ELSEVIER

International Journal of Pharmaceutics xxx (2006) xxx–xxx

PHARMACEUTICS

www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Preparation of ethyl cellulose/methyl cellulose blends by supercritical antisolvent precipitation

Ana Rita C. Duarte [a,*], M.D. Gordillo [b], M. Margarida Cardoso [c], Ana Luísa Simplício [a], Catarina M.M. Duarte [a]

[a] *Nutraceuticals and Delivery Laboratory, ITQB/IBET, Aptd. 12, 2781-901 Oeiras, Portugal*
[b] *Departamento de Ingeniería Química, Tecnología de Alimentos y Tecnologías del Medio Ambiente, Universidad de Cádiz, Facultad de Ciencias, Campus Rio San Pedro, 11510 Puerto Real, Cádiz, Spain*
[c] *REQUIMTE/CQFB-Departamento de Química, FCT-UNL, 2829-516 Caparica, Portugal*

Received 15 July 2005; received in revised form 24 November 2005; accepted 5 December 2005

Abstract

The supercritical antisolvent (SAS) technique was used to prepare ethyl cellulose/methyl cellulose blends, two biocompatible polymers commonly used as drug carriers in controlled delivery systems. Ethyl cellulose is widely used as a drug carrier. The drug release of the delivery devices can be controlled to some extent by addition of a water-soluble or water swellable polymer, such as methyl cellulose. This leads to the solubility enhancement of poorly water-soluble molecules. SAS experiments were carried out at different operational conditions and microspheres with mean diameters ranging from 5 to 30 μm were obtained. The effect of CO_2 and liquid flow, temperature and pressure on particle size and particle size distribution was evaluated. The microspheres were precipitated from a mixture of dichloromethane (DCM) and dimethylsulfoxide (DMSO) (4:1 ratio). The best process conditions for this mixture were according to our study 40 °C and 80 bar.

Keywords: Biocompatible polymers; Micronization; Supercritical fluid antisolvent (SAS); Release systems

1. Introduction

The importance of biocompatible and biodegradable polymers is continuously increasing in pharmaceutical applications, namely to prepare new controlled drug delivery systems (Shariati and Peters, 2003). For such systems size and morphology of the polymer matrix assumes an extremely important role in the drug release and pharmacokinetics. Although several polymers are used in the pharmaceutical industry, cellulose derivatives are among the most commonly used for better drug delivery efficiency, reduced toxicity and an improvement in patient compliance (Reverchon et al., 2000; Rekhi and Jambhekar, 1995). Ethyl cellulose is a hydrophobic material used in a variety of applications such as sustained release and taste masking. Furthermore, it is also widely used to prepare controlled delivery systems. Drug release can be controlled and enhanced to some extent by addition of a water-soluble or water swellable polymer, such as methyl cellulose (Handbook of Pharmaceutical Excipients, 2003). In order to gastrointestinal fluids permeate through the polymeric matrix and dissolve the drug enabling it to diffuse out at a rate dependent on the physicochemical properties of both the drug and the matrix, a water insoluble polymer (e.g. ethyl cellulose) needs to be combined with a water-soluble ingredient (e.g. methyl cellulose). Blends of different cellulose derivatives are often used for sustained release coatings and enteric coatings. Mixed polymer drug delivery systems must possess the appropriate morphology to facilitate the required drug release profile (Sakellariou and Rowe, 1995). Moreover, enhancement of bioavailability of poorly water-soluble compounds is achieved by inclusion of the active principle in a faster dissolving hydrophilic excipient like ethyl/methyl cellulose blends. The changes in the porosity of the system allow a stable inclusion of poorly soluble molecules of an adapted size (Perrut et al., 2005; Nam et al., 2002).

Intensive worldwide research related with the application of high pressure and supercritical fluids to particle formation,

* Corresponding author.
E-mail address: rduarte@itqb.unl.pt (A.R.C. Duarte).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.12.010

encapsulation and impregnation of polymeric matrixes has proven the efficiency of supercritical fluid (SCF) technology to generate improved delivery systems. Production of micro- or nanoparticles using supercritical fluid technology is very attractive since it provides an alternative solution to the various problems encountered in traditional techniques (Yeo and Kiran, 2005). The possibility of producing very small particles with a narrow size distribution using mild and inert conditions represents a major improvement over the conventional processes (Elvassore et al., 2003).

One of the available particle formation technique based on supercritical fluids is the supercritical antisolvent process, referred as SAS, ASES, PCA or SEDS in literature (Yeo and Kiran, 2005; Foster et al., 2003) depending on the process arrangements and apparatus. Nevertheless, the principle inherent to all these processes is the same, i.e., to decrease the solvent power of the liquid by addition of an antisolvent in which the solute is insoluble. The selection of a proper combination of the organic solvent and the antisolvent for a particular polymer is essential for the success of the process. The organic solvent should have a reasonable miscibility towards the polymer and also a high solubility in the supercritical fluid under moderate operating conditions. This method of particle formation is based on two mechanisms that take place simultaneously, on one hand, the fluid penetrates into the droplets where it acts as an antisolvent for the dissolved material and on the other hand the organic solvent evaporates on the supercritical fluid so that precipitation occurs (Mukhopadhyay and Dalvi, 2004). Since the diffusivity of the supercritical fluid is higher than the diffusivity of a liquid, the diffusion of the fluid into the organic solvent produces a faster supersaturation of the solute solved in the liquid and therefore its precipitation into micronized particles.

The low solubility of polymers in carbon dioxide and their relatively high solubility in organic solvents provide suitable conditions to preferably employ this process for particle formation and design of improved controlled delivery systems.

Process variables, such as temperature, pressure and flow rate, have a strong influence in the morphology of the particles, as well as their particle size and particle size distribution. These variables directly interfere with the basic mechanisms that control particle formation, which are fluid dynamics, mass transfer, nucleation kinetics and thermodynamics (Reverchon et al., 2003).

The aim of this study was to evaluate the influence of such variables in the precipitation of ethyl cellulose/methyl cellulose blends, in order to optimize the process conditions.

2. Experimental procedure

2.1. Materials

Ethyl cellulose (CAS 9007-57-3) and methyl cellulose (CAS 9007-67-5) were purchased from Fluka. Dichloromethane, DCM (CAS 78-09-2, 99.9% purity), dimethylsulfoxide, DMSO (CAS 67-68-5, 99.9% purity) and acetone (CAS 67-64-1, 99.5% purity) were purchased from Vaz Pereira. Carbon dioxide (99.998 mol%) was supplied by Air Liquide. All chemicals were used with no further purification.

2.2. Microsphere preparation

The precipitation experiments were carried out in a SAS apparatus, schematically presented in Fig. 1.

The apparatus works in a continuous co-current mode and it consists of a precipitator in which the antisolvent and the liquid solution are separately fed to the top of the chamber and are continuously discharged from the bottom. The liquid solution is pumped into the chamber by a high pressure piston pump (Knauer HPLC pump K-501). The antisolvent is delivered by means of a high pressure piston pump (Haskel model MCPV-71).

The precipitator is a cylindrical vessel with an inner volume of 500 cm^3. The liquid solution is delivered into the chamber through a stainless steel nozzle. The supercritical carbon dioxide is heated, up to the temperature of the experiment, before entering the precipitator in a tube section by an electric cable (CS 12854), which is connected to a temperature controller (Ero Electronic LMS-491-13).

The precipitator is heated by means of two electric thin bands heater (Watlow STB3J2J1) also connected to a temperature controller. The pressure in the chamber is measured by a pressure gauge manometer (Bourdon-Haenni model MVX7 D30 B38). The outflow is regulated by a micrometric valve (Hoke 1315G4Y) located at the bottom of the precipitator. This valve is heated with an electric cable (CS 12854) in order to prevent

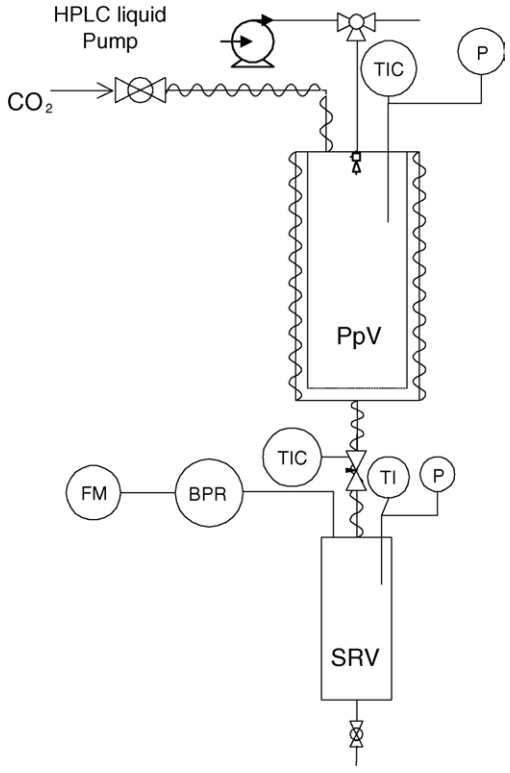


Fig. 1. SAS apparatus (TIC, temperature transducer; TI, temperature indicator; P, pressure transducer; BPR, back pressure regulator; FM, flow meter; PpV, precipitation vessel; SRV, solvent recuperation vessel).

the freezing of carbon dioxide due to the rapid depressurization (50 °C). A filter of sintered steel with 0.1 μm porosity is placed at the bottom of the vessel to collect the particles produced.

The solvents are separated and recovered from a second vessel. Usually the temperature of the vessel is around 15 °C and pressure 5–10 bar. The pressure in the separator is measured by a pressure gauge manometer (Bourdon-Haenni model MVX7 D30 B29) and regulated by a back pressure valve (Tescon Europe).

The carbon dioxide flow rate and the total quantity of antisolvent used are measured by a flow meter (Aalborg GFM 17S-VADL2-E).

2.3. Particle characterization

2.3.1. Scanning electron microscopy (SEM)

Samples of the precipitated powder were observed by a ZAISS 960 scanning electron microscope. The particles were fixed by mutual conductive adhesive tape on aluminium stubs and covered with gold–palladium using a sputter coater.

2.3.2. Particle size and size distribution

The particle size and size distribution of the prepared microparticles were measured by laser diffraction spectrometry (Coulter LS 130, Coulter Electronics). The dried powder samples were suspended in deionized water with a surfactant solution (Coulter Dispersant, Coulter) and sonicated for 1 min with an ultra-sound probe (500 W, Vibra Cell, Sonics & Materials Inc.) before measurement. The obtained homogeneous suspension was determined for the volume mean diameter, size distribution and polydispersity. Each sample was analyzed three times.

3. Results and discussion

In this study the possibility of precipitating biocompatible polymer blends (ethyl cellulose/methyl cellulose) using supercritical fluid technology is evaluated. The selection of a proper combination of the organic solvent and the antisolvent for a particular polymer is essential for the success of the process. To determine the best organic solvent for ethyl cellulose two preliminary experiments were carried out. Dichloromethane and acetone were the solvents tested. Particles precipitated from the DCM solution using CO_2 as an antisolvent did not agglomerate as the ones precipitated from acetone as it can be seen in Fig. 2. Therefore, DCM was the selected organic solvent to precipitate ethyl cellulose using SAS technique.

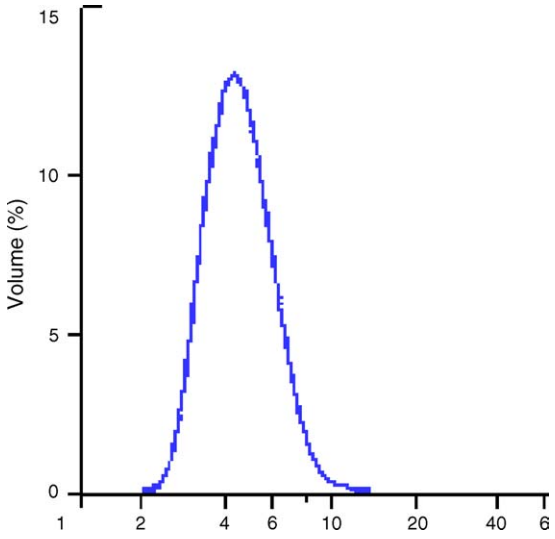
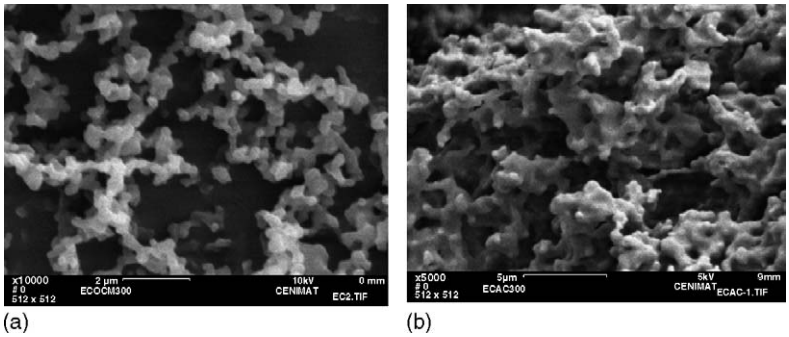


Fig. 3. Particle size distribution of ethyl cellulose micronized from dichloromethane.

Furthermore, particles of ethyl cellulose precipitated from dichloromethane solution through a 100 μm nozzle present a narrower size distribution (Fig. 3) with a mean particle size of 4.71 μm.

3.1. Ethyl cellulose/methyl cellulose blends

A mixture of two solvents had to be used to perform the SAS precipitation experiments, as the solubilization of the two polymers was only possible in a mixture of DCM/DMSO (4:1). Different ratios of ethyl cellulose/methyl cellulose were tested. Methyl cellulose, because it is a hydrophilic polymer, was very difficult to solubilize in the organic solution and for concentrations higher than 35% (w/w) it forms a gel. A blend containing 33% (w/w) of methyl cellulose was precipitated. However, the particles obtained were extensively agglomerated (Fig. 4). Therefore, blends at lower concentration (20%, w/w) of methyl cellulose were prepared and studied. Ethyl cellulose/methyl cellulose blends have been successfully obtained from supercritical antisolvent precipitation, as it could be confirmed by the SEM analysis.



(a) (b)

Fig. 2. Ethyl cellulose micronized from (a) dichloromethane and (b) acetone.

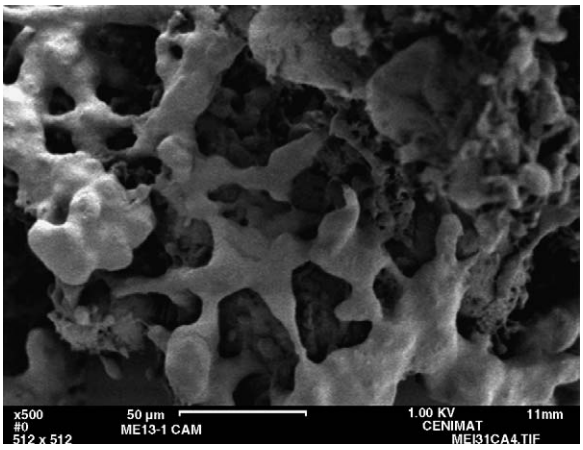


Fig. 4. Ethyl cellulose/methyl cellulose 33% (w/w) micronized.

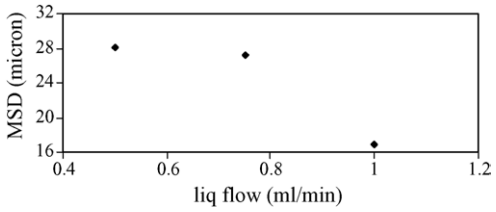


Fig. 5. Effect of liquid flow rate on the mean particle size (experiments 1–3).

A summary of the experiments, performed and the mean size diameter of the particles obtained is listed in Table 1.

The experiments were designed in order to determine the best operational conditions for the production of ethyl cellulose/methyl cellulose microspheres. In each set of experiments one of the variables was modified so that, the effect of the different variables on the particle size could be evaluated. In a first approach the liquid solution flow (experiments 1–3) was evaluated and from the experiments performed we could conclude that a higher liquid flow favours the precipitation of particles with smaller size diameter. An increase in the liquid solution flow leads to a better mixing between the organic solution and the surrounding medium and therefore to a stronger turbulence. This results in higher supersaturation rates and consequently to smaller particle diameter (Fig. 5).

Fig. 6 corresponds to the scanning electron microscopy of the particles obtained in experiment 6. In experiments 1, 4 and 5, the liquid flow and the CO_2 flow varied, maintaining constant the ratio between them. From the results obtained, 1 mL/min liquid flow and 8.5 L/min CO_2 flow were chosen to continue the study. Experiments at different temperatures and pressures were then performed.

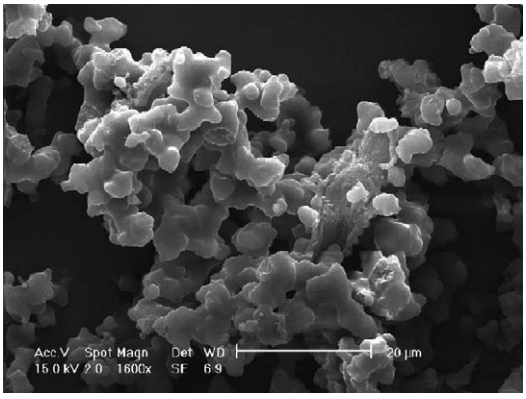


Fig. 6. SEM images of experiment 6.

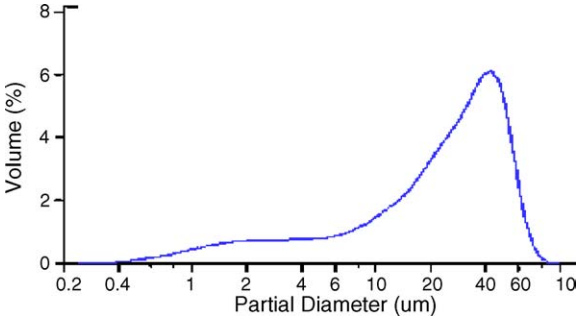


Fig. 7. Particle size distribution from experiment 2.

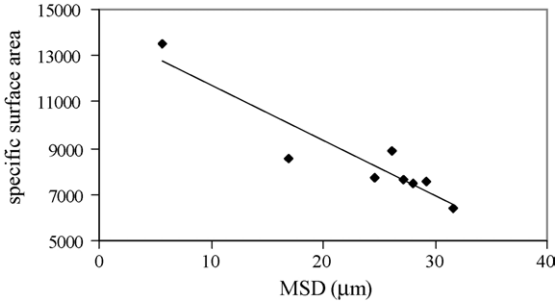


Fig. 8. Specific surface area vs. particle size.

Table 1
Summary of the experiments performed

Experiment	P (bar)	T (°C)	CO_2 density (kg/m^3)	Liquid flow (mL/min)	CO_2 flow (L/min)	MSD (µm)
1	80	35	422.06	1.00	8.5	16.91
2	80	35	422.06	0.75	8.5	27.12
3	80	35	422.06	0.50	8.5	28.13
4	80	35	422.06	0.75	6.5	29.29
5	80	35	422.06	1.50	13.0	28.08
6	80	40	277.80	1.00	8.5	3.03
7	80	30	702.50	1.00	8.5	31.12
8	90	30	744.77	1.00	8.5	24.61
9	75	30	662.43	1.00	8.5	26.11

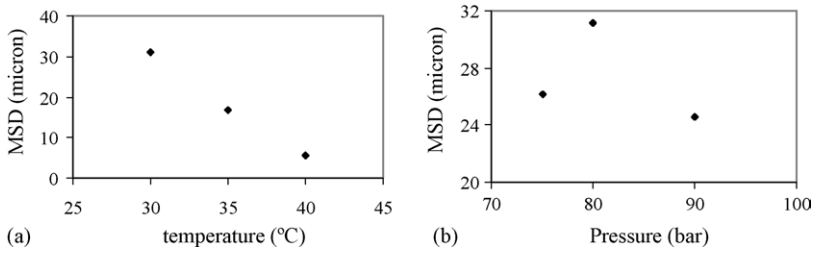


Fig. 9. Effect of (a) temperature and (b) pressure on the mean size diameter.

Particle size distribution of the blends precipitated showed a greater polydispersity when comparing to the micronized particles of ethyl cellulose (Fig. 7), this result is due to the fact that in the blends two polymers are being co-precipitated. Nevertheless, the supercritical antisolvent process still presents enormous advantages when comparing with conventional techniques such as solvent evaporation (Duarte et al., in press).

As the study of the preparation of these blends is directly concerned with the development of controlled release systems, a characteristic of major importance is their surface area. A higher surface area will lead to the increase in bioavailability of a drug impregnated in the system. Fig. 8 represents the relationship of the specific surface area with the particle mean size distribution. As predictable a lower particle size corresponds to a larger surface area.

Several parameters affect the final particle size distribution in the supercritical antisolvent process. Particle size of ethyl cellulose/methyl cellulose microspheres is strongly influenced by temperature. The density of the solution is more significantly affected by temperature than pressure. From the experiments performed it is possible to conclude that lower densities favour the precipitation of smaller particles (experiments 1, 6, 7 and 9). An isobaric increase in temperature results in a sharp decrease of the particle size, on the contrary the effect of the pressure is not very significant (Fig. 9(a and b)).

With the results obtained it is possible to conclude that for this system the best operating conditions involve higher temperatures, lower carbon dioxide densities and a higher liquid flow.

4. Conclusions

Ethyl cellulose/methyl cellulose microspheres were successfully precipitated from an organic solution using the supercritical antisolvent process. Operational conditions that affect the particle size and particle size distribution, such as liquid and carbon dioxide flow, pressure and temperature, were evaluated and smaller particles were obtained at 40 °C and 80 bar with 1 mL/min liquid flow and 8.5 L/min CO_2 flow rate, nevertheless in this experiment the yield was not as high as when the temperature was 35 °C.

Acknowledgments

Ana Rita C. Duarte wants to thank Prof. Ernesto Reverchon for the transfer of knowledge related with the technique.

This work was financially supported by FCT-MCES and FEDER, Portugal, under contract POCTI/EQU/46715/2002. Ana Rita C. Duarte is grateful for the SFRH/BD/10780/2002. M.D. Gordillo thanks Interreg Program (through Supermat Network) for financial support.

References

Duarte, A.R.C., Costa, M., Cardoso, M.M., Simplício, A.L., Duarte, C.M.M., 2005. Preparation of controlled release microspheres using supercritical fluid technology for delivery of anti-inflammatory drugs, Int. J. Pharm., available online.

Elvassore, N., Parton, T., Bertucco, A., Di Noto, V., 2003. Kinetics of particle formation in the gas antisolvent precipitation process. AIChE J. 49, 859–868.

Foster, N., Mammucari, R., Dehghani, F., Barrett, A., Bezanehtak, K., Coen, E., Combes, G., Meure, L., Ng, A., Regtop, H.L., Tandya, A., 2003. Processing pharmaceutical compounds using dense gas technology. Ind. Eng. Chem. Res. 42, 6476–6493.

Handbook of Pharmaceutical Excipients, 4th ed., American Pharmaceutical Association, Washington, 2003.

Mukhopadhyay, M., Dalvi, S.V., 2004. Mass and heat transfer analysis of SAS: effects of thermodynamic states and flow rates on droplet size. J. Supercrit. Fluids 30, 333–348.

Nam, K.W., Lee, S., Hawang, S.J., Woo, J.S., 2002. Enhancing water-solubility of poorly soluble drug itraconazole with water-soluble polymer using supercritical fluid processing. In: Proceedings of the C.R.S. 29th Annual Meeting.

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.

Rekhi, G.S., Jambhekar, S.S., 1995. Ethylcellulose—a polymer review. Drug Dev. Ind. Pharm. 21, 61–77.

Reverchon, E., Porta, G.D., De Rosa, I., Subra, P., Letourneur, D., 2000. Supercritical antisolvent micronization of some biopolymers. J. Supercrit. Fluids 18, 239–245.

Reverchon, E., et al., 2003. Role of phase behaviour and atomisation in the supercritical antisolvent precipitation. Ind. Eng. Chem. Res. 42, 6406–6414.

Sakellariou, P., Rowe, R.C., 1995. Interactions in cellulose derivative films for oral drug delivery. Prog. Polym. Sci. 20, 889–942.

Shariati, A., Peters, C.J., 2003. Recent developments in particle design using supercritical fluids. Curr. Opin. Solid State Mater. Sci. 7, 371–383.

Yeo, S.-D., Kiran, E., 2005. Formation of polymer particles with supercritical fluids: a review. J. Supercrit. Fluids 34, 287–308.