Supercritical CO_2 as Novel Particle Formation Media: 1. Applications to the Formation of Organic and Inorganic Materials

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Numerous results of multitude investigations indicate that the particular properties of supercritical fluids (SCFs) can be conveniently exploited for the formation of submicron particles for a large number of applications such as pharmaceutical technology and material science. In case of the former one, the poor dissolution behaviour and therewith bioavailability of drugs in biological media can be enhanced dramatically by reduction of the particle size. For catalytic applications, a high dispersion, i.e. the preparation of noble metal nanoparticles on porous catalyst supports improves the activity of the catalyst. The disadvantages of the common particle size reduction techniques (milling and grinding, spray-drying, freeze-drying, high-pressure homogenization, ball and air jet milling) are often degradation of the product, a broad particle size distribution and cumbersome solids handling.

Furthermore, catalysts prepared by the conventional aqueous impregnation of diverse supports yields to large metal particles with broad particle size distribution. To overcome this, innovative SCF based particle size reduction processes are gaining an importance in material science and pharmaceutical technology and are currently investigated in our laboratory. The paper is organized as follows:

After an introduction into the basic principles of the processes, typical results obtained from RESS-experiments (Rapid Expansion of Supercritical Solutions) with poorly soluble drugs such as *RS*-(±)-Ibuprofen, Naproxen and of Carbamazepine are presented. In addition, it is shown that the improved dissolution behaviour of these particles depends on the reduced particle size and hence increased surface area of the processed powders and on the pH-value of the dissolution media.

After this, results obtained from SFRD-experiments (Supercritical Fluid Reactive Deposition) are presented and discussed. The experimental results show that metallic nanoparticles can directly be deposited on a wide range of solid substrates by SFRD. This process enables the deposition of small, uniform Pt- or Au-particles with improved activity of the catalyst. The particle size and size distribution can be affected by the reduction conditions, type and amount of precursor, surface area of the substrate and chemical nature of the surface. The main conclusions and further perspectives are summarized at the end of the paper.

INTRODUCTION

The production and utilization of nanoparticles is an increasing field for industrial and scientific applications, such as advanced materials, catalysts, semiconductors, optical components and precursor materials used in ceramic and pharmaceutical industry. Various investigations show that both, particle formation and chemical synthesis in SCFs is very attractive for materials processing [1-4]. SCFs are characterized by densities very close to those of liquids and mass transfer properties (viscosities and diffusivities) lying between those of gases and liquids, which make them attractive solvents for separations and reactions. At the same temperature, the viscosity of a gas is typically less than one order of magnitude lower than the viscosity of SCFs, but the gas density is at least two orders of magnitude higher. Thus, depending upon the fluid density, the fluid behaves as a specific solvent for a specific substance at one pressure, but as a non-solvent at another pressure. In addition, processes

using SCFs are characterized by their ease of solvent and product recovery; solvent-free products can be obtained in a single processing step by partial system depressurization. Among the SCFs, supercritical carbon dioxide (sc-CO_2) is particularly attractive since it is inexpensive, non-flammable, non-toxic, and leaves no residue in the treated medium [1].

Formation of submicron organic particles

The particular properties of SCFs can be conveniently exploited for the production of submicron particles for pharmaceutical application such as injectable, inhalable, and controlled release drug formulations. However, an increasing number of newly developed pharmaceutical substances are poorly soluble in both aqueous and organic media. The low bioavailability of such drugs can be improved by reducing the particle size. A large number of studies demonstrated that RESS is a promising method for the fabrication of submicron particles (see overview in [5]). In RESS, the material to be processed is dissolved at high pressure (p_0) in a SCF (usually CO_2). After heating to the desired pre-expansion temperature (T_0) an extremely fast phase change from the supercritical to the gas-like state takes places during the expansion through a heated nozzle to ambient pressure and temperature. The decrease in density brings high supersaturation values (10^5 – 10^8) and therewith high nucleation rates ($\leq 10^{26}$ $cm^{-3} \cdot s^{-1}$). This leads to uniform crystal growth which enables the formation of submicron (< 1 µm) particles. In case that nucleation occurs, particles grow by coagulation, which is the growth by collision of particles, and by condensation, which is the deposition of molecules on the particles surface. The particle size, size distribution and morphology (crystalline or amorphous) of the obtained RESS product can be influenced by various process parameters:

a) extraction and pre-expansion temperature and pressure
b) nozzle geometry, diameter and length
c) residence time, pressure and temperature in the expansion unit
d) solubility in SCF and nature of solute-solvent interaction.

Prior to precipitation, the degree of supersaturation depends strongly on the solutes equilibrium mole fraction at the prevailing temperature and pressure during the expansion and hence on the phase behaviour of the respective binary mixture.

Preparation of supported metallic nanoparticles

Experimental investigations show that metallic nanoparticles can directly be deposited on various solid substrates by SFRD [6-9]. The SFRD-technique involves the dissolution of the precursor in a SCF and the exposure of a substrate to the solution. The precursor will be transformed to its metal form with a reducing agent, such as hydrogen (H_2). Both highly dispersed and uniformly distributed metal crystallites and agglomerated metal clusters with a wide size distribution supported on different inorganic and organic substrates for a multitude of applications can be produced. Different methods can be used to convert the organometallic precursor to its metal form:

a) chemical reduction in sc-CO_2 with a reducing agent (H_2),
b) chemical reduction at atmospheric pressure with a reducing agent (H_2),
c) thermal reduction in sc-CO_2,
d) thermal reduction at atmospheric pressure in an inert atmosphere.

The average particle size and size distribution can be affected by the precursor reduction method and conditions, type and amount of precursor in the system, the surface properties of the substrate such as surface area and chemical nature of the surface. For the preparation of high-purity supported metallic nanoparticles a number of organometallic precursors can be used as starting materials as long as they have some solubility in the SCF. More details of the different concepts that are currently employed in the preparation of

metallic nanoparticles using SCFs are summarized in various reviews [see e.g. 6-9]. However, the preparation of supported metal alloy catalysts and binary metallic films using supercritical fluid deposition is a great unexplored area which merits attention in the future.

MATERIALS AND METHODS

CO_2 (Linde AG; Germany) was chosen as supercritical solvent since it is a non-flammable, inexpensive, and non-toxic solvent. Supercritical CO_2 (sc-CO_2) allows processing at moderate temperatures (Tc = 304.1 K), is particularly attractive for a wide variety of applications because it is chemically inert, non-toxic, and environmentally acceptable. Hydrogen (H_2) with a purity of 99.999% was purchased from Linde AG (Karlsruhe, Germany)

Racemic Ibuprofen (RS(±)-Ibuprofen) is a non-stereoidal anti-inflammatory drug and was generously supplied from Knoll Pharmaceuticals (Nottingham, UK). RS(±)-Ibuprofen contains S(+)-Ibuprofen and R(-)-Ibuprofen, generally in equal amounts. Carbamazepine and Naproxen was obtained from Sigma Aldrich (Taufkirchen, Germany). The precursor complex selected for the SFRD-experiments was dimethyl-(1,5-cyclooctadien)-platinum, Pt(COD)Me_2, which was purchased from ABCR (Karlsruhe, Germany)

Differential Scanning Calorimetry (DSC 204 Phoenix, Netzsch; Selb, Germany) was used for physical characterization (melting point and enthalpy of fusion) of the unprocessed and the processed powders. The sample (≈5 mg per run) was heated in an aluminium standard pan under a nitrogen gas flow of 20 ml / min. Usually a heating rate of 5 K / min was used up to a maximum temperature of 473 K.

The powder X-ray diffraction (XRD) pattern of the unprocessed solutes and the micronized substances were determined by using a Guinier instrument (System G600, mono-chromate CuKα radiation, $\lambda = 1.54056\times10^{-10}$ m, Huber Diffraktionstechnik GmbH, Rimsting; Germany). Typically the diffractograms have been collected in a 2θ range of 5 to 60°.

Since in case of non- spherical and / or agglomerated particles on-line measurement technique can lead to incurrent results of the particle size distribution, Scanning Electron Micrographs (SEMs) were made using a scanning electron microscope (DSM 940 A, Carl Zeiss, Oberkochen; Germany; or Stereoscan S4-10, Cambridge Scientific Instruments; UK). The samples were coated with gold by means of a Sputter Coater (E 5100, Bio-Rad, München; Germany).

The average particle size (d_{50}) and particle size distribution (PSD, expressed as d_{10}, d_{50}, and d_{90}) were statistically determined from SEM images using image analysis (ImageJ Version 1.38). d_{10} is defined as the diameter where 10 % of the particles have a smaller diameter, and the other 90 % have a larger diameter. d_{50} and d_{90} are defined accordingly. As a rule, about 600 particle diameters were considered in each PSD calculation. The span Δ was defined by: $\Delta = (d_{90} - d_{10})/d_{50}$ to describe the polydispersity of the various samples.

A USP dissolution apparatus [10, 11] was used for in vitro testing of drug dissolution at 310±0.5 K. An excess amount of the poorly soluble drug was placed into the dissolution medium (250 ml). Samples were withdrawn, during the initial stage (≤ 10 min) every 2 minutes, after that every 10 min, and always replaced with an equal amount of fresh dissolution medium. A similar procedure was used for solubility measurements: Excess amounts of the drugs were added to the thermostated (310±0.5 K) dissolution vessel containing 250 ml of dissolution medium. These mixtures were then agitated with magnetic pieces for a period of 24 h on a magnetic stirrer at a temperature of 310±0.5 K. All samples were filtered through a membrane filter with pore size of 0.2 μm and the drug content was determined by HPLC (Agilent Technologies; Waldbronn, Germany, Typ 1100, Agilent LiChrospher 100-5 RP18, 125x4 mm).

The average mass percentages of the deposited platinum was measured gravimetrically

(Mettler-Toledo, Giessen, Deutschland) with an accuracy of ±0.2 mg. The precise platinum contents of the substrate were determined by means of X-ray fluorescence analysis (Spectrace 5000, 50 kV, Rh Target).

The supported metal particles were characterized by ICP-AES, XRD, TGA, N_2 adsorption, and HRTEM in order to study the influence of various process parameters on dispersion and particle size.

All materials and solvents were of the purest grade available and were used without further purification. In Table 1 some important physical properties of the materials used in this study are summarized.

Table 1: Physical properties of the substances investigated.

Substance	M [g/mol]	CAS-Nr.	T_M [#][K]	$\Delta h_i^{fus\#}$ [J/g]
RS(±)-Ibuprofen	206.3	15687-27-1	348.6	123.5
Naproxen	230.3	22204-53-1	423.3	127.5
Carbamazepine	236.3	298-46-4	458.3	99.4
$Pt(COD)Me_2$	333.3	12266-92-1	380.0	57.6

[#]measured with DSC

EXPERIMENTAL

1) RESS-process

The laboratory scale RESS-apparatus is shown schematically in Figure 1. The continuous apparatus is designed for experiments in the temperature range from 300 to 600 K and pressures up to 40 MPa. A more detailed description of the RESS-apparatus and the experimental procedure can be found elsewhere in literature [12, 13].

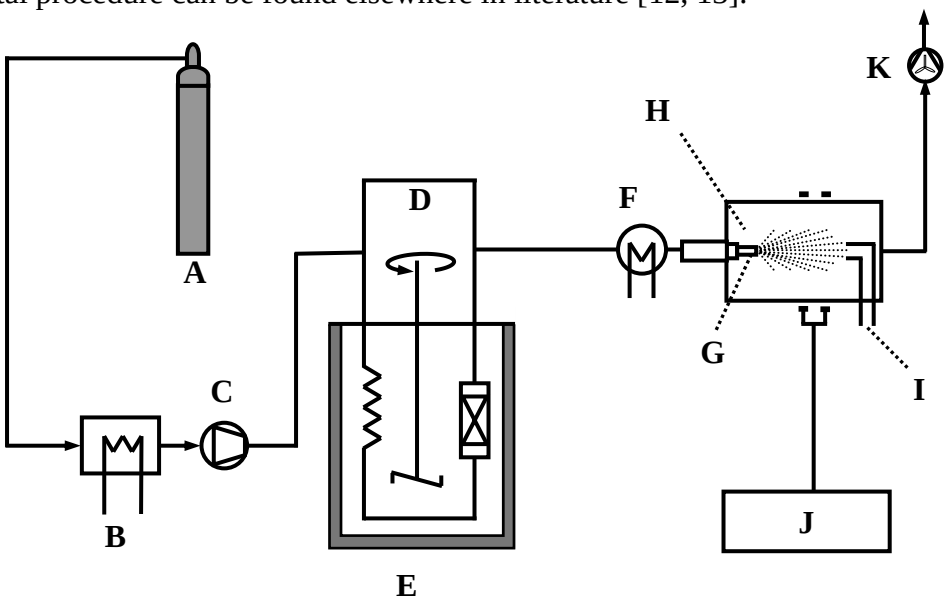

Figure 1: Schematic diagram of the RESS-apparatus: **A**, solvent supply; **B**, chiller; **C**, diaphragm pump; **D**, bypass; **E**, extraction unit; **F**, heating; **G**, capillary nozzle; **H**, expansion chamber; **I**, sample for SEM; **J**, 3-WEM; **K**, vent.

In all experiments, the gaseous CO_2 is liquefied, sub-cooled, and pressurized to the desired pressure with a diaphragm pump. Thereby the mass flow rate of CO_2 is measured with

a mass flow meter. To minimize the unsteadiness of the flow and to accelerate thermal equilibrium, pure CO_2 flows through the bypass section into the high-pressure vessel and is expanded through a capillary nozzle into the expansion chamber. After equilibrium, the bypass section is closed and the sc-CO_2 flows through the pre-heater and the extraction column where the solute is dissolved in sc-CO_2. The pre-expansion pressure (p_0) was maintained at the same pressure as the extraction column. Then, the supercritical solution flows through a tube into a high-pressure vessel where the pre-expansion temperature (T_0) is adjusted and is expanded through a capillary nozzle (L/D = 10, D = 50 µm) down to ambient conditions inside the expansion chamber. Samples are collected onto SEM stages located on the sampling device at a distance of 300 mm to the nozzle exit [12, 13].

In case of Naproxen, the extraction temperature was fixed to 313 K, while T_0 was varied from 323 to 363 K, and p_0 from 20 to 30 MPa. In case of Carbamazepine, the extraction temperature was fixed to 323 K, while T_0 was varied from 333 to 383 K, and p_0 from 15 to 30 MPa. For both substances, the influence of p_0 and T_0 on particle characteristics was studied.

2) SFRD-process

SFRD is an alternative and promising way to deposit metal nanoparticles onto the surfaces of porous solid supports. Thereby the metallic precursor is converted to its metal form as shown in Fig. 2.

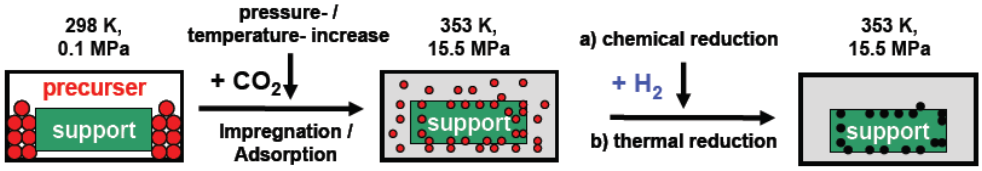

Fig. 2: Scheme of using CO_2 as processing solvent to synthesize supported Pt-nanoparticles.

In a typical experiment, Pt(COD)Me_2 and the support were placed in a tubular reactor in two separate open recipients. The mixture was treated in sc-CO_2 at 353 K and 15.5 MPa for 20 h. During this time the precursor is dissolved in CO_2 and adsorbed on the support. A magnetic agitator was placed between the recipients for an enhanced mixing of the solution. Subsequently, 1.17 vol.-% H_2 was added to the Pt(COD)Me_2/support-mixture in sc-CO_2 at constant temperature and pressure, and the mixture was kept for another 2 h. During this process, the precursor is reduced and the organic ligands are transformed to cyclooctane and methane. Then, the system was slowly depressurized and cooled down to ambient pressure and temperature.

RESULTS

a) RESS-Experiments

Typical experimental results are depicted in Fig. 3 and show that particle size and PSD of both, Naproxen and Carbamazepine were significantly reduced by the RESS. Unprocessed Naproxen had a median diameter (d_{50}) of approximately 5.6 µm with a wide PSD ranging from 1.8 (d_{10}) and 13.5 (d_{90}) µm, whereas the Carbamazepine particles used as starting material had a median diameter of around 40 µm and a PSD between 20 (d_{10}) and 89 (d_{90}) µm. Under the different operating pressure and temperature conditions, RESS processed particles were similar in size and PSD. In case of Naproxen the d_{50} is around 0.16 µm with a narrow PSD between 0.11 and 0.23 µm. The PSD profile of Carbamazepine shows that the particle sizes range from 0.5 µm (d_{10}) to 1.1 µm (d_{90}), with a median particle diameter of 0.7

µm (d_{50}). Obviously the particles produced by RESS are by the factor of 35 (Naproxen) and of 57 (Carbamazepine) smaller than the unprocessed particles.

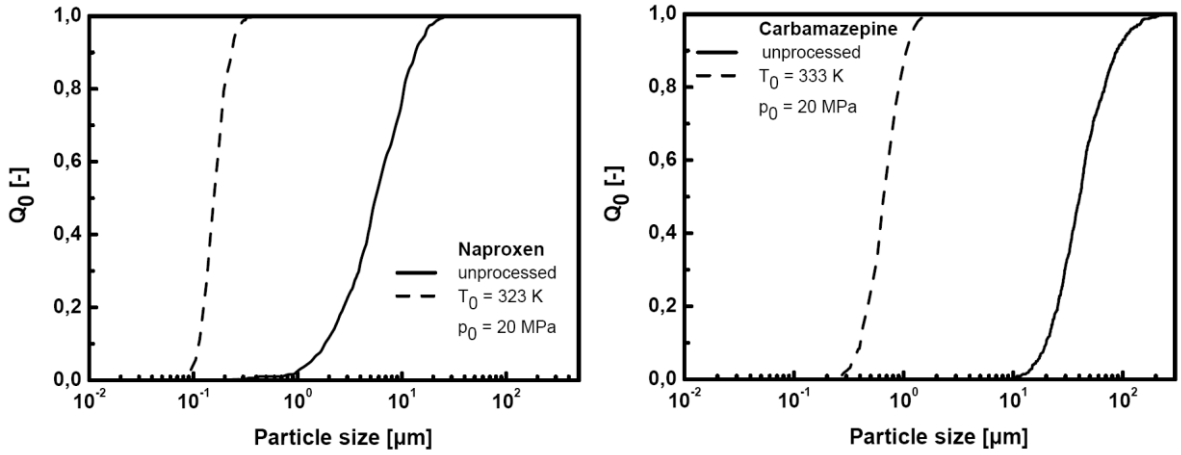

Fig. 3: PSD of unprocessed and of micronized Naproxen (left) and Carbamazepine (right).

For both substances similar melting behaviour and X-ray diffraction patterns were observed for the original material and the precipitated particles obtained by RESS. However, the heat of melting and melting temperature obtained from DSC analysis and the intensity of the XRD peaks of the processed substances were slightly lower compared with the unprocessed material. These results indicated a slight reduction in the degree of crystallinity after processing with RESS. For Carbamazepine Gosselin et al. [14] show that the polymorphic characteristics of micro-particles produced by RESS are slightly different from the unprocessed particles. In agreement with our results, no correlation between the particle size and different operating conditions was noticed.

b) RESS-Modelling

In addition, the RESS-process is investigated numerically for a better understanding of the mechanisms of particle formation and growth, and therefore, to be able to identify optimised process conditions with regard to particle size and distribution.

Fig. 4 shows the calculated mean particle size of Naproxen as a function of the residence time, t, the pre-expansion pressure and Naproxen mole fraction, y_2. For these calculations, a steady-state flow field model was used [15-17]. The modelling consists of mass, momentum and energy balance and an equation of state. In the inlet region to the capillary nozzle an additional pressure drop is included while for the flow inside the capillary nozzle, friction and heat exchange is considered. Particle formation and growth is considered by solving the general dynamic equation for simultaneous nucleation, condensation, and coagulation. Thus, the simulation program is able to predict nucleation rate, particle number concentration, and average particle size, and the standard deviation as functions of the axial distance along the expansion path. The nucleation rate is obtained using the classical nucleation theory within this modelling approach. The obtained values for the nucleation rate rely hence on the validity of the classical nucleation theory. Molecular dynamics simulations of the RESS process [18] presented in the subsequent paper provide nucleation rates based on molecular interactions only. They can be used as input for the fluid dynamics modelling of the complete process. The calculations here are based on the following process conditions: L/D =1, D = 50 µm and l = 0.3 m. The air supply to the expansion chamber was set to 300 dm^3 / h. The results depicted in Fig. 4 clarify the influence of two process parameters on particle size. Both, a lower solubility and a shorter residence time of the particles in the expansion chamber results in smaller particles. The former one leads to a higher dilution of the particles which inhibit post-expansion particle growth while the latter one leads to less time available for

particle growth in the expansion chamber. Similar findings were previously published by various authors (see [5]). Thus, from the calculations discussed above follows, that it should be possible to form particles smaller than 50 nm. The inability to approach the theoretical lower limit is likely due to particle growth during collisions in the free jet. Thus, measures such as spraying the supercritical solution directly into an aqueous surfactant solution should result in smaller particles due to minimizing flocculation and agglomeration resulting from particle collisions.

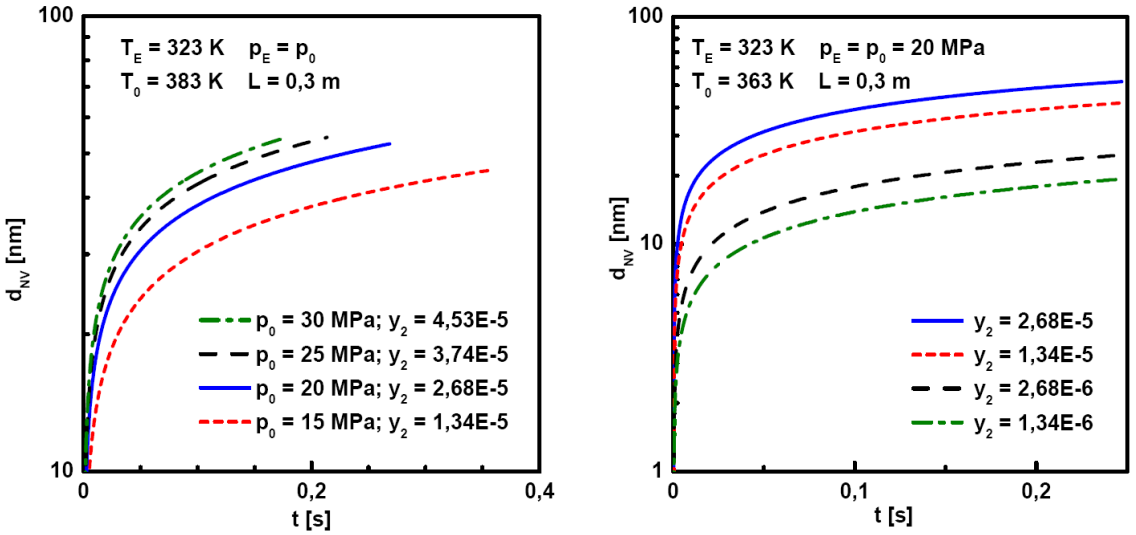

Fig. 4: Effect of pre-expansion pressure (left) and solute mole fraction (right), y_2, of Naproxen in CO_2 on calculated particle size, d_{NV}, inside the expansion chamber.

c) Dissolution Kinetics Studies

First of all, solubility measurements of Ibuprofen [19], Naproxen and Carbamazepine were conducted at different pH-values. In case of Carbamazepine no influence of the pH-value was observed and a mean saturation concentration of 303±25 mg/ml was determined at 310 K [20]. In opposite thereto, the solubility of Ibuprofen and of Naproxen increases with increasing ph-value of the dissolution medium. As shown in Fig. 5 (left) for Ibuprofen, the solubility increases from 0.04 mg/mL at pH = 2.0 to 0.18 mg/mL at pH = 6.8. For Naproxen an increase in solubility from 28 mg/mL at pH = 2.0 up to 175 mg/mL at pH = 6.8 was observed [20].

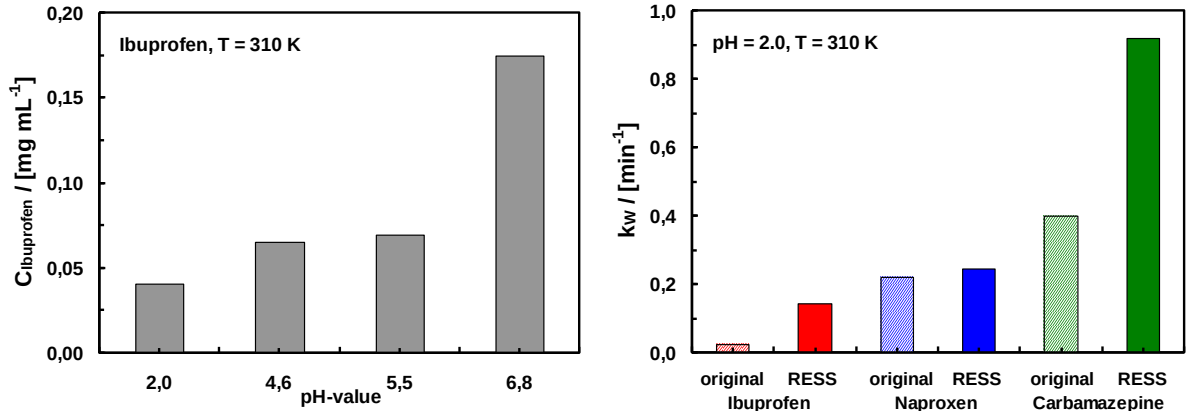

Fig. 5: Saturation concentration of Ibuprofen vs. pH-value of the dissolution medium (left) and k_w of unprocessed and micronized Ibuprofen, Naproxen, and Carbamazepine at pH =2.0 and T = 310 K (right).

Dissolution testing of the three poorly water-soluble drugs, Ibuprofen, Naproxen, and Carbamazepine was performed at 310 K and pH = 2.0. As a basis for comparison, the dissolution rate coefficient (k_W) is calculated as the reciprocal of the time after which 63.2% of the original amount of drug has dissolved. In Fig. 5 (right) the dissolution rate of the original material and the processed drugs are shown. The dissolution rate coefficient of the micronized Ibuprofen was found to be 0.14 min^{-1} which is 6 times higher than that of the original material. In case of Naproxen the k_W of the RESS product is 1.2 times higher and for Carbamazepine 2.3 times higher than that of the unprocessed material.

Additional dissolution experiments were performed with Ibuprofen and pH = 4.5, 5.5 and 6.8. In agreement with our previous results [5], the difference in the dissolution rate between unprocessed and micronized particles becomes smaller with increasing pH-value of the dissolution medium. However at present it should be noticed that it is not always clear whether the improved dissolution behaviour is due to the reduced particle size and degree of crystallinity, and / or change in the physical form (from crystalline to amorphous state), and / or more or less effective wetting due to adding surfactant to the dissolution media, and / or change of pH-value of the dissolution media. Molecular dynamics simulation as described in the subsequent paper show that the structure of small particles formed by RESS is different to those obtained from the liquid phase, especially for molecules with hydrogen bonds.

d) SFRD

Among others, SFRD-experiments were carried out with $Pt(COD)Me_2$ and β-Cyclodextrin (β-CD) as a water soluble solid substrate [21,22]. In a first experiment, $Pt(COD)Me_2$ and β-CD were filled into two separate open recipients (Pt-1) inside the high pressure reactor. In the second experiment, a physical mixture of $Pt(COD)Me_2$ and β-CD were placed in the reactor (Pt-2). For comparison, $Pt(COD)Me_2$ was converted to its metal form by chemical reduction at 353 K and atmospheric pressure with H_2 (Pt-3). In all SFRD-experiments, the ratio between $Pt(COD)Me_2$ and β-CD was kept constant at 0.044 g/g.

The left chart of Fig.6 summarizes the different PSD of the Pt-particles obtained from TEM and SEM analysis [23].

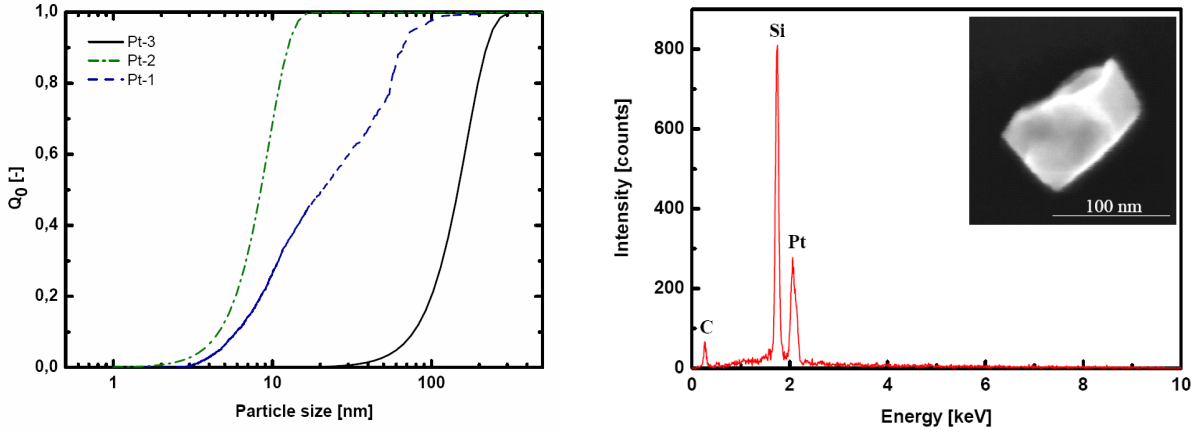

Fig. 6, left: Influence of process conditions on PSD of Pt-particles obtained from SFRD experiments performed at T = 353 K, p = 15.5 MPa (Pt-1, -2) and 353 K and 0.23 MPa (Pt-3); right: EDXS analysis of an individual Pt particle on Si substrate [23].

Obviously, for sample Pt-1 a very broad PSD (Δ = 2.9) was found. The particle size covers a range from 6 to 66 nm (d_{50} = 20.6 nm). Sample Pt-2 shows the smallest particles ranging from 4.7 to 12.2 nm with an average size of d_{50} = 7.7 nm and an extremely narrow size distribution (Δ = 1). For sample Pt-3 the particle size range from 88 to 210 nm (d_{50} = 155

nm), however the variation in particle size is rather small (Δ = 0.8). TEM and SEM investigations were complemented with energy-dispersive X-ray spectroscopy (EDXS) for chemical analyses as shown in the right chart of Fig. 6.

Incera Garrido et al. [21] investigated the deposition of Pt on SnO_2-coated Al_2O_3 foams. In this work, the influence of pressure and temperature and therewith the phase behaviour of the binary system Pt(COD)Me_2 / CO_2 on catalytic performance was investigated. The authors show that SFRD performed at 353 K and 15.5 MPa yields to highly dispersed Pt-particles with an average diameter of 3.2 nm. Increasing the temperature up to 373 K leads to a PSD shifted to larger particles in the range up to 13 nm. In addition, these elongated particles show signs of particle coalescence, indicating the appearance of a liquid phase after adsorption of the Pt-complex. Additional experiments show that the catalysts prepared by SFRD possess a superior activity towards oxidation of carbon monoxide in comparison to a catalyst prepared by the conventional aqueous impregnation of Pt. Thus, these results demonstrate that particle size plays an important role in the catalytic properties, since a higher dispersion of the particles leads to an increased activity.

CONCLUSION

RESS-experiments and modelling results show that:

a) Increasing T_0, (p_0 = constant), leads often to an increase in particle size. When $T_0 < T_M$ particle formation followed traditional nucleation and growth theory.

b) Increasing the pressure, (T_0 = constant), increases the CO_2 mass flow rate which decreases the residence time of the particles in the expansion chamber. This results in less time available for particle growth and therewith smaller particles.

c) Increasing the nozzle diameter, (T_0 and p_0 = constant), increases the CO_2 mass flow rate and leads therefore to smaller particles.

d) A lower solubility in the SCF results in smaller particles. This is caused by the fact that the particle collision rate is directly proportional to the square of particle concentration.

e) RESS is a very attractive and simple process for the production of submicron and uniform particles with improved dissolution behaviour.

SFRD experiments

An attractive alternative to the conventional liquid-phase impregnation route is the application of SFRD to achieve high dispersions of noble metals on different porous supports. Since in SCFs, both the metal precursor complex and H_2 can be dissolved, the metallic nanoparticles can be deposited on a support in one single step. The average particle size and size distribution can be affected by the reduction conditions, type and amount of precursor, surface area of the substrate and chemical nature of the surface. In addition SFRD provides an environmentally benign, efficient and rapid alternative to conventional liquid-phase impregnation techniques as commonly encountered in the preparation of noble metal catalysts.

5. ACKNOWLEDGMENTS

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