Incorporation of X-ray Contrast Agent into Microcontainers Used for Oral Drug Delivery

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Introduction

Polymeric cylindrical microcontainers can be used to protect orally administered drugs from physical, chemical, and biological challenges found throughout the gastrointestinal (GI) tract until they reach the desired location for drug release and absorption [1-3]. Previous work, carried out in our research group, showed easy and fast GI tracking of microcontainers [4]. These microcontainers were loaded with a contrast agent of barium sulfate ($BaSO_4$) and tracked with planar x-ray imaging and computed tomography scanning, respectively. A disadvantage of this approach is that the $BaSO_4$ contrast agent takes up the void space inside the microcontainer where a potential drug should be loaded instead. The purpose of the present study is to incorporate $BaSO_4$ into the microcontainer shell in order to make GI tracking of drug-loaded microcontainers possible in future studies.

Experimental and Results

Microcontainers (~322 µm in diameter and ~267 µm in height) were fabricated in a negative epoxy-based photoresist, SU-8, using two steps of photolithography [1], loaded with $BaSO_4$ using a simple brush method and coated with poly(lactic-co-glycolic acid) (PLGA) by spray coating (Figure 1a-c). These microcontainers loaded with $BaSO_4$ were easily observed in the stomach of a rat 3 h post-administration by planar x-ray imaging (Figure 1d). Microparticles with incorporated $BaSO_4$ were made in different sizes (diameters of 150 µm, 300 µm and 500 µm and with a height of 100 µm) using a single step of photolithography (Figure 2a). Here, ~5 wt% of $BaSO_4$ was mixed into the SU-8 solution prior to spin coating. The microparticles sitting side-by-side on small wafer chips were investigated with planar x-ray imaging and we found that the contrast from all three types of microparticles seemed very weak (Figure 2b). For a direct contrast evaluation, a chip of microcontainers loaded with $BaSO_4$ and a chip of microparticles with a diameter of 500 µm were studied with planar x-ray imaging (Figure 3a). Here, it was seen that the contrast from microcontainers was much higher than the contrast from microparticles which could be due to the rather high (~20 wt%) amount of $BaSO_4$ loaded into the microcontainers. In comparison for the case of microparticles, the dispersion of $BaSO_4$ into the SU-8 solution was challenging due to precipitation of $BaSO_4$ and thus, the true amount of $BaSO_4$ in the microparticles was expected to be much lower than 5 wt%. Additionally, x-ray photoelectron spectroscopy (XPS) was utilized for the determination of barium (Ba) present on the microparticle surfaces which primarily showed carbon (C) and oxygen (O), originating from SU-8, and an at% in the order of 10^{-2} for Ba (Figure 3b).

Conclusion

Microcontainers loaded with $BaSO_4$ have been easily localized by planar x-ray imaging in the stomach of a rat post-administration. In order to provide space for drug loading inside the microcontainer cavity in future studies, but still enabling simultaneous imaging, an approach with $BaSO_4$ incorporated into the microcontainer shell was proposed. Until now, microparticles in three different sizes with less than 5 wt% of $BaSO_4$ have been successfully fabricated. The contrast from the microparticles was very low compared to the contrast from microcontainers loaded with $BaSO_4$. Therefore, the fabrication process for incorporation of $BaSO_4$ has to be further optimized. As a next step, we are going to work on increasing the amount of $BaSO_4$ without subsequent precipitation. In relation to this, we will evaluate the use of $BaSO_4$ nanoparticles, instead of so far used $BaSO_4$ powder, for photolithography, but we also try other fabrication methods such as mold casting and 3D printing.

Acknowledgement

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References
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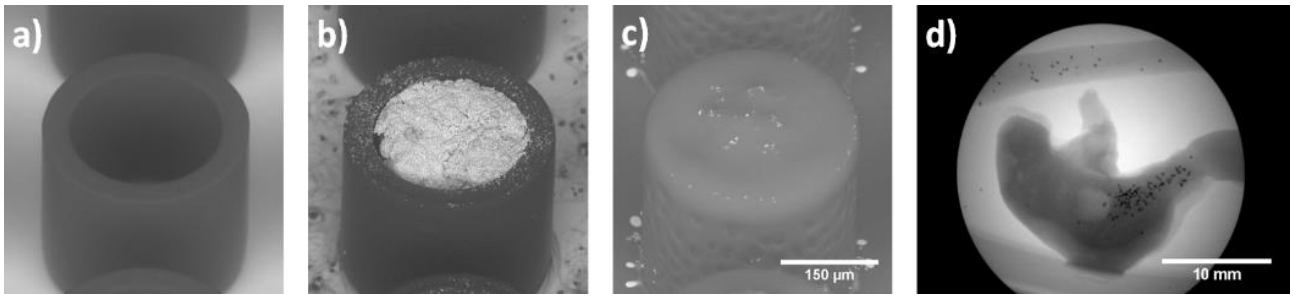

Figure 1. a-c) SEM images of a single microcontainer being empty, loaded with $BaSO_4$ and coated with PLGA. d) Planar x-ray image of $BaSO_4$-loaded microcontainers observed in a rat stomach 3 h post-administration. [4]

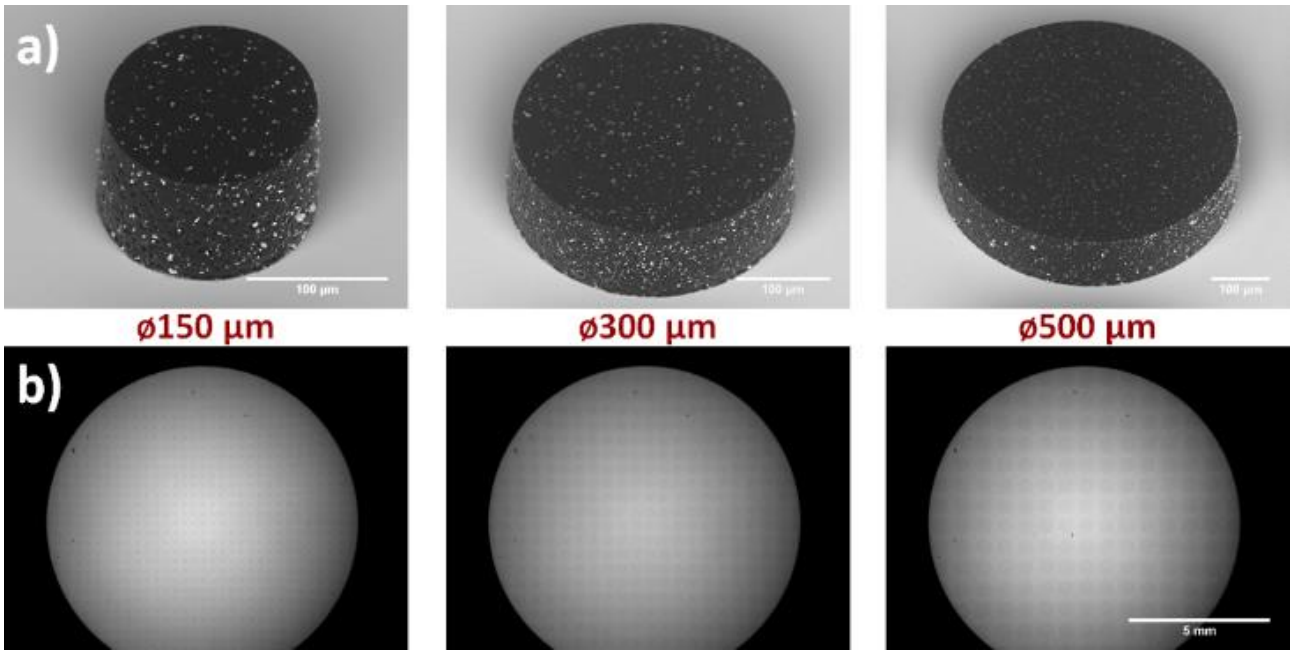

Figure 2. a) SEM images of fabricated microparticles with incorporated BaSO4 (diameters of 150 µm, 300 µm and 500 µm, respectively). b) X-ray images of chips with the three different types of microparticles.

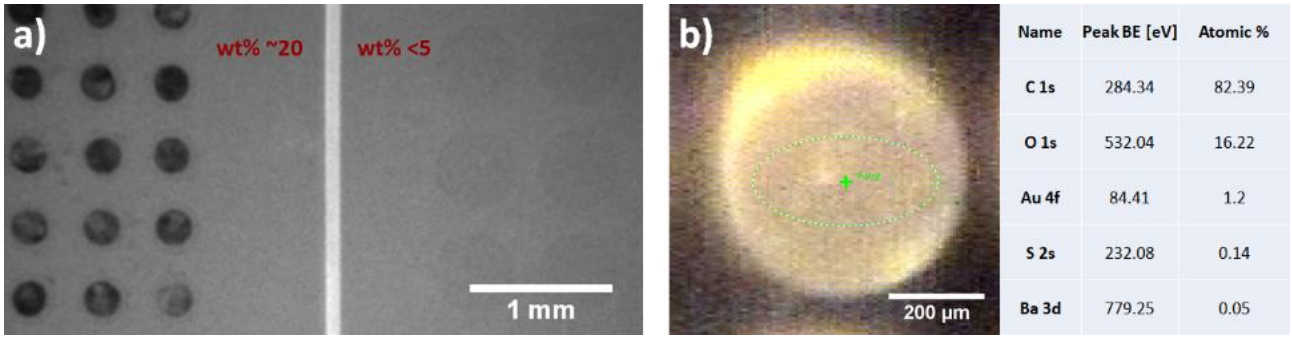

Figure 3. a) Planar x-ray images comparing microcontainers loaded with $BaSO_4$ (left) to microparticles having a diameter of 500 µm (right). b) XPS of microparticle surface and corresponding at% from the survey scan.