CONSTRUCTION OF A PHASE DIAGRAM FOR ITRACONAZOLE/EC 20 CPS SOLID DISPERSIONS PREPARED BY HOT STAGE EXTRUSION WITH AND WITHOUT INJECTION OF PRESSURIZED CO_2.

Geert Verreck[1,*], Annelies Decorte[1], Liesbeth Theunissen[1], Jef Peeters[1], Guy Van den Mooter[2], Marcus E. Brewster[1]

1: Johnson & Johnson Pharmaceutical Research & Development, Turnhoutseweg 30, B-2340 Beerse, Belgium
2: Laboratorium voor Farmacotechnologie en Biofarmacie, K.U.Leuven, Campus Gasthuisberg O+N, 49 Herestraat, B-3000 Leuven, Belgium
*: phone: +3214603165, fax: +3214607083, gverreck@prdbe.jnj.com

Introduction

Although a significant number of pharmaceutical examples of hot stage extrusion have been described in literature [1, 2], one of the major drawbacks of hot stage extrusion is its limited applicability to thermally stable products. For a number of active substances (and excipients), hot stage extrusion cannot be used due to thermal degradation and subsequent loss of its activity [3]. In these cases, a plasticizer can be added in order to reduce the viscosity of the mixture in the extruder and therefore to lower the process temperature settings. However, added plasticizers usually remain in the product, thus affecting its properties and performance. Typically, conventional plasticizers such as triacetin or polyethylene glycol are used in a concentration range of 5 up to 30 wt% of the extrudable mass [4-6]. Therefore, it is beneficial to have a temporary plasticizer that lowers the processing temperature during hot stage extrusion without being present in the final formulation.
Previous work has shown that pressurized carbon dioxide, when injected during hot stage extrusion, worked as a temporary plasticizer for a number of pharmaceutically acceptable polymers, including PVP-VA 64, eudragit® E100 and EC 20 cps [7]. Verreck et al. also describe the injection of carbon dioxide during hot stage extrusion of itraconazole with PVP-VA 64 and itraconazole with EC 20 cps and confirm the plasticization of the product by pressurized carbon dioxide [8,9]. To better understand the solid dispersion, a phase diagram of itraconazole and EC 20 cps was constructed using hot stage extrusion with and without CO_2 injection.

Materials and Methods

Itraconazole (purity more than 99%) was obtained from Janssen Pharmaceutica (Beerse, Belgium) and EC 20 CPS was obtained from Keyser & Mackay (Keyser & Mackay, Brussels, Belgium). CO_2 (≥ 99.9 vol%, purity grade 3.0) was supplied in gas cylinders with dip tube (Messer, Machelen, Belgium).

Physical mixtures

The physical mixtures of itraconazole and EC 20 cps were prepared by blending both components in a planetary blender (Collette MP20, Collette, Belgium) for 10 minutes at a mixing speed of 20 rpm.

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 4 barrel segments of 5 L/D each and 1 barrel element of 20 L/D. The extruder set up and screw configuration are shown in Figures 1 and 2. The barrel segment adjacent to the powder feeder was water cooled. The first two barrel segments were set at 180°C, while the remainder of the barrel was kept at 140°C. The screw speed and feed rate were kept constant at 100 rpm and 1 kg/hr, respectively. The physical mixtures of drug and polymer were 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), at a constant pressure rate (CPR) of 40 bar. CO_2 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). The 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 into the barrel through an injection nozzle located in barrel segment 3 (see Figure 1).

Modulated differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) was performed using a TA Instruments modulated DSC Q1000 differential scanning calorimeter and thermal analysis controller (TA Instruments, New Castle, DE, USA). The samples were analysed in duplicate in standard (open) aluminum TA Instruments pans. Approximately 2 to 3 mg of the melt extrudate samples was heated from 35°C to 200°C with an underlying heating rate of 2°C/min, at a period of 60 s and an amplitude of ± 0.32°C.

X-ray powder diffraction (XRPD)

XRPD analyses were carried out on a Philips X'PertPRO MPD diffractometer PW3050/60 with generator PW3040 and Bragg-Brentano geometry (Philips, Almelo, the Netherlands). The instrument was equipped with a Cu LFF X-ray tube PW3373/00 and operated at a voltage of 45 kV and a current of 40 mA. A zero background holder was used as sample holder. The samples were exposed to monochromatic Cu Ka1 (wavelength of 1.54056 Å) and scanned continuous from 3 to 53º 2theta with a step size of 0.01675º/step and counting time of 10s.

Hot stage X-ray powder diffraction (hot stage-XRPD)

The experimental conditions were identical as the XRPD analysis, with the exception of the sample stage. For the XRPD hot stage experiments the XRPD instrument was equipped with an Anton Paar TTK hotstage. The samples were heated from 25°C and 180°C at a heating rate of 2°C/min. During the XRPD measurements the temperature was kept isotherm.

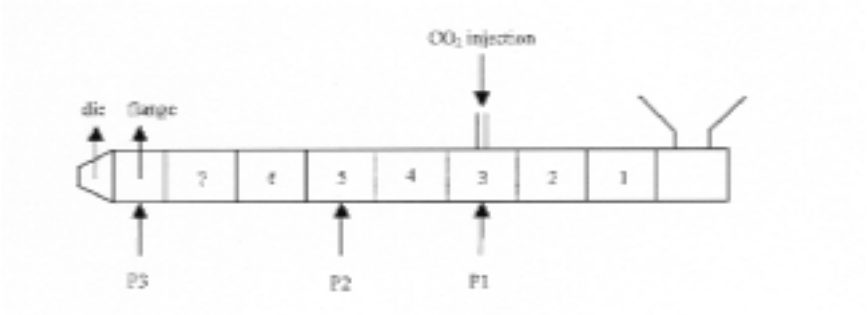

Figure 1: Schematic set up of the Leistritz twin screw extruder. Carbon dioxide was injected in segment 3. Further downstream, the barrel is completely closed. Pressurized carbon dioxide is released back to atmospheric pressure upon exiting the die.

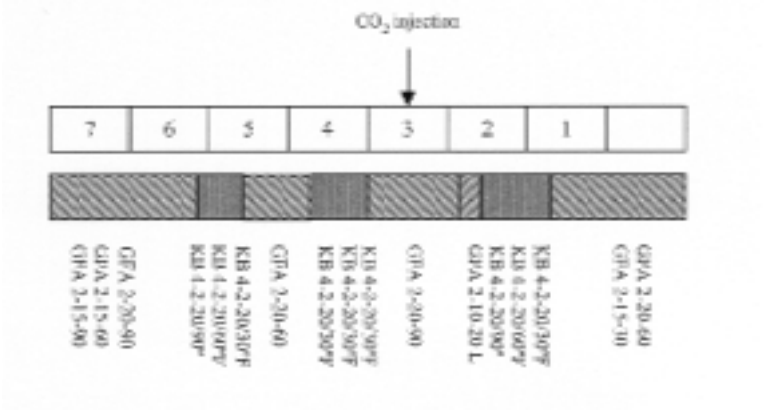

Figure 2: Schematic set up of the screw configuration. The descriptions represent the properties of the transport elements (GFA) and kneading blocks (KB), respectively, as well as the length and angle of each element.

Results and discussion

The hot stage extrusion process was feasible for all concentrations without CO_2 injection and up to 40% w/w drug loading with injection of carbon dioxide. At higher drug loadings, the melt seal could not withstand the high pressure resulting in leakage of the pressurised gas. This is probably due to the reduced viscosity of the melt at higher drug loadings since itraconazole works as a plasticizer for EC 20 cps itself.

DSC analysis of crystalline itraconazole shows that in the first heating run, an endothermic melting peak with its maximum at 172°C and an enthalpy of fusion (ΔH_f) of about 85 J/g is obtained. During cooling and subsequent reheating, a glass transition (T_g) at 60° C and two endothermic peaks at 76°C (ΔH = 0.7 J/g) and 92°C (ΔH = 1.0 J/g), respectively, are observed. Investigation showed that itraconazole transforms into the glassy state with the formation of chiral nematic mesophase when cooled from the melt [11-14]. EC 20 cps on the other hand, is a semi-crystalline polymer with a glass transition temperature of 131°C and a melting endotherm at 182°C; the corresponding enthalpy of fusion (ΔH_f) is 4.9 J/g [7,15].
Tables 1 and 2 show the MDSC results for the different itraconazole/EC 20 cps solid dispersions with and without CO_2 injection. These tables show that a number of thermal events are measured in the different solid dispersions. Up to a drug loading of 20% w/w itraconazole, the solid dispersions show one glass transition and one endothermic transition with a low enthalpy. This indicates the formation of mainly amorphous dispersions (glass solutions) with a low concentration of a crystalline fraction. From a drug loading of 30% w/w

and higher, the solid dispersions show two glass transitions and three endothermic transitions. This indicates that solid dispersions are formed with a number of different phases including glassy itraconazole (lowest T_g), chiral nematic mesophase of itraconazole (the two lowest endothermic transitions), crystalline itraconazole (the highest endothermic transition) and an amorphous mixture (the highest T_g). From 40% w/w and higher, cold crystallization was observed in all samples, as indicated by one or more exothermic transitions. Also, the amount of crystalline itraconazole increases with increasing drug loading.

These observations were made irrespective of the injection of pressurized carbon dioxide during hot stage extrusion of itraconazole with EC 20 cps. In other words, these data show that the thermal properties of the solid dispersion were not influenced by injecting CO_2 under subcritical pressures.

XRPD patterns of the different solid dispersions show a broad halo up to a 30% w/w drug loading with and without carbon dioxide injection (data not shown). Above 30% w/w, diffraction peaks were observed indicating the presence of crystalline itraconazole in these dispersions and confirming the MDSC data. Also, all XRPD patterns show a small diffraction peak at a 2θ value of approximately 12 which can be contributed to the crystalline fraction of EC 20 cps. This shows that all samples still contain a crystalline fraction of the polymer and that the highest endothermic transition, measured using MDSC, possibly consists of a combined melting of both crystalline itraconazole and EC 20 cps. To further elucidate this endothermic transition, hot stage-XRPD was performed within the temperature range of 25 to 180°C. The XRPD patterns show a change as a function of the temperature. At 170°C, the crystalline diffraction peaks of itraconazole disappear while at 180°C, the diffraction peak of EC 20 cps at a 2θ value of approximately 12, is formed. This strongly suggests that the melting peak observed during MDSC analysis of this sample, represents the melting of crystalline itraconazole.

Table 1: The glass transition temperature (T_g), the temperature of the endo/exothermic transitions (T_t) and the enthalpy of the endo/exothermic transition (ΔH_t), for the 10 to 70% w/w solid dispersions prepared by hot stage extrusion without CO_2 injection. Results are average values (n=2).

% w/w itraconazole	T_g (°C)	T_t (°C)	ΔH_t (J/g)
10	106.0	165.6	2.1
20	115.0	158.0	3.1
30	58.6	73.2	0.1
	111.4	90.3	0.1
		157.6	2.2
40	58.8	73.6	0.2
	118.7	90.1	0.5
		109.0	-9.7
		166.6	22.8
50	60.0	74.0	0.3
	122.0	90.2	0.4
		123.5	-18.6
		167.7	27.0
70	58.1	73.7	0.1
	114.4	92.2	0.3
		98.7	-7.3
		128.5	-3.0
		172.2	34.6

Table 2: The glass transition temperature (T_g), the temperature of the endo/exothermic transitions (T_t) and the enthalpy of the endo/exothermic transition (ΔH_t), for the 10 to 40% w/w solid dispersions prepared by hot stage extrusion with CO_2 injection. Results are average values (n=2).

Nr.	T_g (°C)	T_t (°C)	ΔH_t (J/g)
10	104.7	165.9	1.6
20	96.6	157.3	2.9
30	58.8	74.2	0.1
	118.4	90.3	0.1
		166.2	2.0
40	58.3	73.6	0.1
	111.0	89.6	0.1
		96.8	-3.9
		125.5	-4.9
		164.7	28.5

Conclusion

Based on the experiments it is concluded that the itraconazole/EC 20 cps solid dispersions prepared by hot stage extrusion consist of amorphous dispersions up to 20-30% w/w drug loading. Higher concentrations result in solid dispersions consisting of a mixture of glassy itraconazole, chiral nematic mesophase and crystalline itraconazole. The thermal properties of the solid dispersions were not changed when CO_2 was injected under subcritical pressure.

References

1 BREITENBACH J., Eur. J. Pharm. Biopharm., 54, **2002**, 107-117.

2 VERRECK G., BREWSTER M.E., Bulletin Technique Gattefosse, 97, **2004**, 85-95.

3 FOLLONIER N., DOELKER E., COLE E.T., Drug. Dev. Ind. Pharm., 20 (8), **1994**, 1323-1339.

4 FOLLONIER N., DOELKER E., COLE E.T., J. Control. Rel., 36, **1995**, 243-250.

5 MC GINITY J.W., ZHANG F., Pharmaceutical extrusion technology, Marcel Dekker, New York, **2003**, 183-208.

6 REPKA M.A., GERDING T.G., REPKA S.L., MC GINITY J.W., Drug Dev. Ind. Pharm., 25(5), **1999,** 625-633.

7 VERRECK G., DECORTE A., LIU D., TOMASKO D., ARIEN A., PEETERS J., ROMBAUT P., VAN DEN MOOTER G., BREWSTER M. E., J. Supercritical Fluids, accepted **2005**

8 VERRECK G., DECORTE A., HEYMANS K., ADRIAENSEN J., CLEEREN D., JACOBS A., LIU D., TOMASKO D., ARIEN A., PEETERS J., ROMBAUT P., VAN DEN MOOTER G., BREWSTER M. E., Eur. J. Pharm. Sci., accepted **2005**.

9 VERRECK G., DECORTE A., HEYMANS K., ADRIAENSEN J., LIU D., TOMASKO D., ARIEN A., PEETERS J., ROMBAUT P., VAN DEN MOOTER G., BREWSTER M. E., J. Pharm. Pharmacol., submitted **2005**

10 PEETERS J., NEESKENS P., TOLLENAERE J.P., VAN REMOORTERE P., BREWSTER M., J. Pharm. Sci., 91, **2002**, 1414-1422.
11 VERRECK G., SIX K., VAN DEN MOOTER G., BAERT L., PEETERS J., BREWSTER M.E., Int. J. Pharm., 251, **2003**, 165-174.
12 SIX K., BERGHMANS H., LEUNER C., DRESSMAN J., VAN WERDE K., MULLENS J., BENOIST L., THIMON M., MEUBLAT L., VERRECK G., PEETERS J., BREWSTER M., VAN DEN MOOTER G., Pharm. Res. 20 (7), **2003**, 1047-1054.
13 SIX K., VERRECK G., PEETERS J., AUGUSTIJNS P., KINGET R., VAN DEN MOOTER G., Int. J. Pharm., 213, **2001**, 163-173.
14 SIX K., VERRECK G., PEETERS J., BINNEMANS K., BERGHMANS K., AUGUSTIJNS P., KINGET R., VAN DEN MOOTER G., Thermochim. Acta, 376, **2001**, 175-181.
15 DE BRABENDER C., VAN DEN MOOTER G., VERVAET C., REMON J.P., J. Pharm. Sci., 91, **2002**, 1678-1684.