 1994; Knez, 2000). 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 15–60 min (Weidner et al., 1994) up to seven times at 60 min (Knez, 2000).
- *Felodipine* has been processed by PGSS-CO_2 similarly to nifedipine (Knez, 2000). 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

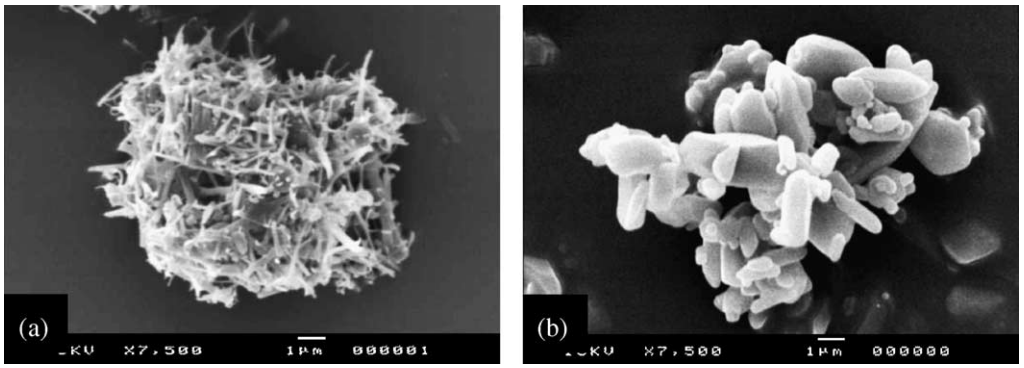

Fig. 6. Celecoxib particles by RESS-dimethyl ether (a) and Rofecoxib particles by RESS-carbon dioxide (b). Bars = 1 μm (Courtesy of SEPAREX).

0.33 m^2/g area. However, both the unprocessed and micronized particles exhibit similar very low dissolution rates in pure water of 0.26 and 0.29 mg/l after 1 h, once again due to the very low wettability of the compound.

5. Discussion

From the results cited in this publication on 13 active compounds by a variety of researchers, we would conclude:

a. Although the accepted theory tends to predict a rate quasi-proportional to the specific surface area *a*, micronisation alone cannot guarantee a significant enhancement of dissolution rate or bio-availability of hydrophobic drugs.
b. Many other factors play a major role in the dissolution phenomenon among which the most important one is *wettability*; addition of a surfactant in the excipient mixture is of prime importance.

We would conclude that this does not mean that SCF-micronization is not valuable; on the contrary, we would emphasize that an optimized formulation does permit us to take advantage of the resulting specific surface area increase. On the other hand, SCF processes can be used to generate composite particles with attractive dissolution properties, as discussed in Part II (Perrut et al., 2005).

Acknowledgements

The authors are grateful to Professor Jacques Fages (Ecole des mines d'Albi-Carmaux, France) for valuable discussions and for reviewing this article.

References

Charoenchaitrakool, M., Dehghani, F., Foster, N.R., Chan, H.K., 2000. Micronization by RESS to enhance the dissolution rates of poorly water soluble pharmaceuticals. In: Eckert, C., Teja, A. (Eds.), Proceedings (CD-ROM) of the Fifth International Symposium on Supercritical Fluids.

Crison, J.R., 2000. Biopharmaceutical aspects of water-insoluble drugs for oral delivery. In: Liu, R. (Ed.), Water-Insoluble Drug Formulation. Interpharm Press, Denver, pp. 97–110.

Cristini, F., Delalonde, M., Joussot-Dubien, C., Bataille, B., 2003. Elaboration of ibuprofen microcomposites in supercritical CO_2. In: Brunner, G., Kikic, I., Perrut, M. (Eds.), Proceedings of the Sixth International Symposium on Supercritical Fluid, pp. 1917–1922.

Foster, N.R., Bezanehtak, K., Charoenchaitrakool, M., Combes, G., Dehghani, F., Sze Tu, L., Thiering, R., Warwick, B., Butsami, R., Chan, H.K., (2000), Processing pharmaceuticals using dense gas technology. In: Eckert, C., Teja, A. (Eds.), Proceedings (CD-ROM) of the Fifth International Symposium on Supercritical Fluids.

Foster, N.R., Dehghani, F., Charoenchaitrakool, M., Warwick, B., 2003. Application of dense gas techniques for the production of fine particles. AAPS Pharm. Sci. 5, 105–111.

Frank, S.G., Ye, C., 2000. Small particle formation and dissolution rate enhancement of relatively insoluble drugs using rapid expansion of supercritical solutions (RESS) processing. In: Eckert, C., Teja, A. (Eds.), Proceedings (CD-ROM) of the Fifth International Symposium on Supercritical Fluids.

Gerard, D., Quirin, K.W., 1986. In: Stalh, E., Quirin, K.W., Gerard, D. (Eds.), Dense Gases Extraction and Refining. Springer-Verlag, Berlin, pp. 226–227.

Higuchi, T., 1985. Remington's Pharmaceutical Sciences, 17th ed. Mack Publishing Company, Easton, Pennsylvania.

Jiang, S.Y., Chen, M., Zhao, Y.P., 2003. A study on micronization of phytosterol by the RESS technique with supercritical CO_2. In: Brunner, G., Kikic, I., Perrut, M. (Eds.), Proceedings of the Sixth International Symposium on Supercritical Fluid, pp. 653–1658.

Jung, J., Perrut, M., 2001. Particle design using supercritical fluids: literature and patent survey. J. Supercrit. Fluids 20, 179–219.

Kikic, I., Moneghini, M., Perissutti, B., Voinovich, D., 2000. Improvement of carbamazepine dissolution characteristics using supercritical carbon dioxide. In: Perrut, M., Reverchon, E. (Eds.), Proceedings of the Seventh Meeting on Supercritical Fluids. Tome, vol. 1, pp. 95–100.

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

Knez, Z., 2000. Micronization of pharmaceuticals using supercritical fluids. In: Perrut, M., Reverchon, E. (Eds.), Proceedings of the Seventh Meeting on Supercritical Fluids. Tome, vol. 1, pp. 1–26.

Liu, R., 2000. Water-Insoluble Drug Formulation. Interpharm Press, Denver.

Loth, H., Hemgesberg, E., 1986. Properties and dissolution of drugs micronized by crystallization from supercritical gases. Int. J. Pharm. 32, 265.

Martin, H.J., Schmidt, P.C., Wahl, M.A., Hils, P., Helfgen, B., Turk, M., Schaber, K., 2000. Nanoscale particles for pharmaceutical purpose by rapid expansion of supercritical solutions (RESS). Part II: Characterization of the product and use. In: Perrut, M., Reverchon, E. (Eds.), Proceedings of the Seventh Meeting on Supercritical Fluids. Tome, vol. 1, pp. 53–57.

Perrut, M., Jung, J., Leboeuf, F., (2002). Solid state morphology of particles prepared by a supercritical fluid process. In: Venice, Bertucco, A. (Eds.), Proceedings of the Fourth International Symposium on High Pressure Process Technology and Chemical Engineering, pp. 711–716.

Perrut, M., 2003a. Supercritical fluids applications in the pharmaceutical industry. STP Pharm. Sci. 13, 83–91.

Perrut, M., Clavier, J.Y., 2003b. Supercritical fluid formulation: process choice and scale-up. Ind. Eng. Chem. Res. 42, 6375–6383.

Perrut, M., Jung, J., Leboeuf, F., 2005. Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes. Part II: Preparation of composite particles. Int. J. Pharm, 288, 11–16.

Prentis, R.A., Lis, Y., Walker, S.R., 1999. Pharmaceutical innovations in the seven UK-owned pharmaceutical companies (1964–1985). Br. J. Clin. Pharmacol. 25, 387–396.

Turk, M., Hils, P., Helfgen, B., Schaber, K., Martin, H.J., Wahl, M.A., 2002. Micronization of pharmaceutical substances by rapid expansion of supercritical solutions (RESS): a promising method to improve bio-availability of poorly soluble pharmaceutical agents. J. Supercrit. Fluids 22, 75–84.

Warwick, B., Dehghani, F., Foster, N.R., Biffin, J.R., Regtop, H.L., 2002. Micronization of copper–indomethacin using gas antisolvent processes. Ind. Eng. Chem. Res. 41, 1993–2004.

Weidner, E., Knez, Z., Novak, Z., 1994. PGSS—a new process for powder generation. In: Brunner, G., Perrut, M. (Eds.), Proceedings of the Third International Symposium on Supercritical Fluids. Tome, vol. 3, pp. 229–234.