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Research paper

Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants

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ABSTRACT

The 3D printing technique of fused deposition modeling® (FDM) has lately come into focus as a potential fabrication technique for pharmaceutical dosage forms and medical devices that allows the preparation of delivery systems with nearly any shape. This is particular promising for implants administered at application sites with a high anatomical variability where an individual shape adaption appears reasonable. In this work different polymers (Eudragit®RS, polycaprolactone (PCL), poly(L-lactide) (PLLA) and ethyl cellulose (EC)) were evaluated with respect to their suitability for FDM of drug loaded implants and their drug release behaviour was evaluated. The fluorescent dye quinine was used as a model drug to visualize drug distribution in filaments and implants. Quinine loaded filaments were produced by solvent casting and subsequent hot melt extrusion (HME) and model implants were printed as hollow cylinders using a standard FDM printer. Parameters were found at which model implants (hollow cylinders, outer diameter 4–5 mm, height 3 mm) could be produced from all tested polymers. The drug release which was examined by incubation of the printed implants in phosphate buffered saline solution (PBS) pH 7.4 was highly dependent on the used polymer. The fastest relative drug release of approximately 76% in 51 days was observed for PCL and the lowest for Eudragit® RS and EC with less than 5% of quinine release in 78 and 100 days, respectively. For PCL further filaments were prepared with different quinine loads ranging from 2.5% to 25% and thermal analysis proved the presence of a solid dispersion of quinine in the polymer for all tested concentrations. Increasing the drug load also increased the overall percentage of drug released to the medium since nearly the same absolute amount of quinine remained trapped in PCL at the end of drug release studies. This knowledge is valuable for future developments of printed implants with a desired drug release profile that might be controlled by the choice of the polymer and the drug load.

1. Introduction

The use of 3D printing technologies for the preparation of drug delivery devices has gained great interest over the last decade, as demonstrated by a rapidly increasing number of open publications linked to "3D printing" and "Drug Delivery" from 2000 to 2015 [1]. Besides powder based 3D printing, selective laser sintering, stereolithography and inkjet printing, fused deposition modeling® (FDM) has become a very popular technique to create solid objects. FDM is an extrusion-based additive manufacturing technique, whereby in most cases plastic filaments are advanced through a heated nozzle and the molten polymer strands are placed layerwise on the printing table. Thus nearly every shape can be printed, taking into account the size limitations for very small objects. The use of FDM in the field of pharmaceuticals is relatively new compared to consumer goods. In the pharmaceutical field research efforts are mainly focused on the fabrication of oral dosage forms.

The starting point for FDM-printing of dosage forms is a drug-loaded polymer filament. First filament loading processes were performed by incubation of commercial polyvinyl alcohol (PVA)-filaments in a high concentrated drug solution [2–4]. Goyanes et al. investigated the influence of different printing infill rates of PVA tablets on the release of fluorescein, mesalazine and 4-aminosalicylic acid and showed that a higher infill percentage could prolong the release of the drug [2,3]. The advantage of drug loading by impregnation is a lower risk of drug or polymer degradation as there is no thermal load during filament fabrication. Even though fluorescein accumulated at the surface of the filament, fluorescein

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distribution in printed tablets appeared uniformly [2]. Clear disadvantages are the highly concentrated and thus expensive drug solutions that are needed and the very low drug load, that could be reached by drug diffusion in the polymer, ranging from only 0.063% m/m (mesalazine, [3]) to 1.9% m/m (prednisolone, [4]) in PVA filaments. For this reason and since only a few drugs and polymers are accessible via impregnation process, different workgroups have started to produce drug-loaded filaments by hot melt extrusion (HME). Goyanes et al. continued the work with PVA and evaluated drug release of acetaminophen from printed dosage forms with different geometries (cube, pyramid, cylinder, sphere and torus), where the release behaviour was dependent on the surface area to volume ratio [5]. Thus FDM enabled here the precise fabrication of difficult shaped tablets that are not feasible to obtain with for example powder compaction. This workgroup also demonstrated successfully the ability of double extrusion of two different filaments for the FDM of capsule-shaped oral devices, which allows the combination of two different drugs in layers or in coat-core-designs [6]. Besides the water soluble PVA Pietrzak et al. evaluated other polymers for example hydroxypropyl cellulose and the methacrylic polymers (Eudragit® RL, RS and E) for FDM of theophylline immediate or extended release tablets with an individualized dose [7]. Mellocchi et al. evaluated commonly used pharmaceutical polymers as polyethylene oxide, Kollicoat® IR, hydroxypropyl methylcellulose (HPMC), Soluplus®, hydroxypropyl methylcellulose acetate succinate, Eudragit® L, Eudragit RL and ethyl cellulose as materials for HME of filaments and for printing discs that were tested regarding their barrier function for acetaminophen [8]. Apart from oral dosage forms FDM can also be used for the preparation of implantable devices as demonstrated for ethylene vinyl acetate and polycaprolactone intrauterine systems containing indomethacin [9,10] or nitrofurantoin loaded polylactic acid implantable discs [11–13]. The major advantage of implant 3D printing is the ability to form geometries with nearly any shape so that the implant could be printed individualized for each patient. This shape adaption might be especially important for application sites with a high variability in patient's anatomy, e.g. the paranasal sinuses [14,15]. Data for the implant shape can be obtained from medical imaging as computerized tomography or magnetic resonance imaging [16,17]. In the field of dental/orthopaedic reconstruction this approach is already used successfully [18,19] and is therefore also conceivable for drug delivery devices. The aim of this work is to evaluate different polymers for their use in hot melt extrusion of drug loaded filaments and their suitability for FDM of implants. Successfully printed implants were characterized concerning their drug release behaviour. In fact, PCL was already used to print indomethacin containing intrauterine devices [10], EC was already printed to drug free barrier discs [8], polylactide was already printed from commercial filaments to either drug free or nitrofurantoin containing discs [8,12,13] and Eudragit® RS was already printed to theophylline containing tablets [7]. But a coherent view and a comparison of drug releases for printed dosage forms that are identically produced, have the same geometry, contain the same drug and are intended for the use as an implant have, to our knowledge, not been reported in literature. In addition the influence of different drug loadings on the printability and the drug release was investigated. The findings may serve as a basis to produce an implant with a customized shape and a controllable drug release via FDM.

2. Materials and methods

2.1. Materials

Quinine (anhydrous, ≥98.0%) was purchased from Sigma Aldrich, Germany. Eudragit® RS PO and poly(L-lactide) (PLLA, Resomer® L206S) were kindly provided by Evonik Industries, Germany. Polycaprolactone (PCL, weight average molecular weight (Mw) ≈ 14,000, number average molecular weight (M_n) ≈ 10,000 by GPC) was obtained from Sigma Aldrich, Germany. Ethyl cellulose (EC, ETHOCEL™Standard 45 Premium) was purchased from Colorcon, UK. The plasticizer triacetin (≥99%) was obtained from Carl Roth, Germany. Solvents and all other substances used were of analytical grade.

2.2. Methods

2.2.1. Preparation of drug loaded polymer films

The incorporation of quinine into the polymer was performed by a solvent casting technique. PCL and PLLA were dissolved in methylene chloride (final concentration 0.18 g/mL). Eudragit® RS PO and EC were dissolved in acetone (final concentration 0.35 g/mL and 0.1 g/mL). An ethanolic solution of quinine (0.1 g/mL) was added to each polymeric solution yielding a quinine load of approximately 5% (m/m) referring to the solid fraction. This mixture was homogenized under stirring for a few minutes. The solution was poured onto a glass plate as a thin layer and the volatile solvent was evaporated in a drying oven at 50 °C for at least 12 h. The resulting film was cooled down, removed from the dish and cut into small pieces.

2.2.2. Filament extrusion

Quinine containing films were loaded into a self-constructed filament extruder. It consists of a heated metal sleeve with an internal thread (M16) and a stepping motor with a precisely fitting external thread (M16, 0.94 rpm) that pushes the molten polymer through the terminal nozzle (diameter 3 mm). Extrusion temperatures are shown in Table 1. A second motor with a rotating cylinder is winding up a string that is mounted to the tip of the filament. The rotation speeds of both motors were adjusted to achieve a sufficient stretching of the filament and to obtain the desired and uniform diameter of the filament. Filaments were stored at 20 °C under protection from light. Filament diameters were measured with a digital calliper (accuracy ±0.02 mm) in 10 mm distances over the whole filament length and given as mean diameters.

2.2.3. 3D printing

Implants were produced from the quinine-loaded filament with the standard FDM printer Multirap M420 (Multec GmbH, Germany). The hot end was equipped with a nozzle with a diameter of either 0.5 mm (PLLA, Eudragit® RS) or 0.35 mm (PCL, EC). The printing geometry was designed with FreeCAD 0.14 and imported as a stereolithography file into the slicing software Simplify3D® (version 2.2.2, Simplify3D, USA). As the printing geometry a hollow cylinder with an outer diameter of 5 mm, an inner diameter of 3 mm and a height of 3 mm (for Eudragit® RS $Ø_{outer}$ = 4 mm, $Ø_{inner}$ = 2 mm, h = 3 mm) was chosen. Printing parameters were set as follows: layer height 0.1 mm, movement and extrusion speed 1440 mm/min (X/Y axis), 400 mm/min (Z axis), outline underspeed 50%, only outline shells without infill, 100% cooling from layer 2, support and raft options inactivated. Varying printing parameters for different polymer filaments are shown in Table 1. Blue painters tape was applied to the printing table to improve first layer adhesion. Implants were also stored at 20 °C under protection from light.

2.2.4. Imaging

The surface morphology of the printed implants was examined with a reflected-light microscope (Zeiss Stemi 2000-C with light source Zeiss CL 1500 ECO, camera Zeiss AxioCam and AxioVision software, all Carl Zeiss Microscopy GmbH, Germany). The fluorescence imaging was performed by the fluorescence microscope