Preparation of Polymer Micro-particles based on Supercritical Fluids Expansion Depressurization Process

JIANG JING-ZHI[2,3], MIAO KAI[2], CUI HAI-TING[2],
PENG PEI-YING[2], ZHU HAI-RONG[2]

Abstract. Poly (methyl methacrylate) (PMMA, model material) micro-particles can be prepared successfully by supercritical fluid expansion depressurization (SFED) process. The obtained microparticles were characterized by scanning electron microscope. The influence of the process parameters, including the temperature and pressure in the mixing vessel, the solution concentration and the solution feed rate, on the particles were investigated experimentally. The results indicated that the pressure in the mixing vessel, the solution concentration and the solution feed rate had signi?cant effect on the microparticles. The temperature in the mixing vessel has a little influence on the prepared PMMA particles but they directly influence the yield of the final production. With the increase of the mixing vessel pressure in the range of 8-10MPa, the particle diameters decrease obviously and the distributions become narrower. The increase of the solution concentration and solution feed rate lead to an increase of particle diameter, wide diameter distribution and irregular particle morphology. The optimal operation parameters for preparing PMMA microparticles in the range of this work are: the pressure of 10MPa and the temperature of chmetcnvUnitNameCSourceValue60HasSpaceFalseNegativeFalseNumberType1TCSC060∘C in the mixing vessel, the solution feed rate of 3ml/min, and the solution concentration of 10mg/ml.

Key words. Supercritical Fluids, Micro-particles, PMMA.

1. Introduction

The production of polymer micro-particles is relevant in many industrial fields, such as in cosmetics, biomedical engineering and analytical methodologies. Particularly, biocompatible and biodegradable polymers can be largely used in medical

[2] Workshop 1 - College of Mechanical & Electronic Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, China
[3] Corresponding author: Jiang Jing-zhi ;email:jjzhi2000@126.com

applications. For example, biologically active ingredients can be encapsulated in a polymer matrix to be used as controlled drug delivery systems of bioactive agents and drugs. They can be used for this purpose in form of films, sponges, micro-particles[1,2]. However, the most interesting route seems to be the use of micro- and nano-particles[3−5]. Recently, the preparation of the polymer micro- and nano-particles is attracting increasing attention of a considerable number of researchers.

To obtain the polymer micro-particles, some conventional processes, such as sol-vent evaporation, emulsion polymerization, jet-milling and spray drying, were pro-posed. However, the dominated challenges associated with these technologies are solvent residue and non-control of the particle morphology (PM), particle size (PS) and particle size distribution (PSD). At the same time the solvent impurities and surfactants are often toxic and also degrade medicines within polymer matrix[6−7]. In recent years, there are several techniques for the preparation of polymer parti-cles using supercritical fluids (SCFs) to overcome the limitations of the conventional processes. Among these processes, the rapid expansion of supercritical solutions (RESS) process and the supercritical antisolvent (SAS) process are most typical. They take advantage of the specific characteristics of SCF such as the strong solvent power, large diffusivity, low viscosity and surface tension, and inert and nontoxic property if CO is used as SCF. However, the application of RESS process is largely limited by the low solubility of the most polymers solids of interest in supercritical CO_2 ($ScCO_2$). Several researchers have studied the feasibility of preparing polymer microparticles by SAS. The main limitation of this process on its application is the difficulty in the selection of the solvent which can dissolve the polymer and also can be dissolved by $ScCO_2$.

In recent years, a novel supercritical technology named supercritical fluids ex-pansion depressurization (SFED) process has been developed to prepare drug mi-croparticles. Tetracycline, griseofulvin and erythromycin drug microparticles with narrow diameter distribution less than 3m have been obtained. In SFED process, the solute is dissolved in a solvent to form a solution at a certain temperature and pressure. The solution contacts with $ScCO_2$ in a mixing vessel and a solid–liquid–gas ternary phase mixture is formed as the $ScCO_2$ dissolves into the solution. The mixture is sprayed through a nozzle and primary micro-droplets are generated at the exit of the nozzle in a precipitator. The droplets"burst" into the smaller secondary droplets when the $ScCO_2$ is rapidly released from the primary droplets via expan-sion depressurization process. Rapid gasification of the $ScCO_2$ and the solvent in the droplets results in the precipitation of ultimately fine solute particles with the help of the heated gas for evaporation.. In this process $ScCO_2$ as solute has three functions: blowing up the droplets to form smaller ones when it expand to gas from the droplets, decreasing the viscosity and surface tension of the liquid mixture to intensify atomization effect and decreasing the partial pressure of solvent in the gas phase to make solvent gasification easy. In this paper, polymethyl methacrylate (PMMA) was selected as model material to study the feasibility of the preparation of polymer microparticles using this technology. The influences of the operation parameters, such as the temperature and pressure in the mixing vessel, the solution feed rate, the solution concentration and the precipitation temperature, on the par-

ticle morphology, diameter and diameter distribution is investigated in detail and the optimal operation condition of the process is determined.

2. Experimental

2.1. Apparatus and procedures

The experimental apparatus is schematically shown in Fig. 1. It includes three feed lines for CO_2, polymer solution and heating N_2respectively. CO_2 from the cylinder was compressed with a membrane compressor (Beijing Huizhi model G443, country-regionplaceChina) and heated with a heat exchanger, then delivered into a mixing vessel (I.V.500ml) to reach to a desired pressure. The mixing vessel was put into the water bath whose temperature was controlled by a temperature indicator and controller to keep a constant temperature. Through a high-pressure pump (Xingda model LB-10H, China), the polymer solution was simultaneously sent into the mixing vessel where $ScCO_2$ contacts with the liquid solution rapidly to form the polymer-solvent-$ScCO_2$ ternary mixture. The ternary mixture was then sprayed into the precipitator (I.V.4.5L) through a nozzle (I.D.150 μm, 1Cr18Ni9Ti) to produce fine liquid droplets. N2 as heating gas was also introduced into the precipitator to assist evaporating the solvent in the liquid droplets synchronously. Microparticles of polymer were precipitated on the bottom of the precipitator, separated from the gas-solid mixture by a separator and then collected. The gaseous mixture of solvent vapor, CO_2 and N_2 flowed through a condensator where the solvent vapor is condensed. The residual gaseous mixture of CO_2 and N_2 passes through the rotor flowmeter and the flow rate is measured.

1 CO2 cylinder; 2 membrane compressor; 3 solution container; 4 high pressure pump; 5 mixing vessel; 6 heater; 7 N2 cylinder; 8 heat exchanger; 9 precipitator; 10 separator; 11 condensator; 12 flowmeter

2.2. Materials and solvents

PMMA was obtained from Heilongjiang Longxin Chemical Co.Ltd.. Acetone (analytical purity) was obtained from Xinxing Reagent Plant of Shenyang. CO_2, N_2 (high purity, 99%) was supplied by School of Mechanical Engineering, Hebei University of Science Technology. All reagents were used without any further purification.

2.3. Operation condition

As reported in the paper, the phase behavior of the ternary mixture in the mixing vessel plays an important role in the subsequent atomization and particles formation. The polymer concentration and CO_2 mole fraction in the liquid solution should be as high as possible in order to enhance yield of polymer microparticles and to improve the atomization effect to obtain smaller particles with narrow particles size distribution. However, the increase of either polymer concentration or CO_2 content in the solution may results in previous precipitation of particles in the mixing vessel.
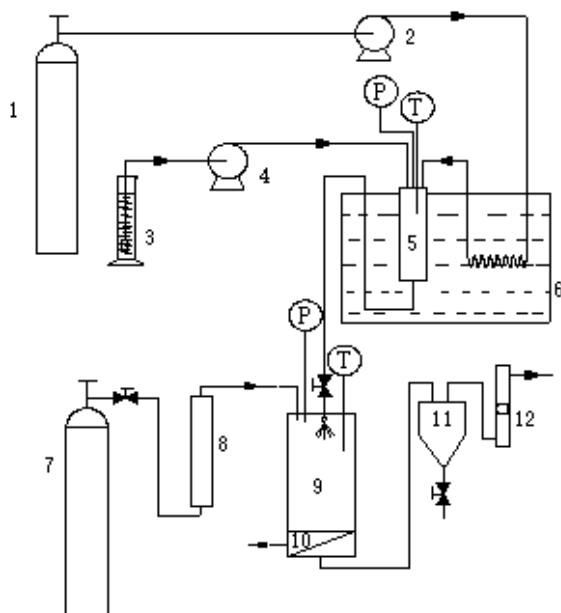
Fig. 1. Schematic drawing of the SFED experimental apparatus

It is reasonable to determine the range of the operation parameters according the ternary phase equilibrium data. Whereas, the exact ternary phase equilibrium data were scarcely presented in the literature. Further, the formation of a homogenous liquid phase in the saturator is required, but in presence of the solute the vapor–liquid equilibrium could become complexity and be significantly modified, especially in the case of high-molecular weight compounds like polymers. Therefore, an experimental study of the feasibility of SFED process to prepare polymer particles is very necessary. Based on above consideration the experimental conditions were determined as shown in table 1. In addition, acetone boiling point and PMMA glass transition temperature is about 57 °C and 110 °C respectively. The temperature was set at 60 °C in the precipitator to ensure complete evaporation of liquid acetone and to prevent the plasticization of micronized polymer particles for obtaining well-dried and well-dispersive micro-particles.

Table 1. Operating parameters of SAA process on PMMA

Polymer	Mixing vessel pressure (MPa)	Mixing vessel temperature (℃)	Solution concentration (mg/ml)	Solution feed rate (ml/min)
PMMA	6, 8, 10, 12	50, 60, 70	10, 20, 30	3, 6, 9

2.4. Particle characterization

The morphology of PMMA particles prepared by the SFED process was characterized with scanning electron microscope (SEM) (KYKY-2800B, KYKY, country-regionplaceChina) at 30KeV. Samples were deposited on carbon sticky tabs and gold coated prior to analysis (KYKY-SDC-12 KYKY ?China). The particles size and the size distribution were measured by the KYKY-SemImage software, and about 200 particles were accounted in each calculation of particles size distribution.

3. Results and discussions

3.1. Influence of the mixing vessel pressure

Fig.2 presents the SEM images of PMMA particles prepared at the mixing vessel pressure of 6MPa(a), 8MPa(b), 10MPa(c) and 12MPa(d) respectively, while other operation parameters were set at: the mixing vessel temperature of 60 °C, the solution concentration of 10mg/ml and the solution feed rate of 3ml/min. Different PM, PD and PDD particles were obtained at different pressures in the mixing vessel as shown in Fig.2. The well-defined sphere particles were obtained only at the mixing vessel pressure of 10MPa and the particles obtained at 6MPa, 8MPa and 10MPa are irregular and tend to doughnut shape. The PDD of obtained at different pressures are shown in Fig.3. The mean PD is 1.1 m, 0.9 m, 0.6 m and 1.0 m. The PDD are in the range of 0.5-2.0 m, 0.4-1.7 m, 0.3-1.1 m and0.6-2.1 m. With the increase of mixing vessel the PD decrease gradually and the PDD become narrower in the range of 6-10MPa while the larger diameter and wider diameter distribution particles in the precipitator and some previous precipitated particles in the mixing vessel were obtained at the mixing vessel pressure of 12MPa.
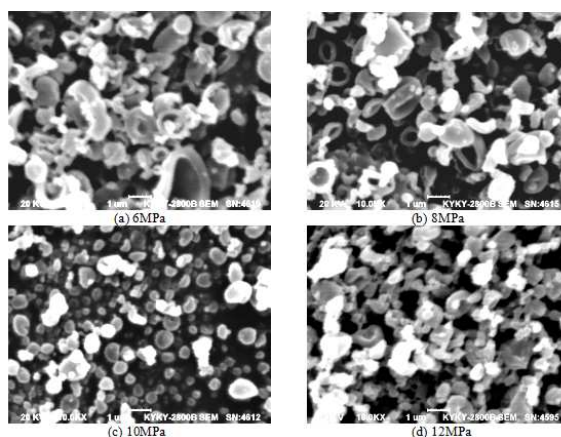

Fig. 2. SEM images of PMMA microparticles prepared at different pressures in the mixing vessel

As mentioned above, in the presence of polymer in the ternary system the phase
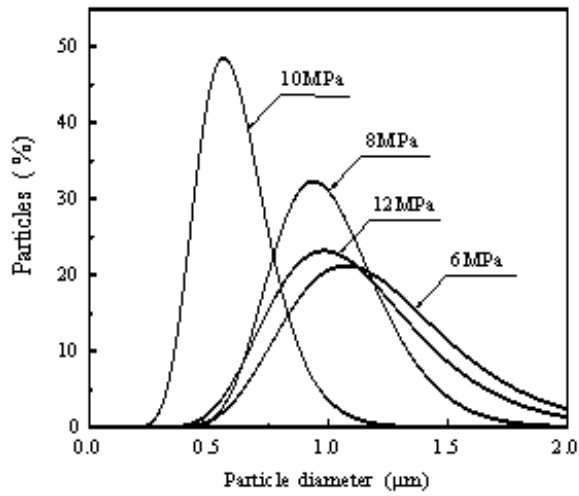
Fig. 3. PMMA micro-particle diameter distribution curves at different pressures in the mixing vessel
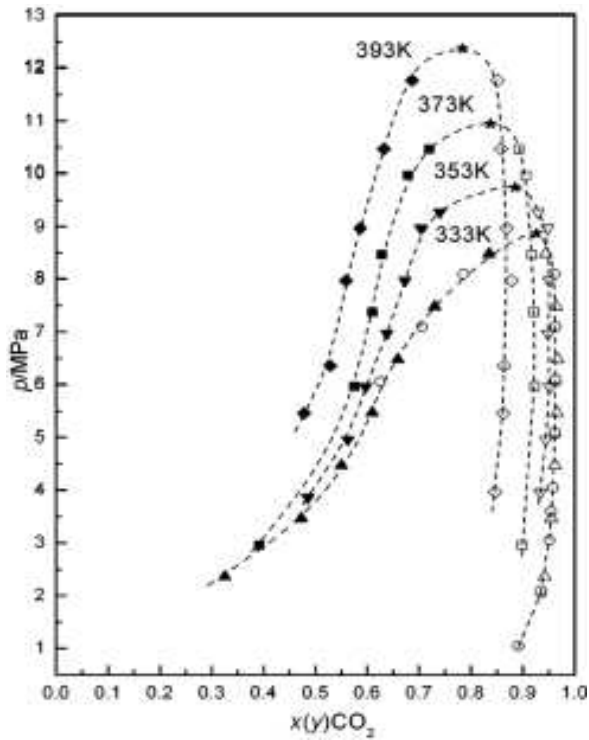

Fig. 4. diagram of the carbon dioxide acetone system

behavior may become complexity. The phase separation phenomena in the initial

polymer solution may take place when supercritical CO_2 dissolved in the initial polymer solution. Han et al provided the vapor-liquid equilibria curves of the CO_2-acetone system at pressure from 2.36 to 11.77MPa and temperature from 333.15 to 393.15K as shown in Fig.4. It can be seen that at the mixing pressure of 6 and 8MPa, there is two phase of vapor and liquid which reach to equilibrium state in CO_2-acetone system. When the polymer solution flow through the mixing vessel which is filled by supercritical CO_2, it is probable that the polymer solution was separated into polymer-lean phase (consisting of abundant CO_2, acetone and less polymer) and polymer-rich phase (consisting of abundant polymer, acetone and less CO_2). Polymer-lean phase can be atomized into droplets perfectly through the nozzle because of high mole fraction of CO_2in the liquid solution and some nano-particles can be obtained. When the polymer-rich phase sprayed into the precipitation through the nozzle, the high surface tension and viscosity lead to a bad atomization and some irregular polymer particles were obtained. When the pressure rose to 10MPa, the operation parameters (temperature and pressure) are near the critical points of liquid phase and gas liquid and the dividing line between the liquid and gas phase even the polymer-rich phase and polymer-lean phase. The total system can be takes as approximately homogenous phase in which enough CO_2 (about mole fraction of 0.8)dissolved into the system to reduce the surface tension and viscosity and enhance the subsequent atomization. The well-defined sphere polymer micro-particles were obtained in the precipitation. At the mixing vessel pressure of 12MPa, the operating condition is located in the complete miscibility region in which a mass of acetone dissolved into supercritical CO_2 rapidly and supercritical CO_2'santi-solvent function become significant. Some previous polymer particles were obtained in the mixing vessel and the yield of final product reduced. With dissolving of acetone into supercritical CO_2 the polymer solution presents an increasing surface tension and viscosity. So some irregular micro-particles were observed in the precipitator for bad atomization through the nozzle at the mixing vessel pressure of 12MPa.

3.2. Influence of the mixing vessel temperature

Fig.5 presents the SEM images of PMMA particles prepared at the mixing vessel temperature of 50°C (a), 60°C (b) and 70°C (c)respectively, while others operation parameters were set at: the mixing vessel pressure of 8MPa, the solution concentration of 10mg/ml, the solution feeding rate of 6ml/min and the precipitation temperature of 60°C. The diameters and diameter distribution of the particles prepared at the different temperatures in the mixing vessel are shown in Fig. 6. From Fig.3, we can see that the morphology of the particles prepared at the three different temperatures in the mixing vessel is spherical or approximately spherical. There is little change in the PD and PDD at the mixing vessel temperature of 60 and 70°C as shown in Fig.6. When the temperature decreased to 50°C, the PD increase and the PDD become wider. The diameters of micro-particles prepared at three different mixing vessel temperatures lie probably in the range of 1-3μm.

At the higher pressure and lower temperature, the anti-solvent function of supercritical CO_2 is very prominent. Dissolving of a mass of acetone into supercritical
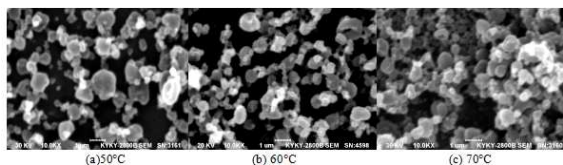
Fig. 5. SEM images of PMMA microparticles prepared at different temperatures
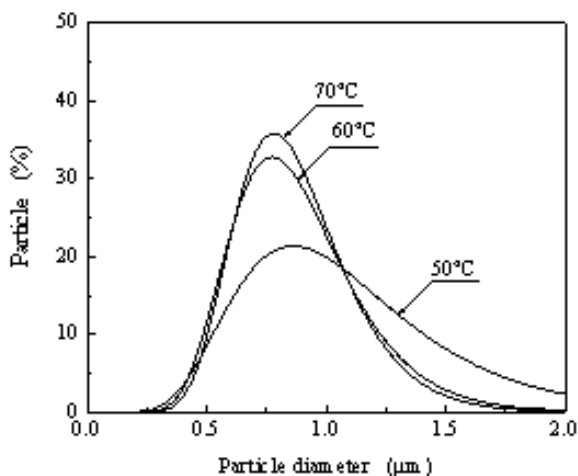in the mixing vessel

Fig. 6. PMMA micro-particle diameter distribution curves at the different
temperatures in the mixing vessel

CO_2 and lower temperature all lead to the increase of the surface tension and viscosity of PMMA solution. The larger diameter and wider diameter distribution micro-particles were obtained at the mixing vessel temperature of 50°C. At the temperature of 60°C, the operating parameters is near the critical point of vapor and liquid of CO_2-acetone system as shown in Fig.4. The enough CO_2 mole fraction and uniform ternary solution lead to the preparation of smaller diameter and narrow diameter distribution particles. When the temperature increase to 70°C, although the phase separation is probably to take place because operating conditions is located in two phase region and the surface tension and viscosity of polymer-rich phase is probably to increase, while the increase of the temperature results possibly in the decrease of the surface tension and viscosity of polymer-rich phase. These two opposite effects might offset each other and weaken the influence of the mixing vessel temperature on the particle to a certain extent. There is little change in the PD and PDD at the mixing vessel temperature of 60 and 70°C.

3.3. Influence of the solution concentration

Fig.8 presents the SEM images of PMMA particles prepared at the solution concentration of 10mg/ml(a), 20mg/ml(b) and 30mg/ml(c) respectively, while others

operation parameters were set at: the pressure of 10MPa and the temperature of 60℃ in the mixing vessel, the solution feed rate of 3ml/min. The diameters and diameter distribution of the particles prepared at different solution concentration are shown in Fig.9. It can be seen from Fig.8 and Fig.9 that, there is a remarkable difference in the PD and the PDD of micro-particle prepared at different solution concentration. At the solution concentration of 10mg/ml, smaller PD, narrower PDD and well-defined spherical micro-particles were obtained. Larger PD, wider PDD and disk-like shape or doughnut-like micro-particles were at 20mg/ml and 30mg/ml. with the increase of the solution concentration the PD increases, the PDD becomes wider and the particles become irregular.

The increase of the polymer solution concentration enhances greatly the density, the viscosity and surface tension of the mixture solution in the mixing vessel[24]. While, according to the mechanism of atomization, the droplet shapes obtained from atomization are decided by the viscosity and surface tension of the mixture when the atomization process Web number remains a constant.

These factors would lead to an imperfect atomization effect and the droplets tend to turn into the disc-shaped objects

The increase of the solution concentration enhances the viscosity of the mixture in the mixing vessel, which might make the subsequent atomization process imperfect. At the same time, with the increase of the solution concentration, it is easy to take place that phase separation resulting from the dissolving of CO_2 into PMMA solution and higher surface tension and viscosity polymer-rich phase formed. With the continuing dissolving and diffusing between acetone and CO_2, the polymer-rich phase is possible to form gel-like solution even to vitrify or solidify in the presence of polymer. When such solutions were sprayed into precipitation through the nozzle the bad atomization process and irregular micro-particles were obtained. The polymer solution concentrations have remarkable influences on microparticles. In the range of this work, the optimal solution concentration should be set at 10mg/ml.
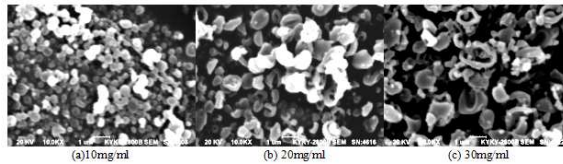

Fig. 7. SEM images of PMMA microparticles prepared at the different solution concentrations

3.4. Influence of the solution feed rate

Fig.10 presents the SEM images of PMMA particles prepared at the solution feed rate of 3ml/min(a), 6ml/min (b) and 9ml/min(d) respectively, while others operation parameters were set at: the mixing vessel pressure of 10MPa, the temperature of 60℃, the solution concentration of 10mg/ml and the precipitation temperature of 60℃. The diameters and diameter distribution of the particles prepared at different solution feed rates are given in Fig.11. It can be seen that, there are also great
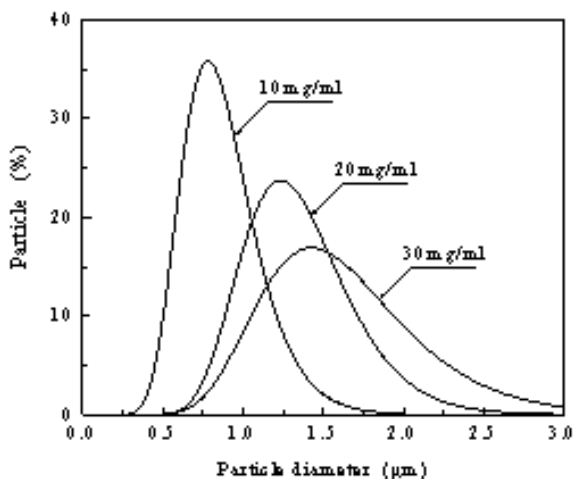
Fig. 8. PMMA microparticle diameter distribution curves at the different solution concentrations

influences of the solution feed rate on the PM, PD and PDD. At the solution feed rate of 3ml/min, most of particles are well dispersive and their shapes are spherical. The diameters of most particles are in the range of 0.5-1.3μm. When the solution feed rate rises to 6ml/min, the PD obtained becomes larger, the PDD becomes wider with the diameter between 0.5 2.0μm, the PSs become irregular and the particles tend to cohere together. At the solution feed rate of 9ml/min, few particles present spherical shape and most irregular and disk-like particles were obtained.

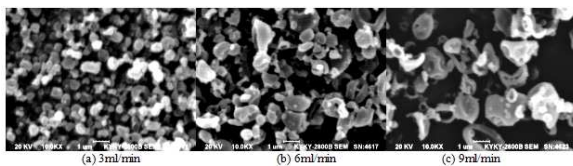In the range of this work, the optimal solution feed rate should be set at 3ml/min.

Fig. 9. SEM images of PMMA microparticles prepared at the different solution feed rates

At the lower solution feed rate the thickness of the liquid film in the nozzle is thinner, the mixing solution can be effectively atomized assisted by ScCO$_2$ and the original droplets can be successfully blown up into secondary ones. At the higher solution feed rate the thickness of the liquid film becomes thicker and polymer solution has a higher viscosity and surface tension. These are the possible reasons that the mixture solution in the mixing vessel can not be atomized successfully to spherical droplets by flow velocity difference between gas and liquid and the particles obtained tend to disk-like.
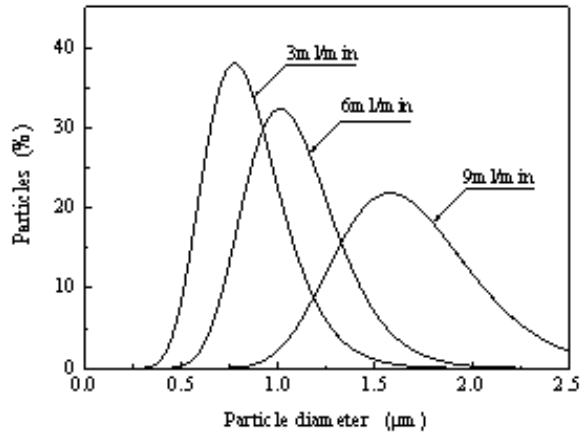
Fig. 10. PMMA microparticle diameter distribution curves at the different
solution feed rates

4. Conclusions

PMMA micro-particles can be prepared by SFED process successfully. Most of particles are spherical or approximately spherical with the diameter less than 3 m and a narrow diameter distribution. The pressure in the mixing vessel and the solution concentration are two most effective operation parameters while the solution feed rate is the less effective one. The temperatures in the mixing vessel and the precipitator have a little influence on the particles. The PM, PS and PSD could be controlled by adjusting operation parameters. With the increase of the mixing vessel pressure, the PS decreases obviously and the PSD becomes narrower. There is a more notable effect of the pressure on the particles in the range of 6-8MPa than 8-10MPa. With the increase of the solution concentration, the PS becomes larger, PSD becomes wider and the PM becomes more irregular. The higher solution feed rate results in more irregular morphology of the particles, the larger particle size and the wider size distribution. Although the temperatures in the mixing vessel and the precipitator have little effect on the PM, PS and PSD, they have great influence on the yield of the final product. The optimal operation parameters for preparing PMMA micro-particles in the range of this work are: the pressure of 8MPa and the temperature of 60℃ in the mixing vessel, the solution feed rate of 6ml/min, the solution concentration of 10mg/ml and the precipitation temperature of 60 ℃.

References

[1] A. GRECE, S. SENHORINI: *Farago Microparticles of poly(hydroxybutyrate-co-hydroxyvalerate) loaded with andiroba oil: Preparation and characterization.* Materials Science and Engineering *32* (2012), 1121–1126.

[2] G. C. BAZZO,   E. LEMOS-SENNA,   A. T. N. PIRES: *Poly(3-*

hydroxybutyrate)/chitosan/ketoprofen or piroxicam composite microparticles. Preparation and controlled drug release evaluation 77 (2009), 839–844.

[3] M. STEVANOVIC, I. BRACKO, M. MILENKOVIC: *nanoparticles and ascorbic acid with simultaneous antioxidative and prolonged antimicrobial activity.* Acta Biomaterialia 10 (2014), 151–162.

[4] R. BAI, T. QIU, F. HAN: *Preparation and characterization of emulsifier-free polyphenylsilsesquioxane-poly .* Applied Surface Science 282 (2013), 231-235.

[5] D. CAITLIN, D. LEMKE, M. SEANGEARY, B. VIJAYA: *Antigen-coated polya-hydroxy acid based microparticles for heterologous prime-boost adenovirus based vaccinations.* Biomaterials 34 (2013), 2524–2529.

[6] A. MART, M. J. COCERO: *Micronization processes with supercritical ?uids: Fundamentals and mechanisms.* Drug Deliv 60 (2008) 339–350.

[7] K. MISHIMA: *Biodegradable particle formation for drug and gene delivery using supercritical uid and dense gas.* Adv 60 (2008),411–432.

[8] K. MATSUYAMA, Z. D. HUI, T. URABE: *Formation of l-poly(lactic acid) microspheres by rapid expansion of CO2 saturated polymer suspensions.* J. of Supercritical Fluids 33 (2005) 275–288.

[9] J. MOHAMMED, MEZIANI, P. PATHAK, F. BEACHAM, F. LAWRENCE: *Nanoparticle formation in rapid expansion of water-in-supercritical carbon dioxide microemulsion into liquid solution.* J. of Supercrit Fluids 34 (2005) 91–97.

[10] E. REVERCHON, R. ADAMI, G. CAPUTO, I. D. MARCO: *Spherical microparticles production by supercritical antisolvent precipitation: Interpretation of results.* J. of Supercrit Fluids 47 (2008) 70–84.

[11] S. CHOI, K. LEE, S. KWON: *Preparation of fine particles of poly(N-vinyl-2-pyrrolidone-co -2-methylene-1,3-dioxepane) using supercritical antisolvent.* J. of Supercrit Fluids 37 (2006) 287–291.

[12] L. Z. YI, J. J. ZHI, L. X. WU: *Preparation of tetracycline microparticles suitable for inhalation administration by supercritical fuid expansion depressurization.* Chemical Engineering and Processing 47 (2008) 1311–1316.