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Single step fabrication and loading of biopolymer microcontainers for oral drug delivery

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Abstract: A novel strategy of hot punching has been developed for single-step fabrication of high aspect ratio biodegradable microcontainers for oral drug delivery. This method is up-scalable and can be used for various types of drugs and polymers. In addition to fabrication of microcontainers, in this abstract loading of the container cavities has been successfully demonstrated.

In recent years, microfabricated devices have been proposed as advanced drug delivery systems [1]. In particular, microcontainers have been demonstrated as promising new oral drug delivery systems with the potential to significantly enhance the bioavailability of drugs [2]. The microcontainers are preferentially fabricated with biocompatible or biodegradable polymers [3]. Previously, we introduced hot punching as a method to fabricate discrete poly-L-lactic acid (PLLA) microcontainers [4]. In this study, we propose an advanced hot punching technique for the fabrication of microcontainers in polycaprolactone (PCL). As a major advancement, the previously used combination of embossing and thermal bonding are replaced with a single-step process, leading to a higher yield and a more time-efficient method.

Due to their small dimensions, one of the major challenges is to load drug into the cavities of the microcontainers. Earlier, we introduced the powder embossing as novel method for reproducible loading of arrays of microcontainers with drug powder [5]. This loading method has previously proved a successful loading of the entire cavities as visualized by x-ray microtomography. In this work, the shadow mask required for this process is replaced by the already existing polymer film between the containers before peeling it off. This allows a fast, gentle and precise loading of the cavities without need for alignment of containers with shadow mask.

The fabrication process is illustrated in fig. 1. First, the substrate is prepared by spin coating a PolyAcrylic Acid-Polyethylene glycol (PAA-PEG) solution on a clean silicon wafer. After drying for 12 hours, a layer of PCL solution is spin coated at 800 rpm to achieve a thickness of 100 μm which is also dried for 12 h. Then the sample is embossed with a Ni stamp for 30 min at a room temperature of 70°C and a pressure of 1.9 MPa. In this step, the stamp features penetrate the PCL film until they reach the PAA-PEG film below, thereby punching out the microcontainers. Before peeling the surrounding polymer film off, the loading with microparticles into the cavities is performed by the powder embossing method; Drug powder is placed in a recess and a pressure of 1.9 MPa is applied with a bonding press. The powder is embossed inside the container cavities after which the pressure is removed and the remaining PCL film is peeled off.

Fig. 2 shows a single empty PCL container after the demolding and peeling of a single, empty container. The adhesion between the PAA-PEG and PCL film is stronger than between Ni stamp and PCL film and therefore the microcontainers remain on the PAA-PEG film after the punching. The hydrophilic properties of the PAA-PEG films facilitate the demolding from the hydrophobic PCL film after the embossing procedure. A large array of the fabricated containers is observed in fig. 3. Fig. 4 demonstrates small lipid-based microparticles that have been loaded into the cavities. After demolding, the PCL film from the PAA-PEG film, individual microcontainers loaded with the powder formulation are observed (fig. 5).

In conclusion, it is shown how to fabricate discrete biopolymer microcontainers in a single step and time efficient way. Furthermore, loading of the microcavities has been shown by using the punched PCL film as stencil and by using the powder embossing method.

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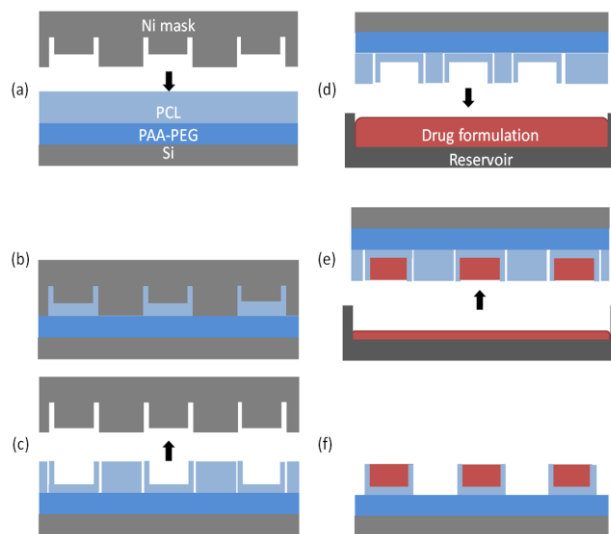


Figure 1: Graphical illustration of the single step fabrication of microcontainers where a) films of PAA-PEG and PCL are spin coated on a Si wafer, b) the Ni mask applied with an elevated temperature and pressure, c) the stamp is removed and containers are punched out with surrounding PCL film., d) powder formulation is placed in a holder and the containers are used as a stamp to load powder inside the cavities, e) the pressure is released, f) the surrounding PCL film is removed and the containers are uniformly loaded

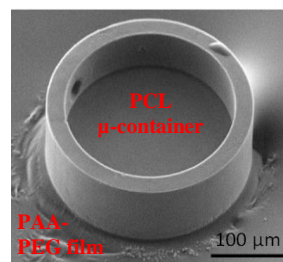


Figure 2: SEM image of a single PCL container on a PAA-PEG substrate

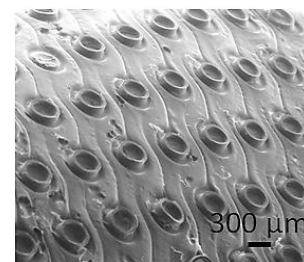


Figure 3: SEM image of arrays of PCL microcontainers with the diameter of 300 μm

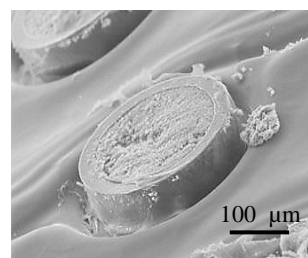


Figure 4: SEM image of a single PCL container loaded with powder

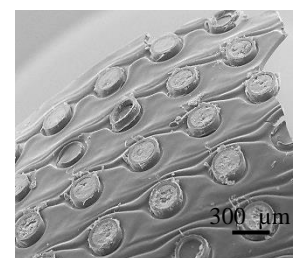


Figure 5: SEM image of arrays of loaded PCL microcontainers