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Micronization of Theophylline by a New Spray Drying Using Supercritical Carbon Dioxide as an Atomizing Medium

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----------*ABSTRACT*----------
We report on the production of theophylline fine particles by a new spray drying using supercritical carbon dioxide as an atomizing medium. The powders produced were agglomerates, composed of spherical, columnar or plate-like primary crystals with a mean size of around 250 nm, which was 280 times smaller than that of the virgin particles. There were no liquid solvents (i.e. residual solvents) in the crystals produced. The crystal structure of the theophylline powders did not change after the micronization by the present technique: it was the kinetically stable form at room temperature, i.e. form II. This process is a versatile process, applicable for several substances, and can be operated at low processing costs due to the relatively low operating pressures, low gas consumption and operation in a continuous mode. Compared with conventional spray dryings, the present technique can also be used at much lower drying temperatures, resulting in less degradation and lower energy consumption.
KEYWORDS;-*supercritical carbon dioxide, spray drying, microparticles, theophylline, atomization*

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I. INTRODUCTION

Micro or nanoparticles produced by micronization cause a change in their surface areas, structures, and functional properties due to the reduction of particle sizes. Micronization processes motivate the academic research as well as industrial research [1]. The application of micronization in pharmaceutical industries is important because most pharmaceutical compounds are poor water soluble [2]. It has been reported that approximately 40% of currently marketed drugs and up to 75% of currently developing compounds have been suggested to be poorly water soluble [3]. Furthermore, the problem of low solubility in water may well be increasing [3, 4]. Therefore, the bioavailability is low, and the dosage used is high [2]. As a solution to this problem, a micronization of pharmaceutical compounds is effective to improve solubility and dissolution rates of drugs into the living body. Particles with very high surface area per mass compared to large particles are more biologically active, i.e. high bioavailability. This is supported by the Gibbs-Thomson equation (also called Ostwald-Freundlich equation) [5] which shows that solubility of drugs increases exponentially as a function of particle sizes [6]. In addition, the Noyes-Whitney equation [5] demonstrates that the dissolution rate is directly proportional to the increasing the surface area of the pharmaceutical compounds. Conventional micronization processes are mechanical comminution (i.e. crushing, grinding, and milling), solute recrystallization, and spray drying. For example, spray drying is one of the most interesting technology used in the pharmaceutical fields [7]. However, these processes have some disadvantages such as impurity contamination from a comminution device, difficulty in controlling the particle size and particle size distribution, excessive use of solvents, thermal and chemical degradation of solutes, and high residual solvents [2, 8–12]. As an alternative to the conventional processes, the micronization of drugs using supercritical fluids techniques has been proposed and is gaining much attention [1, 2, 6, 10]. The technique using supercritical fluids has been developed in order to minimize the undesirable problems caused by conventional processes [1]. Supercritical fluids are an attractive medium due to the moderate solvent power and favorable transport properties in mass transfer rates. In particular, carbon dioxide (CO_2) is the most common and useful for pharmaceutical applications because it has some advantages such as relatively low critical point (304.12 K and 7.374 MPa), non-toxic, nonflammable, easy to recycle, and relatively safe [1, 6, 13]. Supercritical CO_2 for micronization can be used as: 1) a solvent for drugs in the rapid expansion of supercritical solutions (RESS); 2) an anti-solvent for the precipitation of drugs dissolved in organic solvents in the supercritical anti-solvent recrystallization (SAS); 3) a solute in the particles from gas saturated

solution (PGSS). However, these processes have some problems of low applicability to drugs and difficulty to produce submicron sized particles and to control the particle sizes [14–18]. Recently, atomization processes using supercritical CO_2 as atomizing media have been proposed as the effective micronization processes. The processes can be considered to be modifications of the conventional spray drying. For example, CO_2 assisted nebulization-bubble dryer (CAN-BD) has been proposed by Sievers et al. [19–21]. This process is based on the mixing of a liquid solution and supercritical CO_2 in a low dead volume tee and subsequent atomization to near atmospheric pressure though a capillary flow restrictor. Supercritical assisted atomization (SAA) has been proposed by Reverchon et al. [22–25]. This process is based on the solubilization of supercritical CO_2 in liquid solutions in which a solute is dissolved using a saturator that contains high surface packing and ensures long residence times. A near equilibrium solution is subsequently atomized through a nozzle into a near atmospheric precipitator. This process has two-step atomization contained in which primary droplets are generated by pneumatic atomization at the outlet nozzle and are further divided into secondary droplets by rapidly releasing CO_2. In addition, many similar methods such as PGSS-drying [26], supercritical fluids assisted atomization introduced by hydrodynamic cavitation mixer (SAA-HCM) [27], supercritical CO_2 assisted solubilization and atomization (SCASA) [28], supercritical CO_2-assisted spray-drying (SASD) [29], and modified PGSS [30, 31] processes have been proposed.

We propose a new spray drying using supercritical CO_2 as an atomizing medium which is similar to CAN-BD and SAA. However, unlike the techniques, a solution and supercritical CO_2 can perform contact and mixture moderately in a mixing part in the present technique for preventing clogging of piping by precipitated crystals and creation of finer droplets. This work aims to elucidate the applicability of the present technique using supercritical CO_2 as an atomizing medium to the production of fine powders of a drug (model compound; theophylline) and to analyze the crystal characteristics of particles produced by the present technique. Theophylline, shown in Fig. 1, is one of the xanthine derivatives, which is bronchodilator to treat asthma and is however a poorly water-soluble compound.

II. EXPERIMENTAL

Materials

High-purity CO_2 (supplied by Showa Denko Gas Products Co., Ltd., its purity is greater than 99.99%) was used as an atomizing medium, and was supplied through a dryer, in which 5A molecular sieve particles were packed to remove impurities such as water. Nitrogen (supplied by Okaya Sanso, Co., Ltd.) was used as a drying gas in a drying chamber. A mixture of ethanol (supplied by Kanto Chem., Co., Inc.; its purity is 99.5%) and dichloromethane (supplied by Kanto Chem., Co., Inc.; its purity is 99.5%) were used as a liquid solvent in 1:1 volume ratio. Theophylline (supplied by Wako Pure Chem., Ind., Ltd.; its purity is greater than 99%) was used as a solute. Figure 2 shows the SEM photograph of the virgin theophylline particles. The morphology of virgin particles was plate-like and the mean size of those was 71 μm with the particle size distribution (CV: 65%) as shown in Fig. 3.

Apparatus and Procedures

The apparatus was basically a flow-type arrangement consisting of three sections, i.e. 1) a section for supplying CO_2 and a liquid solution, 2) a section of contact and mixing of supercritical CO_2 and the liquid solution, and 3) a section of drying and collection of particles produced. The apparatus is shown schematically in Fig. 4. Carbon dioxide was supplied from a CO_2 cylinder (1) and liquefied via the cooling unit (5). The liquefied CO_2 was sent to the pre-heater (8) by the feed pump (6) (Nihon Seimitsu Kagaku Co. Ltd., NP-FX-40(J)). The CO_2 passed through the preheater which is a tube of 2 m-length and 1/8 inch-outer diameter heated using glass fiber heating tapes (AS ONE Co.), which was controlled using a proportional integral derivative (PID) controller thermostat (AS ONE Co., TC-1000) at an experimental temperature controlled to within ±1 K, and became a supercritical fluid. After opening valve V2, the supercritical CO_2 was introduced into the low volume tee (i.e. the mixing section) (9) (Swagelok Co., Union cross of SS-400-4 in which an upper fitting was sealed with a cap). After opening valve V3, a prepared liquid solution adjusted to the desired concentration (10) was introduced into the low volume tee by high-pressure pump (11) (Tokyo Rikakikai Co. Ltd., KP-12-13) through the preheater which is a SUS316 tube of 2 m-length and 1/8 inch-outer diameter heated using glass fiber heating tapes (AS ONE Co.), which was controlled using a proportional integral derivative (PID) controller thermostat (AS ONE Co., TC-1000) at an experimental temperature controlled to within ±1 K. The temperature of the low volume tee was also heated using glass fiber heating tapes (AS ONE Co.), which was controlled using a proportional integral derivative (PID) controller thermostat (AS ONE Co., TC-1000) at an experimental temperature controlled to within ±1 K, and the temperature was measured with a type K thermocouple connected to the temperature indicator (TI) (Yokogawa Test & Measurement Co., TX10-01) with accuracy of ±0.1 K.

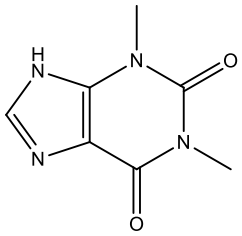


Fig. 1 Chemical structure of theophylline.

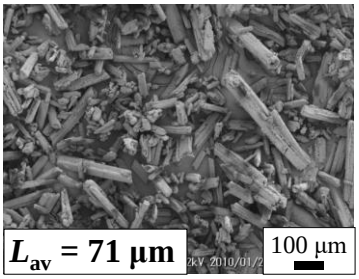


Fig. 2 SEM photograph of virgin theophylline particles.

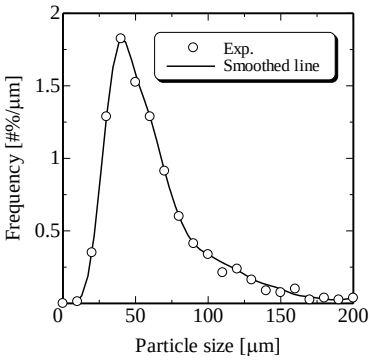
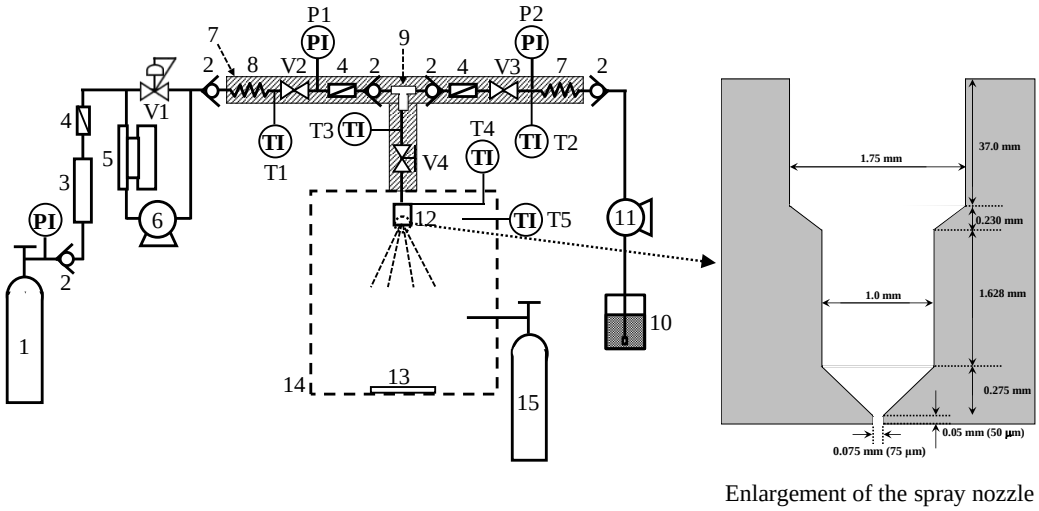


Fig. 3 Particle size distributions (PSD) of virgin theophylline particles.

The pressure in the low volume tee was controlled by the back-pressure regulator (TESCOM, 26-1762-24). The pressure was measured using a pressure transducer (Kyowa Electronic Instruments Co., Ltd., PG-500KU) with accuracy of ±0.1 MPa, which was connected to the pressure indicator (PI) (Kyowa Electronic Instruments Co., Ltd., WGA-710A). The liquid solution was intimately mixed with the supercritical CO_2 through the low volume tee to generate a gas-liquid emulsion or a solution in which CO_2 is dissolved. The resultant solution was rapidly expanded through a 75-µm-diameter and 50-µm-long drilled capillary spray nozzle (12) into a drying chamber (14) filled with a heated nitrogen gas at atmospheric pressure, forming a primarily aerosol of microbubbles and microdroplets which were further broken by the expansion of dissolved CO_2 in the solution. Dry powders produced by rapid drying of the aerosol droplets were collected on a glass tray (13) placed at the bottom of the drying chamber.

The parameters of the section which supplies supercritical CO_2 and a liquid solution (i.e. the CO_2 temperature, T_{CO2}, the liquid solution temperature, T_{sol}, the flow rate of the liquid solution, q_{sol} and the concentration of the liquid solution, C_{sol}) were as follows: T_{CO2} = 308.2 K, T_{sol} = 308.2 K, q_{sol} = 5.0 mL/min, and C_{sol} = 10.0 kg/m^3. The parameters of the mixing section of supercritical CO_2 and a liquid solution (i.e. the mixing temperature, T_{mix} and the mixing pressure, P_{mix}) were as follows: T_{mix} = 308.2 K and P_{mix} = 10.0 MPa. The temperature of spray nozzle and drying chamber, T_{noz} and T_{dry} was 343.2 K.



Enlargement of the spray nozzle

Fig. 4 Schematic diagram of the experimental apparatus; (1) liquefied CO_2 cylinder, (2) stopper, (3) dryer, (4) filter, (5) cooling unit, (6) CO_2 feed pump, (7) heating cables (slanted line parts), (8) pre-heater, (9) low volume tee (mixing section), (10) a liquid solution, (11) liquid solution feed pump, (12) spray nozzle, (13) glass tray (particles collection), (14) drying chamber, (15) N_2 cylinder, (PI) pressure indicator, (TI) temperature indicator, (V1) back-pressure regulator, (V2 and V3) stop valves, (V4) needle valve to control a flow rate.

Analysis

The morphology of unprocessed and produced particles was characterized using a scanning electron microscope (SEM) (Keyence Co., VE-9800). The sputter coater covered a thin layer of Pt/Pd to the SEM samples. Particle sizes was determined by an image analysis of photomicrographs that is the counting at least

800 particles from the photomicrographs and by the diameter based on the Ferret diameter. Fourier transform infrared (FTIR) spectroscopy was also performed using a JASCO FT/IR-4200 spectrophotometer (with a spectral resolution of 4 cm^{-1}) in order to analyze possible residual solvents in particles produced by the present technique. The transmittance was measured according to the KBr technique using potassium bromide pellets. The spectra were collected in the range from 7800 to 350 cm^{-1} range. The crystal structure of the particles produced was analyzed using powder X-ray diffraction (XRD) (Rigaku Co., Miniflex II) with a CuKα radiation source. The diffraction patterns were measured with a voltage of 30 kV and a current of 15 mA in the angle range $2^o < 2\theta < 60^o$ with a scan rate of 0.02º/min. Thermal analysis was performed using a differential scanning calorimetry (DSC) (Rigaku Co., ThermoPlus EVODSC-8230). For the DSC analysis, each sample (2 mg) was placed in an aluminum pan and heated at a rate of 2 K/min from room temperature to 563.2 K.

III. RESULTS AND DISCUSSION

Figure 5 shows an SEM photograph of the micronized particles by the present technique. From this figure, the powders produced were agglomerates, composed of spherical, columnar or plate-like primary crystals with a mean size of around 250 nm. The particle size of the primary particles was very small (the mean size: around 250 nm) with the narrow particle size distribution (CV: around 38%) as shown in Fig. 6, which was 280 times smaller than that of the virgin particles. Moreover, the mean size of particles produced by the present technique was 5 times smaller than that of around 1.3 μm of particles produced by the conventional spray drying [32]. As shown in Fig. 7, there was no residual solvents in the crystals produced because the positions of the absorption peaks in the FTIR spectra of the virgin and the processed theophylline particles are almost the same, i.e. the absorption peaks of ethanol (620–680 cm^{-1}) [33] and dichloromethane (717 cm^{-1}) [33] were not observed after micronization. Table 1 shows the melting temperatures and enthalpies of fusion measured using DSC analysis of virgin particles, particles produced by the present technique with those of literature data [34, 35]. Comparing between the melting temperature and enthalpy of fusion of virgin particles and those of the particles produced by the present technique, the melting temperature and enthalpy of fusion of particles produced by the present technique was almost the same as those of virgin particles and literature data. In Figs. 7 and 8, FTIR and XRD analyses showed that the crystal structure of the theophylline particles did not change after the micronization by the present technique because the positions of the peaks in the FTIR spectra and the XRD patterns of the virgin and the processed theophylline particles are almost the same. Theophylline has one hydrate (Form M) and four anhydrous forms (Form I, II, III and IV) [34–36]. The crystal structure of the particles produced was the kinetically stable form at room temperature, i.e. Form II.

In the present technique, supercritical CO_2 and the liquid solution will be well contacted and mixed in the low volume tee, and became a gas-liquid emulsion or a solution in which CO_2 is dissolved, followed by the forming a primarily aerosol of microbubbles and microdroplets which were further broken by the expansion of dissolved CO_2 in the solution. This would make it possible to produce microparticles. This shows the mixing amount of supercritical CO_2 and a liquid solution is important and the size of particles by the present technique can be controlled by the mixing method and the ratio of the mixture of supercritical CO_2 and a liquid solution.

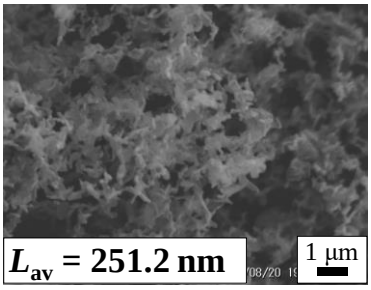


Fig. 5 SEM photograph of processed theophylline particles.

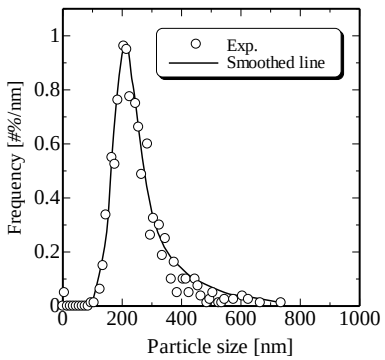


Fig. 6 Particle size distributions (PSD) of processed theophylline particles.

Table 1 DSC analyses of melting points and enthalpy of fusions of virgin particles, particles produced by the present technique, and literature data

	Melting temperature, T_m [K]	Enthalpy of fusion, H_{fus} [J/g]
Literature data [34, 35]	543.9	167.1
Virgin theophylline	543.8	145.2
Theophylline particles produced by the present technique	543.7	142.8

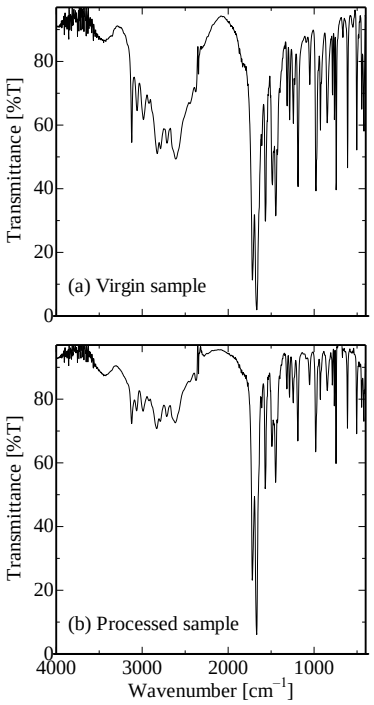


Fig. 7 FT-IR spectra of theophylline; (a) virgin particles, and (b) particles produced.

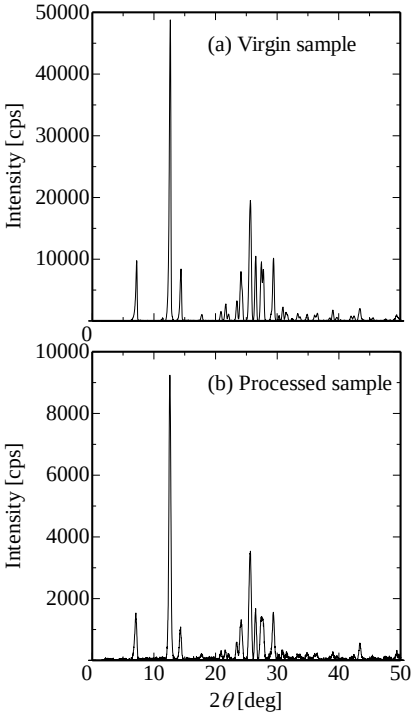


Fig. 8 XRD patterns of theophylline; (a) virgin particles, and (b) particles produced.

IV. CONCLUSION

We elucidated the applicability of the new spray drying using supercritical CO_2 as an atomizing medium to the production of fine particles of theophylline and analyzed the crystal characteristics of particles produced by the present technique. The powders produced were agglomerates, composed of spherical, columnar or plate-like primary crystals with a mean size of around 250 nm, which was 280 times smaller than that of the virgin particles. The crystal structure of the theophylline powders did not change after the micronization by the present technique: it was the kinetically stable form at room temperature, i.e. form II. This technique is versatile process, applicable for several substances, and can be operated at low processing costs due to the relatively low operating pressures, low gas consumption and operation in a continuous mode. Compared with conventional spray drying, the present technique would be used at much lower drying temperatures, resulting in less degradation and lower energy consumption.

REFERENCES

[1]. W.L. Priamo, I. Dalmolin, D.L. Buschetto, N. Mezzomo, S.R.S. Ferreira, J.V. Oliveira, "Micronization processes by supercritical fluid technologies: a short review on process design (2008-2012)", Acta Scientiarum. Technol., 35: 695–709, 2013.
[2]. N. Esfandiari, "Production of micro and nano particles of pharmaceutical by supercritical carbon dioxide", J. Supercrit. Fluids, 100: 129–141, 2015.
[3]. H.D. Williams, N.L. Trevaskes, S.A. Charman, R.M. Shanker, W.N. Charman, C.W. Pouton, C.J.H. Porter, "Strategies to address low drug solubility in discovery and development", Pharmacol, Rev., 65: 315–499, 2013.
[4]. T. Takagi, C. Ramachandran, M. Bermejo, S. Yamashita, L.X. Yu, G.L. Amidon, "A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan", Mol. Pham., 3: 631–641, 2006.
[5]. J.W. Mullin, "Crystallization 4th ed.", Butterworth-Heinemann, Oxford, 2001.
[6]. T. Yasuji, H. Takeuchi, Y. Kawashima, "Particle design of poorly water-soluble drug substances using supercritical fluid technologies", Adv. Drug Deliv. Rev., 60: 388–398, 2008.
[7]. M. Gil, J. Vicente, F. Gaspar, "Scale-up methodology for pharmaceutical spray drying", Chim. Oggi-Chem. Today, 28: 18–22, 2010.
[8]. W.Z. He, Q.L. Suo, Z.H. Jiang, Shan A, H.L. Hong, "Precipitation of ephedrine by SEDS process using a specially designed prefilming atomizer", J. Supercrit. Fluids, 31: 101–110, 2004.

[9]. E. Franceschi, M.H. Kunita, M.V. Tres, A.F. Rubira, E.C. Muniz, M.L. Corazza, C. Dariva, S.R.S. Ferreira, J.V. Oliveira, "Phase behavior and process parameters effects on the characteristics of precipitated theophylline using carbon dioxide as antisolvent", J. Supercrit. Fluids, 44: 8–20 2008.

[10]. A. Martin, M.J. Cocero, "Micronization processes with supercritical fluids: Fundamentals and mechanisms", Adv. Drug Deliv. Rev., 60: 339–350, 2008.

[11]. M. Müler, U. Meier, A. Kessler, M. Mazzotti, "Experimental study of the effect of process parameters in the recrystallization of an organic compound using compressed carbon dioxide as antisolvent", Ind. Eng. Chem. Res., 39: 2260–2268, 2000.

[12]. H. Kröber, U. Teipel, "Materials processing with supercritical antisolvent precipitation: process parameters and morphology of tartaric acid", J. Supercrit. Fluids, 22: 229–235, 2000.

[13]. S. Palakodaty, P. York, "Phase behavioral effects on particle formation processes using supercritical fluids", Pham. Res., 16: 976–985, 1999.

[14]. A. Shariati, C.J. Peters, "Measurements and modeling of the phase behavior of ternary systems of interest for the GAS process: I. The system carbon dioxide + 1-propanol + salicylic acid", J. Supercrit. Fluids, 23: 195–208, 2002.

[15]. E. Reverchon, "Supercritical antisolvent precipitation of micro- and nano-particles", J. Supercrit. Fluids, 15: 1–21, 1999.

[16]. A.H.L. Chow, H.H.Y. Tong, P. Chattopadhyay, B.Y. Shekunov, "Particle engineering for Pulmonary Drug Delivery", Pharm. Res., 24: 411–437, 2007.

[17]. T.K. Fahim, I.S.M. Zaidul, M.R. Abu Baker, U.M. Salim, M.B. Awang, F. Sahena, K.C.A. Jalal, K.M. Sharif, M.H. Sohrab, "Particle formation and micronization using non-conventional techniques– review", Chem. Eng. Process., 86: 47–52, 2014.

[18]. A.S. Silva, M.T. Tavares, A. Aguiar-Ricardo, Sustainable strategies for nano-in-micro particle engineering for pulmonary delivery, J. Nanopart. Res., 16: 1–17, 2014.

[19]. R.E. Sievers, U. Karst, "Methods for fine particle formation", US Patent 5639441, 1997.

[20]. R.E. Sievers, E.T.S. Huang, J.A. Villa, J.K. Kawamoto, M.M. Evans, P.R. Brauer, "Low-temperature manufacturing of fine pharmaceutical powders with supercritical fluid aerosolization in a Bubble Dryer®", Pure Appl. Chem., 73: 1299–1303, 2001.

[21]. S.P. Cape, J.A. Villa, E.T.S. Huang, T.H. yang, J.F. Carpenter, R.E. Sievers, "Preparation of active proteins, vaccines and pharmaceuticals as fine powders using supercritical or near-critical fluids", Pharm. Res., 25: 1967–1990, 2008.

[22]. E. Reverchon, "Supercritical-assisted atomization to produce micro- and/or nanoparticles of controlled size and distribution", Ind. Eng. Chem. Res., 41: 2405–2411, 2002.

[23]. E. Reverchon, G.D. Porta, "Particle design using supercritical fluids", Chem. Eng. Technol., 26: 840–845, 2003.

[24]. E. Reverchon, G.D. Porta, "Micronization of antibiotics by supercritical assisted atomization", J. Supercrit. Fluids, 26: 243–252, 2003.

[25]. E. Reverchon, "Process for the production of micro and/or nano particles", US Patent 7276190 B2, 2007.

[26]. D. Meterc, M. Petermann, E. Weidner, "Drying of aqueous tea extracts using a supercritical fluid spray process", J. Supercrit. Fluids, 45: 253–259, 2008.

[27]. M.Q. Cai, Y.X. Guan, S.J. Yao, Z.Q. Zhu, "Supercritical fluid assisted atomization introduced by hydrodynamic cavitation mixer (SAA-HCM) for micronization of levofloxacin hydrochloride", J. Supercrit. Fluids, 43: 524–534, 2008.

[28]. N. Hijazi, E. Rodier, J.J. Letourneau, H. Louati, M. Sauceau, N.L. Moigne, J.C. Benezet, J. Fages, "Chitosan nanoparticles generation using CO_2 assisted processes", J. Supercrit. Fluids, 95: 118–128, 2014.

[29]. R.P. Cabral, A.M.L. Sousa, A.S. Silva, A.I. Paninho, M. Temtem, E. Costa, T. Casimiro, A. Aguiar-Ricardo, "Design of experiments approach on the preparation of dry inhaler chitosan composite formulations by supercritical CO_2-assisted spray-drying", J. Supercrit. Fluids, 116: 26–35, 2016.

[30]. O.N. Ciftci, F. Temelli, "Formation of solid lipid microparticles from fully hydrogenated canola oil using supercritical carbon dioxide", J. Food Eng., 178: 137–144, 2016.

[31]. R. Couto, V. Alvarez, F. Temelli, "Encapsulation of Vitamin B_2 in solid lipid nanoparticles using supercritical CO_2", J. Supercrit. Fluids, 120: 432–442, 2017.

[32]. A. Alhalaweh, W. Kaialy, G. Buckton, H. Gill, A. Nokhodchi, S.P. Velaga, "Theophylline cocrystals prepared by spray drying: Physicochemical properties and aerosolizaiton performance", AAPS. PharmSciTech., 14: 265–276, 2013.

[33]. The Chemical Society of Japan (Ed.), Kagaku Binran Kisohen II, 5th Ed., Maruzen, Tokyo, 2004.

[34]. P. Szterner, B. Legendre, M. Sghaier, "Thermodynamic properties of polymorphic forms of theophylline. Part I: DSC, TG, X-ray study", J. Therm. Anal. Cal., 99: 325–335, 2010.

[35]. D. Khamar, I.J. Bradshaw, G.A. Hutcheon, L. Seton, "Solid state transformations mediated by a kinetically stable form", Cryst. Growth Des., 12: 109–118, 2012.

[36]. L. Seton, D. Khamar, I.J. Bradshaw, G.A. Hutcheon, "Solid state forms of theophylline: Presenting a new anhydrous polymorph", Cryst. Growth Des., 10: 3879–3886, 2010.

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