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► **To cite this version:**

Zsombor Kristof Nagy, Martial Sauceau, Gy Marosi, Élisabeth Rodier, Jacques Fages. Control of the dissolution rate of an active pharmaceutical ingredient by using melt extrusion coupled with supercritical CO<sub>2</sub>. 12th European Meeting on Supercritical Fluids, ISASF, May 2010, Graz, Austria. 9 p. hal-01757385

**HAL Id: hal-01757385**

**<https://hal.science/hal-01757385>**

Submitted on 6 Aug 2018

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# Control of the Dissolution Rate of an Active Pharmaceutical Ingredient by Using Melt Extrusion Coupled With Supercritical CO<sub>2</sub>

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## INTRODUCTION

Hot-melt extrusion (HME) is a process for converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions [1]. It represents an efficient manufacturing technology to disperse drugs in a melt up to a true molecular solution of a pharmaceutical ingredient into a polymeric matrix [2]. Most of the applications describe the preparation of solid dispersions by HME either to increase the aqueous solubility and oral bioavailability of the active substance or to control its release. The advantages of HME are: (i) avoidance of organic solvent; (ii) reduction of processing steps (one pot method); (iii) elimination of the good compressibility requirement for the active ingredients and excipients; (iv) high level of drug content uniformity; and (v) improved bioavailability through drug solubilization or molecular level dispersion in water soluble matrix [3].

One of the major drawbacks of HME is that it can be applied only for producing thermally stable pharmaceuticals. For a number of drugs, proteins and other excipients, HME cannot be used unless a plasticizer is added in order to reduce the viscosity of the mixture lowering thus the processing temperature in the extruder. However, these additives remain in the product and thus alter its properties and performance.

In this context, supercritical carbon dioxide (scCO<sub>2</sub>) represents an interesting alternative. Indeed, injection of scCO<sub>2</sub> in extrusion process modifies the rheological properties of the polymer in the barrel of the extruder and scCO<sub>2</sub> acts as a blowing agent when flowing through the die [4]. The pressure drop induces a thermodynamic instability in the polymer matrix, generating a large number of bubbles. The cell growth continues until the foam is rigidified (when  $T < T_g$ ). The reduction of viscosity decreases the mechanical constraints and the operating temperature within the extruder. Thus, combining extrusion with scCO<sub>2</sub> allows using fragile or thermally sensitive molecules, like pharmaceutical molecules, with the absence of residue in the final material.

For the extrusion of pharmaceuticals, copolymers derived from acrylic acid and methacrylates, such as Eudragit types, are promising matrices. Due to their multifunctional nature, unique properties and good biocompatibility, these polymers are considered to be of common grades for coating of pharmaceuticals [5]. In particular, Eudragit E, due to its tertiary

amine groups, forms coating soluble in gastric fluid in acidic pH [6]. Eudragit E has already been successfully implemented for HME. Six *et al.* [7] described the HME of the poorly water soluble itraconazole with Eudragit E100 polymeric carrier. Melt extrusion of this drug with Eudragit E polymer resulted in significantly enhanced dissolution rate. More recently, Verreck *et al.* showed that pressurized carbon dioxide, acting as a reversible plasticizer and foaming agent, reduces the melt extrusion temperature of several pharmaceutically acceptable polymers, including Eudragit E100 [8].

Carvedilol is a nonselective  $\beta$ -adrenergic blocking agent with  $\alpha$ -blocking activity [9]. It is a lipid soluble compound, practically insoluble in water and poorly absorbed from the gastrointestinal tract. The slow absorption of Carvedilol was attributed to its poor water solubility. Its absolute bioavailability is 25-35%. Eudragit E100 has been already used to improve the bioavailability of Carvedilol. Indeed, E100 nanoparticles containing Carvedilol were prepared by nanoprecipitation [10]. Finally, high encapsulation efficiency was obtained with a faster rate of release of Carvedilol from the nanoparticles.

In this work a  $scCO_2$  coupled extrusion process has been used to generate solid dosage form based on Eudragit E100 with Carvedilol drug according to the method previously elaborated for producing foams of this polymer [11, 12].

## MATERIALS AND METHODS

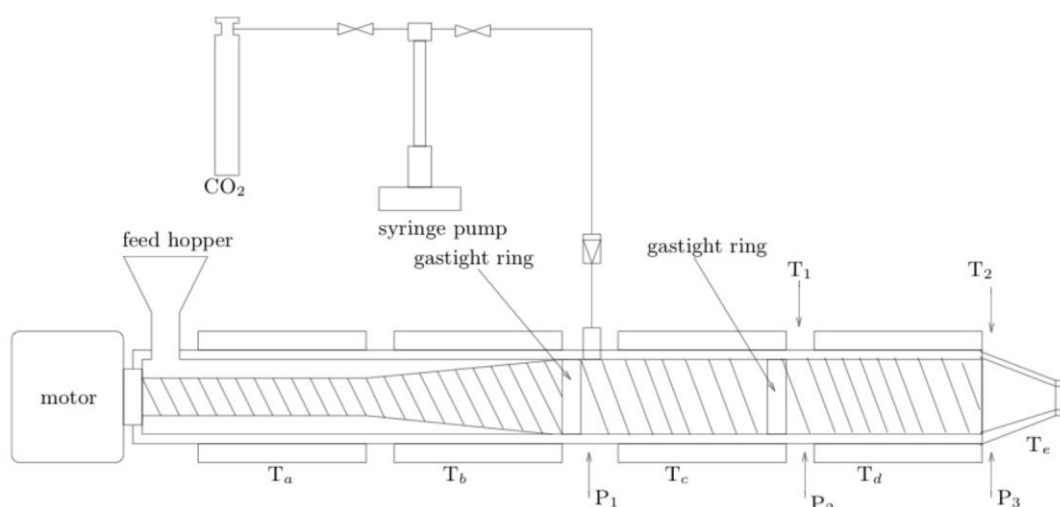
### Materials

Carvedilol (CAR) was kindly provided by EGIS Plc (Hungary). Eudragit E (E100) was purchased from IMCD (France) and  $CO_2$  from Air Liquide (France).

### Extrusion coupled with supercritical $CO_2$

Figure 1 shows the experimental set up, which has previously been detailed elsewhere [9, 10]. The single-screw extruder has a 30 mm-screw diameter and a length to diameter ratio (L/D) of 35 (Rheoscam, SCAMEX). A large L/D ratio generally allows increasing the capacity of mixing and melting but also energy consumption. The first conical part of the screw has a length to diameter ratio of 20 and allows the transport of solid polymers and then, their melting and plasticizing. Then, the screw has a cylindrical geometry from the first gastight ring to the die with a length to diameter ratio of 15. Two restriction rings have been fitted out in order to prevent  $scCO_2$  from backflowing. The diameter of the die was 1 mm and its length was 11.5 mm.

The temperature inside the barrel is measured at five locations:  $T_a$  and  $T_b$  before the  $CO_2$  injection,  $T_c$  and  $T_d$  after the injection and  $T_e$  in the die. In this study, the zone temperatures were fixed as follows:  $T_a=125^\circ C$ ,  $T_b=T_c=T_d=135^\circ C$ , and  $T_e=130^\circ C$ . The temperature and the pressure of the polymer inside the extruder were measured by means of three pressure ( $P_1$ ,  $P_2$  and  $P_3$ ) and two temperature sensors ( $T_1$  and  $T_2$ ). Errors associated to pressure and temperature sensors were about 0.2 MPa and  $3.3^\circ C$  respectively.



**Figure 1. Experimental device**

CO<sub>2</sub> was pumped from a cylinder by a syringe pump (260D, ISCO) regulated at 7°C. It was then introduced at a constant volumetric flow rate of 0.25 cm<sup>3</sup>.min<sup>-1</sup> at a pressure which was kept slightly higher than the pressure P<sub>1</sub>. The CO<sub>2</sub> injector was positioned at a length to diameter ratio of 20 from the feed hopper. The pressure and the volumetric CO<sub>2</sub> flow rate were measured within the syringe pump.

At the beginning of the extrusion process, pure E100 was fed in the extruder. Before the injection of scCO<sub>2</sub>, the torque was controlled by the rotating speed of the screw (higher rotating speed resulted in higher torque) and was kept at high values close to the established alarm limit to ensure high production rate and low residence time. Once steady state conditions have been reached with E100, drug polymer mixture was introduced through the hopper. Two drug mass contents were tested: 5 and 20%. The scCO<sub>2</sub> was introduced into the barrel once the drug polymer mixture had reached the die. During the scCO<sub>2</sub> injection, the torque decreased and the rotation speed could be increased to reach higher production rates and lower residence time.

**Table 1. Compositions and operating conditions of the samples**

Exp	CAR (mass %)	CO <sub>2</sub> (cm <sup>3</sup> .min <sup>-1</sup> )	Mean torque (Nm)	Screw rotation speed (rpm)
1	0	0	104	5
2	5	0	96	5
3	5	0.25	66	5
4	5	0.25	75	7
5	5	0.25	93	10
6	20	0	83	5
7	20	0.25	55	5
8	20	0.25	64	7
9	20	0.25	76	10

When steady state conditions have been reached again, extrudates were collected and air-cooled at ambient temperature. The samples were obtained under the following operating conditions (Table 1). The sampling time and the mass of the collected samples were measured in order to determine the mass-flow. Extrudates were then ground by an IKA MF10 microfine grinder drive with a MF 10.2 impact grinding head. The applied sieve was MF 2.0 mm and the rotation speed was 3000 rpm.

#### Scanning electron microscopy (SEM)

Morphology of the samples was investigated by a JEOL 6380LVa type scanning electron microscope. Each specimen was fixed by conductive double sided carbon adhesive tape and gold-coated by JEOL 1200 in order to avoid electrostatic charging.

#### Fourier transformed infrared spectrometry (FTIR)

KBr pastille sample preparation method was used for the FTIR measurement. The obtained pastilles were analyzed by Bruker Tensor 37 type spectrometer equipped with DTGS detector in the range of 4000-400  $\text{cm}^{-1}$  with a resolution of 4  $\text{cm}^{-1}$ .

#### Determination of drug content

Samples equivalent to 10 mg of CAR were placed into volumetric flask (1  $\text{dm}^3$ ) and were diluted with 0.1 N HCl. After the complete dissolution and homogenization the concentration of CAR was determined by UV spectrophotometry at 242 nm (Hewlett-Packard HP 8452A).

#### In vitro dissolution measurement

The dissolution studies were performed by an Erweka DT6 dissolution tester (USP II apparatus). Samples were placed in the dissolution vessel containing 900 ml 0.1 N HCl maintained at  $37 \pm 0.5^\circ\text{C}$  and stirred at 50 rpm. Samples (5 ml) were collected periodically and the concentration of CAR was determined by UV spectrophotometry at 242 nm (Hewlett-Packard HP 8452A).

## **RESULTS AND DISCUSSION**

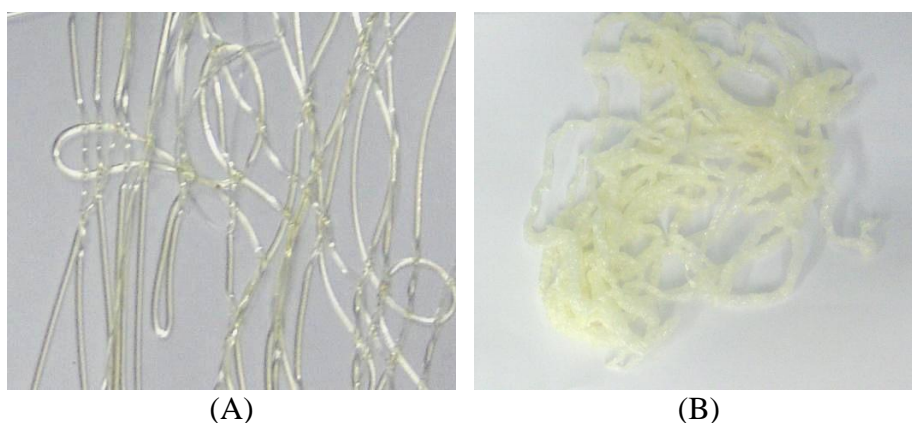
#### Supercritical CO<sub>2</sub> aided extrusion

The application of scCO<sub>2</sub> in the field of pharmaceutical extrusion has two remarkable advantages from the stability point of view. Processing temperature can be decreased [8] and/or the mass flow rate can be increased. If higher mass-flow is achieved, the residence time of the material can be shortened significantly; furthermore, the productivity is higher. A lower temperature and an increased flow rate result in lower risk of decomposition and total amount of impurities (decomposition products) can be kept under the maximum limit.

The aim of this work was to achieve amorphous drug morphology with good homogeneity. Therefore, to be sure that API is melted, the temperature of the process was not decreased (comparing to the reference experiments without scCO<sub>2</sub>). The melting point of Carvedilol is 117°C [13] while the temperatures of the five zones were kept slightly higher (125-135°C) than this temperature. The residence time, however, was shortened in order to preserve the drug stability. The viscosity of the material in the barrel is correlated with the torque. As the rotation speed was increased, the measured torque increased. Without the injection of scCO<sub>2</sub>, a maximum rotation speed of 5 rpm could be used without alarm stop. In contrast, after introducing scCO<sub>2</sub>, the torque decreased significantly and the rotation speed could be increased stepwise up to 10 rpm. Due to the plasticization effect of scCO<sub>2</sub>, the torque at 10 rpm was lower than at 5 rpm without scCO<sub>2</sub> (Table 1). This gain in the maximal throughput demonstrates the valuable plasticizing efficiency of scCO<sub>2</sub>.

Beside the scCO<sub>2</sub>, the addition of the active ingredient provided remarkable plasticizing effect too, which could be detected by measuring the torque (Table 1). Carvedilol, being a relatively small molecule proved to play the role of a plasticizer. E100-CAR mixtures exhibit lower torque than pure E100 owing to the decreased viscosity.

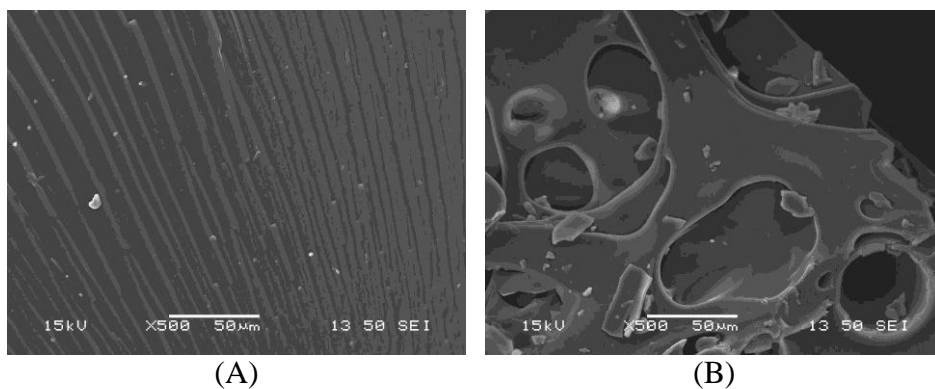
Figure 2 shows the photographs of E100-CAR extrudates. The extrudates made by traditional extrusion process (A) were glassy and transparent. The extrudates made by scCO<sub>2</sub> aided extrusion (B) were opaque due to the newly formed internal surfaces.



**Figure 2. E100-CAR extrudates, (A) exp. 6, (B) exp. 9**

### Scanning electron microscopy (SEM)

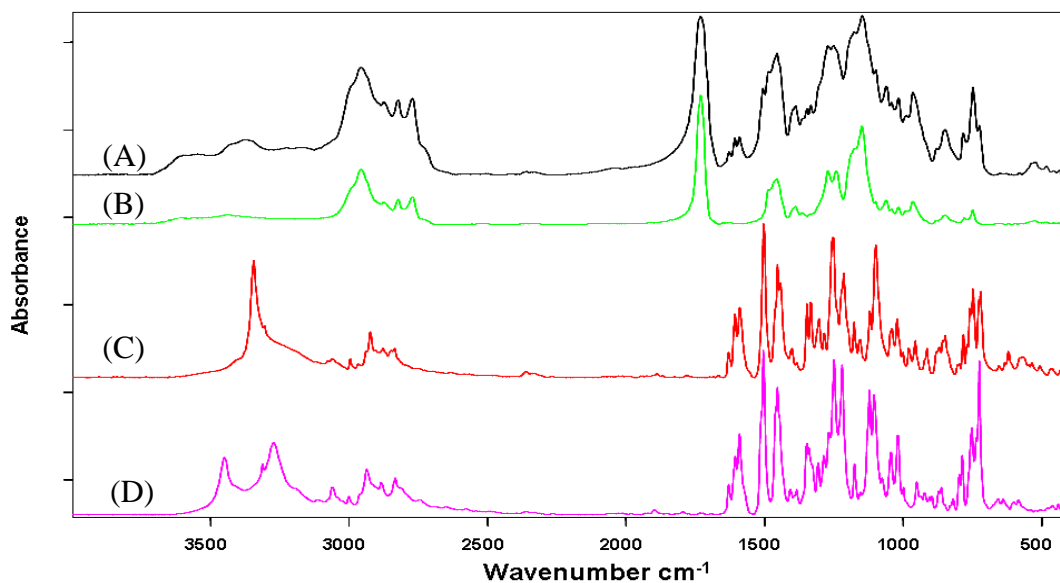
The surface of extrudates, shown in the SEM images of Figure 3, is quite different to the one made by traditional extrusion process, which is smooth compared to the foamed extrudates. The specific surface area is clearly larger in the case of the foamed samples providing extended availability to the dissolving medium, which may increase the dissolution rate.



**Figure 3. SEM images of E100-CAR extrudates, (A) exp. 6 , (B) exp. 9**

### Fourier transform infrared spectrometry (FTIR)

The extruded products were analyzed by FTIR spectrometry in order to check their stability under the processing conditions. The results are shown in Figure 4. Compared to the untreated pristine components appearance, no new peak could be detected in the spectra of the extrudates. It confirms that no detectable decomposition occurred during the extrusion.



**Figure 4. FTIR spectra of samples, (A) Exp. 9 ground, (B) E100 powder, (C) CAR Form II, (D) CAR Form I**

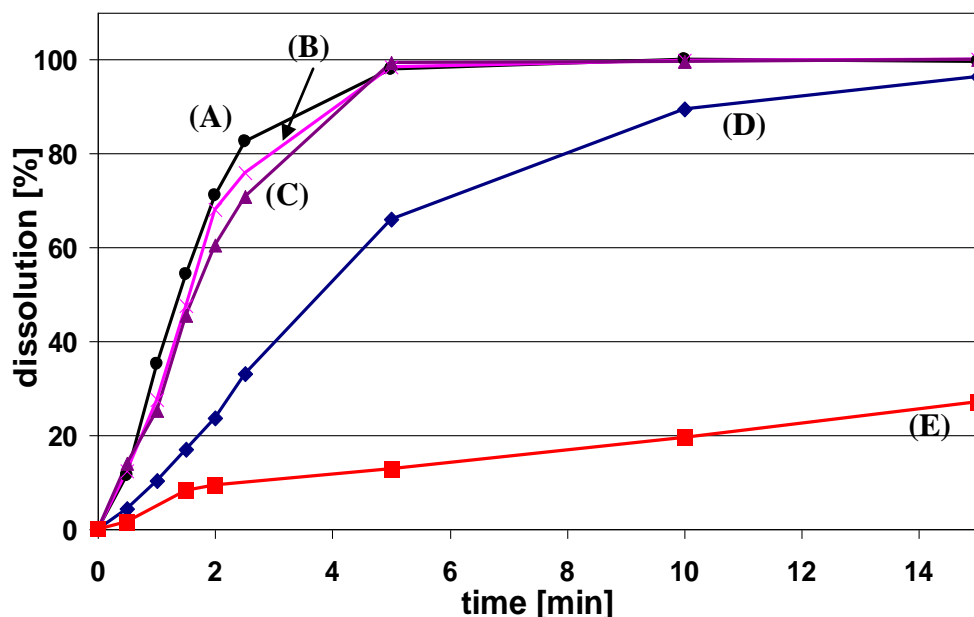
CAR has got two common polymorphic crystalline forms. These are CAR Form I and Form II [14,15]. In the absorption region of O-H and N-H stretching vibration CAR Form II has got one strong band at  $\sim 3340\text{ cm}^{-1}$  and CAR Form I has got two strong bands at  $\sim 3250\text{ cm}^{-1}$  and  $3450\text{ cm}^{-1}$ . E100 has got only two very slight peaks in this region.

In the spectra of E100-CAR extrudates, one broader peak was observable from  $\sim 3300\text{ cm}^{-1}$  to  $3450\text{ cm}^{-1}$  which demonstrates the interaction between the E100 and CAR. It suggests that the CAR is not in crystalline form because the characteristic peaks of Form I and Form II are not present in the spectra. The broad peak indicates probably that CAR is present in amorphous form. This deduction corresponds to the results of Pokharkar *et al.* [16].

Further analyzes were made by X-ray diffraction and differential scanning calorimetry (not presented here) and both techniques verified that CAR is in amorphous phase whatever the drug content is (5% or 20%).

#### In vitro dissolution and drug content determination

The *in vitro* dissolution of the different samples exhibited significant differences. The dissolution curves are shown in Figure 5.



**Figure 5. Dissolution profiles, (A) Exp. 9 ground, (B) Exp. 6 ground, (C) Exp. 6, (D) Exp 9, (E) Crystalline CAR**

Crystalline CAR (curve E) shows moderate dissolution rate which could be improved by HME with E100 (curves A, B C and D). It was found that the E100 matrix governs the dissolution rate of the extrudates. When molecules of E100 matrix were dissolved, the CAR molecules dissolved simultaneously because CAR molecules were in amorphous form (as shown above) and there was no need to overcome the lattice energy. It confirms that CAR was molecularly dispersed or nearly molecularly dispersed in the E100 matrix.

As E100 dissolves in acidic media rapidly the dissolution times of the extrudates were found to be short as well. The dissolution rate depends on the surface area of the material exposed to the dissolution media [17]. Though the foamed extrudates exhibit an increased surface area, the unmilled foams (curve D) had significantly slower dissolution than common extrudates and ground extrudates. The reason for that result lays on the floating of the unmilled foamy samples on the surface of the dissolution media resulting in limited contact between the phases. In contrast the common and the ground extrudates sank into the dissolution media allowing the dissolution process to proceed faster through the fully accessible surfaces. Consequently the dissolution times of ground samples (5 min) is significantly improved compared to that of crystalline CAR.



The drug contents of the extrudates, determined with UV spectrophotometer, corresponded in all cases to the initially introduced CAR and the relative standard deviation (1.31 % RSD) of the measured contents was under the established limit of U.S. Pharmacopeia (4.6 % RSD) [18].

## CONCLUSION

In this work, fast dissolving formulation of a poorly water soluble drug against hypertension was produced by conventional and supercritical CO<sub>2</sub> assisted extrusion process using Eudragit E as a polymer matrix. The manufactured fine solid dispersions of Carvedilol in Eudragit E increased the dissolution rate of Carvedilol. It shows the dissolution improving efficiency of Eudragit E matrix, produced by HME, and its applicability as fast dissolving drug delivery system. Moreover, the mild operating conditions and the productivity of the technology could be improved by decreasing the viscosity with scCO<sub>2</sub> as a temporary plasticizer.

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