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Dispersion of an Active Pharmaceutical Ingredient in Eudragit E100 by Melt Extrusion Coupled with Supercritical Carbon Dioxide

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Abstract

The plasticising effect of supercritical CO_2 during the solvent-free melt extrusion of the cationic copolymer Eudragit E and the heat-sensitive and slowly dissolving active pharmaceutical ingredient, spironolactone was shown to reasonably improve the purity of the prepared solid dispersions by enabling production at lower temperature ranges. By increasing the mass flow of the melt, further enhancement was achieved in purity, but the shorter residence time counteracted the amorphisation (i.e. molecular dispersion) of crystalline drug particles, according to data acquired by confocal Raman mapping. At the same time, supercritical CO_2 aided amorphisation of the lipophilic drug, thus also facilitating the production of fully amorphous glassy solution samples at the lowered temperature. The obtained high amorphicity ensured immediate drug dissolution in acidic medium. Scanning electron microscopy revealed that optimal extrusion parameters enabled the production of foams of low porosity, homogeneous structure and thin walls.

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Keywords: supercritical fluid extrusion; foaming; immediate release; solid solution; decomposition

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1. Introduction

Melt extrusion is a well-known technique to disperse poorly water-soluble crystalline active pharmaceutical ingredients (APIs) in polymers in order to enhance their bioavailability [1]. Dissolution of the API from the resulting solid suspensions or solid solutions can be faster for two reasons in accordance with the Noyes–Whitney equation [2]. On one hand, crystalline APIs can get dissolved in the polymer melt in the course of extrusion, and hence there is no crystalline lattice to be destructed during the dissolution of the formulation in the stomach. The lower the API crystallinity, the faster dissolution can be expected. On the other hand, molten polymers can solubilise the drug molecules, thus improving their apparent solubility and increasing the driving force of molecular diffusion from the extrudate surface. Unquestionable advantages of melt extrusion are that it does not require the use of any solvent, it is a high-throughput continuous manufacturing technology ensuring constant product quality, which is favoured by Process Analytical Technology (PAT) guidelines [3], and finally, the range of producible dosage forms is wide: mini matrices, granules, pellets, foams, films and implants can be prepared this way [4]. At the same time, a clear disadvantage of melt

extrusion is that most pharmaceutical-grade polymers can only be processed at a high temperature due to their high glass-transition temperature (T_g). Despite the growing number of the marketed pharmaceutical products that are produced by melt extrusion (for example Kaletra and Isoptin SR-E [5–7]), the heat sensitivity of some active compounds can be an obstacle to the application of melt granulation methods in their case. Although processing temperature can be lowered by means of plasticisation, plasticisers remain in the extrudate permanently, lowering its glass-transition temperature (T_g), which can reduce physical stability and make further processing impossible.

An interesting alternative of plasticisation achieved by small-molecular additives is the injection and dissolution of supercritical carbon dioxide ($scCO_2$) into the molten polymer conveyed in the extruder [8]. By enabling production at a lower temperature, it can reduce decomposition of thermally unstable compounds [9]. Special attention is given to this plasticiser because it does not remain in the extrudate after processing. Therefore, it only modifies the rheological properties of the polymer during processing – the plasticising effect ceases afterwards, leaving behind a product of high T_g and viscosity. $ScCO_2$ can just as well be used as a physical blowing agent due to the gaseous CO_2 bubbles evolving in the melt after pressure has dropped in the extruder die. Growth of these pores continues until the extrudate rigidifies or until the whole amount of CO_2 diffuses into the atmosphere. This blowing agent leaves no residue in the foams, which is particularly important in the case of pharmaceutical applications [10]. The high specific surface area generated by this foaming process can be extremely beneficial in the case of immediate-release formulations due to the great influence of this property on dissolution rate [11]. Being a nonpolar material, $scCO_2$ can also aid amorphisation of lipophilic drugs, which has not been investigated so far.

This study was aimed to prepare immediate-release foamed solid solutions of spironolactone and Eudragit E, and to examine the effect of extrusion variables on foam structure, the effect of the application of $scCO_2$ plasticiser on the stability of spironolactone and on the molecular dispersion of the drug component in the melt. Formation of solid solutions with Eudragit E would be an effective way to enhance the slow dissolution of the drug compound, but purity issues can be an obstacle to the conventional extrusion processing of this system.

2. Materials and methods

2.1. Materials

Microcrystalline spironolactone with a molar weight of 417 g/mol, a melting point of 198-207 °C, an average particle size of approx. 30 µm and a water solubility of 28 mg/l [12] was kindly provided by Gedeon Richter Plc. (Budapest, Hungary). It is an orally administered steranic BCS II compound with problematic dissolution properties and lipophilic character (its octanol logP is 2.6; [13]). Eudragit® E 100, a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate, with an average molecular weight of 47,000 Da and a glass transition temperature of 62 °C was obtained from Evonik Industries AG (Essen, Germany).

2.2. Melt extrusion

Supercritical CO_2-aided melt extrusion of a mixture of 10% spironolactone and 90% Eudragit E was performed on a single-screw extruder (SCAMEX, Crosne, France), previously described in details [14]. Hopper temperature was fixed at 50 °C. Barrel temperature was controlled separately in 5 zones: T_1 and T_2 before the CO_2 injection point, T_3 and T_4 after it, while T_5 was the temperature set in the die. T_1 was fixed at 100 °C for all experiments, while T_2–T_5 had always the same value, which is hereafter simply referred to as temperature, T. Extrudates were cooled with compressed air at ambient temperature, after leaving the die. Screw speed was adjusted to a value which ensured the desired melt flow rates. Pressure drop was set by constricting the channel in the die using a needle and it was characterised by the value of pressure measured in the die (P_{die}). CO_2 which was cooled to 5 °C and had the pressure in the extruder at the injection point was pumped into the barrel with a constant volumetric flow rate using a pressure bearing syringe pump (260D, ISCO, Lincoln, NE, USA). CO_2 density obtained on NIST website [15] and calculated by Span and Wagner equation of state [16] was used to calculate mass flow rate. Table 1 displays the extrusion operating conditions for all prepared spironolactone formulations. Concerning melt flow rate and the mass percentage of CO_2 in the melt, comparison-aiding groups were defined, each group containing extrudates with similar values. The values of these variables measured when taking samples are also given in brackets. Sample names were composed from extrusion parameters (rounded, without units) in the order of temperature, melt flow rate, P_{die}, and CO_2 percentage, separated by slashes: e.g. S_110/1/250/6.

Table 1. *Extrusion parameters of spironolactone solid dispersions prepared using scCO$_2$-aided and conventional melt extrusion. Composition: 10% spironolactone, 90% Eudragit E*

Sample	T^a, °C	Melt flow rate, g/min	$P_{die}{}^b$, bar	CO_2 mass percentage, %	M^c, N·m
S_130/1/250/0	130	1.3 ± 0.5 (1.67)	250	0.00	123
S_120/1/250/0	120	1.3 ± 0.5 (0.85)	250	0.00	158
S_130/10/150/3	130	9.7 ± 0.9 (9.41)	150	2.7 ± 0.8 (2.10)	100
S_130/10/250/3	130	9.7 ± 0.9 (10.45)	250	2.7 ± 0.8 (1.90)	145
S_130/10/250/6	130	9.7 ± 0.9 (10.03)	250	6.3 ± 0.8 (5.70)	143
S_130/1/250/6	130	1.3 ± 0.5 (1.75)	250	6.3 ± 0.8 (5.46)	145
S_110/10/150/3	110	9.7 ± 0.9 (8.80)	150	2.7 ± 0.8 (2.24)	173
S_110/6/250/3	110	6.4 ± 0.7 (5.67)	250	2.7 ± 0.8 (3.44)	205
S_110/6/250/6	110	6.4 ± 0.7 (5.80)	250	6.3 ± 0.8 (6.51)	193
S_110/1/250/6	110	1.3 ± 0.5 (1.34)	250	6.3 ± 0.8 (7.01)	151

a: temperature, ***b***: pressure, ***c***: torque

2.3. Purity testing of extrudates

Spironolactone-Eudragit E extrudates were dissolved (1 mg spironolactone/ml) in a 1:1 mixture of methanol and 0.1 M acetic acid. 20 µl of the solution was chromatographed on an Agilent Eclipse XDB-C18 5-µm column thermostated to 40 °C, using an Agilent 1200 HPLC coupled with an Agilent 6140 Quadrupole MS system (Santa Clara, California, USA). The eluent having the composition of 1.5% acetonitrile, 2.0% tetrahydrofurane, 42.5% methanol and 54.0% 0.1 M acetic acid had a flow rate of 0.4 ml/min. Molar ratios of spironolactone and canrenone were calculated using a calibration for 254-nm UV chromatograms. Detected compounds were identified by their characteristic MS peaks as well as their UV absorption peaks.

2.4. Measurement of foam porosity

The porosity (ε) of foams was calculated from their density (ρ_1) and that of a non-foamed extrudate (ρ_2) as $\varepsilon = 1 - (\rho_1 / \rho_2)$. ρ_1 was determined from weight and dimensional measurements (repeated 3 times), while ρ_2 was measured using helium pycnometry (AccuPYC 1330, Micromeritics, Norcross, GA, USA).

2.5. Scanning electron microscopy

Morphology of samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope (SEM). Each specimen was fixed by conductive double-sided carbon adhesive tape and sputtered by a gold-palladium alloy (using a JEOL 1200 instrument) in order to avoid electrostatic charging.

2.6. Confocal Raman mapping

Backscattering Raman spectra were collected using a Horiba Jobin-Yvon LabRAM system coupled with an external 785-nm diode laser source and an Olympus BX-40 optical microscope. Confocal objectives of 10× and 100× magnifications were used. Extrudates were compressed into flat discs (Camilla OL95, Manfredi, Torino, Italy) and their surface was mapped in order to determine amorphous fraction. Acquisition, spectrum processing and visualization of maps were performed using LabSpec 5.41 (Horiba Jobin-Yvon) software. As a general rule, spectra were collected in 24×24 equidistant points, those being 50 µm away from each other. The ratio of amorphous and total spironolactone content (i.e. the amorphous API fraction) was calculated from the average spectrum by modelling based on component spectra and the method of classical least squares (CLS).

2.7. *In vitro* drug dissolution

Dissolution measurements were performed on an Erweka DT6 dissolution tester (USP I, Erweka, Heusenstamm, Germany). Ground extrudates equivalent to 10 mg spironolactone were placed in the dissolution vessel containing 900 ml 0.1 M hydrochloric acid maintained at (37.0 ± 0.5) °C and stirred at 100 rpm. Samples (3 ml) were taken after 0, 1, 2, 3, 4, 5, 10, 15, 30, 45 and 60 min and were analysed on a Hewlett-Packard HP 8452A UV-VIS spectrophotometer (Palo Alto, USA) at 242 nm, using diode array detector. Concentration was calculated with the help of the calibration curve of pure spironolactone in 0.1 M hydrochloric acid. The calibration curve was found linear in the range of 0.7 and 17.0 mg/l.

3. Results and discussion

3.1. Purity and processability

In this study, the extrudability of the spironolactone–Eudragit E system, the behaviour of the heat-sensitive API and the achievable purity improvement by the application of supercritical CO_2 ($scCO_2$) as a plasticiser were investigated. Plasticisation is desirable because Eudragit E requires high temperature for extrusion [17]. The 10%-API mixture was first extruded without $scCO_2$. 130 °C was the optimal temperature of extrusion, while melt flow rate dropped at 120 °C (S_120/1/250/0, Table 1), and no extrusion was possible at 110 °C. According to HPLC/MS chromatograms, processing at 120 °C resulted in a 15.1% decomposition as shown in Table 2 and Fig. 1. The product of this reaction was supposed to be canrenone, based on its UV spectrum and the characteristic *m*/*z* values in the mass spectrum.

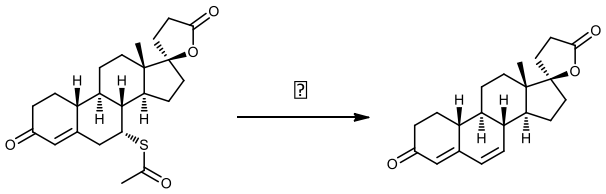


Fig. 1. *Decomposition of spironolactone to canrenone*

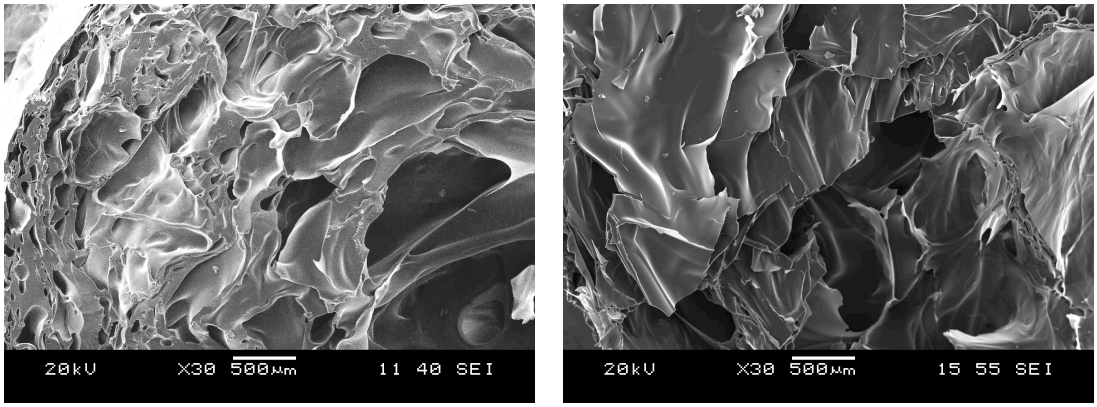
Although the plasticised system S_130/10/150/3 was extruded at a higher temperature, the degree of decomposition decreased remarkably due to the increased melt flow rate. Injection of the supercritical fluid also made possible foam extrusion at 110 °C (Table 1) with constant quality and without difficulty, and the melt was extrudable even at 100 °C. At 110 °C, decomposition decreased reasonably to 2.5% (S_110/10/150/3). However, when melt flow was slower at this temperature (S_110/6/250/6), the possibility of the undesirable degradation reaction was higher due to longer residence times (Table 2). These results show that $scCO_2$-aided extrusion can be an appropriate tool to enhance the purity of melt extruded products.

Table 2. *Decomposed spironolactone in different extruded foams (HPLC/MS)*

Sample name	S_120/1/250/0	S_130/10/150/3	S_110/10/150/3	S_110/6/250/6
Conversion, mol%	15.1	3.4	2.5	2.8

3.2. Foam structure

Foam morphology on fractured cross sectional surfaces was examined by SEM. Reasonable difference was shown between the structure of extrudates prepared at 130 and 110 °C. As opposed to the extreme high porosity (95%, Table 3) and thin walls obtained at 110 °C (S_110/10/150/3), only 75% porosity was measured for the sample prepared at 130 °C (S_130/10/150/3) and the wall width distribution was also broad. The above mentioned effect of temperature was also confirmed by the comparison of samples S_130/1/250/6 (Fig. 2a) and S_110/1/250/6 (Fig. 2b).



A B

Fig. 2. *SEM image of (A) S_130/1/250/6 and (B) S_110/1/250/6*

In addition, the cells in these samples were of irregular shape and their diameters were various (Table 3). Optimal was the structure of S_110/6/250/6 of high porosity; its spherical cells had a narrow wall width distribution and thin (5–10 µm), in many cases even submicronic (400–1000 nm) walls (Fig. 3).

Table 3. *Structural attributes of extruded spironolactone–Eudragit E foams*

Sample	Cell size, µm	Characteristic wall width, µm	Porosity, %	Cell shape
S_130/10/150/3	400–600	1–50	75	spherical
S_110/10/150/3	300–500	0.5–10	92	spherical
S_130/1/250/6	10–300	1–100	64	irregular
S_110/1/250/6	100–800	0.5–5	85	irregular
S_110/6/250/6	200–600	5–10	87	spherical

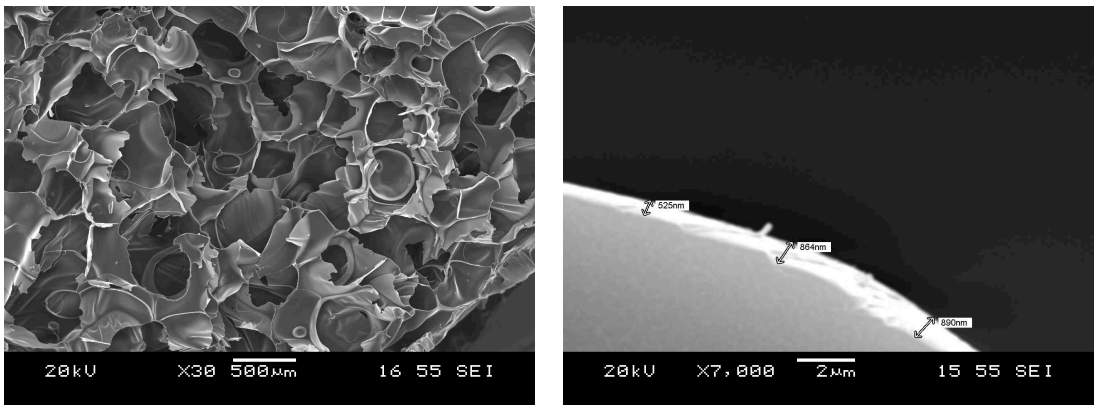


Fig. 3. *SEM images of S_110/6/250/6*

3.3. Amorphicity of samples

The amorphous API fractions in the extrudates were compared using Raman spectrometry. It is an eligible technique to distinguish amorphous spironolactone from its crystalline form because the scattering spectrum of the API changes when the crystalline lattice is destructed. For the correct and representative determination of the amorphous API fraction in the samples, a larger part of the sample was examined by performing Raman mapping.

Table 4. *Amorphous API fractions of foams, measured by Raman mapping*

Sample	Amorphous API fraction, %
S_130/1/250/0	96
S_130/1/250/6	100
S_130/10/250/6	96
S_130/10/250/3	94
S_110/1/250/6	100
S_110/6/250/3	95

Table 4 shows that only an amorphous fraction of 96% could be achieved at 130 °C when $scCO_2$ was not introduced into the melt (S_130/1/250/0). The fact that a solid solution could be produced at the same temperature when 5.5% $scCO_2$ was used (S_130/1/250/6) is a proof for the ability of the nonpolar supercritical fluid to enhance the molecular dispersion of the lipophilic API. At the same time, amorphous fraction was found to decrease slightly when the melt flow rate was increased and residence time decreased (S_130/10/250/6), and when less CO_2 was injected (S_130/10/250/3). The plasticising effect of the supercritical fluid also enabled sample preparation at 110 °C where conventional melt extrusion is not even possible. It must be highlighted that full amorphisation could be reached at 110 °C (S_110/1/250/6), as opposed to the 96% amorphous API fraction achievable at 130 °C with conventional melt extrusion. Residence time and CO_2 percentage had an influence on amorphisation at this temperature as well (S_110/6/250/3).

3.4. Dissolution tests

The degree of dissolution enhancement achieved by forming solid dispersions was characterised by *in vitro* dissolution tests. In comparison with the extremely slow dissolution rate of microcrystalline spironolactone (Fig. 4), the dissolution of ground S_110/6/250/3 was considerably fast despite the fact that spironolactone was not entirely amorphous in that case (Table 4). 91% was released in the first 5 min, while the remaining 9% dissolved much more slowly. Even at this rate, nearly complete dissolution was reached in 30 min.

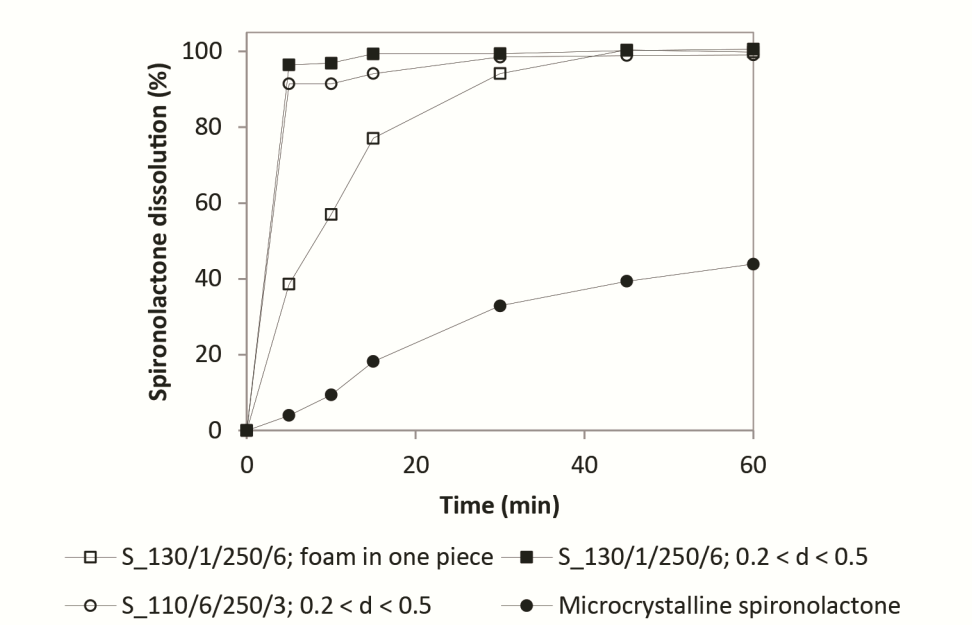


Fig 4. *Dissolution of spironolactone from extruded formulations in comparison with the curve belonging to pure microcrystalline spironolactone*

Even faster dissolution was observed for the solid solution sample S_130/1/250/6. It was found that particle size greatly determined release kinetics. 5 min were enough for >90% dissolution when the fine-ground

particles (0.2 mm < d_p < 0.5 mm) of S_130/1/250/6 having high specific surface area were tested. When dissolution started from a single large foamy particle, drug release could be prolonged to 45 min. This kind of release control can hinder precipitation in the case of APIs having extreme low solubility compared to their dose.

4. Conclusion

The growing interest for melt extrusion in pharmaceutical development and drug manufacture is indicated by the high number of scientific papers published about the achievable benefits of this continuous technology. At the same time, the possible disadvantages as well as the ways to overcome these are less frequently discussed. Decomposition of heat-sensitive APIs and the difficulty of glass solution formation in the case of higher drug loadings are considered to be the major issues of conventional melt extrusion.
This study proved on the example of spironolactone–Eudragit E foamed solid dispersions that a special kind of melt extrusion, in which supercritical (sc) CO_2 is injected and dissolved into the melt, can have three main benefits regarding product properties. (1) The degree of API decomposition could be lowered because $scCO_2$ enabled processing at lower temperature ranges. (2) As a physical blowing agent, $scCO_2$ increased the specific surface area of the extrudates remarkably. The effect of temperature was found to be of major importance, and by optimisation, 87–92% porosity and submicronic cell walls could be obtained. (3) Finally, as a nonpolar solvent, $scCO_2$ could aid the amorphisation of lipophilic spironolactone during processing. The increased specific surface area and the formation of solid solutions made a 5-minute drug release possible in acidic medium. The presented results of this article can contribute to the deeper understanding of the effect of extrusion variables on decomposition processes occurring in the course of melt extrusion. By hindering decomposition and improving purity by supercritical fluid extrusion, the circle of melt extrudable compounds can be extended.

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