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Hot stage extrusion of *p*-amino salicylic acid with EC using CO_2 as a temporary plasticizer

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Abstract

The aim of the current research project was to explore the possibilities of combining pressurized carbon dioxide with hot stage extrusion during manufacturing of solid dispersions of the thermally labile *p*-aminosalicylic acid (*p*-ASA) and ethylcellulose 20 cps (EC 20 cps) and to evaluate the ability of the pressurized gas to act as a temporary plasticizer. The thermal stability of the *p*-ASA was investigated using DSC, TGA and HPLC. The compound decomposes completely upon melting. Below 110 °C and under atmospheric conditions, the compound is thermally stabile for 10 min.

Pressurized carbon dioxide was injected into a Leistritz Micro 18 intermeshing co-rotating twin-screw melt extruder using an ISCO 260D syringe pump. Carbon dioxide acted as plasticizer for *p*-ASA/EC 20 cps, reducing the processing temperature during the hot stage extrusion process. HPLC showed that without carbon dioxide injection, approximately 17% of *p*-ASA degraded, while less than 5% degraded with CO_2 injection. The experiments clearly showed that injecting pressurized carbon dioxide broadens the application of hot stage extrusion to thermally labile compounds in a one step process.

Keywords: Hot stage extrusion; *p*-Aminosalicylic acid; Ethylcellulose; Solid dispersion; Pressurized gas; Supercritical fluid

1. Introduction

The application of hot stage extrusion in the pharmaceutical industry has gained more and more attention in the development of drug delivery systems with improved physicochemical properties. These include the preparation of solid dispersions to increase dissolution rate and oral bioavailability, to control the release of an active ingredient or a combination of both (Breitenbach, 2002; Verreck and Brewster, 2004). Although the hot stage extrusion process is broadly applicable to a number of active substances and excipients, one of its major drawbacks is its limitation to thermally stable products. A number of active compounds decompose below or during melting, which may lead to loss of activity or functionality of the active substance or excipient (Follonier et al., 1994). To reduce the melt viscosity in the extruder and to be able to decrease the temperature settings, a plasticizer can be added to the formulation. Typically, conventional plasticizers such as triacetin or polyethylene glycol are used at a concentration range of 5–30 wt.% of the extrudable mass (Follonier et al., 1995; McGinity and Zhang, 2003; Repka et al., 1999). This is a major limitation, since this additional weight adds to the total weight of the formulation, which may result in unacceptably large dosage forms. Therefore, it would be beneficial to have a plasticizer that lowers the processing temperature during hot stage extrusion without being present in the final formulation. It is well known that carbon dioxide can act as a temporary plasticizer during hot stage extrusion (Elkovitch et al., 1999, 2000; Royer et al., 2000; Lee et al., 1998, 1999). At the die of the extruder, expansion occurs to atmospheric pressure which will result in a transformation

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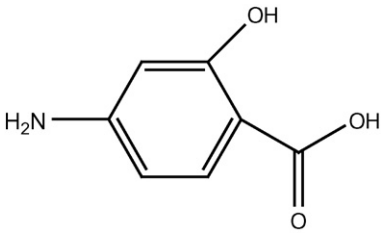

Fig. 1. Chemical structure of *p*-amino salicylic acid.

of carbon dioxide to the gaseous phase. As a consequence, CO_2 will escape from the extruded mass and will not be present in the final product. Previous work has shown that pressurized carbon dioxide, when injected during hot stage extrusion, works as a temporary plasticizer for a number of pharmaceutically acceptable polymers, including polyvinylpyrrolidone-co-vinylacetate 64 (PVP-VA 64), Eudragit® E100 and ethylcellulose 20 cps (EC 20 cps) (Verreck et al., in press-b). This investigation shows that with PVP-VA 64 and Eudragit® E100, subcritical pressures could be used, while with EC 20 cps, supercritical pressures could be achieved during hot stage extrusion. The injection of carbon dioxide resulted in temperature setting reductions of 30, 15 and 65 °C for PVP-VA 64, Eudragit® E100 and EC 20 cps, respectively. Verreck et al. also describe the injection of carbon dioxide during hot stage extrusion of itraconazole with PVP-VA 64 (10 and 40% (w/w) drug loading) and confirm the plasticization of this mixture by carbon dioxide under subcritical pressures (Verreck et al., 2005). Under these conditions, glass solutions were obtained (similar to those without CO_2 injection) and dissolution could be controlled by temperature and pressure during the hot stage extrusion process. The macroscopic morphology was changed to a foam extrudate after CO_2 treatment, which resulted in an increased specific surface area, porosity and hygroscopicity. As a consequence, milling of the extrudates was improved. Similar observations were made for the extrusion of itraconazole with EC 20 cps (10 and 40% (w/w) drug loading) (Verreck et al., in press-a). As with pure EC 20 cps, carbon dioxide could be injected at supercritical conditions resulting in dispersion with both amorphous and crystalline domains. Again, the dissolution of itraconazole could be controlled by injection of carbon dioxide during the hot stage extrusion process and macroscopic morphology was altered.

For these experiments, itraconazole was used as a model compound since it is thermally stable during hot stage extrusion. This drug substance is practically insoluble in water and therefore suitable for investigating the influence of injecting carbon dioxide on the physicochemical properties of the solid dispersion.

The aim of the current research project is to investigate the applicability of carbon dioxide as a temporary plasticizer for a thermally labile active substance. *p*-Amino salicylic acid (*p*-ASA) was used as a model compound. This active substance melts at 147 °C with decomposition. The chemical structure is shown in Fig. 1. *p*-ASA is a specific bacteriostatic agent used to treat pulmonary tuberculosis. EC 20 cps was selected as a model polymeric carrier, since previous work has shown the highest effect of CO_2 as a temporary plasticizer for this polymer when injected at supercritical pressures (Verreck et al., in press-a, in press-b).

2. Materials and methods

2.1. Materials

p-ASA (purity more than 99%) was obtained from Acros Organics (Geel, Belgium) and EC 20 cps from Keyser & Mackay (Keyser & Mackay, Brussels, Belgium). CO_2 (≥99.9 vol.%, purity grade 3.0) was supplied in gas cylinders with a dip tube (Messer, Machelen, Belgium).

2.2. Thermogravimetric analysis (TGA)

The samples were measured with a TA Instruments Hi-Res TGA 2950 (TA instruments, New Castle, DE, USA) equipped with a data station TA2100. Approximately 10 mg of sample was weighed in an aluminum pan of 30 μl volume and heated from room temperature at a heating rate of 20 °C/min. The endpoint was set at 350 °C or at a weight loss of 20%.

2.3. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed using a TA Instruments DSC Q1000 differential scanning calorimeter and thermal analysis controller (TA Instruments, New Castle, DE, USA). Cooling was provided with a TA Instruments refrigerated cooling system (RCS, TA Instruments). Data were treated mathematically using the resident TA Q-series software. Calibration was carried out using indium, octadecane and sapphire as reference materials. The sample was analysed in standard (open) aluminum TA Instruments pans. Nitrogen was used as the purge gas at 50 ml/min.

Approximately 2–3 mg of *p*-ASA was heated from 25 to 150 °C at a heating rate of 10 °C/min.

2.4. Drug substance thermal stability

The drug substance thermal stability was assessed using a TA Instruments DSC Q1000 differential scanning calorimeter and thermal analysis controller (TA Instruments, New Castle, DE, USA). Cooling was provided with a TA Instruments refrigerated cooling system (RCS, TA Instruments). Calibration was carried out using indium, octadecane and sapphire as reference materials. Approximately 5 mg *p*-ASA was weighed in standard aluminum Perkin-Elmer pans and transferred in the DSC oven. The sample was kept isothermally at 80, 100, 110, 120, 130 and 140 °C, respectively, up to 10 min in open conditions. The sample was then removed from the DSC oven and analysed for degradation using HPLC.

2.5. HPLC

The analysis was performed using a Waters 2690 HPLC (Waters, Milford, MA, USA) with Millennium 32 Software. The column used was a Hypersil BDS RP18, 3 μm, 10 cm × 4.6 mm

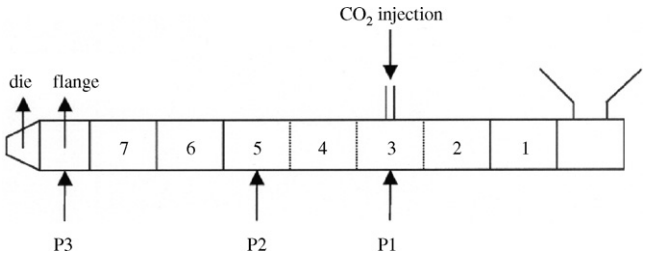

Fig. 2. Schematic set up of the Leistritz twin-screw extruder. Carbon dioxide was injected in segment 3. Further downstream, the barrel is sealed. Pressurized carbon dioxide is released to atmospheric pressure upon exiting the die. P1–P3 are pressure probes to measure the pressure inside the extruder at these three locations.

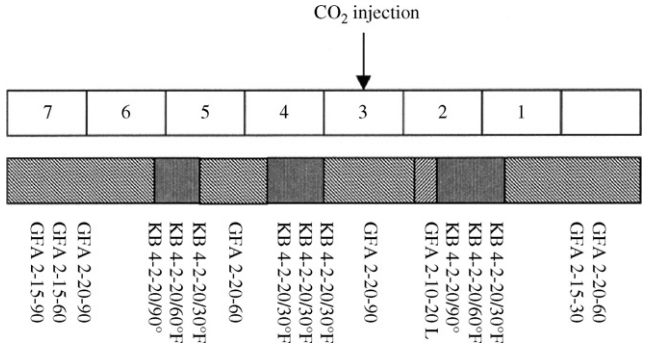

Fig. 3. Schematic set up of the screw configuration. The descriptions represent the properties of the transport elements (GFA) and kneading blocks (KB), respectively, as well as the length and angle of each element.

ID. The mobile phase consisted of 0.1% trifluoroacetic acid in water and acetonitrile using a gradient elution at a flow rate of 1.2 ml/min. Samples were dissolved in water/acetonitrile 10/90 (v/v). Concentration determination was performed using a diode array detector at a wavelength of 304 nm, a bandwidth of 4 nm and an attenuation of 0.1 AU. Samples were analysed in triplicate.

2.6. Physical mixture

A physical mixture of *p*-ASA and EC 20 cps in a ratio 10% (w/w) was prepared by blending both components in a planetary blender (Collette MP20, Collette, Belgium) for 10 min at a mixing speed of 20 rpm. Prior to blending, the *p*-ASA was sieved using a 870 μm mesh.

2.7. Hot stage extrusion

The hot stage extrusion trials were performed using 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 four barrel segments of 5 L/D each and one barrel element of 20 L/D. The extruder set up and screw configuration are shown in Figs. 2 and 3. The barrel segment adjacent to the powder feeder was water cooled. The temperature settings are shown in Table 1. The screw speed and feeding rate were kept constant at 100 rpm and 1 kg/h, respectively. At each new condition, at least 10 min were allowed between runs to achieve equilibrium. The pressure inside the barrel was measured at three locations: before and after the CO_2 injection port and at the flange. The torque of the extruder was recorded as a function of the temperature settings. Experiments were performed at least in duplicate. The physical mixture was fed with a K-Tron loss-in-weight feeder system (K-Tron, Switzerland). Carbon dioxide was pressurized and injected into the extruder using an ISCO 260D syringe pump (ISCO, Lincoln, NE, US), operating at a constant pressure. CO_2 was provided as liquid ($T = 25\,^{\circ}C$; $P = 56$ 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). The cooling medium was a mixture of isopropanol/water 50/50 (v/v). The cylinder of the pump was cooled to 1.5 °C. Carbon dioxide was injected into the barrel through an injection nozzle located in barrel segment 3 (see Fig. 2).

3. Results and discussion

DSC analysis of the pure drug substance shows a melting endotherm with its maximum at 135 °C (see Fig. 4). This melting peak is followed by a number of endothermic transitions

Table 1
Minimum temperature settings for hot stage extrusion of *p*-ASA/EC 20 cps 10% (w/w) with and without CO_2 injection

T_{1-2}[a] (°C)	T_3 (°C)	T_4 (°C)	T_5 (°C)	T_6 (°C)	T_7 (°C)	T_{die}[b] (°C)	T_{flange}[c] (°C)	Torque (%)	P_{pump} (bar)	% *p*-ASA[d] ($n = 3 \pm$ R.S.D.)
Without CO_2 injection										
180	115	115	115	115	115	115	115	87–100	–	36.4 ± 0.6
130	130	130	130	130	130	130	130	78–93	–	83.7 ± 0.2
130	130	130	130	130	130	130	130	75–91	–	83.3 ± 0.3
With CO_2 injection										
130	80	80	80	80	80	80	80	88–100	90	87.9 ± 0.2
130	80	80	80	80	80	80	80	86–100	90	86.4 ± 1.1
125	90	90	90	90	90	90	90	86–100	75	89.6 ± 1.1
110	110	110	105	105	100	100	95	85–100	75	96.3 ± 0.8

The screw speed and feed rate were maintained at 100 rpm and 1 kg/h, respectively.
[a] Temperature settings of barrel segments 1 and 2.
[b] Temperature settings of the die (see Fig. 2).
[c] Temperature settings of the flange (see Fig. 3).
[d] % of *p*-ASA which is not degraded.

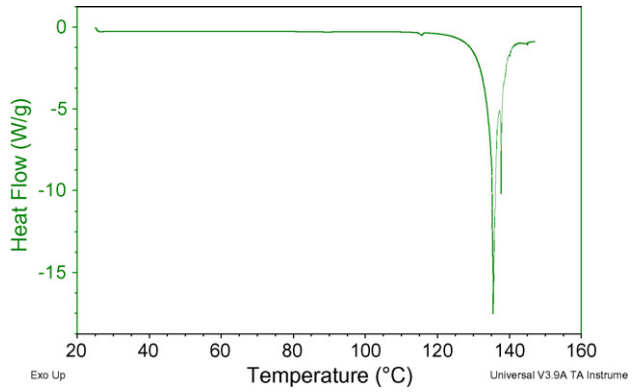

Fig. 4. DSC profile of *p*-amino salicylic acid. Approximately 2–3 mg of the active ingredient was analyzed in perforated and covered aluminum pans under a nitrogen purge. The sample was heated from 25 to 150 °C at a heating rate of 10 °C/min.

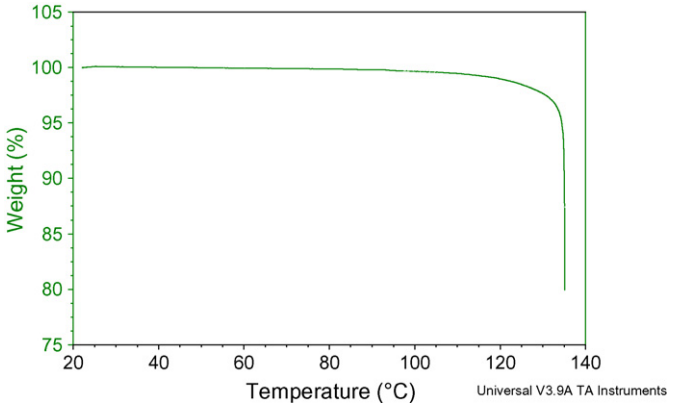

Fig. 5. TGA analysis of *p*-amino salicylic acid. Approximately 10 mg of sample was weighed in an aluminum pan of 30 μl volume and heated from room temperature at a heating rate of 20 °C/min. The endpoint was set at 350 °C or at a weight loss of 20%.

indicating degradation of the *p*-ASA. This is confirmed by TGA, showing a weight loss of 0.4% up to 100 °C, followed by a significant weight loss above 120 °C (see Fig. 5). To further investigate the thermal degradation profile, the drug substance was stored at various temperatures in a DSC pan under open conditions. This was done up to 10 min, which spans the typical residence time in a twin-screw melt extruder (Breitenbach and Magerlein, 2003). The HPLC results are shown in Table 2. This table shows that the active substance is thermally stable for at least 10 min when stored below 100–110 °C. In other words, the temperature inside the extruder should not exceed 110 °C for too long a period in order to prevent degradation of the active substance. The degradation products of *p*-ASA were not identified in this study, but it is assumed that the decomposition pathway includes a decarboxylation of the active ingredient with the formation of carbon dioxide (Rekker and Nauta, 1948; Roy, 2002; Vasbinder et al., 2004). This by-product from the decarboxylation may act as a plasticizer itself, and therefore, care has been taken that there is no interference by it during the hot stage extrusion process.

Table 2
Thermal degradation profile for *p*-amino salicylic acid in open conditions

Temperature (°C)	Time (min)	% *p*-ASA intact
140	5	0
130	5	0
120	5	72.7
110	5	98.5
110	10	96.7
100	10	98.9
80	10	99.4

To prepare a solid dispersion/solution of a drug substance with a polymeric carrier by hot stage extrusion, it is important to obtain intimate contact between drug and carrier. When using CO_2 as a plasticizer, the pressurized gas has to dissolve in the polymer requiring good mixing capabilities. Among the different types of commercial extruders, the co-rotating intermeshing twin-screw extruders possess excellent mixing and conveying characteristics (Mollan, 2003). Therefore, this type of extruder was used for these experiments. Because the screws are intermeshing, the barrel can never be completely filled with product. As a consequence, injection of pressurized CO_2 could cause leakage of the gas. This can be avoided by designing the extruder set up and screw configuration such that pressure fluctuations are minimized to obtain a stable injection of the gas (Lee et al., 1998). Melt seals should be used to prevent leakage of the gas and kneading elements to completely dissolve the gas in the polymer. Previous experiments with PVP-VA 64, Eudragit® E100, EC 20 cps, itraconazole/PVP-VA 64 and itraconazole/EC 20 cps resulted in an extruder set up and screw configuration as shown in Figs. 2 and 3. This set up and configuration allowed for a stable injection of pressurized CO_2, without leakage of the gas. As described by Verreck et al., the torque of the extruder is used as an indicator to evaluate the effect of the carbon dioxide as a plasticizer (Verreck et al., 2005). That is, the minimum temperature settings were determined at which maximum torque was obtained with injection of carbon dioxide compared to that without CO_2 injection (maximum torque is 100% with automatic shut down of the extruder). This was assessed by two different approaches. Proximal to the CO_2 injection port, one melt seal was obtained in barrel segment 2 using a reversing transport element (see Figs. 2 and 3). Such a reversing transport element pushes the material back, until that zone is completely filled with material and as such resulting in positive product flow and a melt seal. This enables mixing, but also requires a high torque from the machine. Therefore, the first approach is to keep these barrel segments (zones 1 and 2) at increased temperature (to reduce the torque in that zone) and try to reduce the temperature in the remaining segments as low as possible. The second approach is to reduce the temperature settings of all segments, while trying to keep the melt seal proximal to the injection port intact.

During the initial extrusion experiments without CO_2 injection, the formation of a foam extrudate was observed at the die of the extruder. This indicated gas formation in the closed extruder barrel originating from the formation of decomposition products. When opening the vent port in the barrel, the foam formation stopped and the extrudate became more dense. This indicates that indeed decarboxylation of *p*-ASA occurs with the subsequent formation of CO_2. To avoid the interference of this

formed carbon dioxide, all experiments without CO_2 injection were performed with the vent port open.

Table 1 lists the minimum temperature settings with and without CO_2 injection during hot stage extrusion of the *p*-ASA/EC 20 cps 10% (w/w) solid dispersion. These are the absolute minimum temperature settings, meaning that any further temperature reduction resulted in a torque of 100% and automatic shut down of the extruder.

This table shows that CO_2 acted as a plasticizer for *p*-ASA/EC 20 cps 10% (w/w). The optimal conditions that allowed for CO_2 to be injected was at pressures exceeding the supercritical pressure (up to 90 bar) resulting in a processing temperature decrease of approximately 30 °C. Further increasing the carbon dioxide pressure caused leakage with the extrudate being expelled from the die plate. As shown in previous work, hot stage extrusion of pure EC 20 cps without carbon dioxide injection was feasible at temperature settings of at least 140 °C, indicating that *p*-ASA worked as a plasticizer for EC 20 cps as well. As discussed by Verreck et al., this was also observed by solid dispersions consisting of itraconazole/PVP-VA 64 and itraconazole/EC 20 cps, whereby a combined plasticizing effect was observed of both the drug substance and CO_2 (Verreck et al., 2005).

HPLC analysis was performed after hot stage extrusion to evaluate the influence of CO_2 as a plasticizer on the thermal degradation of the *p*-ASA. These results show that the percentage of *p*-ASA which is still intact after hot stage extrusion, has significantly increased when using CO_2 as a plasticizer. Without carbon dioxide injection, almost 65% degradation occurs when the first two-barrel segments are kept at increased temperature. Even when the temperature of the initial barrel elements are maintained at reduced temperature, approximately 17% degradation occurred. When CO_2 was injected, the extent of degradation was less than 5%. These assays and the corresponding barrel temperature settings confirm the values obtained during the investigation of the thermal degradation behaviour (see Table 2). Repeating the hot stage extrusion experiments resulted in exactly the same results, no matter whether this was done with or without carbon dioxide injection. This shows the robustness of the hot stage extrusion process, as well as the use of injection of the pressurized gas.

These experiments demonstrate that the hot stage extrusion of *p*-ASA with EC 20 cps became feasible as a result of the injection of CO_2, a temporary plasticizer, which is not present in the final product. Bruce et al. for example describe a hot melt extruded tablet formulation for colonic delivery of 5-amino salicylic acid (Bruce et al., 2005). This compound is thermally stable up to 250 °C. However, to be able to thermally process the brittle polymer Eudragit® S100, plasticizers such as triethyl citrate and citric acid monohydrate or lubricants such as glycerol monostearate were needed. These ingredients were added up to 30% (w/w) of the extruded mass. In addition, with triethyl citrate, a pre-plasticization step was necessary to promote intermolecular interaction between the dry polymer and the plasticizer. This extra step consisted of a granulation of triethyl citrate with the polymer. This indicates the advantages of CO_2 as a temporary plasticizer directly injected during the hot stage extrusion without the need for additional processing steps.

Also Follonier et al. recognized the limitations of conventional hot stage extrusion in cases where the drug or the excipients thermally decompose and described the use of plasticizers such as triacetin, diethylphtalate and polyethylene glycol 400 up to 10% (w/w) (Follonier et al., 1994). These and many other examples show that often excipients are needed (plasticizers, lubricants) that add to the final weight of the solid dosage form and that increase the number of processing steps.

The experiments described in the current research project have clearly demonstrated that injecting pressurized carbon dioxide broadens the application of hot stage extrusion to thermally labile compounds in a one step process.

4. Conclusion

p-ASA is a thermally labile compound which melts with decomposition. Below 110 °C and under atmospheric conditions, the compound is thermally stabile for at least 10 min.

Using a Leistritz Micro 18 intermeshing co-rotating twin-screw melt extruder, it was possible to show that CO_2 acts as a plasticizer during the manufacturing of solid dispersions of *p*-ASA/EC 20 cps 10%(w/w), allowing a reduction in processing temperature. HPLC showed that without carbon dioxide injection, approximately 17% of *p*-ASA decomposed, while this was approximately 5% with CO_2 injection.

The experiments clearly showed that injecting pressurized carbon dioxide broadens the application of hot stage extrusion to thermally labile compounds.

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