MICRO CONTAINERS WITH SOLID POLYMER DRUG MATRIX FOR ORAL DRUG DELIVERY

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ABSTRACT

In this work, we present micro containers for drug delivery and a method for wafer scale filling utilizing hot embossing. Hot embossing of a polymer drug matrix followed by a deep reactive ion etch (DRIE) enables filling and release of individual micro containers. Finally, drug release from the embossed polymer drug matrix is shown.

KEYWORDS Drug delivery, Hot embossing, micro container.

INTRODUCTION

Advances in microtechnology and pharmaceutical engineering have led to the proposition of micro containers as carriers for oral drug delivery [1] [2] [3]. Micro containers can be used for oral administration and are able to protect drug from degradation during transit of the gastro-intestinal tract. Further they will enable one-directional drug release at the site of absorption and can thereby enhance the bioavailability of drugs.

Traditionally, micro containers are filled by micro spotting or microinjection [2]. The techniques require liquid solutions and are time consuming. Alternatively, micro containers are filled using hydrogels, a batch method involving several process steps such as deposition, cross-linking, washing, and swelling [2] [3]. Our method enables an easy integration of filling of solid drug formulations into micro container during the fabrication process.

THEORY

Hot embossing is a technique by which an amorphous or semi-crystalline material is molded with a stamp to achieve a wanted shape. Hot embossing is possible due to lowering of the Young's moduli of materials when the temperature approaches the melting point, T_m. The point where the softening sets is known as the glass transition temperature, T_g. The glass transition is a reversible transition from a hard state into a molten state. Hot embossing takes advantage of that reversible process by molding the material above the T_g and below the T_m. A stamp is used to mold the material in the desired shape by pressing the stamp in the material. Once the stamp is filled with material, the system is cooled below the T_g, thus hardening the material before the stamp is withdrawn.

EXPERIMENTAL

The micro containers are fabricated in SU-8 by a two step photolithography process using a silicon wafer as substrate, as shown in figure 1. The micro containers have an outer diameter of 300 µm and an inner diameter of 200-250 (design variation). The total height is measured to be 105±5µm with a container depth of 60±5µm. The polymer-drug film is fabricated by spin coating of a solution of polycaprolactone (PCL) and furosemide (furosemide is a diuretic drug used for the treatment of e.g. edema) on a silicon wafer with a fluorocarbon anti-sticking coating [4]. The solution consists of 20 ml dichloromethane, 40 ml acetone, 8 g PCL, 2 g furosemide. The spin coating parameters are 1000 rpm for 60 s with a ramp of 2000 rpm/s. The resulting film is 15 µm thick. To achieve the desired thickness of 45 µm, the spin coating procedure is performed 3 times.

Figure 2 shows the major process steps in the micro container filling. First, the polymer-drug film is embossed into the micro containers at a temperature of 60 ºC and a force of 15 kN for 1 hour, figure 2.1. Embossing at 60 ºC, which is just below the melting point of PCL, ensures an optimal hot embossing and pattern transfer [4]. The system is then cooled to 20 ºC and the silicon wafer is removed, as shown in figure 2.2 and figure 3. The anti-sticking coating ensures that separation takes place between the coating and the polymer-drug film. The next process step is a deep reactive ion etch (DRIE) that separates the micro containers from the excess polymer-drug film, figure 2.3 and figure 4. The etching is performed with a DRIE using the following parameters for an anisotropic etch: O_2 flow of 20 sccm, Ar flow 20 sccm, platen power 150 W, coil power 600, pressure of 4 mTorr, temperature of 10 ºC and time of 12 min. Finally, the individual containers are detached from the carrier wafer mechanically, figure 2.4.

Drug release of the embossed polymer drug matrix is performed using a Pion µDISS profiler that utilizes UV spectroscopy to measure concentration over time. The drug release is performed using the biorelevant dissolution media Fasted State Simulated Intestinal Fluid (FaSSIF), to simulate the gastrointestinal fluids, and with a pH that is adjusted to pH 6.5 before the release. Experiments are conducted in beakers containing 10 ml FaSSIF media held at a temperature of 37 ºC.

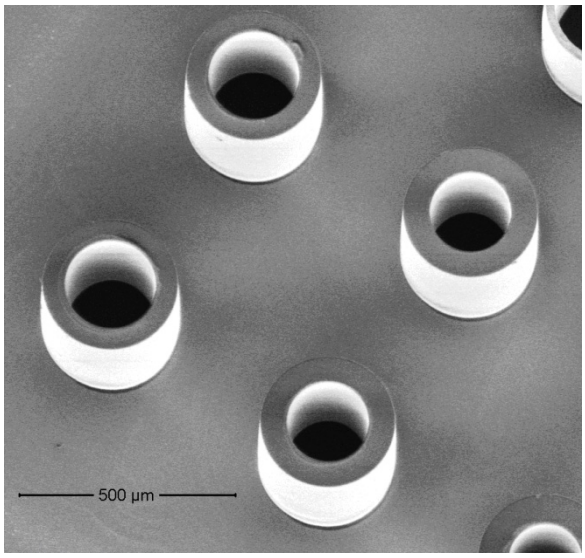

Figure 1. SEM image showing micro containers fabricated in SU-8 by a two step photolithography process

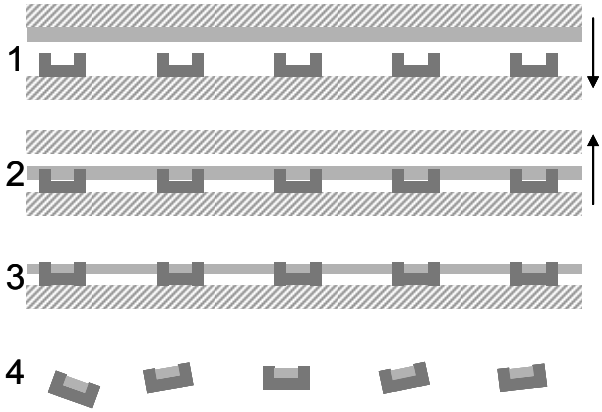

Figure 2. Micro container filling process. 1-2 Embossing polymer drug matrix into containers and removing the carrier wafer. 3 Etching of polymer drug matrix. 4 Mechanical release of containers

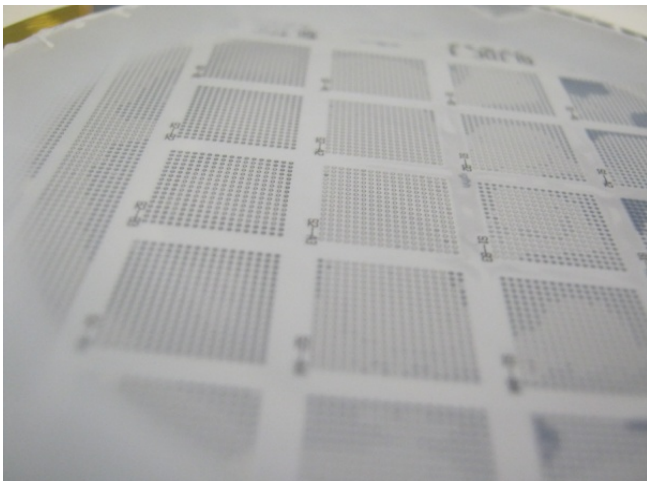

Figure 3. Wafer with micro containers after polymer drug matrix embossing.

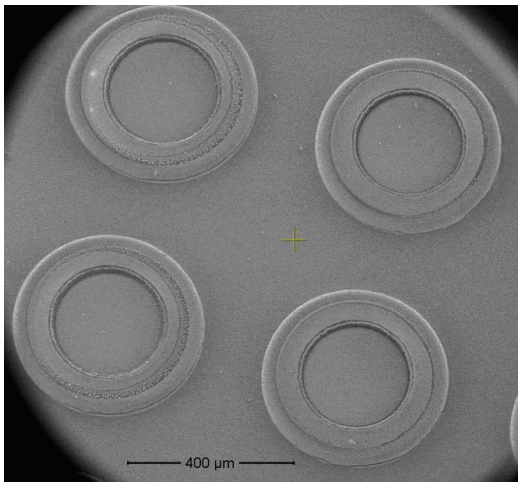

Figure 4. SEM image showing polymer drug matrix embossed into micro containers and etched by DRIE.

RESULTS & DISCUSSION

The result of the fabrication process is SU-8 micro containers filled with a film consisting of polycaprolactone and furosemide, as shown in figure 5. The method is demonstrated to work on wafer scale level with 4 inch wafers. Our method for filling containers with a drug matrix can be applied to any polymeric drug that presents the following fabrication requirements. . The T_g of the polymer drug matrix must be lower than the one of the micro container material. The embossing temperature should be in-between the T_g polymer drug matrix material and the T_g of micro container material. This ensures a reflow of the polymer drug matrix without effect on the structural stability of the micro containers. Furthermore, the embossing temperature should not exceed T_m of the components to allow separation of the embossed stack following the cooling process.

Drug release test is performed on the embossed drug matrix, as shown in figure 6 together with the release curve for crystalline furosemide powder and an amorphous spray dried furosemide powder. For the embossed polymer drug matrix more than 95% of the furosemide is released within the first 30 minutes. The release of the embossed polymer matrix shows improved drug release compared with crystalline furosemide. The release resembles the fast release seen from the amorphous furosemide. It is known that amorphous furosemide dissolves faster than crystalline [6], thus the furosemide in the embossed filmed exhibits amorphous characteristics. X-ray diffraction spectroscopy confirms the morphology and shows that the PCL furosemide films are amorphous before and after the embossing.

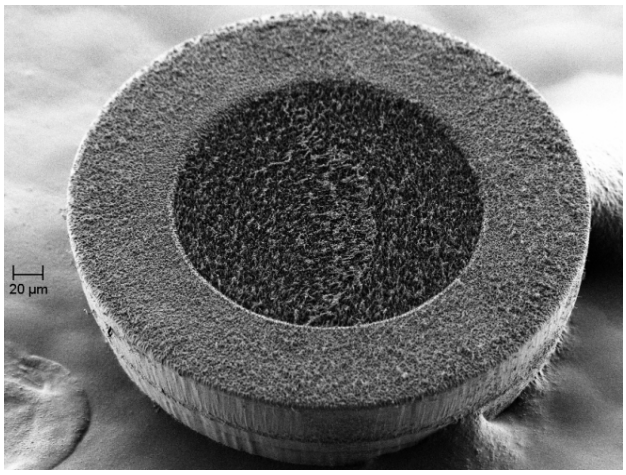

Figure 5. SEM image of released micro container filled with polymer drug matrix. The micro container is placed on carbon foil for ease of handling.

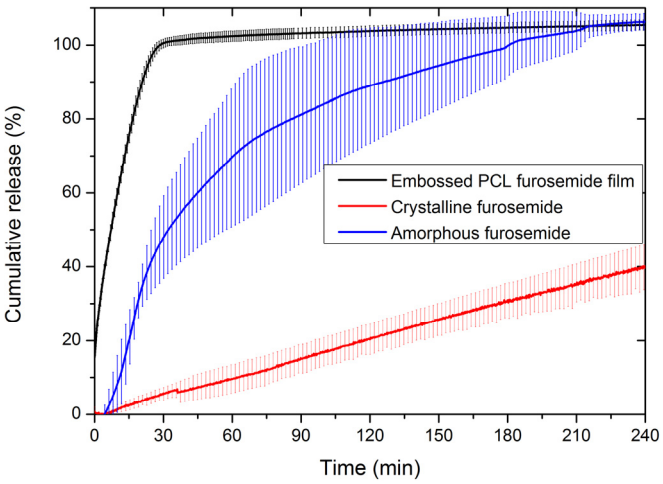

Figure 6. Release curve of embossed furosemide polycaprolactone matrix showing cumulative release. As a reference the cumulative release for an amorphous furosemide powder and a crystalline is plotted. Release test is performed with pion µdiss profiler. Standard curve R^2 value of 0.996.

CONCLUSION

We have shown that it is possible to integrate filling of micro containers as part of the fabrication on a wafer scale level, thus enabling high volume production. The embossed PCL furosemide film shows fast drug release and the furosemide is found to be amorphous. Further development of micro containers for drug delivery includes the addition of a lid for controlled release and the exchange of SU-8 as container material with a biodegradable polymer

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REFERENCES:

[1] "Microfabricated drug delivery systems: Concepts to improve clinical benefit", F.J. Martin, C. Grove, Biomedical Microdevices 3:2 97-108 (2001).
[2] "Bioadhesive microdevices with multiple reservoirs: a new platform for oral drug delivery", A. Ahmed, C. Bonner, T. A. Desai. Journal of Controlled Release 81, 291–306 (2002).
[3] "Microfabrication technologies for oral drug delivery", S. Sant, S. L. Tao, O. Z. Fisher, Q. Xu, N. A. Peppas, A. Khademhosseini, Advanced Drug Delivery Reviews 64:6, 496-507 (2012).
[4] "Optimized plasma-deposited fluorocarbon coating for dry release and passivation of thin SU-8 cantilevers" S. Keller, D. Haefliger, A. Boisen, Journal of Vacuum Science & Technology B, Vol. 25, 1903-1908 (2007).
[5] "3D microstructuring of biodegradablepolymers" J. Nagstrup, S. Keller, K. Almdal, A. Boisen, Microelectronic Engineering 88, 2342–2344 (2011).
[6] "Mechanisms of dissolution of furosemide/PVP solid dispersions" C. Doherty and P. York, International Journal of Pharmaceutics, 34, pp. 197–205 (1987).

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