Drug Dissolution Chip (DDC): A Microfluidic Approach for Drug Release

*Maike Windbergs and David A. Weitz**

The effectiveness of drug delivery relies on the drug being released from its pharmaceutical dosage form, such as a tablet or capsule, and dissolving in body fluids prior to absorption, and transport to the therapeutic target.[1] The analytical investigation of drug release from its dosage form is called dissolution testing and is essential in development as well as in manufacturing and quality control of pharmaceutical dosage forms.[2] The fundamental methodology of dissolution testing entails a defined amount of the dosage form immersed in a predetermined volume of dissolution medium. The concentration of the released drug in the medium is measured in distinct time intervals, yielding time-dependant dissolution profiles. The compartment containing the dosage form is typically a vessel or chamber equipped with mechanical barriers, such as filters or a bed of glass beads, which retain the solid sample. The dissolution medium is pumped through this compartment at a constant flow rate, and the drug concentration in the dissolution medium is determined with high-performance liquid chromatography or UV–vis spectroscopy. Unfortunately, the drug can undergo changes in its solid state which can have marked effects on its dissolution rate.[3,4] For example, the drug might recrystallize at the surface of the dosage form into another polymorphic form which has reduced solubility, therefore leading to a significantly reduced dissolution profile.

These effects cannot correctly be interpreted with concentration analysis alone, and this would have considerable implications for the proposed therapy in the human body. Thus, methods to identify such effects are essential for the development of new pharmaceuticals as they would offer increased process understanding, thereby improving safety for the patient.[5,6] There have been analytical attempts to monitor the behavior of pharmaceutical samples in fluid that use different analytical techniques.[7,8] A suitable approach for tablet dissolution testing was realized in a Teflon flow-through device allowing simultaneous analysis of the dissolved drug concentration and visualization of the solid sample through a combination of UV–vis spectroscopy and Raman spectroscopy,[9] or coherent anti-Stokes Raman scattering,[10] respectively. However, these devices are restricted to large monolithic dosage forms such as tablets, which can easily be immobilized in such a device. Unfortunately, the majority of dosage forms under current development are small multiparticulate systems; and for these systems, the aforementioned devices are unsuitable. Indeed, there is currently no suitable dissolution testing device for such small multiparticulate systems, which facilitates simultaneous visualization of the particulate samples and concentration analysis.[11–13] While many different geometries are used to measure dissolution profiles without visualization, there is no way to precisely compare results among these geometries.[14–16] Thus, there is a strong demand for a versatile dissolution testing device that provides simultaneous measurements of dissolution rate and sample visualization.[17]

In this paper we present a novel flow-through cell fabricated on a microfluidic chip, which is a versatile dissolution testing apparatus for small multiparticulate dosage forms. The chip consists of a hollow chamber equipped with specific mechanical barriers to immobilize the particles and prevent their aggregation, thereby mimicking the fate of such a dosage form in the human body. The dissolution medium is continuously pumped through the cell providing contact to the dosage form. The chip is constructed from polydimethylsiloxane (PDMS) bonded to a thin glass slide; it therefore allows simultaneous visualization of the sample and monitoring the concentration of dissolved drug. This approach can be used to visualize changes of the sample to augment the concentration analysis.

The inherent goal of dissolution testing is to mimic the fate of a dosage form with a drug in the human body. To accomplish this, the sample compartment should be large enough to allow random distribution of the particles; moreover, the compartment should provide mechanical barriers to retain the solid parts of the sample within it. At the same time, the dissolution medium, which mimics the body fluids, must be pumped through the device with a sufficiently large flow rate to avoid saturation and to mimic the behavior within the body. Many samples require sink conditions which necessitates the volume of dissolution medium to exceed, by 5 to 10 times, the volume at the saturation point of the drug. In addition, other important considerations for the device include ease of use, scale-up potential, low cost, and reproducibility of the results. We use a drug dissolution chip (DDC), which consists of a microfluidic device fabricated from PDMS. It has a hollow chamber that is oval in shape, which was found experimentally to be the optimal shape for a dissolution flow-through cell within a systematic investigation of different potential geometries. By contrast,

Dr. M. Windbergs, Prof. D. A. Weitz
Department of Physics and School of Engineering and Applied Sciences
Harvard University
Cambridge, MA 02138, USA
E-mail: weitz@seas.harvard.edu

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a straight-channel structure provides purely laminar flow, which is inappropriate as an analytical approach to simulate processes in the human body. Similarly, a rectangular shape risks sample accumulation in the corners having stagnation zones in the flow resulting in local supersaturation of the drug, thereby producing artefacts in the measurements. All these potential artefacts are avoided by the oval shape. The inlet and outlet are connected to either side of the oval chamber, where it narrows, and dissolution medium is continuously pumped through the chamber using polyethylene tubing. We design substructures in the interior of the hollow chamber to randomly separate sample particles and prevent aggregation or clustering while spreading the sample over the full chamber. A similar approach has been used for separation of single cells in microfluidic devices,[18] where small cavities retain single cells in a basket-like structure; an analogous strategy was used to immobilize aqueous drops in a continuous oil phase.[19] However, for dissolution testing the barrier structure must not only retain the particles, but must also ensure constant contact to the dissolution medium as it flows through the device. One suitable approach to immobilize a solid sample within a microfluidic chamber has been realized by pillar stoppers.[20] In our device this sieve principle is realized by integrating small PDMS blocks in rows within the hollow chamber forming shelf-like structures that spread over the interior. A schematic of one of the microfluidic chips, with red spheres representing the sample particles, is depicted in **Figure 1**a. A light microscopy image of one of the substructure barriers in the PDMS chamber, loaded with glass beads to mimic the drug particulates, is shown in Figure 1b. To avoid particles escaping from the interior of the cell, the outlets are designed with similar structures that act as filters, as depicted in Figure 1c.

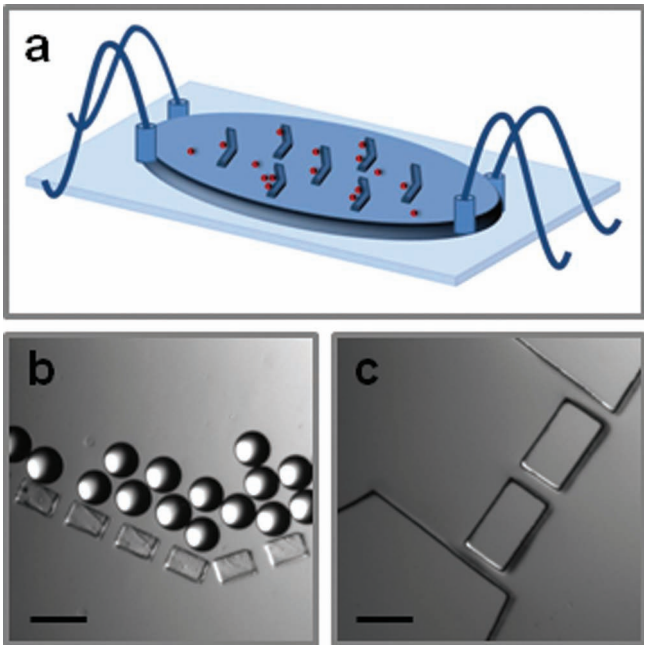

Figure 1. a) Schematic of a microfluidic chip for dissolution testing connected to tubing; b) light microscopy image of a mechanical barrier structure in the cell with glass beads; and c) light microscopy image of one outlet with two PDMS blocks as mechanical barriers. The scale bars denote 200 μm.

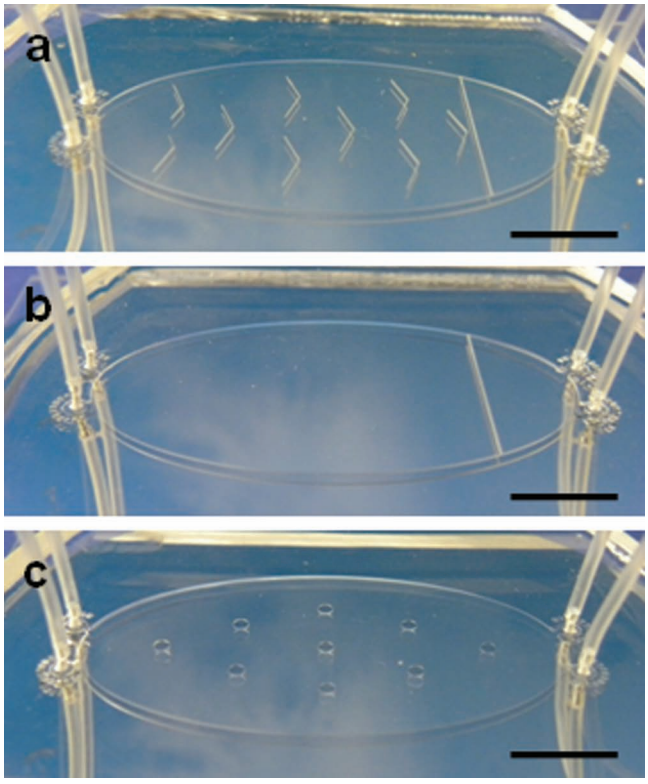

Figure 2. Dissolution chips with different interior designs: a) various barriers distributed in the chamber and one central barrier, b) one central barrier, and c) pillars distributed in the chamber. The scale bars denote 10.000 μm.

We use several modifications of the basic device consisting of the hollow oval camber with inlets and outlets for the dissolution medium fluids allowing to mimic different immobilization and flow conditions. We present three different varieties of the interior device substructure to show the variability of this new analytical approach. The PDMS blocks are either be arranged in the shelf-like structures or in simple straight rows to form a barrier structure (**Figure 2**a,b). It is also possible to use an assembly of pillars within the chamber (Figure 2c).

The DDC is based on a variable platform technology; the choice of the structure and the dimensions of the chip are flexible and can be adapted to the particular requirements of each specific drug delivery system. Using soft and photolithography, the size limitations for the device are on the one hand defined by the characteristics of the photoresist that is used to fabricate the master and hence defines the maximum dimensions, which is around 900 μm for the height of the chamber. On the other hand, the minimum dimensions are defined by the resolution of the printer used to fabricate the photomask, which generates the interior substructure of the device and is around 1 μm. For the production of smaller or bigger chambers other materials such as glass and other fabrication techniques such as etching can be used. A specific DDC can easily be reproduced once the initial mold is

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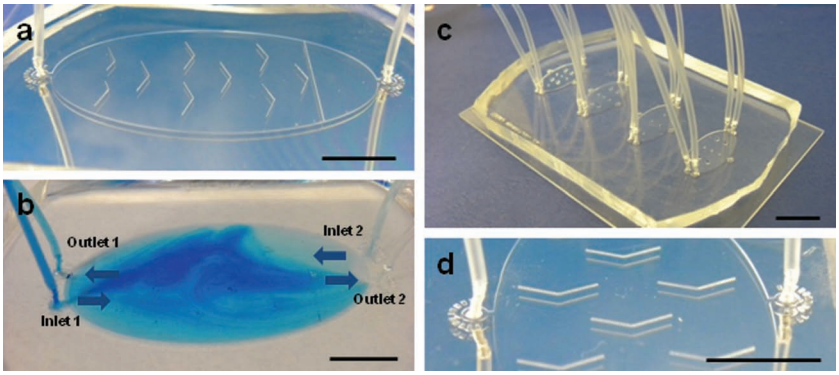

Figure 3. a) Dissolution chip having one inlet and one outlet, b) two different counterpart fluids (water and methylene blue solution) pumped through the chip, c) four chambers on one chip in parallel, and d) side inlet and outlet for sample injection. The scale bars denote 10.000 μm.

formed, this ensures reproducible dissolution results. Furthermore, the sample chamber provides excellent optical access for observation of the dissolution process. Thus, the DDC represents a valuable new dissolution setup for small multiparticulate dosage forms.

Furthermore, we vary the flow condition of the dissolution medium. We either operate the chip with one inlet and outlet (**Figure 3**a) or two inlets and outlets as shown in Figure 3b. The latter case offers additional possibilities to vary the dissolution testing procedure. We use two counter flows to generate turbulence, which occurs more frequently in human body than does laminar flow. To visualize this effect, we flow purified water through one inlet and an aqueous methylene blue solution through the counter inlet. Both liquids mix in the middle of the flow-through cell, as depicted in Figure 3b (see video in Supporting Information). This arrangement is particularly valuable for those chip structure which have only a central barrier to retain the solid particles or an arrangement of pillars, as depicted in Figure 2b and c, respectively. Furthermore, we realized a parallel array of four flow-through cells on one chip to simultaneously compare data from different samples as shown in Figure 3c. The size of the chip can be adjusted to optimize each system.

Loading the sample into the chamber is either accomplished through an inlet at the narrow sides or through additional side inlets on the broad sides (Figure 3d). Hence, the sample can even be injected into the chamber while continuously circulating the medium through the flow-through cell. By adding additional inlets and outlets to allow the dissolution medium to be pumped in a direction transverse to the barrier, the particles themselves can be transported between different chambers. This allows the particles to be exposed to different conditions such as other values of pH. Such a procedure is more gentle and easier than removing the sample completely from the DDC and reloading it in a second device.[21]

Analysis of the drug release with the DDC can be performed with several different analytical methods. For example, we connect a UV–vis spectrometer with a flow-through cuvette for concentration analysis can be connected to the outlet of the chip, similar to that of commercially available dissolution systems for large pharmaceuticals. In addition, the DDC allows the sample to be operated on a microscope stage for direct and simultaneous visualization with an optical microscope, providing additional valuable information and analysis options.

To illustrate the capability of the DDC, we perform release studies with two different systems. For this purpose we use the device depicted in Figure 3a. The first drug delivery system consists of core–shell hydrogel particles with a non-thermoresponsive polyacrylamide core and a thermo-responsive poly(*N*-isopropylamide) shell loaded with fluorescent Rhodamine B isothiocyanate (RITC)–dextrans. At temperatures above 34 °C the poly(*N*-isopropylamide) shell is not swollen, retaining the dextrans inside of the gel structure. As soon as the temperature is decreased below 34 °C the shell structure swells, releasing the encapsulated dextrans.[22] This release process **is** visualized in real time in the DDC as the dissolution medium is slowly cooled below 34 °C. The release of dextrans, as measured by monitoring the time-dependant decrease of the fluorescence intensity of the particles, is depicted in **Figure 4**a–f. The second release system consists of core–shell particles comprised of a solid lipid shell encapsulating an aqueous droplet containing Allura Red solution. The particles are filled into the device in dry conditions directly through the tubing. The release of the dye Allura Red is visualized as the particles come into contact with the heated dissolution medium (37 °C). The lipid shell has a melting point at 33.5–35.5 °C and releases its content while melting, as shown in Figure 4g–l.[23] The corresponding concentration data of the released dye in the dissolution medium are analyzed with UV–vis spectroscopy and shown in Figure 4m. In addition to light and fluorescence microscopy other spectroscopic techniques, such as infrared or Raman spectroscopy,[24,25] can be used for monitoring the drug or carrier. Furthermore, as a potential future development of the DDC different analytical sensors, for instance to determine pH value or temperature, can directly be incorporated within the device chamber.

This DDC provides a novel, versatile platform technology for comprehensive release studies of multiparticulate pharmaceutical dosage forms. It can be designed with a flexible structure, using different mechanical barriers to immobilize the particles and separate them from each other, thereby mimicking the fate of such a dosage form in the human body. Chip production is highly reproducible, and the chip is inexpensive to fabricate and is easy to use. The DDC enables simultaneous visualization of the physical properties of the sample through different microscopy techniques and monitoring of the dissolution concentration through different spectroscopic techniques. Thus, the DDC should contribute to the optimization of the therapeutic effectiveness of small multiparticulate release systems during development and stability studies. Furthermore, it can be used for routine assessment of

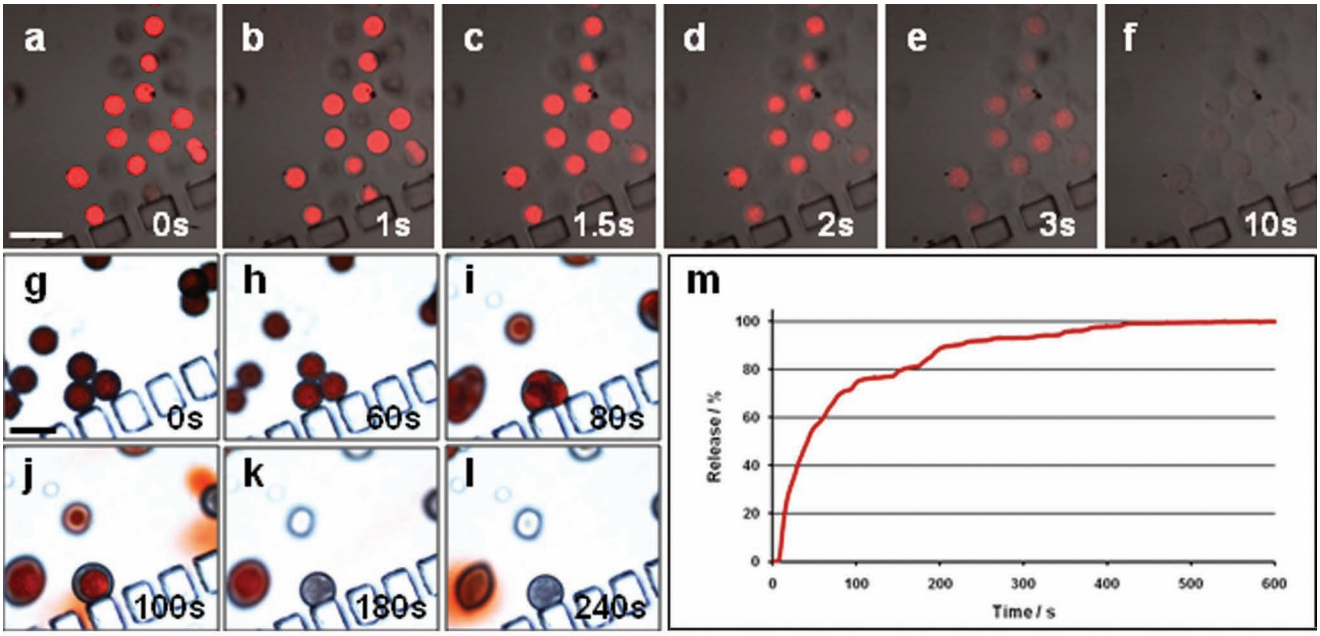

Figure 4. Release studies of different core–shell particles in the dissolution chip over time: a–f) poly(*N*-isopropylacrylamide) hydrogel particles containing a core of poylacrylamide loaded with fluorescent RITC–dextrans and the release detected by fluorescence microscopy, and g–l) particles with a solid lipid shell and an aqueous core containing Allura Red, detected by light microscopy, and m) the corresponding cumulative concentration of the released dye in the dissolution medium, detected by UV–vis spectrometry. The scale bars denote 200 μm.

manufacturing quality to ensure safety and uniformity of different production batches.

Experimental Section

Device Fabrication: The drug dissolution chips are fabricated by soft lithography in PDMS.[26] A specific photomask is designed and printed on a transparency (CAD/Art Services, Bandon, OR). A clean silicon wafer is spin-coated with negative photoresist SU-8 2100 (MicroChem, Newton, MA) to a final height of 300 μm and exposed to UV light covered with the photomask to crosslink exposed patterns. The non-cross-linked parts are removed with propylene glycol monoethyl ether acetate (PGMEA). PDMS (Sylgard 184, Dow Corning, Midland, MI) is mixed with its cross linking agent (ratio 10:1 w/w) and degassed before pouring it onto the photoresist mold in a petri dish. After curing for at least 1 h at 65 °C, the replica is peeled off and holes for inlets and outlets are punched with a biopsy needle (diameter 1.2 mm). Finally, the replica is bonded to a glass slide after surface activation with oxygen plasma.

Dissolution Testing and Detection of Drug Release: The PDMS chip is connected to the medium reservoir via polyethylene tubing (PE 5, Scientific Commodities Inc., Lake Havasu City, AZ). Pumps (Minipuls 3, Gilson, Middleton, WI) circulate the medium through the chip. Purified water and an aqueous methylene blue solution are used as dissolution medium and test fluid, respectively. For temperature control the medium reservoir is placed onto a heating plate. Release processes are investigated with the following systems: hydrogel core–shell particles consisting of a polyacrylamide core and a thermoresponsive poly(*N*-isopropylacrylamide) shell loaded with fluorescent RITC–dextrans (mean diameter 120 μm)[22] as well as core–shell particles with a solid triglyceride shell and a liquid core (aqueous Allura Red solution) with a mean diameter of 130 μm. The microfluidic device is operated on a microscopy stage. Detection of RITC–dextrans is performed with a confocal microscope (Leica TCS SP5, Bannockburn, IL) exciting the fluorescence with the 543 nm line of a HeNe laser, whereas detection of Allura Red is realized with a Eclipse TE 200-E microscope (Nikon, Melville, NY) equipped with a color camera. The release of Allura Red from the particles was detected with a UV–vis Spectrometer (Perkin Elmer Lambda 40) at 504 nm.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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