Enhanced Drug Delivery across the Intestinal Epithelium using Planar Bioadhesive Microdevice

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ABSTRACT SUMMARY
There is a great need for the production of novel delivery systems that improve the bioavailability of orally delivered therapeutics. Herein, we demonstrate the use of microfabricated thin, asymmetric, multi-reservoir, poly(methyl methacrylate)-PMMA microdevices to facilitate the delivery of oral drugs across the epithelium.

An in vitro caco-2 monolayer was used as the intestinal epithelium model to study the controlled release of multiple drugs from the microdevices. An in vivo mouse model was also used to study the bioadhesion, retention, and delivery of a poorly absorbable and poorly soluble model drug Acyclovir across the intestine.

INTRODUCTION
Oral delivery is a preferred route of administration as it is less invasive, provides patient compliance, and less costly. However, the harsh physiological conditions of the gastrointestinal tract, along with an array of intestinal enzymes and high shear fluid flow reduce the therapeutic efficacy of oral drugs. Although delivery paradigms such as enteric-coated capsules, liposomes, and permeation enhancers, have been developed, most drugs delivered orally have limited bioavailability. Also, the absence of targeting strategies for treating intestinal diseases (IBD, IBS, Crohn’s) provides a motivation for development of novel microfabricated bioadhesive vehicles for enhanced permeation and controlled release of oral drugs.

Precise engineering and design control needed to overcome the above issues can be achieved using microfabrication. Microparticles, the most widely studied approach, suffer from non-uniform size distributions and release profiles [1]. Further, the multi-directional drug release due to the microparticles’ symmetry results in drug loss into the lumen, thereby reducing the overall bioavailability of drug. To overcome these issues, herein, we developed asymmetric unidirectional drug releasing planar microdevices [2, 3]. Multiple reservoirs were introduced into biocompatible PMMA microdevices for an independent and controlled release of differentially tagged model drugs (BSA). GI epithelial specific targeting protein, tomato lectin was also conjugated to the microdevice surface to provide enhanced bioadhesion. Microdevices loaded with poorly soluble and poorly absorbable drug Acyclovir was studied for drug permeation across the mouse intestine.

EXPERIMENTAL METHODS
Microdevice Fabrication: The fabrication of the microdevice is shown in figure 1. Briefly, a series of PMMA spin coating followed by positive photoresist was conducted to control the device thickness. Photolithography using a device-shape-defining mask followed by reactive ion etching under oxygen plasma was done initially to get the microdevice body. A second photolithographic step with a reservoir-defining mask followed by partial reactive ion etching resulted in the formation of the multi-reservoir PMMA microdevice.

RESULTS AND DISCUSSION
The thickness of the fabricated microdevices can be varied by varying the spin speed and number of spinning steps. The parameters of reactive ion etching (power and time of etching) were found to vary the depth of the reservoirs. For this study, the microdevice features were optimized to 200 μm circular devices, having three 60 μm circular reservoirs of 5 μm depth. The thickness of the microdevice was around 9 μm in depth.

Conjugation of Tomato Lectin: Bioadhesive property was introduced to the microdevices by conjugating targeting protein, tomato lectin to the surface. Briefly, amine groups were introduced using pre-synthesized N-lithioethylenediamine. Carbodiimide chemistry was then used to form amide bonds between the carboxylic groups of the protein and the amine groups of the PMMA device.

Drug Loading of Microdevices: Single or multiple drugs were loaded via photolithography. Briefly, a prepolymer solution of MMA, poly(ethylene glycol) dimethacrylate (PEGDMA), photoinitiator, and model fluorophore tagged BSA in PBS or Acyclovir in 1 M HCl were spun onto the microdevices. Specific negative masks were employed to polymerize the solution into a drug encompassing hydrogel matrix.
Figure 2.a. shows the presence of multiple model drugs (FITC-BSA; green, Texas red-BSA; red, and DNP-BSA; blue) loaded using a series of photolithographic steps. It is observed that the drugs are loaded specifically to their respective reservoirs. This enables the use of different drug releasing systems such as pH and temperature responsive hydrogels, or degradable polymeric materials in the same device.

The devices were made bioadhesive by the by the conjugation of the intestinal epithelial cell surface targeting protein, tomato lectin. To confirm the conjugation of lectin to the surface of the amine introduced PMMA microdevices, FITC conjugated lectin was used. Figure 2.b. shows the presence of carbodiimide conjugated FITC-lectin to the microdevice surface, the side where the reservoirs are open for drug release.

Figure 3 shows the in vitro release profile of single drug loaded microdevices. Relative to the control (hydrogel bolus) sample, the microdevices show an enhanced permeation of drug across the caco-2 monolayer. This may be attributed to the fact that unlike the bolus, asymmetric microdevices release drug in a unidirectional way, thereby providing an increased concentration of drug across the device-cell interface.

The presence of multiple reservoirs proves advantageous in terms of releasing different drugs at different time points and at different rates. Figure 4 shows the release of different model drugs using different responsive hydrogels (increasing PEG amounts) loaded in the respective reservoirs.

Figure 3. The enhanced permeation of different single drug loaded microdevices as compared to their respective drug loaded hydrogel bolus (control; without devices) through a caco-2 epithelial monolayer on collagen treated Transwells®. (N=3) [3].

Figure 4. Controlled release and permeation of different model drugs loaded into their respective reservoirs of the same device using different crosslinking ratio/amounts of crosslinker (PEGDMA). (N=3) [3].

Table 1. In vivo bioadhesion or retention studies using mice. Mice were gavaged with 150 μm spherical PMMA microparticles, of same surface area as that of PMMA microdevices.

CONCLUSION
A thin, asymmetric, multi-reservoir microdevice was fabricated using photolithography and RIE of PMMA. The devices were rendered bioadhesive by conjugating them with lectin. In conjunction with the enhanced permeation of drug, the increased retention of devices in the GI resulted in an increased absorption of oral drugs.

REFERENCES
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