

INVESTIGATION OF THE INFLUENCE OF INJECTING PRESSURIZED CO₂ ON THE HOT MELT EXTRUSION PROCESS AND THE EXTRUDATE PROPERTIES OF PVP-VA 64.

Geert Verreck*¹, **Hongbo Li**², **Albertina Ariën**¹, **Jef Peeters**¹, **David Tomasko**², **Guy Van den Mooter**³, **Marcus E. Brewster**¹

1: Johnson & Johnson Pharmaceutical Research & Development, Turnhoutseweg 30, B-2340 Beerse, Belgium

*: gverreck@prdbe.jnj.com, phone: +32/14603165, fax: +32/14607083

2: Department of Chemical Engineering, Ohio State University, 125 Koffolt Lab, 140 W. 19th Ave., Columbus, OH 43210, USA

3: Laboratorium voor Farmacotechnologie en Biofarmacie, K.U.Leuven, Campus Gasthuisberg O+N, 49 Herestraat, B-3000 Leuven, Belgium

The aim of the current research project was to explore the possibilities of combining a pressurized gas with hot melt extrusion of polyvinylpyrrolidone-co-vinyl acetate 64 (PVP-VA 64), to evaluate the ability of the pressurized gas to act as a temporary plasticizer as well as to produce a foamed polymeric matrix. Pressurized carbon dioxide was injected into a Leistritz Micro 18 co-rotating twin-screw melt extruder using an ISCO 260D syringe pump. The physicochemical characteristics of the polymer before and after treatment with carbon dioxide were evaluated using specific surface area measurement, polymer dissolution and SEM. An extruder set up and screw configuration were optimized which allowed for injection of a pressurized gas without leakage and a reduction of the processing temperature by 30°C when the CO₂ was injected at 55 bar. The specific surface area of the polymer was increased after treatment with carbon dioxide, resulting in faster dissolution. The macroscopic morphology was changed due to foaming upon expansion of the carbon dioxide at the extrusion die.

INTRODUCTION

More and more drug candidates tend to have higher molecular weights, higher lipophilicities, and lower aqueous solubilities, usually resulting in poorer oral bioavailability [1,2]. One approach to increase dissolution rates and therefore oral bioavailability for BCS Class II drugs is the generation of supersaturated drug solutions using solid dispersions [3-5]. In the last decade, hot melt extrusion has gained significant interest in pharmaceutical industry as a valuable technique to prepare solid dispersions of a drug substance and carrier(s) [6,7]. In general, co-rotating twin-screw extruders are most often applied since they have excellent mixing capacities as the surfaces of the screws move towards each other. Therefore, these types of extruders are preferred to counter-rotating instruments with regard to solid dispersions and mixing/dissolving drug into a polymeric carrier [8].

Applications of pressurized gases to hot melt extrusion are not new in polymer science. The applications have generally focused on viscosity reduction and foam formation [9]. Examples include the viscosity reduction and improved blending of polystyrene and poly(methyl methacrylate) (PMMA) by supercritical carbon dioxide when processed in a single screw extruder [10,11]. Lee et al. investigated the viscosity reduction of polyethylene/polystyrene (PE/PS) blends and observed a significant plasticisation effect when

measured in a twin-screw extruder [12]. Park et al., studied the continuous micro-cellular foam formation of polystyrene using a single screw extruder [13].

The aim of the current research project was to explore and investigate the combined possibilities of pressurized carbon dioxide and hot melt extrusion of pharmaceutically acceptable polymers. The influence of injecting pressurized carbon dioxide as a temporary plasticizer for the polymer was investigated, as was the ability to form a foam upon expansion of the pressurized gas.

MATERIALS AND METHODS

PVP-VA 64 was obtained from BASF (BASF, Ludwigshafen, Germany). CO₂ (≥ 99.9 vol%, purity 3.0) is supplied in gas cylinders with dip tube (Messer, Machelen, Belgium).

The melt extrusion trials were performed with a Leistritz Micro 18 co-rotating intermeshing twin-screw extruder. The screw diameter was 18 mm and the length to diameter ratio (L/D) was 40, divided over 4 barrel segments of 5 L/D each and 1 barrel element of 20 L/D. The first barrel segment was water cooled only. Temperature settings varied between 180°C and 120°C while screw speed (n) and feed rate (F) were kept constant at 100 rpm and 1 kg/hr, respectively. At each new condition, at least 10 minutes were allowed to achieve equilibrium. The pressure inside the barrel was measured at three locations: before and after the CO₂ injection port and in the flange. The torque of the extruder (T) was recorded as a function of the temperature settings. The extruder set up and screw configuration are shown in Figures 1 and 2. Polymer was fed with a K-Tron loss-in-weight feeder system (K-Tron, Switzerland). Carbon dioxide was pressurized and injected in the extruder using an ISCO 260D syringe pump (ISCO, US). CO₂ was provided as liquid (T=20°C ; P=56 bar) from a gas cylinder with a dip tube and cooled to 1.5°C with a spiral tube in a cooling bath (Analis Heto, CBN 8-30, Denmark). Cooling medium was a mixture of isopropanol/water 50/50 v/v. Also the cylinder of the pump was cooled to 1.5°C. Carbon dioxide was injected in the barrel through an injection nozzle located in barrel segment 3 (see Figure 1).

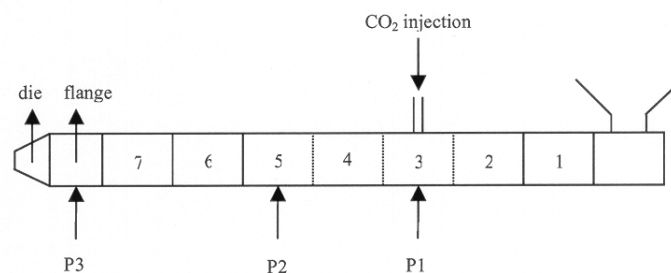


Figure 1: Schematic set up of the Leistritz twin screw extruder. Carbon dioxide was injected in segment 3. Further downstream, the barrel is completely closed. Pressurized carbon dioxide is released back to atmospheric pressure upon exiting the die.

Prior to analysis, the polymer samples were milled using a Bamix lab scale mill (Bamix, Mettlen, Switzerland) and the fraction below 500 µm (ASTM E11-61: 35 mesh/inch) was retained for further characterization.

Scanning electron microscopy (SEM) was performed with a JEOL JSM- 5510 (Japan Electron Optics Laboratory LTD) scanning electron microscope. The sample was fixed on the stub with adhesive tape. The mounted samples were coated with a layer of gold using a

Balzers sputtering device. The samples were placed in a multiple specimen holder of the scanning electron microscope and scanned at 10-20 kV. Digital images were processed using Adobe Photoshop.

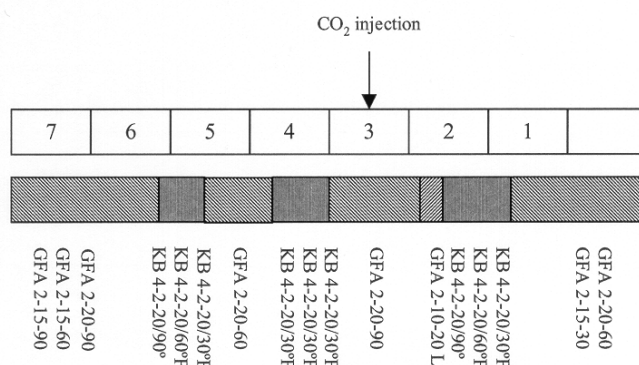


Figure 2: Schematic set up of the screw configuration. One melt seal is obtained by using a reversing transport element before carbon dioxide injection and another melt seal is obtained in the die plate. To better distribute the carbon dioxide in the polymer, two mixing zones were provided downstream of the melt seal. The descriptions represent the properties of the transport elements (GFA) and kneading blocks (KB), respectively, as well as the length and angle of each element.

The specific surface area was measured with a Quantachrome surface area analyser (Quantachrome, Greenvale, NY, USA) using Kr/He gas mixtures (0.1, 0.2 and 0.3 mole fraction) at 1.5 bar and 25 ml/min flow rate. Adsorption time was between 20 and 30 minutes. Calibration was done with a known quantity of Kr. Samples were degassed repeatedly (6 times) prior to analysis by adsorption and desorption using a constant flow of the Kr/He 0.3 mole fraction gas mixture.

Dissolution of PVP-VA 64 was measured by adding 10 g of a sample to 500 mL purified water (37°C), while stirring with a paddle at 50 rpm (USP II apparatus). The dissolution was followed for 1 hour with samples of the dissolution medium taken after 5, 15, 30, 45 and 60 minutes. An aliquot of 3 ml was filtered through a Millex HV 0.45 µm filter (Millipore SLHV R04 NL) and diluted with purified water. The sample was not replaced with fresh solvent. The concentration of PVP-VA 64 was measured photometrically by the formation of the iodine complex [14]. Therefore, 5 mL of the diluted sample solution was mixed with 2.5 mL of 0.2 M citric acid solution and 1 mL of 0.006 N iodine solution (0.81 g of freshly sublimed iodine and 1.44 g of potassium iodide dissolved in 1000 mL of water). The absorbance was measured using UV at 470 nm after exactly 30 minutes. The experiments were performed in triplicate.

RESULTS AND DISCUSSION

Table 1 and 2 show the parameter settings and read outs of the melt extrusion process before and after injection of carbon dioxide. These tables show that the torque increases when the temperature settings are lowered which is as expected since the melt viscosity increases at lower temperatures. For the extrusion without carbon dioxide injection, the maximal torque (i.e. > 100%, resulting in automatic shut down of the extruder) is reached below 150°C. For

the extrusion with carbon dioxide injection, maximal torque is reached below 120°C. This was obtained when injecting CO₂ at 55 bar, that is at subcritical conditions. Under these conditions, steady state in the extruder and polymer foaming at the exit of the extruder were obtained. These results show that carbon dioxide acts as a plasticizer reducing the processing temperature by 30°C when extruding PVP-VA 64.

Table 1: Parameter settings for extrusion experiments of PVP-VA 64 without CO₂ injection. Investigation of the effect of the temperature settings on the torque of the extruder.

T ₁ -T ₂ (°C)	T ₃ -T _{die} ¹ (°C)	P ₁ (bar)	P ₂ (bar)	P ₃ (bar)	T _m (°C)	n (rpm)	F (kg/h)	T (%)
180	180	3	1	12	186	100	1	31-41
180	170	3	2	15	174	100	1	35-46
180	160	2	1	28	165	100	1	50-63
180	150	2	1	44	157	100	1	70-82
180	140	2	1	55	153	100	1	>100

1: T₃-T_{die}: all zones between T₃ and T_{die} were kept at the same temperature.

Table 2: Parameter settings for extrusion experiments of PVP-VA 64 with CO₂ injection. Investigation of the effect of CO₂ pressure and temperature settings on the torque of the extruder.

T ₁ - T ₂ (°C)	T ₃ - T _{die} ¹ (°C)	P ₁ (bar)	P ₂ (bar)	P ₃ (bar)	T _m (°C)	N (rpm)	F (kg/h)	T (%)	P _{pump} (bar)
180	180	3	1	12	186	100	1	31-41	-
180	170	10-22	7-20	14-22	174	100	1	35-45	35
180	160	18-28	15-25	21-31	162	100	1	48-59	45
180	150	26-34	23-31	28-36	153	100	1	53-69	50
180	140	26-42	23-40	36-56	142	100	1	60-80	40
180	130	40-49	37-45	41-49	132	100	1	65-80	45
180	120	47-55	45-53	48-56	125	100	1	74-92	55
180	110	- ²	-	-	-	100	1	> 100	60

1: T₃-T_{die}: all zones between T₃ and T_{die} were kept at the same temperature

2: maximum torque was obtained before the temperature settings were reached

Figure 3 shows the dissolution profile of the polymer before and after treatment with carbon dioxide in the extruder. Comparison of the dissolution profiles, shows that the samples treated with CO₂ dissolve significantly faster at the 30 minutes time point (t-test, n=3, P<0.05). At all other time points, the dissolution of the carbon dioxide treated polymer is higher, although not significantly. This faster dissolution rate may be attributed to a change in morphology through foam formation when CO₂ is expanded at the exit of the extruder.

Measurement of the specific surface area shows that the processed sample has a specific surface area of 0.381 m²/g compared to 0.261 m²/g for the unprocessed sample.

SEM confirms that the morphology of the carbon dioxide-treated polymer has changed from sphere like particles, before treatment, to very thin platelets after treatment (see Figure 4). These platelets are formed during the foaming step when CO₂ expands at the exit of the

extruder. The very thin morphology of the platelets, explains the differences observed in the dissolution profile and the specific surface area.

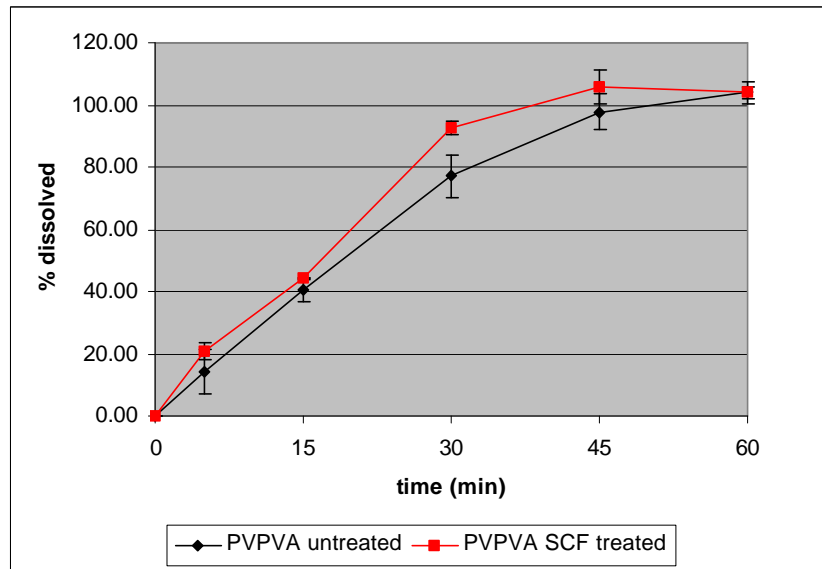


Figure 3: Dissolution of PVP-VA 64 untreated and treated with CO₂. The dissolution of 10 g polymer is measured in 500 mL purified water at 37°C while stirring with a paddle at 50 rpm. Error bars represent the standard deviation based on measurements in triplicate.

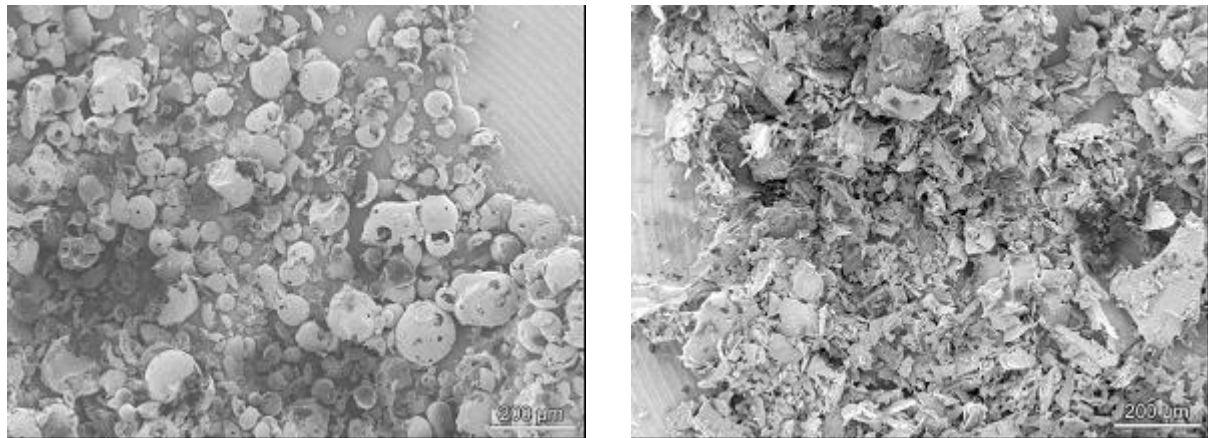


Figure 4: SEM of PVP-VA 64 before treatment (left) and after carbon dioxide assisted extrusion (right) of the milled foam.

CONCLUSION

Based on these experiments with PVP-VA 64, an extruder set up and screw configuration were found which allow for the injection of pressurized carbon dioxide. Injection of the pressurized gas, building up pressure and polymer foaming were obtained with an extruder and screw set up whereby a melt seal was obtained using a reversing transport element and the die opening and whereby CO₂ is expanded after the die plate.

Furthermore, it can be concluded that CO₂ acts as a plasticizer for PVP-VA 64 since the process temperature can be lowered by at least 30°C. Steady state is obtained as a function of optimal pump pressure and temperature settings. The maximal pressure that could be obtained with PVP-VA 64 was approximately 55 to 60 bar, which means that the extrusion was performed under subcritical conditions.

The physicochemical characterization of the polymer revealed that the specific surface area was increased due to a morphology change, which probably provides for increased dissolution of the polymer.

REFERENCES

- [1] LIPINSKI, C.A., LOMBARDO, F., DOMINY, B.W., FEENEY, P.J., *Adv. Drug Deliv. Rev.*, Vol. 23, **1997**, p 3
- [2] LIPINSKI, C.A., *Curr. Drug Disc.*, Vol. 1, **2001**, p. 17
- [3] SHEEN, P., KHETARPAL, C., ROWLINGS, C., *Int. J. Pharm.*, Vol. 118, **1995**, p. 221
- [4] SERAJUDDIN, A.T., *J. Pharm. Sci.*, Vol. 88, **1999**, p. 1058
- [5] LEUNER, C., DRESSMAN, J., *Eur. J. Pharm. Biopharm.*, Vol. 50, **2000**, p. 47
- [6] GRUENHAGEN, H. H., *Pharmaceut. Manufact. International*, **1995**, p. 167
- [7] BREITENBACH, J., *Eur. J. Pharm. Biopharm.*, Vol. 54, **2002**, p. 107
- [8] GHEBRE-SELLASSIE, I., MARTIN C., *Pharmaceutical Extrusion Technology*, Marcel Dekker, **2003**, New York, NY, USA
- [9] CHIOU, J.S., BARLOW, J.W., PAUL, D.R., *J. Appl. Polym. Sci.*, Vol. 30, **1985**, p. 2633
- [10] ELKOVITCH, M.D., LEE, L.J., TOMASKO, D.L., *ANTEC*, **1998**, p. 1407
- [11] ELKOVITCH, M.D., TOMASKO, D.L., LEE, L.J., *Polym. Eng. Sci.*, Vol. 39 (10), **1999**, p. 2075
- [12] LEE, M., TZOGANAKIS, C., PARK, C.B., *Polym. Eng. Sci.*, Vol. 38, **1998**, p. 1112
- [13] PARK, C.B., BALDWIN, D.F., SUH, N.P., *Polym. Eng. Sci.*, Vol. 35, **1995**, p. 432
- [14] BUHLER, V., *Polyvinylpyrrolidone for the pharmaceutical industry*, BASF Aktiengesellschaft, **1992**