CONTRIBUTIONS to SCIENCE, **3** (1): 11–18 (2005)
Institut d'Estudis Catalans, Barcelona

New technologies for the preparation of micro- and nanostructured materials with potential applications in drug delivery and clinical diagnostics

N. Ventosa*, J. Veciana*, S. Sala, M. Muntó, M. Cano and M. Gimeno

Departament de Nanociència Molecular i Materials Orgànics, Institut de Ciència de Materials de Barcelona, CSIC.

Resum

L'obtenció de nous materials micro– i nanoestructurats, i la possibilitat de manipular materials ja existents a escala nanoscòpica, tenen un paper crucial en els avenços assolits durant els darrers anys dins del món farmacèutic i de la diagnosi clínica. Dins d'aquest context s'ha observat que els progressos en la preparació de materials amb propietats excepcionals derivades de la seva estructura nanoscòpica, com ara les nanoesferes, les nanosuspensions, els materials compostos nanoparticulats, etc., poden contribuir molt significativament a reduir la toxicitat de fàrmacs i agents de contrast, augmentar-ne l'absorció i fer més eficient el perfil de lliurament del principi actiu. Ara bé, per a poder explotar comercialment l'enorme potencial de les nanomedicines és necessari dissenyar i desenvolupar tecnologies eficients i respectuoses amb el medi ambient, que permetin obtenir, a escala industrial, aquests materials farmacèutics micro– i nanoestructurats.

En aquesta revisió, pretenem donar a conèixer diferents mètodes de precipitació, recentment desenvolupats, els quals permeten obtenir directament materials micro– i nanoparticulats. En aquests procediments, en lloc de dissolvents orgànics nocius per a les persones i el medi ambient, s'empren fluids comprimits com a medi dissolvent, els quals estan considerats dissolvents verds. A més a més, aquests mètodes de preparació permeten l'obtenció de materials amb una estructura interna (polimorfisme, porositat, etc.) que no és possible d'assolir mitjançant procediments de preparació realitzats en dissolvents líquids convencionals.

Paraules clau: Fluids comprimits, materials farmacèutics, materials nanoestructurats, alliberament controlat de fàrmacs, agents de contrast.

Abstract

Obtaining new micro– and nanostructured molecular materials, and understanding how to manipulate existing materials at the nanoscopic level, is crucial to the development of drug delivery and clinical diagnostics. Advances in the preparation of materials characterised by exceptional properties attributable to their nanoscopic structure, such as nanosuspensions, nanospheres, nanoparticulate composites, etc., can significantly contribute to reducing the toxicity of drugs and contrast agents, increase their absorption, and improve their release profile. However, in order to be able to exploit the enormous potential of these nanomedicines, it is necessary to develop efficient and environmentally respectful technologies for its manufacture at an industrial scale. In this review, we endeavour to present various recent eco-efficient precipitation procedures, which have been proved to be effective for the straightforward preparation of micro– and nanoparticulate materials. In these procedures, instead of hazardous organic solvents, «green» compressed fluids are used as solvent media, which allow the preparation of materials with physico-chemical characteristics unachievable by conventional procedures performed in conventional liquid media.

Keywords: Compressed fluids, pharmaceutical materials, nano-structured materials, drug-delivery, contrast agents.

* Authors for correspondence: Nora Ventosa and Jaume Veciana. Departament de Nanociència Molecular i Materials Orgànics, Institut de Ciència de Materials de Barcelona (CSIC). Universitat Autònoma de Barcelona. 08193 Bellaterra, Catalonia, EU. Tel. 34 935801853. Fax: 34 935805729. Email: ventosa@icmab.es; vecianaj@icmab.es

From an esthetical perspective, it is attractive to build all desirable pharmacological features of a drug or a diagnostic agent - such as solubility, permeability to biological membranes, and targeting towards particular tissues, cells, and intramolecular compartments – into the drug or the diagnostic agent molecule itself. However, it is simpler and perhaps more powerful to obtain these features by decoupling the biological action from the other biochemical and physicochemical characteristics that determine such key features of their pharmacology [1]. Following this strategy, during the past two decades, it has been observed that advances in the preparation of materials characterised by exceptional properties attributable to their nanoscopic structure, can significantly contribute to the development of new drug delivery routes, of more selective and efficient disease-detection systems, and to the preparation of pharmaceuticals with a higher permeability to biological membranes, with controlled release profiles and with enhanced targeting towards particular tissues or cells, combining diagnostic and therapeutic actions for instantaneous administration of therapy [2, 3].

For example, a surprisingly large proportion of new drug candidates emerging from drug discovery programmes are water insoluble, and therefore have poor bioavailability, which often leads to development being abandoned. These so-called «brick-dust» candidates can now be rescued by formulating them into crystalline nanosuspensions [4]. Nanosuspensions overcome delivery issues by obviating the need to be dissolved, and maintaining the drug in the preferred crystalline state, at a size small enough for pharmaceutical acceptability. In addition to overcoming issues of solubility, nanosuspensions have shown additional benefits. For example, nanosuspensions enable a higher mass per volume loading in comparison to solutions, allowing reduced administration volumes, which is crucial for low-volume intramuscular and ophthalmic applications [5]. On the other hand, the particulate nature of the dosage form might offer alternative pharmacokinetic profiles; both in intravenous delivery, where one might expect lower toxicity and more efficacious regimens, and in oral delivery, where we might find potential for first-pass hepatic metabolism.

Similarly, the use of nanoparticles (particles with dimensions in the range of 10nm to a few hundred nanometers), is gaining momentum in drug delivery and diagnostic imaging. Emulsions and liposomes are perhaps better-known particulate carriers with comparatively long histories of research. Recently, various other types of nanoparticles have been investigated in the search for alternative carriers. Most of those carriers accumulate to the target site during continuous systemic circulation, delivering the drug substance thereon: so-called «passive targeting», the behaviour of which depends highly upon physicochemical characteristics. However, much effort has been made to achieve «active targeting», delivering drugs more actively to the target site by utilizing specific physical forces such as magnetic attraction or biochemical interactions (such as receptor-ligands or antigen-antibody interactions). The application of micro– and nanoscale polymer particles and spheres in therapeutic systems has been well documented, and various systems have been designed for intelligent modulated delivery [6,7,8]. The incorporation of therapeutic and diagnostic pharmaceuticals to these nanoparticulate carriers might lead to advantages such as increased water solubility of sparingly soluble agents, enhanced permeability across physiological barriers, substantial changes in drug distribution, increased bioavailability and reduction of adverse side effects. For example, self assembled core/shell spherical aggregates of block copolymers recently emerged as a possible alternative to liposomes as carriers of drugs and diagnostic agents (Figure 1).

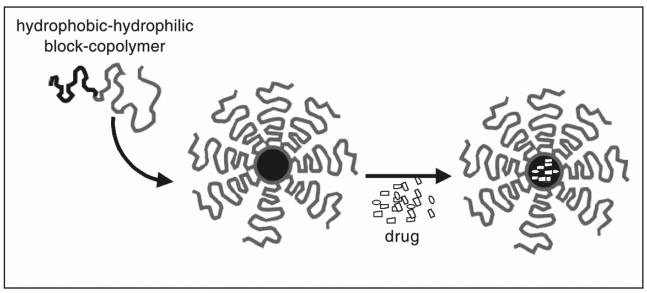

Figure 1. Individual block-copolymers can self-assemble into nanoparticles with a hydrophobic core and hydrophilic corona. The drug is selectively loaded into the core, and the corona protects it until its delivery.

Davis and Illum have conducted extensive investigations on biodegradable nanospheres with polylactides and poly(lactide-co-glycolide) as carriers for achieving the efficient delivery of drugs and diagnostic agents to the lymphatic system. To enhance lymphatic drainage and lymphatic node uptake of nanospheres, various surface engineering methods have been tried, including surface coating with poloxamides or poloxamers [9] and the use of polyethylenglycols [10]. Besides the drug delivery purpose, magnetite-dextran nanoparticles have been investigated for diagnostic use and found potentially useful as contrast agents in magnetic resonance imaging [11]. Wang and co. have reported a new strategy for amplifying electrical DNA sensing based on the use of microsphere tags loaded internally with a «redox marker». Such electroactive beads offer great potential for multitarget detection (in connection to spheres loaded with different redox markers) and for enhancing the sensitivity of other bioassays [12].

However in order to be able to commercially exploit the enormous potential of nanomedicines such as the ones described above, it is necessary the development of efficient technologies for the manufacture of these contaminant-free nanostructured materials, at an industrial scale, in an environmentally responsible manner. Presently, the different methods for the preparation of nanoparticulate materials can be divided into two main categories: «top-down» strategies where the raw material is subsequently broken down using physical methods (i.e. dry or wet milling) until nanoscopic dimensions are reached; and «bottom-up» approaches where nanomaterials are built from their constituent units (polymers, macromolecules, molecules, atoms) by synthetic or self-assembly procedures.

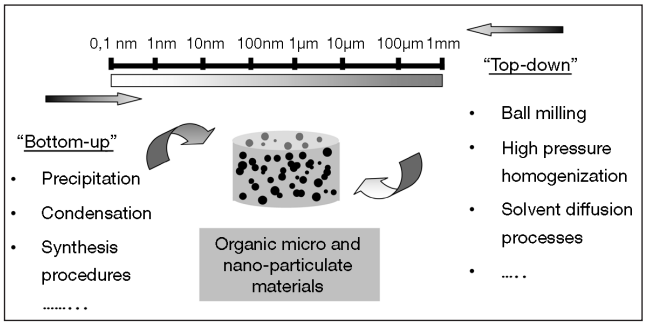

Figure 2. Schematic representation of different preparation strategies to obtain nanoparticulate materials.

The potential of «bottom-up» strategies for material engineering is much larger than that of «top-down» approaches. As Feynman put it, very simply, *«What would the properties of materials be if we could arrange the atoms and molecules the way we want them?»* [13]. Such a dream, up till now, remains unfulfilled in general, at least in terms of molecular self-assembly in the crystalline state. Through «bottom-up» technologies it should be possible to design and control particle size and size distribution, morphology and the internal structure of the final nanoparticulate material, whereas using «top-down» procedures we can only control the final particle size, whilst the internal structure of the raw material cannot be modified, and it is very difficult to govern the particle morphology.

In any «bottom-up» process involving precipitation from solution, particle size, particle size distribution, morphology, and internal structure (polymorphs, solvates, etc.) are strongly dependent on the evolution during the precipitation process of the supersaturation rate (β), which drives nucleation rate and crystal growth, at each point in the solution [14]. For instance, in those precipitation processes where large levels of supersaturation are attained rapidly (trace A of Figure 3), and where there is a high homogeneity of this supersaturation profile throughout the bulk solution, nucleation phenomena will dominate crystal growth, and very small and essentially monodisperse particles will be produced. On the contrary, in those precipitation processes with a β profile more comparable to trace B of Figure 3, the solute in solution is depleted by both nucleation and crystal growth mechanisms resulting in large crystals being formed, with a broad particle size distribution.

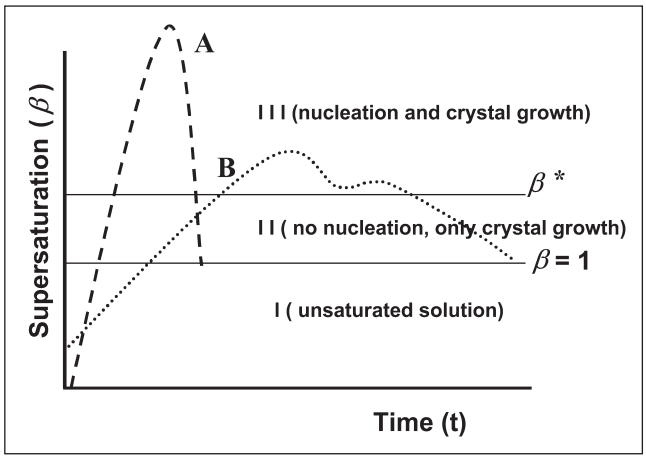

Figure 3. Trace A: qualitative supersaturation profile corresponding to a crystallization process where nucleation phenomena are dominant over crystal growth. Trace B: qualitative supersaturation profile corresponding to a crystallization process where crystal growth is dominant over nucleation.

Again different are those precipitation processes occurring far from equilibrium conditions, where large β values are attained over short periods of time –allowing the preparation of internal structures favoured by kinetic factors rather than thermodynamic ones. In contrast, in those precipitation processes which take place near equilibrium conditions, thermodynamically stable internal structures are more likely.

In processes involving precipitation from conventional liquid solvents, supersaturation is generally triggered by temperature or system composition changes (e.g. solvent evaporation, addition of anti-solvents, addition of salts). By using such solvent-based precipitation processes, it is very difficult to straightforward produce micro– and nanoparticulate materials, since temperature and composition variations are only slowly transmitted in liquid media, and efficient and expensive stirring systems are required in order to achieve large values of β homogeneously. Thus, additional downstream operations, such as milling and sieving, are required to achieve the desired particle size.

In contrast with liquid solvents, the solvent power of compressed fluids (CFs), either in the liquid or supercritical state, can be tuned by pressure changes, which propagate much more quickly than temperature and composition solvent changes. Therefore, using compressed solvent media, it is often possible to synthesize materials with unique physicochemical characteristics (size, porosity, polymorphic nature, morphology, etc.) unachievable with classical liquid media [15, 16]. CFs are substances that exist as a single phase, and offer several advantages over both liquids and gases. CFs often have liquid-like densities and, hence, solvating characteristics that are similar to those of liquids, but mass transfer properties that are more similar to those of gases. Small changes in temperature and pressure result in large changes in the fluid's density, and hence, its solvent power. This tuneable range in density (solvation ability) cannot be achieved so easily with any conventional solvent. The most widely used CF is compressed CO_2 (cCO_2), which is non-toxic, non-flammable, cheap and easy recyclable. It has gained considerable attention, during the past few years as a «green substitute» to organic solvents and even water in industrial processing. During the past two decades, «bottom-up» approaches using cCO_2 as a solvent medium have attracted scientific and technological interest for the preparation of nanostructured materials (particles, fibres, templates, porous materials, etc.) [17] . The use of cCO_2 as a solvent medium for fine particle formation is an active research field, in which considerable technological development is expected [18]. In these «green» precipitation processes with cCO_2, much larger and more abrupt changes of β can be achieved than with conventional solvents. As a consequence, micro– and nanoparticulate materials with a narrow size distribution, unachievable through conventional processes, can be prepared without problem. Further, it is often possible to prepare, at a large scale, materials with a specific internal structure

(polymorph, nanostructured composite material, porosity, degree of crystallinity, etc.) unachievable by traditional methods. Moreover, in these procedures, precipitation occurs in a non-oxidising atmosphere, and without the need for the application of high shear forces. Hence, these procedures are particularly suited to the processing of thermally, chemically or physically unstable materials, such as biological compounds, chemical intermediates and pharmaceuticals.

Precipitation technologies using cCO_2 hold a great deal of promise in the pharmaceutical industry, which is currently facing the challenge of drug formulation involving active ingredients or diagnostic agents with low solubilities, high toxicities, low stabilities, and short in vivo half-lives. Some potential applications of these new particle engineering methodologies in the pharmaceutical industry include:

– Generation of micro– and nanosized drug particles to enhance dissolution and therefore bioavailability of sparingly water-soluble or insoluble drugs.
– Encapsulation of proteins, peptides, vaccines and toxic diagnostic agents.
– Targeted delivery of biological or diagnostic agents.
– Parenteral formulations (e.g. injectable) applications.
– Metered dose and dry powder inhaler applications.

There are various precipitation processes involving compressed CO_2, leading to different particles in terms of size, shape, and morphology, and offering various possible solutions to the different problems faced, and allowing the preparation of various forms or formulations of any given drug or diagnostic agent [19,20]: dry inhalable powder, nanoparticle suspension, microspheres or microcapsules of the drug embedded in a carrier, drug-impregnated excipient or matrix, etc. As summarized in Table 1, these precipitation processes can be classified in three different groups according to the solvating behavior of the CO_2 in the process: as a solvent, as an anti-solvent, or as a co-solvent. Next, we briefly describe the most significant methodologies of these three categories, their advantages and limitations.

Rapid expansion of supercritical solutions (RESS) – CO_2 as a solvent

The RESS process involves the dissolution of the solute to precipitate in cCO_2, generally under supercritical conditions, followed by the rapid expansion of the resulting solution to atmospheric pressure through a nozzle. During the expansion, the density and the solvent power of the cCO_2 decreases dramatically, resulting in a high degree of solute supersaturation (see trace A in Figure 3) and subsequent precipitation of solute particles free of residual solvents. As can be inferred from the SEM images of naproxen in Figure 4, the RESS procedure has found success in the preparation of micro– and nanosized drug actives and drug carriers such as, naproxen [21], carbamazepine [22], griseofulvin [23], phytosterol [24], ibuprofen [21], nifedipine [25] or poly(L-lactic acid) (L-PLA) [26].

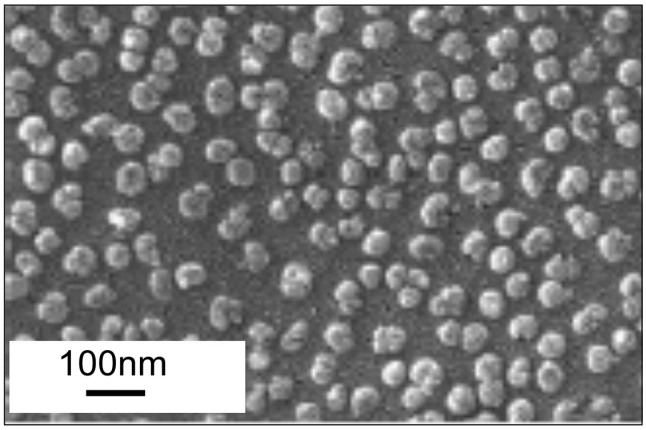

Figure 4. RESS processed naproxen nanoparticles (from ref. [21])

The particle shape, size distribution, and crystalline pattern of the final materials can be tuned by playing on the process parameters (atomization pressure and temperature, and fluid velocity through the nozzle) and equipment design (nozzle type and dimensions, and atomization chamber dimensions). Nanostructured microspheres of drug or contrast agent embedded in an excipient for controlled-release delivery can be prepared, on the condition that both the active substance and the carrier are soluble in cCO_2. For example, Kim et al. have used the RESS method to coprecipitate poly(l-lactic acid) (L-PLA), as drug-carrier, with the antiinflamatory naproxen [27]. Although RESS is a simple and effective method to produce micro– and nanoparticulate materials, with a relatively narrow particle size distribution, the major limitation of this process is the low solubility of many materials (e.g. polymers, polar molecules) in pure cCO_2. A large amount of fluid is needed to produce a small yield. Frequently, RESS is therefore a comparatively costly technique.

Gas Antisolvent (GAS) – CO_2 as an anti-solvent

Whereas the low solubility in cCO_2 of a large number of therapeutics and contrast agents for diagnosis has a negative impact on the large-scale production of micronized particles using the RESS technique, it can be turned into an advantage

Table 1. Major «bottom-up» precipitation procedures using compressed CO_2 in order to obtain micro– and nano-particulate pharmaceutical materials.

	CO2 solvation behavior	*Processable material*	*Material/CO_2 ratio*	*Working pressures*	*Stirring requirements*	*Scale up*	*Use of organic solvents*
RESS	Solvent	Apolar	Very low	> 20MPa	No	Difficult	No
GAS	Anti-solvent	Apolar/polar	High	5–10MPa	Yes	Favourable	Yes
ASES	Anti-solvent	Apolar/polar	Low	6–30MPa	No	Difficults	Yes
DELOS	Co-solvent	Apolar/polar	High	5–10MPa	No	Favourable	Yes

when cCO_2 is used as an antisolvent. The ability of CFs, such as cCO_2, to dissolve and expand organic solvents, thus lowering their solvent power, allows the use of cCO_2 for the precipitation of micro– and nanosized pharmaceutics from organic solutions. Compressed fluids are characterized by densities intermediate to gases and liquids. As well as this, CFs have a negligible surface tension between the liquid and vapour phases close to the critical point, and allow solutes to exhibit relatively high diffusivities (with respect to the solvent density). These physical properties in combination allow for the generation of extremely small uniform particulate materials due to the unusually high supersaturation concentrations that can be induced. The favourable transport properties of CFs, and the existence of a homogeneous phase in situ, allow for the rapid removal of trace amounts of organic solvent. The Gas Antisolvent (GAS) [28] process and the Aerosol Solvent Extraction System (ASES) [29,30] are two different high pressure crystallization techniques where the CO_2 behaves as an anti-solvent. In the GAS process, shown schematically in Figure 5 left, a volume of liquid solution of the compound to crystallize is expanded several-fold by mixing it with cCO_2. This expansion produces a decrease of the solvent power, the solution becomes supersaturated, and the solute precipitates as finely divided particles.

As is illustrated in Figure 5 right, in the ASES process, an organic solution of the compound to crystallize is sprayed through a nozzle, as fine droplets, into a vessel pressurized with cCO_2. In this process the CO_2 diffuses into the sprayed droplets causing a rapid expansion of the solvent, decreasing its solvating capacity and therefore forcing the solute to precipitate or crystallize as particles. «Engineering» new types of particles with different morphologies has been achieved with a wide range of molecules, leading to nanoparticles (50–500nm), microparticles (0.5–5μm), or empty «balloons». This permits a very significant increase in the bioavailability of sparingly water-soluble drugs, as well as the preparation of drugs with a narrow particle size distribution suitable for pulmonary delivery. Moreover, microspheres of a drug embedded in an excipient for controlled-release delivery can be prepared by these processes, without the limitations encountered with the RESS process, because most active substances and carriers can be easily dissolved in an organic solvent or an appropriate combination

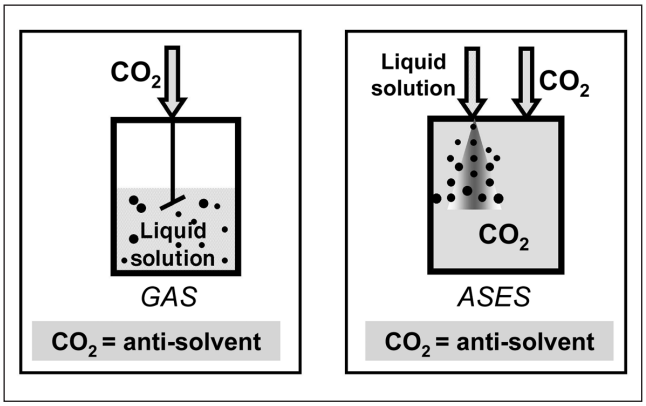

Figure 5. Schematic representation of two different configurations used to perform CO_2 antisolvent precipitation: Gas Antisolvent (GAS) (left); Aerosol Solvent Extraction system (ASES).

of organic solvents. There are several systems of pharmaceutical interest that have been shown to be procesable through cCO_2 antisolvent techniques. Indeed, these techniques have been used for the straightforward production of micro– and nanoparticulate drugs, as well as for the formation of drug/polymer micro-composites [20]. For instance, the ASES technique has been assessed for the production of micronized steroids for lung delivery. Budesonide, triamcinolone, acetonide, fluticasone-17-propionate, prendisolone, and flunisolide were all precipitated with average particle sizes of less than 5μm [31]. Insulin, lysozyme, albumin, and recombinant human DNase are examples of proteins that have been precipitated using cCO_2 antisolvent techniques [32]. All have been precipitated in the form of microparticles. Particle size reduction of proteins with compressed fluids can produce smaller particles than spray and freeze-drying techniques while preserving enzymatic activity [33]. Mammucari et al. have co-precipitated cyclodextrins (CDs) with a drug through the ASES process, in order to improve their stability, solubility, dissolution rates and reducing side effects [34]. The small particle size they achieved makes the application of ASES potentially suitable and advantageous for systems containing CDs in which the particle size is an important aspect. Another example of co-precipitation using CFs antisolvent techniques, is the encapsulation of insulin with PLA and PEG/PLA in nanospheres, in the range of 400–600nm, that Elvassore et al. have performed using the GAS technique [35]. Rantakyla et al. made an estimate of the cost of cCO_2 antisolvent precipitation on the industrial scale. This cost analysis suggests that the use of cCO_2 antisolvent precipitation should be considered only for high-value-added products. Although the versatility of the process does allow the unit to be used for the processing of different materials, in its current operation, CFs antisolvent precipitation is not a continuous process because the collection of the product requires the depressurization of the collecting chamber [36].

Depressurization of an Expanded Liquid Organic Solution (DELOS) CO_2 as co-solvent

We have developed a new precipitation procedure, called Depressurization of an Expanded Liquid Organic Solution (DELOS) [37,38], where cCO2 is used for the straightforward production of micron-sized and sub-micron-sized crystalline particles from an organic solution. This process differs from the other high-pressure techniques in that the cCO_2 acts as co-solvent being completely miscible, at a given pressure and temperature, with the organic solution of the solute to be crystallized [39]. The driving force behind precipitation in a DELOS process is the large, rapid and extremely homogeneous temperature decrease experienced by a CO_2-expanded solution of the compound to crystallize, when its is depressurized.

The DELOS process comprises the following three steps, which are schematized in Figure 6. 1) Dissolution of the solute to be crystallized in a conventional organic solvent, at atmospheric pressure and at a working temperature, T_W. 2) Addition of a CF (e.g. CO_2) over the organic solution in order to obtain a volumetric expanded liquid solution, at the working temperature (T_W) and at a high working pressure (P_W) containing a given

molar fraction of the cCO2 (X_W), named as the working composition of cCO2. The solute concentration in this step (C_W) must remain below the saturation limit in the expanded mixture of the organic solvent and the cCO2 (C^S_W); that is to say that the supersaturation ratio, β_W, of the expanded solution must be less than one. 3) Rapid reduction of the pressure of the liquid expanded solution, from the working pressure to the atmospheric one through a non-return valve. During this depressurization process, the cCO2 evaporates from the expanded solution, producing a large, fast and extremely homogeneous decrease of the solution temperature down to the final temperature, T_F. As a consequence, there is a pronounced and homogeneous increase of the supersaturation ratio, throughout the solution, triggering the phenomenon of catastrophic nucleation and causing the precipitation of sub-micron– or micron-sized crystalline particles with a narrow particle size distribution.

In a DELOS process, the extent of CO_2 vaporization at any point in the liquid solution is exactly the same. As a consequence, the solution temperature decrease and the evolution of the supersaturation profile are extremely uniform throughout the system. This has important technological implications, since there is no need for efficient stirring systems which would otherwise be needed to avoid inhomogeneous solution cooling, and prevent a precipitation with a wide particle size distribution and non-homogeneous internal structure. Moreover, since precipitation in the DELOS process occurs far from equilibrium conditions, it is possible to produce materials with an internal structure not achievable by thermodynamically-controlled processes [40]. Compared to other high-pressure crystallization techniques, such as RESS and ASES, the DELOS process method requires only moderate operating pressures, which is an important advantage when considering scale-up and the economic evaluation of the process. The design of the process is simpler than that of other techniques with cCO2. No stirring is required, in contrast with the GAS technique, because of the homogeneous cooling during the depressurization stage [41]. Finally, the operation of the DELOS process in a continuous mode is easier than the CF antisolvent techniques, since in the former method the collection of the precipitated material is performed at atmospheric conditions, whereas in the later it should be done at high pressure. The

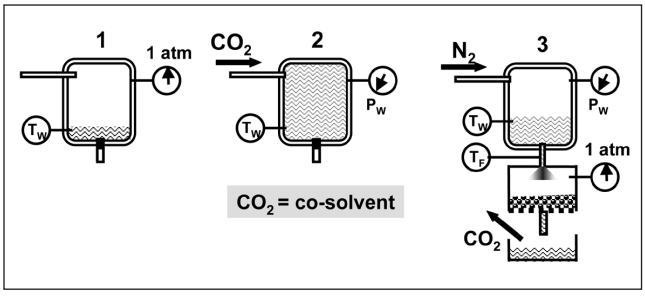

Figure 6. Steps of a DELOS process: (1) A liquid solution of the compound to be crystallized is added to the autoclave. (2) Addition of CO_2 produces a new expanded liquid solution which fills all the autoclave volume at a given pressure, P_W, and temperature, T_W, giving rise to a solution with a molar fraction of CO_2 of X_W. (3) Depressurization of the expanded liquid solution through a valve leading to precipitation of nano– or micron-sized particles, with a narrow size distribution.

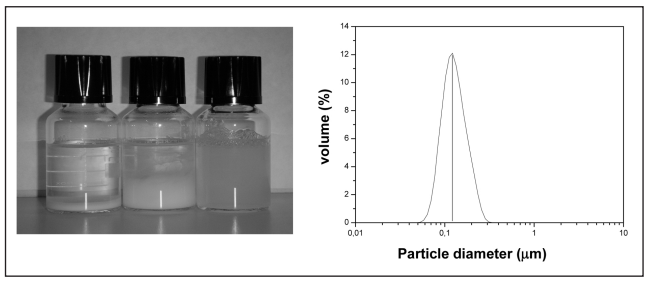

Figure 7. a) Photographs of cholesterol in water suspensions prepared by mixing methods (left two samples) and by the DELOS-SUSP procedure (right sample). b) Laser light diffraction analysis of a cholesterol nanosuspension in water, obtained through the DELOS-SUSP method.

DELOS process has been demonstrated to be an efficient high-pressure crystallization method for the straightforward production of micron– and nano-sized pharmaceutical actives, such as ibuprofen, acetaminophen, acetyl-salicylic acid, naproxen, steroids, etc. with a high polymorphic purity [42], and work is on-going, in order to test the feasibility of this new method for the preparation of micro– and nanoparticulate drug/polymer composites.

Recently we have developed a new efficient procedure based on DELOS, for the preparation of drug nanoparticles stabilized in an aqueous phase [43]. In the preparation of colloidal systems by precipitation procedures, the size and size distribution of the dispersed nanoparticles is strongly dependent on the homogeneity of the supersaturation level, at any point of the liquid solution and at any time of the procedure. In the DELOS-SUSP method, the cooling of the solution, which is the precipitation driving force, takes place to the same extent at any point of the solution, favoring the production of nanosuspensions with a narrow-dispersed particle size distribution. As can be observed in Figure 7, using this technique we have been able to prepare stable nanosuspensions of cholesterol with a mean particle size of 100nm.

The DELOS-SUSP technique has been shown to be effective for the preparation of aqueous nanosuspensions of different non-water soluble polymeric excipients and pharmaceutical actives.

Conclusion

Precipitation techniques using compressed fluids are efficient procedures for the preparation of micro– and nanostructured materials with applications in drug-delivery and clinical diagnosis. These «bottom-up» preparation procedures have many advantages compared to conventional processes, including rapid one-step processing, moderate operating temperatures (essential for thermally labile compounds), and control of particle size and material internal structure. Some of these techniques, such as GAS, ASES and RESS, have been modified for drug encapsulation, impregnation and coating, and others, like DELOS, for the preparation of nanosuspensions of non-soluble therapeutically active compounds. It has been demonstrated that pharmaceutical materials, prepared by techniques

with cCO_2, are efficient for many drug delivery systems, such as aerosol, and intravenous or subcutaneous delivery, because of the dramatic particle size reduction, as well as for oral delivery, as a result of the significant improvement in dissolution rates of sparingly water soluble drugs. The main obstacle to the application of CFs as solvent media in industrial processes is the lack of fundamental studies accurately describing the phase behaviour of the multi-component systems involved in the process. The practical implementation of precipitation procedures with CFs for fine-particle production on the commercial scale requires predictability of product characteristics. Therefore, understanding the influence of all relevant process parameters on the size and shape of the particles formed by these processes is important. However, with improved understanding of current techniques and continued innovation, it is foreseeable that the use of CFs for the processing of pharmaceutical materials will soon become commercially available.

Acknowledgments

We are grateful for the financial support of *S.E. Carburos Metálicos (Air Products)*, the *Centre d'Innovació i Desenvolupament Empresarial* (*CIDEM*) of the Catalan Government, the *Direcció General de Recerca* (*DGR*) of the Catalan Government, project 2001SGR00362, and the *Dirección General de Investigación* (*DGI*) of the Spanish Government, project MAT2003–04699. Nora Ventosa would like to thank the Ramon y Cajal Program of the *Ministerio de Ciencia y Tecnología* (Spain) for her contract. Santi Sala and Mary Cano express their thanks to the *Ministerio de Ciencia y Tecnología* (Spain) for their PhD grants, and Maria Muntó is grateful to the *Consejo Superior de Investigaciones Científicas* (*CSIC*) for her PhD bursary.

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About the authors

The group of Molecular Nanoscience and Organic Materials at the Institut de Ciència de Materials de Barcelona *of* CSIC*, lead by Prof. Jaume Veciana, has broad expertise in the fields of functional molecular material synthesis and processing, crystal engineering and organic physico-chemical characterization. Their research has lead to important contributions to the fields of molecular magnetism and molecular electronics. They have participated in a large number of national and international research projects, financed by national agencies (CICyT, DGCyT, DGI, CIRIT), international agencies (EU HCM/TMR programmes, ESF network, NEDO (Japan) and NATO) and private corporations and industries (IQV, Exxon Chemicals, Raytheon Technologies (USA), Henkel). In 1997, they started a new research line, directed by Dr. Nora Ventosa, devoted to the design and development of green and sustainable processes for the preparation of micro– and nanostructured molecular materials, using compressed fluids as solvent media. In order to pursue this research line, they have actively contributed to the set-up of the Laboratory of Supercritical Fluids of MATGAS AIE, which is a joint research centre between the private enterprise Carburos Metálicos– Air Products, the* Universitat Autònoma de Barcelona *and the* ICMAB *of the* Consejo Superior de Investigaciones Científicas*. The work done following this research has lead to the development of the DELOS® process, a new eco-efficient precipitation procedure for the straightforward preparation of micro– and nano-particulate materials. This new procedure has been patented by Carburos Metálicos S.A., and licensed to the spin-off Activery Biotech S.L. for its commercial exploitation. The DELOS® process has proved to be very effective for the preparation of different pharmaceutical materials, such as micro– and nanoparticulate powders, and nanosuspensions, with potential applications in drug-delivery and clinical diagnosis, unachievable by conventional procedures.*