# Dissolution Enhancement of Active Pharmaceutical Ingredients in Eudragit E100 by Melt Extrusion Coupled with Supercritical Carbon Dioxide

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## ABSTRACT

Melt extrusion is a well-known technique to disperse poorly water-soluble crystalline active pharmaceutical ingredients (APIs) in polymers for dissolution enhancement, which is achieved by destructing their crystal lattice. Its unquestionable advantages are that it is a solvent-free and high-throughput continuous manufacturing technology ensuring constant product quality, which is favoured by Process Analytical Technology guidelines, and the range of producible dosage forms is wide. At the same time, a clear disadvantage of conventional melt extrusion is that the heat sensitivity of some active compounds can be an obstacle to its application because most pharmaceutical-grade polymers can only be processed at a high temperature.

The most promising way of providing milder processing conditions and hence reducing drug degradation is the utilization of supercritical carbon dioxide ($scCO_2$) as a reversible plasticizer [1]. In addition, it acts as a physical blowing agent and leaves behind a well-grindable, rigid product of high specific surface area, which can be extremely beneficial in the case of immediate release formulations owing to the great influence of this property on dissolution rate.

In this study, BCS II classified thermally sensitive drugs, which need dissolution enhancement, were extruded with an acid-soluble, methacrylate-based polymer, Eudragit E100. We studied the influence of different operating parameters on the production of foamy extrudates: melt throughput, $scCO_2$ mass fraction, extrusion temperature and pressure. The samples were analysed for their physical properties: rigidity, porosity and characteristic pore size. API dispersion within the polymer matrix has also been characterized by X-ray diffraction, Raman mapping and dissolution tests.

## INTRODUCTION

To face the lack of bioavailability of numerous active pharmaceutical ingredients, the use of hot melt extrusion (HME) has been extensively described [2]. High temperatures employed, resulting from the glass transition and/or melting point of the polymer used, require however the use of plasticizers which may exhibit some drawbacks. In this respect, the use of supercritical carbon dioxide $scCO_2$ as a removable plasticizer has emerged as a new and effective practice [3]. In addition, the coupling of $scCO_2$ technology with HME has been

described as a promising route for the manufacture of new galenical forms with enhanced dissolution or release-controlled properties of active ingredients embedded into a foamy polymeric matrix [1].

In this paper, we describe two dissolution kinetics enhancement using $scCO_2$-assisted hot melt extrusion with an acrylic polymer of pharmaceutical grade, Eudragit E, and two active ingredients, Carvedilol and Spironolactone. Both molecules belong to the class II of the Biopharmaceutics Classification System, meaning that their dissolution is poor leading to a lack of bioavailability.

## MATERIALS AND METHODS

### Materials: Active ingredients and Polymer

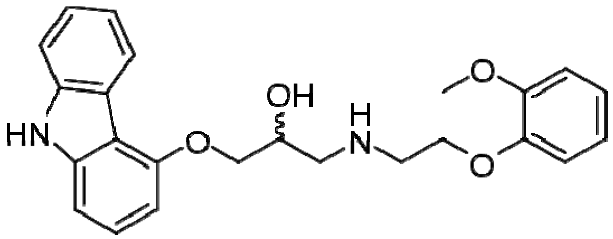



**Figure 1. Formula of Carvedilol**

Carvedilol (Fig. 1) purchased from Sigma-Aldrich (Budapest, Hungary) with purity ≥ 98% was used in this work. Its molecular weight is 406 g/mol and its melting point is 117 °C. It is a beta-blocker used to treat congestive heart failures.

Spironolactone (Fig. 2) is a diuretic and anti-hypertensive molecule having a molar mass of 417 g/mol and a melting range of 198–207 °C. It was kindly provided by Gedeon Richter Plc. (Budapest, Hungary).

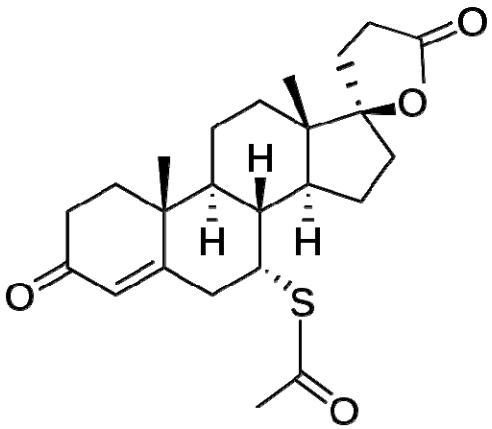



**Figure 2. Formula of Spironolactone**

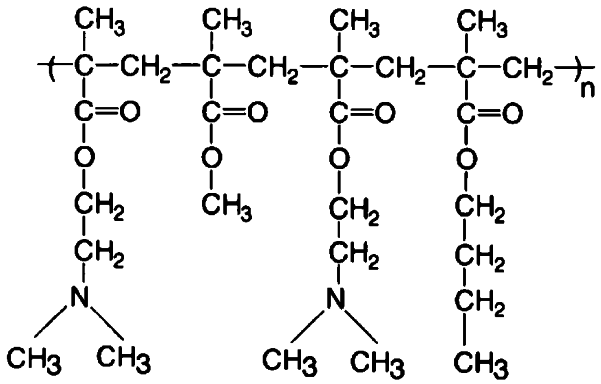
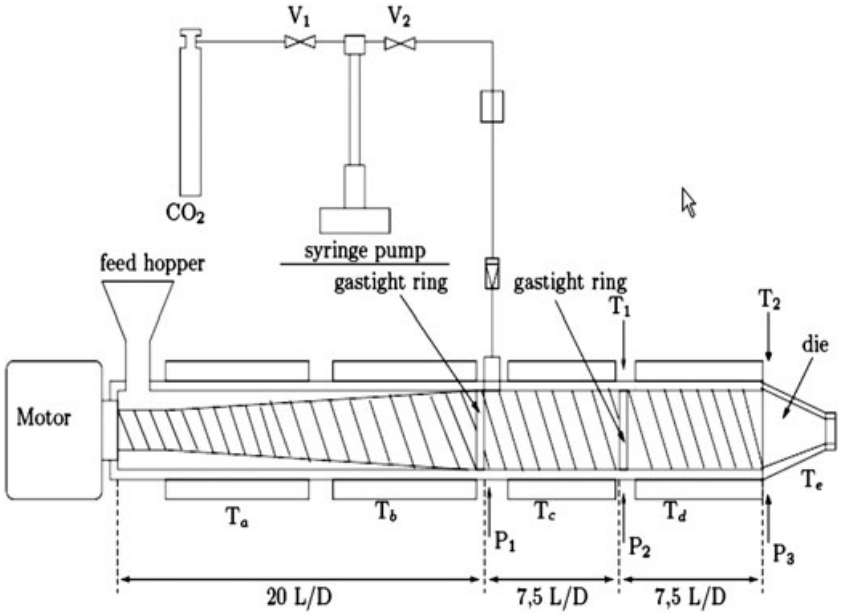



**Figure 3. Formula of Eudragit E100**

Eudragit E (E100, Fig. 3) purchased from IMCD (Saint-Denis La Plaine, France). Eudragit is an amorphous acrylic polymer with an average molecular weight of 150 kg/mol and a glass transition temperature in the range 45-52 °C.

**Methods:**




$ScCO_2$-assisted extrusion of a mixture of active molecule and Eudragit E was performed on a single-screw extruder (SCAMEX, Crosne, France), with a large L/D ratio of 35.

$CO_2$ was injected into the extruder barrel by means of a syringe pump (ISCO, USA).

A detailed description of the system can be found in [3].

**Figure 4. Experimental apparatus**

Several methods -not presented here- were used for characterization of the dispersion of the active into the polymer matrix (i.e. amorphisation of the drug in the extrudates) as well as the foamy structure of the extrudates [4].

**In vitro dissolution tests**

The concentration of active molecules in the samples was determined by UV spectrophotometry at 242 nm (Hewlett-Packard HP 8452A) using a diode-array detector. Six parallel tests were performed and analysed statistically. The test samples were obtained as follows:

- For Carvedilol, using an Erweka DT6 dissolution tester (USP II apparatus, Heusenstamm, Germany). Samples equivalent to 12.5 mg of carvedilol were added as a powder directly in the dissolution vessel containing 900 ml 0.1 M HCl maintained at 37±0.5 °C and stirred at 50 rpm. Samples (5 ml) were collected periodically.
- For Spironolactone, using a PTWS 600 dissolution tester (USP II apparatus, Pharma Test Apparatebau AG, Hainburg, Germany). Samples equivalent to 8 mg of Spironolactone were placed in the dissolution vessel containing 900 ml of 0.1 M hydrochloric acid maintained at 37±0.5 °C and stirred at 100 rpm. Samples were collected periodically.

**RESULTS**:

Figures 5 and 6 give the dissolution profiles of Carvedilol and Spironolactone samples respectively.

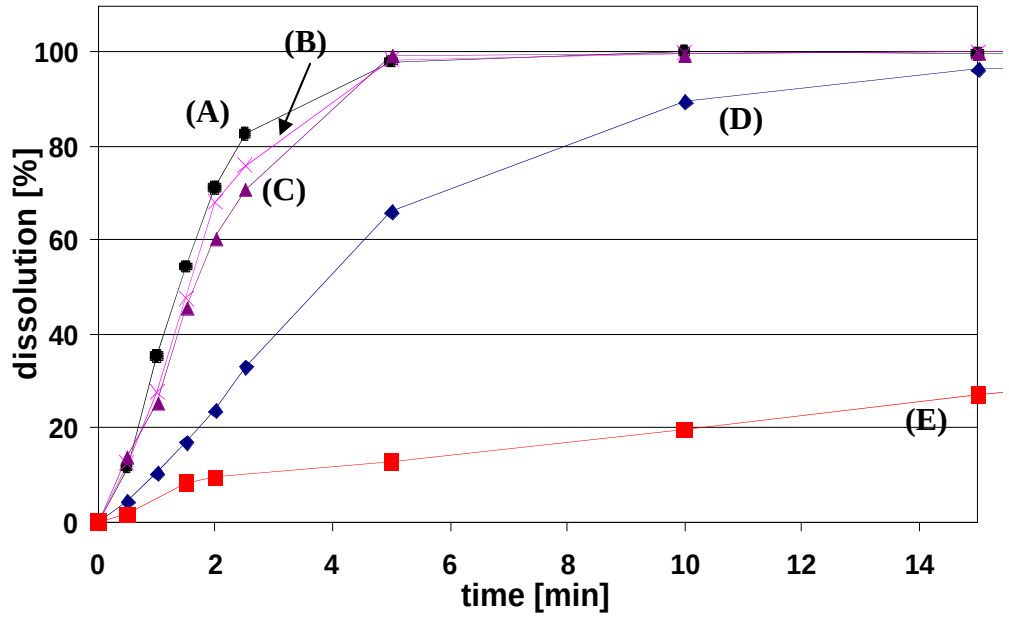



**Figure 5. Dissolution of Carvedilol from HME formulations (A, B, C, D) in comparison to unprocessed crystalline Carvedilol (E). (A) $CO_2$-foamed-extruded and ground, (B) extruded and ground, (C) extruded, (D) $CO_2$-foamed sample.**

Figure 5 shows that the E100 polymer matrix governs the dissolution rate of the Carvedilol extrudates. Carvedilol molecules dissolved simultaneously with the matrix. It confirms that Carvedilol was molecularly dispersed or nearly molecularly dispersed in the matrix by HME. As the matrix 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. The $CO_2$-foamed extrudates exhibit an increased surface area already in unmilled foams (curve D). This area could be however further increased by grinding (curve A). In the very first minutes, the A sample is even slightly more rapid in comparison with the unfoamed samples B, C. This is probably because of the inner porosity, leading to an increased surface area accessible to the solvent: the dissolution rate depends on the surface area of the material exposed to the dissolution medium.

The reason for the slower dissolution of the unmilled foamed extrudate D compared to the ground one A is its low apparent density causing floating of the particles on the surface of the dissolution media. It results in limited contact with the solvent. In contrast, B and C samples sank into the dissolution media allowing the dissolution process to proceed faster through the fully accessible surfaces [5]. Consequently the dissolution time of ground samples (5 min) is significantly lower compared to that of unprocessed Carvedilol.

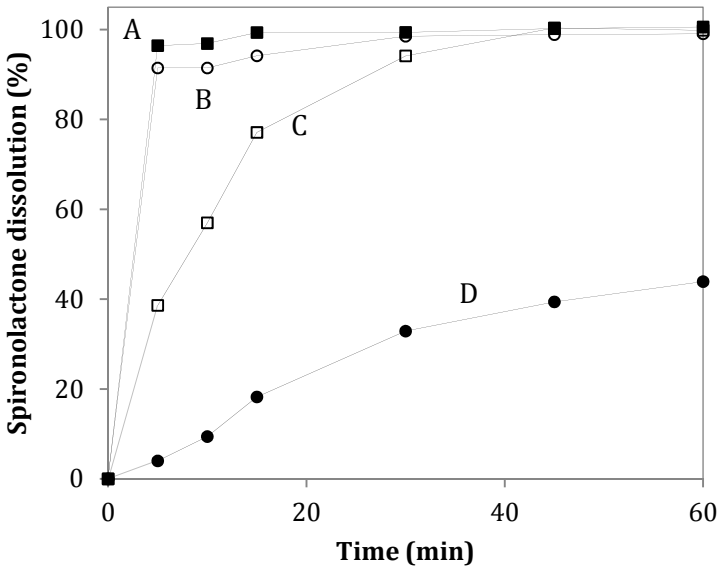



**Figure 6. Dissolution of Spironolactone from HME formulations (A, B, C) in comparison with unprocessed microcrystalline Spironolactone (D). (A, B) $CO_2$-foamed-extruded and ground, (C) $CO_2$-foamed sample.**

In comparison to the extremely slow dissolution rate of microcrystalline Spironolactone (curve D), the dissolution of $CO_2$-foamed extruded and ground samples (curves A and B) was considerably faster. Amorphisation of Spironolactone and the solubilizing effect of Eudragit E enabled the immediate release of approx. 90 % of the API content dissolved in 10 min. The difference between A and B samples lies in the porosity (data not shown), A having a higher porosity than B and exhibiting therefore a larger surface area. The $CO_2$-foamed extruded (without grinding) dissolved at an intermediate rate (Curve C).

## CONCLUSION

This study shows through both examples of Carvedilol and Spironolactone–Eudragit E foamed solid dispersions that HME assisted by supercritical-$CO_2$ can lead to large dissolution rate enhancements. Fast-dissolving formulations of poorly water-soluble drugs can thus be achieved. In addition, by tuning the inner porosity and with an additional grinding step, a wide range of dissolution speed can be reached.

This dissolution rate enhancement is due to an amorphisation of the drug into the polymer matrix [4], which resulted in a drug release rate governed by the polymer dissolution, which in turn depends on the specific surface area of the sample.

Future developments of this process include the manufacture of new solid formulations with improved properties.

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