Published in final edited form as:

Adv Healthc Mater. 2014 October ; 3(10): 1648–1654. doi:10.1002/adhm.201300676.

Planar Microdevices for Enhanced In Vivo Retention and Oral Bioavailability of Poorly Permeable Drugs

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Abstract

The development of novel oral drug delivery platforms for administering therapeutics in a safe and effective manner through the harsh gastrointestinal environment is of great importance. Here, the use of engineered thin planar poly(methyl methacrylate) (PMMA) microdevices is tested to enhance oral bioavailability of acyclovir, a poorly permeable drug. Acyclovir is loaded into the unidirectional drug releasing microdevice reservoirs using a drug entrapping photocross-linkable hydrogel matrix. An increase in acyclovir permeation across in vitro caco-2 monolayer is seen in the presence of microdevices as compared with acyclovir-entrapped hydrogels or free acyclovir solution. Cell proliferation studies show that microdevices are relatively nontoxic in nature for use

in in vivo studies. Enhanced in vivo retention of microdevices is observed as their thin side walls experience minimal peristaltic shear stress as compared with spherical microparticles. Unidirectional acyclovir release and enhanced retention of microdevices achieve a 4.5-fold increase in bioavailability in vivo as compared with an oral gavage of acyclovir solution with the same drug mass. The enhanced oral bioavailability results suggest that thin, planar, bioadhesive, and unidirectional drug releasing microdevices will significantly improve the systemic and localized delivery of a broad range of oral therapeutics in the near future.

1. Introduction

Oral administration of pharmaceuticals is often the preferred route of delivery due to the advantages of high patient compliance, low invasiveness, and low cost of manufacturing. However, the acidic environment of the stomach, combined with an array of intestinal digestive enzymes, and a poorly permeable mucous layer have made the oral delivery of therapeutics challenging.^[1,2] While the development of enteric-coated capsules, liposomes, and permeation enhancers have been pursued for nearly a decade, constant peristalsis and shear flow conditions in the gastrointestinal (GI) has limited the translation of these delivery approaches into the clinic.^[3–7] Also, in the case of micro- and nanoparticles, the most commonly studied oral drug carriers, issues of polydispersity, and aggregation exist. This nonuniformity among particles result in nonuniform loading and drug release.^[8–10] Therefore, there is an inherent need for the development of new platforms for the oral delivery of pharmaceuticals.

The well-established microfabrication techniques of the semiconductor industry have been used by our laboratory and others to manufacture en masse, reproducible, monodispersed, unidirectional releasing, microdevice platforms for oral delivery of pharmaceuticals.^[11–18] We believe that the particle shape and size plays a significant role in the efficacy of oral administration. As shown in Figure 1a, an asymmetrically releasing thin microdevice should experience minimal shear stress from constant peristalsis and intestinal fluid flow on its sides than spherical particles. Unlike spherical particles that have only a fraction of their surface area in contact with the GI epithelium, a large portion of the microdevice surface can remain in contact with the epithelium. Also, the surface chemistry of devices can be uniformly or selectively modified with intestinal cell targeting agents during on-wafer fabrication.^[19] We have recently shown that in addition to releasing multiple drugs from a layer-by-layer drug-loaded microdevice reservoir, microdevices with multiple reservoirs can be fabricated to release multiple drugs independently.^[1,20] This independent multidrug release from microdevices can be harnessed for combinatorial therapy applications.^[21] We have also shown that the unidirectional release from microdevices results in an increased in vitro permeation of model proteins across Caco-2 monolayer as compared with hydrogel particles.^[20] The results presented here show that microdevices enhance in vivo oral bioavailability of a poorly permeable drug. Acyclovir is an anti-viral drug used primarily in the treatment of Herpes simplex, Varicella (chickenpox), and Herpes zoster (shingles) and has a low permeability and absorption in the GI tract.^[22,23] The aforementioned advantages of thin microdevices along with the feasibility of using polymeric biomaterials during

microfabrication make biocompatible microdevices an ideal candidate for oral delivery of multiple drugs.

2. Results and Discussion

2.1. Fabrication of Acyclovir-Loaded Microdevices

Thin PMMA microdevices with three reservoirs were fabricated using a series of photolithographic and reactive ion etching steps (5625 devices/wafer).^[20] We have previously shown that the thickness of the microdevice can be controlled to a few microns by varying the PMMA spin speed, number of PMMA layers, and baking steps that are involved in designing the dimensions of the microdevice body. Also, by controlling the reactive ion etching parameters (power and time of etch), we were able to obtain microdevice reservoirs with different depths. In this work, we used circular microdevices and reservoirs of 8 and 4 μm thicknesses, respectively. The chosen dimension of the microdevice (200 μm diameter) is small enough to aid in better contact with the undulations of the intestinal wall, but large enough to avoid endocytosis. Also, the microdevice thickness was small enough to reduce shear force per mass, experienced by the sides of the microdevice to intestinal flow conditions, thereby reducing the dislodgement of microdevices from its therapeutic release site. Acyclovir was loaded into the reservoirs using a photo-polymerizing hydrogel solution made up of monomer monomethyl methacrylate (MMA) and cross-linker poly(ethylene glycol) dimethacrylate (PEGDMA) and the polymerized reservoir hydrogel is not affected by changes in intestinal conditions (changing pH and enzymatic degradation). Since the saturation mass of acyclovir in water is low, concentrated acyclovir was introduced to the prepolymer hydrogel solution by dissolving first in HCl (140 mg mL^{-1}). UV photopolymerization of the drug-prepolymer solution resulted in the entrapment of acyclovir in the hydrogel matrix. Figure 1b shows the representative scanning electron microscopic (SEM) image of a microdevice loaded with acyclovir-hydrogel. Since the surface area of the reservoir bottom is 300% more than that of reservoir wall, most of the hydrogel (dehydrated state right after polymerization and before development) is adhered to the bottom of the reservoir rather than with the wall. In the presence of a fluid medium, the hydrogel absorbs, swells, and occupies the entirety of the reservoir. The swelling of the hydrogel opens up the hydrogel matrix, thereby releasing the drug and the reservoir allows the drug to release only in one direction—the open side of the reservoir.

2.2. Enhanced In Vitro Permeation of Acyclovir

The ability of unidirectional drug releasing microdevices to enhance transport of acyclovir was studied using a monolayer of confluent caco-2 cells grown on Transwell inserts. About 5500 microdevices loaded with a total of 8.5 μg acyclovir were used per well for this study. An acyclovir-loaded hydrogel bolus (hydrogel pellet with no microdevices) and free acyclovir solution of the same concentration were used as controls for in vitro studies. The microdevices and control samples were added to the apical side of a caco-2 monolayer that possesses in vivo-like tight junctions (1–3 nm) and acyclovir concentration was measured in the basal side.^[24] Figure 2 shows the in vitro permeation profile of acyclovir from the respective samples. Although acyclovir is a small molecule drug with a molecular weight

(225 Da) well below the gastrointestinal limit of epithelial absorption (20 kDa), it is classified as a BCS III—low permeability drug.^[25] Absorption of acyclovir occurs mainly by passive diffusion mechanism, which is slow, variable, and happens in an incomplete manner. This extremely slow permeation of Acyclovir is the reason for minimal presence of the drug on the basolateral side from the acyclovir control solution that is administered on the apical side (Figure 2). It is also observed that the use of a drug-entrapping hydrogel somewhat increases acyclovir permeation across the caco-2 monolayer. This increase may be attributed to the physicochemical interactions between the hydrogel surface and the epithelial surface leading to increased paracellular transport across the intestinal epithelium as seen by others.^[26–28] Relative to the hydrogel bolus, microdevices show a further enhancement of acyclovir permeation across the monolayer. This is probably due to the fact that the control hydrogel bolus swells and releases acyclovir in all directions. Therefore, a majority of the drug is released from those areas of the hydrogel that are not in contact with the epithelium and eventually behave similar to that of the control acyclovir solution. However, in the case of microdevices, acyclovir is released in a unidirectional manner from the reservoir and provides an increased drug concentration at the device-cell interface, thereby leading to an enhanced permeation effect.

2.3. Relative In Vitro Biocompatibility of Acyclovir-Loaded Microdevices

Evaluating biocompatibility by measuring cell viability is important for administering polymeric microdevices in vivo. High amounts of nonregulated intestinal cell death, in conjunction with a foreign material may lead to a heightened inflammation response. This results in a broad chronic inflammation and may further lead to a nonspecific systemic attack of other cells and tissues in the intestine.^[29,30] Any prolonged inflammation and nonspecific systemic attack by immune cells may result in the occurrence/aggravation of intestinal diseases including inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS). Figure 3 represents cell viability in the presence of microdevices and its drug-hydrogel content. The cells in this study were incubated for 4 h with the respective samples, which was well beyond the typical GI transit time of 2 h.^[31] The empty PMMA microdevices at concentrations used (5000 devices) did not cause significant change in cell number. Similar nontoxic results were observed by others who used PMMA microspheres for oral drug delivery applications.^[32–34] Also, PEG used in the drug-entrapping reservoirs is well known for its biocompatible properties.^[35–37] This biocompatibility of different polymeric materials is confirmed by the no change in cell viability in the presence of acyclovir-hydrogel (PEG-PMMA)-loaded microdevices, thereby making them useful for in vivo delivery of oral drugs.

2.4. Enhanced In Vivo Retention of Microdevices via Targeted Bioadhesion

The majority of prior work on improving oral retention has been focused on using bioadhesive spherical particles.^[38] However, we believe that the high surface area of microdevices ($23\,000\ \mu\text{m}^3$) can be harnessed to increase oral residence time. We have previously shown that epithelia-targeting-lectin-conjugated microdevices significantly enhanced in vitro bioadhesion compared with microparticles of same surface area.^[11,12,20] This is because lectin binds specifically to the *N*-acetylglucosamine groups present on the intestinal epithelial lining, thereby increasing bioadhesion/retention and eventual drug transit

time.^[39] Furthermore, the microdevice sides are thin enough to experience low peristaltic shear stress as compared to the thick surface of spherical microparticles.^[40] Figure 4 shows the in vivo retention of PMMA microdevices (with and without lectin) and PMMA microparticles of same surface area available for contact. In this study, a large number of microparticles ($\approx 35\,000$) or microdevices ($\approx 11\,000$) are gavaged into mice stomach (cumulative total surface area is the same). Therefore, there is a steady flow of particles or microdevices into the proximal intestine, after which they interact with intestinal epithelium. From Figure 4, it is observed that about 28% and 37% (cumulative retention of medial intestine and colon together) of the spherical microparticles get pushed downstream from the proximal intestine due to high peristaltic shear stress within 45 and 90 min of gavage time, respectively. This low residence time of microparticles can reduce the overall oral bioavailability as drugs are best absorbed systemically in the proximal intestine within the first hour of oral gavage.^[41] On the other hand, only 14% and 21% of microdevices (with no lectin) experiencing low peristaltic shear stress are downstream of the proximal intestine within the 45 and 90 min of gavage, respectively. Therefore, a significant portion of microdevices (28% and 32% at 45 and 90 min, respectively) are still retained in the proximal intestine, illustrating a significantly increased residence time of microdevices in the GI tract. In the presence of bioadhesive lectin, it is observed that a further enhancement of micro device retention (49% and 64% at 45 and 90 min, respectively) was achieved in the proximal intestine. This enhanced retention of lectin-conjugated microdevices should therefore significantly improve the oral bioavailability of drug/s by increasing the residence time of drug/s available for permeation and systemic absorption. Also, unlike microparticles, we observed a significant number of microdevices (27% without lectin and 41% with lectin) to remain in the proximal intestine 2 h after initial gavage, which may make thin, planar microdevices more suitable than symmetrical microparticles for oral drug delivery.

2.5. Increased In Vivo Oral Bioavailability of Acyclovir

The ability of microdevices to enhance oral bioavailability by providing high concentrations of drug at device-cell interface and an increased intestinal residence time was then tested. Figure 5 shows the pharmacokinetic plasma concentrations of acyclovir over a period of 6 h from microdevices loaded with 17 μg of acyclovir/mice (0.8 mg per kg mice), 17 μg of oral acyclovir solution (1 $\times$ control; 0.8 mg per kg mice), and 85 μg of oral acyclovir solution (5 $\times$ control; 4.0 mg per kg mice). While absorption, distribution, and elimination phase of acyclovir was observed from microdevices, a similar trend was not noticed for the 1 $\times$ oral control. This may be attributed to the fact that acyclovir from the 1 $\times$ oral solution transited faster downstream from the upper intestine, thereby allowing less time for drug absorption to occur. Therefore, drug elimination overcame drug absorption and resulted in a concentration profile with no differentiable pharmacokinetic stages in the majority of time points. But in the case of microdevices, enhanced device retention increased the time of absorption and the amount of drug absorbed in the upper intestine. A similar profile was also evident in the 5 $\times$ oral control, where, in spite of the downstream flow, the concentration of acyclovir was high enough to be absorbed before it reached the colon. The area under the curve (AUC), which represents a measurement of drug exposure, was calculated using the trapezoid rule. The AUC values for microdevices, 1 $\times$ oral control, and 5 $\times$ oral control were 110, 24, and 247 $\mu\text{g min mL}^{-1}$, respectively. Although it appears that the drug exposure

from 5× oral control is twice as much as that of microdevices, it is to be noted that five times the initial dose was required to achieve this value. This requirement of high doses necessary to achieve a therapeutic effect could represent an issue for expensive or toxic drugs that cause severe side effects possibly related to their peak concentrations. The mean residence time, which represents the average amount of time a drug stays in plasma was significantly higher for microdevices ($MRT_{\text{device}} = 88 \text{ min}$) than the 1× oral control ($MRT_{1\times} = 37 \text{ min}$). This means that the controlled release of acyclovir from microdevices was effective enough to maintain a therapeutic drug concentration for an extended period of time. This reduces the inherent need for frequent drug administration as is the case for conventional oral administration. The bioavailability of acyclovir from conventional oral administration is about 21% due to its low permeability values.^[42] The calculated bioavailability from microdevices is about 458% in comparison to the bioavailability of the 1× control (or 223% and 49% for microdevices and 1×, respectively, when normalized to 5× control). This about 4.5-fold enhanced bioavailability in comparison to the 1× oral solution arising from unidirectional release, high concentration of drug at the device-cell interface, and enhanced bioadhesion and retention makes microdevices an attractive platform for oral delivery.

3. Conclusion

Although a variety of drug delivery platforms including enteric-coated capsules, liposomes, permeation enhancers, and micro- and nanoparticles have been developed for improving the oral bioavailability of various drugs; many gastrointestinal barriers hinder their effective translation into the clinic. This present study has demonstrated the successful use of thin, planar, multireservoir PMMA microdevices for the enhancement of oral bioavailability of a poorly permeable drug. The high surface area of the thin, planar microdevice enables high contact area with the intestinal epithelium as compared with spherical microparticles. Acyclovir was entrapped inside the microdevice hydrogel-filled reservoirs by photolithography, thereby allowing unidirectional release of acyclovir. This unidirectional release results in a high drug concentration at the microdevicecell interface and allows for increased permeation of acyclovir across the caco-2 monolayer in vitro. Unlike spherical microparticles that experience a high intestinal and peristaltic shear, planar microdevices experience a low shear stress and remain for a longer duration in the upper intestine. The retention of microdevices in the upper intestine is further enhanced by conjugating GI-targeting bioadhesive lectin to microdevice surface. The increased drug permeation from unidirectional release and enhanced microdevice retention in the intestine leads to an increase in the oral bioavailability of acyclovir in mice. Also, the sustained/controlled release of acyclovir from microdevices enabled the use of a low dosage acyclovir-loaded microdevice to attain similar bioavailability as that of a concentrated solution of acyclovir, which at peak concentrations may cause systemic side effects. Therefore, the use of microdevices holds promise in augmenting the range of oral therapeutics used, while solving pharmacokinetic issues associated with low permeability and avoiding toxic concentrations.

4. Experimental Section

Fabrication of Microdevices

Unless otherwise indicated, all chemicals were purchased from Sigma–Aldrich (St. Louis, MO) and used as received. All plastic ware and disposables were purchased from Fisher Scientific (Pittsburg, PA). Fabrication of 200 μm circular microdevices (8 μm thick) with three 60 μm reservoirs (4 μm deep) are described elsewhere.^[20] Briefly, a series of poly(methyl methacrylate); PMMA spin casting, positive-resist lithography, and reactive ion etching were used to fabricate the microdevices. In the case of lectin-conjugated microdevices, bioadhesive lectin was introduced to the surface of the microdevice using a standard EDC-NHS chemistry after introducing amine groups to the surface of microdevices via aminolysis as described elsewhere.^[20]

Loading of Acyclovir into Microdevices

The drug acyclovir is loaded to the microdevice reservoirs using photolithography.^[20] Briefly, hydrogel-drug prepolymer solution was prepared by mixing cross-linker poly(ethylene glycol) dimethacrylate (PEGDMA; 750 mol wt; 1 mL) with photoinitiator dimethoxyacetophenone (DMPA; 300 μL of 60 mg mL^{-1}) in monomer monomethyl methacrylate (MMA). Acyclovir was then dissolved via vortexing in 1 M HCl to get a final concentration of 140 mg mL^{-1} . 600 μL of acyclovir was then added to the PEGDMA prepolymer solution and sonicated (5 min) to ensure equal distribution of initiator and drug. The prefabricated wafers were then spin coated (1500 rpm, 30 s) with the acyclovir-prepolymer solution (300 μL) and exposed to UV light (405 nm; 16 mW cm^{-2} ; 90 s) using a mask aligner (Karl Suss MJB3; VT). The photomask used for loading in all three reservoirs is a negative photomask (CAD art services; Badon, OR) designed to allow light to pass through all three 60 μm reservoirs for photopolymerization of the prepolymer solution into an acyclovir-entrapping hydrogel matrix. Development was done using DI water (30 s) and blown dry using nitrogen. The wafers were stored in a dry place until further use. Control acyclovir hydrogel bolus was fabricated by pipetting an equal volume of acyclovir-prepolymer solution that contained the same mass of acyclovir as that of microdevices from a single wafer and carrying out UV photopolymerization for 90 s.

In Vitro Acyclovir Permeation Studies

Acyclovir-loaded microdevices were detached from the silicon wafer with a razor blade and added to PBS. Human colorectal adenocarcinoma epithelial cells (caco-2 ATCC) were grown to confluency (transepithelial electrical resistance plateau at 900–1000 Ω) on 50% collagen-ethanol (Type 1, Becton Dickinson, Franklin Lakes, NJ) treated 24-well Transwell inserts. The caco-2 cells were maintained in Modified Eagle's Media (MEM) with fetal bovine serum (Invitrogen; 20%), L-glutamine (2×10^{-3} M), sodium bicarbonate (1.5 g L^{-1}), glucose (2.5 g L^{-1}), HEPES buffer (10×10^{-3} M), sodium pyruvate (1.0×10^{-3} M), and penicillin/streptomycin (1 mg mL^{-1}) for 7 d prior to seeding. The microdevice solution containing about 5500 microdevices was equally added (500 μL) to Transwell inserts. Discrete time (20 min) samples were taken from the basolateral chamber of the Transwell and stored at -20°C until further HPLC analysis.

In Vitro Biocompatibility Study

Caco-2 cells were seeded on 12 well plates at a seeding density of 4×10^5 cells cm^{-2} and grown to confluency in 2 weeks. For obtaining a standard curve, Caco-2 cells of varying seeding densities ($1, 2, 5, 10 \times 10^5$ cells cm^{-2}) were grown to confluency on 12 well plates. Prior to incubation with the different samples—acyclovir-loaded microdevices (≈ 5000 devices/well in PBS; dosage of $8.5 \mu\text{g}$ acyclovir), empty microdevice control, and 20% DMSO negative control; the culture medium was removed and the cells were rinsed with PBS. The cells were incubated with the device sample and controls for 4 h at 37°C . After removal of the devices and controls by washing twice with PBS, 1 mL of PBS was added to the wells. The cells were then incubated for 4 h with 0.1 mL of MTT 5655 solution that form formazan crystals with the mitochondria of viable cells. The crystals were then dissolved using 1 mL of MTT 8910 solution. The UV absorbance was measured at 570 nm using a Spectra Max 190 absorbance microplate reader (Molecular Devices, Sunnyvale, CA). Results are expressed as viable cell number with respect to just cells (TCPS control) grown and assayed under the same conditions.

In Vivo Retention Study

Wild-type C57BL/6 mice (JAX, Bar Harbor, MA), aged 8–12 weeks, were used in this study. Prior to oral gavage of microdevices, mice were fasted for 24 h. Sterile $18 \text{ ga} \times 38 \text{ mm}$ plastic feeding tubes (Instech Solomon, Plymouth Meeting, PA) were used to instill 500 μL of PBS solution containing microdevices or the control. The control solution consisted of spherical PMMA microspheres (150 μm diameter, Cospheric Inc., Santa Barbara, CA) of same surface area as that of the planar microdevices. Mice were then euthanized at 0, 20, 45, 90, 120 min according to IACUC guidelines, using intraperitoneal injection of $150\text{--}400 \text{ mg kg}^{-1}$ of 2,2,2-tribromoethanol at a concentration of 2.25% followed by cervical dislocation. The study protocol (AN082875–03) was approved by and all animal studies were conducted in accordance with the University of California, San Francisco Institutional Animal Care and Use Committee. Intestines were dissected and divided into different sections including the stomach, proximal, medial, and distal intestine, and the colon and added to glass scintillation vials. Tissue digesting Proteinase K (Roche, Indianapolis, IN) at a concentration of 1 mg mL^{-1} was added to the vials and incubated with gentle rocking at 56°C overnight. Lysates were passed through 40 μm cell strainers (BD Falcon, Franklin Lakes, NJ), rinsed with copious amounts of DI water, and collected as 5 mL solutions prior to quantitation of microdevices. Multiple 100 μL samples of the washed lysates were added to glass slides to determine the average number of microdevices in the respective sections of the intestine.

In Vivo Pharmacokinetic Study Using Microdevices

Microdevices from two wafers ($\approx 11\,000$ microdevices) were loaded with $17 \mu\text{g}$ of acyclovir (0.8 mg per kg dosage per mice) for this study. Wild-type C57BL/6 mice were fasted for 24 h prior to oral gavaging with 500 μL of the microdevice or oral control solutions. The control solutions were made up of PBS containing either $17 \mu\text{g}$ ($1\times$ solution) or $85 \mu\text{g}$ ($5\times$ solution; 4.0 mg per kg dosage per mice) of acyclovir without microdevices. After gavaging, mice were euthanized at 20, 45, 90, 150, 240, and 360 min as detailed before. For serum isolation, blood was obtained by right heart puncture and placed in Z-gel microtubes

(Sarstedt, Germany). Samples were then centrifuged at 10 000 g in a tabletop centrifuge for 5 min at 4 °C. Serum was collected and frozen at –20 °C until further HPLC analysis.

HPLC Analysis

The frozen in vitro PBS or in vivo plasma samples were thawed to room temperature prior to HPLC analysis. Perchloric acid (7%) was added to an equal volume of the samples and vortex mixed to get a mixture. Precipitated plasma proteins were separated via centrifugation at 10 000 g for 5 min. The supernatant was filtered using a 0.22 µm filter and 100 µL of the sample was injected into the HPLC analyzer. Analysis was carried out using an Agilent 1260 HPLC (Santa Clara, CA) equipped with a multiple wavelength detector. Separation was performed on a Nucleosil C18 HPLC column (Macherey-Nagel Inc., Bethlehem, PA) equipped with a Nucleosil C18 guard column using a mobile phase comprised of 92% 50 × 10⁻³ M octane sulfonate; pH 2.6 and 8% methanol with a flow rate of 1 mL min⁻¹. Acyclovir was then detected at 254 nm.

Acknowledgments

This work was supported by the Z Cube Zambon Research Venture.

References

1. Ainslie KM, Desai TA. Lab Chip. 2008; 8:1864. [PubMed: 18941687]
2. Eaimtrakarn S, Itoh Y, Kishimoto JI, Yoshikawa Y, Shibata N, Takada K. Int. J. Pharm. 2001; 224:61. [PubMed: 11472815]
3. Saffran M, Kumar GS, Neekers DC, Pena J, Jones RH, Field JB. Biochem. Soc. Trans. 1990; 18:752. [PubMed: 2083667]
4. Ponchel P, Irache JM. Adv. Drug Delivery Rev. 1998; 34:191.
5. Arango MA, Ponchel G, Orecchioni AM, Renedo MJ, Duchene D, Irache JM. Eur. J. Pharm. Sci. 2000; 11:333. [PubMed: 11033077]
6. Lehr CM. J. Controlled Release. 2000; 65:19.
7. Fasano A. Trends Biotechnol. 1998; 16:152. [PubMed: 9586237]
8. Wolters GHJ, Fritschy WM, Gerrits D, Vanschilfagaarde R. J. Appl. Biomater. 1992; 3:281. [PubMed: 10147997]
9. Lai SK, Hida K, Man ST, Chen C, Machamer C, Schroer TA, Hanes J. Biomaterials. 2007; 28:2876. [PubMed: 17363053]
10. Randall CL, Leong TG, Bassik N, Gracias DH. Adv. Drug Delivery Rev. 2007; 59:1547.
11. Ainslie KM, Lowe RD, Beaudette TT, Petty L, Bachelder EM, Desai TA. Small. 2009; 5:2857. [PubMed: 19787677]
12. Tao SL, Lubeley MW, Desai TA. J. Controlled Release. 2003; 88:215.
13. Tao SL, Desai TA. J. Controlled Release. 2005; 109:127.
14. Tao SL, Popat KP, Desai TA. Nat. Protoc. 2006; 1:3153. [PubMed: 17406578]
15. Ahmed A, Bonner C, Desai TA. J. Controlled Release. 2002; 81:291.
16. Guan J, He H, Lee LJ, Hansford DJ. Small. 2007; 3:412. [PubMed: 17285662]
17. Zhang P, Guan J. Small. 2011; 7:2998. [PubMed: 21901832]
18. Zhang P, Liu Y, Xia J, Wang Z, Kirkland B, Guan J. Adv. Healthcare Mater. 2013; 2:540.
19. Grayson ACR, Cima MJ, Langer R. J. Biomed. Mater. Res. Part A. 2004; 69A:502.
20. Chirra HD, Desai TA. Small. 2012; 8:3839. [PubMed: 22962019]
21. White NJ. Antimicrob. Agents Chemother. 1997; 41:1413. [PubMed: 9210658]
22. Clercq ED, Field HJ. Br. J. Pharmacol. 2006; 147:1. [PubMed: 16284630]

23. Susantakumar P, Gaur A, Sharma P. J. Bioequiv. Bioavail. 2011; 3:128.
24. Kitchens K, Kolhatkar R, Swaan P, Eddington N, Ghandehari H. Pharm. Res. 2006; 33:2818. [PubMed: 17094034]
25. Lindenberg M, Kopp S, Dressman JB. Eur. J. Pharm. Biopharm. 2004; 58:265. [PubMed: 15296954]
26. Uskokovic V, Lee PP, Walsh LA, Fischer KE, Desai TA. Biomaterials. 2012; 33:1663. [PubMed: 22116000]
27. Sajeesh S, Bouchemal K, Sharma CP, Vauthier C. Eur. J. Pharm. Biopharm. 2010; 74:209. [PubMed: 19737614]
28. Morishita M, Goto T, Peppas NA, Joseph JI, Torjman MC, Munsick C, Nakamura K, Yamagata T, Takayama K, Lowman AM. J. Controlled Release. 2004; 97:115.
29. Iborra M, Moret I, Rausell F, Bastida G, Aquas M, Cerrillo E, Nos P, Beltran B. Biochem Soc. Transactions. 2011; 39:1102.
30. Padera RF, Colton CK. Biomater. 1996; 17:277.
31. Eaimtrakarn S, Itoh Y, Kishimoto JI, Yoshikawa Y, Shibata N, Takada K. Int. J. Pharm. 2001; 224:61. [PubMed: 11472815]
32. Lemperle G, Ott H, Charrier U, Hecker J, Lemperle M. Ann. Plast. Surg. 1991; 26:57. [PubMed: 1994814]
33. Stampfl S, Stampfl U, Bellemann N, Sommer CM, Thierjung H, Radeleff B, Benitez RL, Berger I, Kauffmann GW, Richter GM. Cardiovasc. Intervent. Radiol. 2008; 31:799. [PubMed: 18214594]
34. Bettencourt A, Almeida A. J. Microencapsul. 2012; 29:353. [PubMed: 22251239]
35. Frazer RQ, Byron RT, Osborne PB, West KP. J. Long Term Eff. Med. Implants. 2005; 15:629. [PubMed: 16393131]
36. Chirra HD, Hilt JZ. Langmuir. 2010; 26:11249. [PubMed: 20486693]
37. Chirra HD, Biswal D, Hilt JZ. Polym. Adv. Technol. 2011; 22:773.
38. Chirra HD, Desai TA. Adv. Drug Delivery Rev. 2012; 64:1569.
39. Rocca J, Shah K. Drug Delivery Technol. 2004:4.
40. Shah S, Liu Y, Hu W, Gao J. J. Nanosci Nanotechnol. 2011; 11:919. [PubMed: 21399713]
41. Pang KS. Drug Metabol. Disposition. 2003; 31:1507.
42. Steingrimsdottir H, Gruber A, Palm C, Grimfors G, Kalin M, Eksborg S. Antimicrob. Agents Chemother. 2000; 44:207. [PubMed: 10602752]

Figure 1.

a) Schematic representation of the advantages of using thin, planar microdevices over symmetric microparticles of same surface area—microdevices experience lower intestinal shear stress, release drug unidirectionally toward the epithelia, and can release multiple drugs independently and b) a scanning electron microscopic image of a microdevice loaded with acyclovir entrapping hydrogel in its reservoirs. The scale bar represents 50 μm.

Figure 2.

The enhanced permeation of acyclovir-loaded microdevices as compared with its respective acyclovir-loaded hydrogel bolus (control: without devices) and conventional oral acyclovir solution through a caco-2 epithelial monolayer on collagen-treated Transwells ($N = 3$).

Figure 3.

In vitro MTT viability data showing that both empty and acyclovir-loaded microdevices are nontoxic in nature as compared with negative control DMSO ($N = 3$).

Figure 4.

In vivo mouse study showing the enhanced retention of thin, planar microdevices in the upper portion of the small intestine as compared with spherical microparticles of same surface area, which are pushed downstream to the colon by the high intestinal shear fluid flow. Also shown, is the further enhancement of retention by using bioadhesive lectin onto microdevices ($N = 3$).

Figure 5.

Pharmacokinetic plot showing the increased in vivo bioavailability of acyclovir using microdevices as compared with an orally gavaged solution of same acyclovir concentration. Enhanced microdevice retention/drug residence time and increased drug permeation from microdevices result in increased oral bioavailability. Also shown for comparison, is the pharmacokinetic profile of a 5 $\times$ concentrated (4 mg kg^{-1}) solution of orally gavaged acyclovir ($N = 3$).