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Drug-eluting coating of extruded polymeric tubular microstructures

Abstract: Extrusion is a common manufacturing process for semi-finished polymer products in various biomedical applications. Extrusion enables processing of a wide range of biomaterials, as well as different cross-sectional geometries. Furthermore, feasibility of drug elution, as it is used for a variety of medical devices, for example microstents for minimally invasive glaucoma therapy, was assessed. The current study deals with manufacturing of polymeric microtubes by extrusion processing. Semi-finished products were made of biodegradable poly-L-lactide (PLLA) and a non-biodegradable polycarbonate-based silicone elastomer (SIL) and covered with a polymer/drug combination, with resveratrol as active ingredient. Three different concentrations of polymer/resveratrol were applied by means of spray-coating. The release behavior of active ingredient was analyzed *in vitro* at 37°C and showed a correlation between the amount of drug and release time. With higher drug content, a faster release was observed. In addition, the release from SIL was faster compared with PLLA.

Keywords: extrusion, PLLA, SIL, tubular semi-finished product, drug eluting, resveratrol, release study.

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1 Introduction

In medicine, implants are often used as a life-saving measure. To prevent the host from reacting to the implant as a foreign body, implant devices are often provided with a specific drug-eluting coating. For example, resveratrol, which is found in significant amounts in grapes, is used as the active ingredient in this coating [1].

Challenges arise from the choice of the coating method as well as the knowledge gained from the drug release from microimplants such as glaucoma stents [2]. Based on previous work, microtubes are manufactured by extrusion and consecutively coated with an appropriate polymer-drug mixture using an airbrush process [3, 4]. Subsequently, the pharmaceutical release *in vitro* is analyzed.

2 Materials and Methods

2.1 Extrusion

A HAAKE MiniLab II (Thermo Fisher Scientific, Karlsruhe, Germany) extruder with counter-rotating twin screws was used to extrude the samples. The outer diameter of the extrudate was monitored during the extrusion process with a 2-axis laser scanner (ZUMBACH Elektronik, Orpund, Switzerland).

Table 1 summarizes the polymers used and the corresponding extrusion parameters. A die with an outer and inner diameter of 2.30 mm and 1.75 mm, respectively, was used to shape the extrudate. To achieve the outer diameters between 300 µm and 400 µm, the haul-off speed was adjusted accordingly [3].

Table 1: Setting parameters of the extrusion process for SIL and PLLA

Material	Extruder setting parameters
SIL	$T_E = 210^\circ\text{C}$, $n_E = 15 \text{ 1/min}$ $T_D = 205^\circ\text{C}$, $n_A = 33 \text{ mm/s}$ $T_{FF} = 16^\circ\text{C}$, $n_{FF} = 5\%$

Material	Extruder setting parameters
PLLA	$T_E = 210^\circ\text{C}$, $n_E = 8$ 1/min
	$T_D = 225^\circ\text{C}$, $n_A = 17$ mm/s
	$T_{FF} = 16^\circ\text{C}$, $n_{FF} = 5\%$

T_E – Temperature of the extruder, n_E – Rotation speed of extruder screws,

T_D – Temperature of the nozzle, n_A – Haul-off speed

T_{FF} – Temperature of the force feeder, n_{FF} – Power of force feeder

2.2 Surface coating by spray process

Semi-finished products obtained from extrusion process were cut into samples with a length of 10 mm. Subsequently, these samples were coated under clean room conditions using a spray coating technique with the RAMSES 1b automatic coating system (University of Rostock). The process took place at a room temperature of 21°C and a humidity of 22%. The following parameters were set on the system (Table 2). Figure 1 illustrates the surface coating of the semi-finished product using the spray method.

Table 2: Setting parameters of the spray process

Airbrush setting parameters	
Pressure in solution reservoir (p_{Solution})	0.3 bar
Pressure in spray nozzle (p_{Nozzle})	0.2 bar
Spray nozzle opening (D_s)	1.7 mm
Distance between spray nozzle and object (a_s)	30 mm
Spray duration (t)	270 s

The spray solution used in the spray process was composed as shown in Table 3. It should be noted that the respective amount of resveratrol was first dissolved in 2 ml methanol and then added to the basic spray solution volume of 24 ml polymer/chloroform.

Table 3: Summary of semi-finished product used, spray solution and spray solution composition as a basis for surface coating of semi-finished product by spray process

Semi-finished product	Polymer/drug formulation	Composition of solutions
SIL	SIL/resveratrol	70/30 (v/v): 0,0560 g / 24,9 mg
		85/15 (v/v): 0,0560 g / 10,09 mg
		90/10 (v/v): 0,0558 g / 5,96 mg
PLLA	PLLA/resveratrol	70/30 (v/v): 0,0581 g / 24,0 mg
		85/15 (v/v): 0,0572 g / 9,88 mg
		90/10 (v/v): 0,0536 g / 6,20 mg

Figure 1: Surface coating of the semi-finished product using the spray process, a_s = distance between spray nozzle and object

2.3 Pharmaconstability to temperature resistance

Resveratrol (Biomol GmbH, Hamburg, Germany; CAS: 501-36-0) was selected as drug. In order to investigate the stability of the active ingredient at body temperature, *in vitro* studies were carried out using four samples of solid resveratrol, each containing approx. 1.5 mg. One sample remained untreated as a reference. Another three samples were heated up to 225°C and hold on at this temperature for 5, 10 and 15 min. Subsequently, all four samples were analyzed using high-performance liquid chromatography, HPLC (KNAUER Scientific equipment GmbH, Berlin, Germany) to determine the resveratrol residual content.

2.4 *In vitro* pharmaceutical release

The study of pharmaceutical release *in vitro* provides information on the pharmaceutical mass released per unit time. Resveratrol-coated semi-finished products were released in 1 ml of isotonic saline solution at a temperature of 37°C . Samples were shaken at a speed of 100 rpm on a laboratory shaker. After the time points 0.25 h, 0.75 h, 1.5 h, 3 h, 6 h, 10 h, 17 h, 33 h, 57 h, 81 h, 105 h, 201 h, 241 h, 338 h, 506 h, 674 h, 842 h, 1034 h and 1,202 h, the medium was removed and 1 ml of fresh medium was added to the samples respectively. A stagnant slope was defined as criterion for termination of the experiments - this was observed between 241 h and 1202 h. Three samples were released for each polymer/drug formulation. The amounts of resveratrol released were analyzed by HPLC.

The following parameters were used: Column: Eurospher 100 C18, grain size 5 μm , 250 x 4 mm ID; Mobile phase: methanol / 0.01 M phosphate buffer pH 6.8 (50/50 v/v) isocratic; Column temperature: 30°C; Flow rate: 0.8 ml/min; Detection: UV, 306 nm; Injected sample volume: 20 μl ; Calibrated measuring range: 0.1 – 50 mg/l (linear); Retention time: ca. 2.8 min.

A typical chromatogram is shown in Figure 2. Here absorption unit is milli – Area Units. From the detected peak area, which is specific for the pharmacone, the released mass can be calculated.

Figure 2: Exemplary resveratrol chromatogram

3 Results and Discussion

Manufacturing by extrusion proved to be a feasible production process for biostable and partially degradable polymer semi-finished products (PLLA and SIL). The *in vitro* investigations regarding the influence of temperature on the active ingredient resveratrol have shown temperature stability up to 225°C (data not shown).

The *in vitro* drug release studies show that a large proportion of resveratrol is released within 1 to 2 days and is characterized by an initial burst release (see Figure 3). Subsequently, there is a continuous slow release until day 8, followed by an almost linear release behavior. This represents a characteristic behaviour of diffusion controlled drug release - the active ingredient near the surface diffuses out of the coating matrix more quickly compared to deeper layers (burst release). A chemically controlled release is not observed within the period under consideration, as PLLA degradation does not yet begin noticeably here.

Figure 3: Cumulative release of resveratrol from differently coated extruded tubular semi-finished samples (relative amounts of active ingredient, normalised to recovered amount of active ingredient of the respective sample)

The release from SIL is faster compared with PLLA. The release behaviour is determined by several parameters like crystallinity of the polymer, the polymer density, the swelling capacity of the polymer or the water permeability. After 50 days of the release study, almost any resveratrol was extracted from the SIL matrix, while 50 – 60% of the active ingredient was still found in the PLLA extract. Therefore, PLLA tends to be more suitable in minimally invasive glaucoma therapy, as long-term releasing materials are needed there.

4 Conclusion

The present study focussed on the production of polymeric microtubes by extrusion processing followed by drug coating using spraying technique. The release behavior studies exhibited different results for PLLA and SIL. Therefore, we concluded that resveratrol is embedded differently in each polymer and, consequently, the release behavior should be investigated individually for each polymer. A disadvantage of surface coating by spraying is the requirement of chloroform. It is recommended to test a chloroform-free active agent coating in the near future. An alternative would be to dust the active ingredient onto the warm extrudate immediately after it exits the die.

Author Statement

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