Printing Tablets with Fully Customizable Release Profiles for Personalized Medicine

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Releasing drugs in a timely manner is important for optimal therapeutic effect in the human body. Different types of timed release are necessary for different types of clinical circumstances. One important type of release profile is the constant rate of release of a drug; this profile is important because there is typically only a narrow range of concentration in which the drug can be effective in the human body. Above the range, undesirable side effects may occur; below the range, the drug may not be effective. Another important profile is the release of a drug in pulses. Certain chemicals (e.g., hormones) need to be released in pulses, at regular intervals, in order for the release to be synchronized with the biological cycles of the human body.[1,2] Other types include an increasing release profile that is important for patients who can develop tolerance of a drug over the course of the medication. A decreasing release profile is needed for cases in which a relatively large dose of drug is needed initially to act against their targets rapidly, followed by gradually lower levels to maintain health (e.g., for arthritis; a large dose of drug is initially required to eliminate pain in the morning, followed by smaller doses to keep the pain from recurring). Thus, a wide variety of release profiles is needed for different circumstances. In addition, the concept of "personalized medicine" has recently gained much attention as an approach that seeks to customize therapy for the needs of specific individuals.[3–5] In order to achieve the most effective personalized treatment, many factors need to be considered: biological differences among different individuals, differences in living/working environment, different types of illness, and the interaction of the administered drug with other substances consumed in the body (e.g., herbs and food).[6,7] It is, therefore, important to design a general and programmable method to fabricate drug carriers that can release drugs of any desired type of profile with respect to time for specific needs.

Conventionally, the typical strategy used to control the release of drugs in the field of drug delivery is to fabricate a carrier that has a specific (or a single type of) release profile. Perhaps one of the simplest ways to fabricate a carrier involves filling a matrix (e.g., polymeric) homogeneously with a drug; however, this method can only release the drug with a rate that decreases with time. This is because as the drug diffuses out of the particle with time, the core of the particle that contains the drug gets gradually smaller—a smaller core releases lesser drug. Hence, in order to achieve profiles that are not decreasing, more complex designs of the carriers are needed. Indeed, a substantial number of methods have been proposed in previous studies to fabricate carriers that release drugs with different types of profiles. A few examples include particles of different geometries,[8,9] particles with some sides protected with different materials,[2] multilayered polymeric particles,[2,10,11] mixtures of particles with different sizes,[12] and particles with other types of complicated designs.[13,14] These drug carriers have been found to release drug with profiles such as constant,[10,12,15] bimodal,[16] pulsatile,[2,17–20] and linear.[21,22] Although carriers can be fabricated to release drugs with a specific release profile, it has been technologically challenging to devise a general method for fabricating customizable carriers that can deliver drugs with any type of release profiles.

Several printing methods reported in previous studies can allow the drug carriers to be fabricated with certain flexibility.[23–25] In particular, 3D printing has been used to construct drug tablets with a few different types of release profiles.[25,26] Briefly, this method involves two main steps: the spreading of layers by layers of powder and the injection of a drug-containing liquid from a custom-made 3D printer that binds the powder together to form the tablet. This method, however, is limited again by the shrinking size of the tablet with respect to the time of dissolution. Essentially, the rate of release tends to decrease with time, hence it is not possible to achieve certain types of release profiles (e.g., release of high doses of drug at a later point in time). Furthermore, this technique is reported to have many other disadvantages such as low dosage of drugs, discontinuous release profiles, rapid initial release of drugs (i.e., "burst release"), and poor mechanical durability of the tablet. It also requires complex mathematical modeling and/or iterative algorithms in order to construct a specific type of carrier for the desired release profile, and may involve the fabrication of complex (e.g., layer-by-layer) structures.[26,27]

Timely release can also be controlled by systems that are not used to deliver drugs orally. Microchips, for example, have been demonstrated to deliver drugs in a controllable pulsatile manner.[17–20] These microchips, however, require the device to be implanted into the human body through surgery—this procedure may not be acceptable to some patients.[28]

In this study, we describe a general method to fabricate customizable tablets that can release drugs with any desired release profiles. The tablet consists of three components: a surface-eroding polymer that contains the drug, a surface-eroding polymer that does not contain the drug, and an impermeable (but biodegradable) polymer that serves as the protective coating around the tablet (**Figure 1**a). The tablet is protected by the impermeable polymer on all sides except for an opening on one of the sides. Importantly, the surface-eroding polymer

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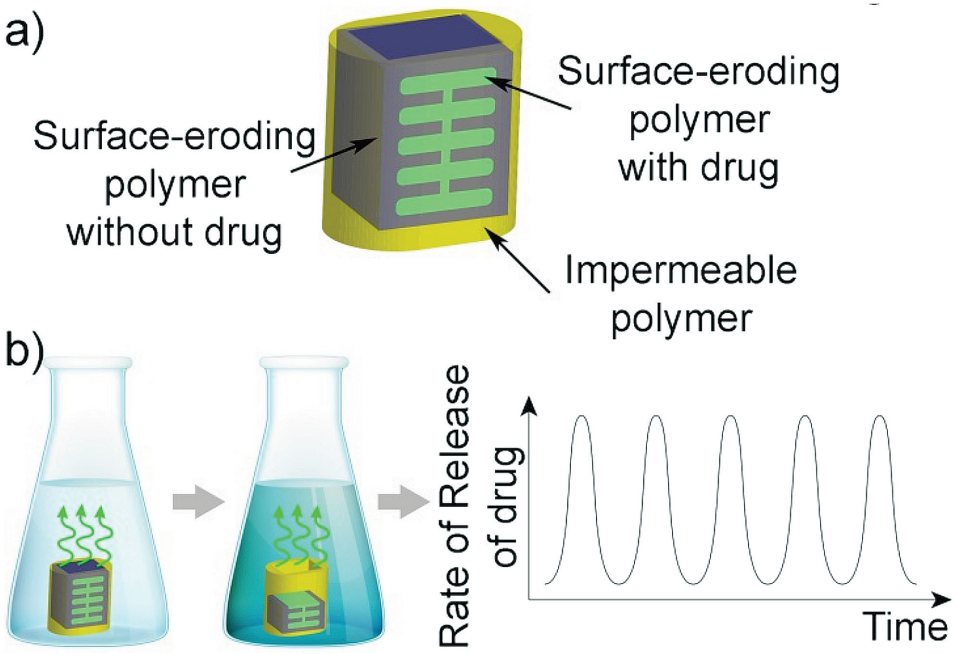

Figure 1. An illustration of the strategy used to deliver a drug with any desired release profile. Shown in this example is the case of releasing a drug with five pulses. a) Scheme of the tablet. The shape of the surface-eroding polymer that contains the drug is specifically designed to deliver the drug of the desired profile. The impermeable polymer serves as a protective coating to all sides of the tablet, except for the opening on the top. b) When this tablet is immersed in an aqueous solution, the degradation is 1-dimensional; thus, the drug releases according to the shape of the surface-eroding polymer that contains the drug.

that contains the drug is fabricated with a specifically designed shape that allows the drug to be released with the desired profile. In the illustration shown in Figure 1a, the shape (indicated in green) consists of five long segments separated by short segments of polymer. When this tablet is immersed in an aqueous medium (Figure 1b), the polymer (both with and without the drug) gradually erodes through the side with the opening. Because the release is 1-dimensional, it is obvious that the rate of release of the drug follows the shape of the drug-containing polymer. In the case of Figure 1, the tablet releases the drug with five pulses over time due to the five long segments of the drug-containing polymer.

Therefore, by fabricating the drug-containing polymer of different shapes, it is possible to release drugs with any desired profiles. We used a commercially available 3D printer for fabricating the polymers of different shapes (**Figure 2**a). 3D printing in drug delivery commonly refers to the direct printing of the drug into the tablet using a custom-made printer; however, in this study, we used a commercially available 3D printer to print the templates for making the polymers instead. The main reasons for choosing to work with a commercially available 3D printer are because it is inexpensive and easy to use. Thus, the main features of this general strategy for making drug tablets are as follows: (1) the tablet is fully customizable for releasing drug of any arbitrary type of profile, (2) the translation of the shape of the drug-containing polymer to the desired release profile is straightforward and intuitive (i.e., it does not require the solution of complex equations or the use of iterative computational algorithms), (3) the procedure for fabricating the tablet is technically simple, and (4) the fabrication is relatively inexpensive.

The general procedure for fabricating the tablets is illustrated in Figure 2b,c (see Supporting Information, Section 1, for a full description of the materials and methods involved). First, we printed a polymeric template with an embossed feature of the desired shape using a 3D printer (Figure 2a). We then poured a polydimethylsiloxane (PDMS) prepolymer mixture onto the template and cured it; thus, this PDMS mold has a cavity with a shape that is complementary to the shape of the embossed feature. For the tablet, the polymer we used was a degradable polyanhydride that undergoes surface erosion (i.e., as opposed to bulk erosion). This characteristic of the polymer means that it erodes much faster at its surface than the diffusion of molecules into its bulk matrix.[29] Specifically, the prepolymer mixture used to make the degradable polyanhydride consisted of 4-pentenoic anhydride, pentaerythritol tetrakis(3-mercaptopropionate) (PETMP) and/or an ethylene glycol-based dithiol (EGDT; 3,5-dioxa-1,8-dithiooctatne) as the cross-linker (the ratio of PETMP:EGDT was varied to different amounts as described later), and 1-hydroxycyclohexyl phenyl ketone as the photoinitiator.[30] As a proof of concept, we mixed a dye (Orange G) into the mixture, instead of a drug, in order for easier quantification of the release. After pouring this mixture into the PDMS mold, it was exposed to UV light for 10 min. The cross-linked polymer was then extracted from the mold, and inserted into another container. This container was also printed by the 3D printer in a separate step. The other advantage of using a 3D printer is that many commercially available models offer the capability to print polylactic acid (PLA). This polymer is known to be biodegradable and biocompatible. We found from our experiments that PLA degraded much slower

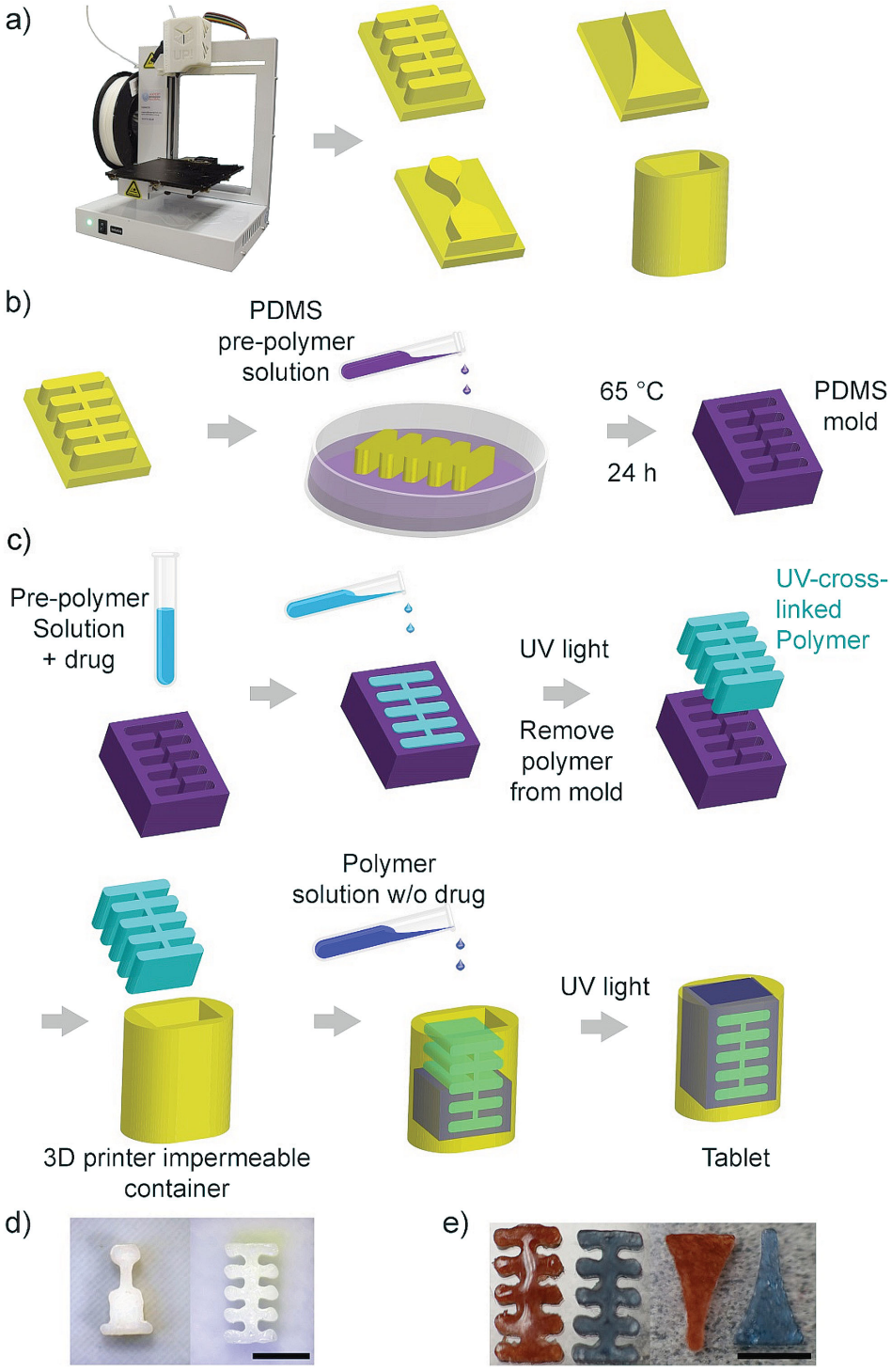

Figure 2. Experimental procedure for fabricating the customizable tablets. a) A 3D printer (image on the left) was used to print templates with embossed features, and the impermeable container (schemes on the right). These embossed features correspond to the shapes needed for delivering the drug of the desired release profiles. b) Method for fabricating the polydimethylsiloxane (PDMS) mold of the desired shape from the 3D-printed template with embossed features. c) Procedure for fabricating the customizable tablet. Refer to the main text for more details. Images of d) the 3D printed templates, and e) the dye-containing surface-eroding polymers of different shapes. Scale bars represent 5 mm.

than the surface-eroding polymer; hence, it is possible to use PLA as the impermeable polymer for protecting the sides of the tablet (see Supporting Information, Section 2, for details of the experiment). After inserting the surface-eroding polymer into the container made of PLA, we filled the remaining void spaces with the same prepolymer mixture, but without the addition

of any dye. In the process of filling the void spaces, we added an additional layer (≈0.5 mm) of this prepolymer solution over the top of the dye-containing polymer. This additional layer was included in order to prevent any possibility of "burst release" (i.e., the initial uncontrollable release of the drug), as it is undesirable for many applications.[31] Burst release is especially disruptive for our purpose since the main objective of this study is to control the release of drugs. Subsequently, the container was placed in a vacuum chamber for 10 min in order to remove any air bubbles in it. The prepolymer mixture was then cured by UV light for another 10 min. The size of the tablet we produced using this method was 11 mm × 7.5 mm × 5.5 mm; this size is modeled after tablets that are commonly found in the market.[32] The thickness of the PLA coating was 1.1 mm.

After fabricating the tablet, we immersed it in a phosphate-buffered saline (PBS) solution (pH = 7.4). The solution was stirred and maintained at 37 °C. The dye typically only released from the tablet after around 10 h; the reasons for the delayed release are due to the presence of the additional layer of polymer (that did not contain any dye) used to prevent burst release, and the characteristic property of the surface-eroding polymer (see Supporting Information, Section 3). After around more than 10 h (we define this time as $t = 0$), small quantities (0.4 mL) of samples were withdrawn from the solution at regular time intervals. For each withdrawal, we added an equivalent amount of fresh PBS into the solution. The samples were analyzed by a UV–vis spectrophotometer in order to determine the concentrations of dye. Based on these concentrations, the rate of release of the dye in the solution was calculated (see Supporting Information, Section 4, for the method of calculating the rate of release).

In order to demonstrate the versatility of the procedure, we repeated the experiment for different shapes of the dye-containing surface-eroding polymer (**Figure 3**, top row). The release profiles of four out of five of these shapes—that is, the constant, pulsed, decreasing, and increasing profiles—are known to be important profiles for drug delivery. The fifth shape we used consisted of a series of constant, decreasing, and increasing profiles; this shape is used to demonstrate that the tablet can be customized to deliver any arbitrary release profile. The translation from the shape of the dye-containing polymer to the actual release profile of the dye is straightforward and intuitive (Figure 3, middle row). As an illustration, we first transformed the shape of the dye-containing polymer into a graph that plots the width, w, of the dye-containing polymer along the direction of degradation (denoted by the x-axis in Figure 3). When the polymer erodes, the rate of release of the dye is expected to be linearly proportional to w. Through taking into account of the shape, rate of degradation, and thickness of the polymer, together with the concentration of dye in the

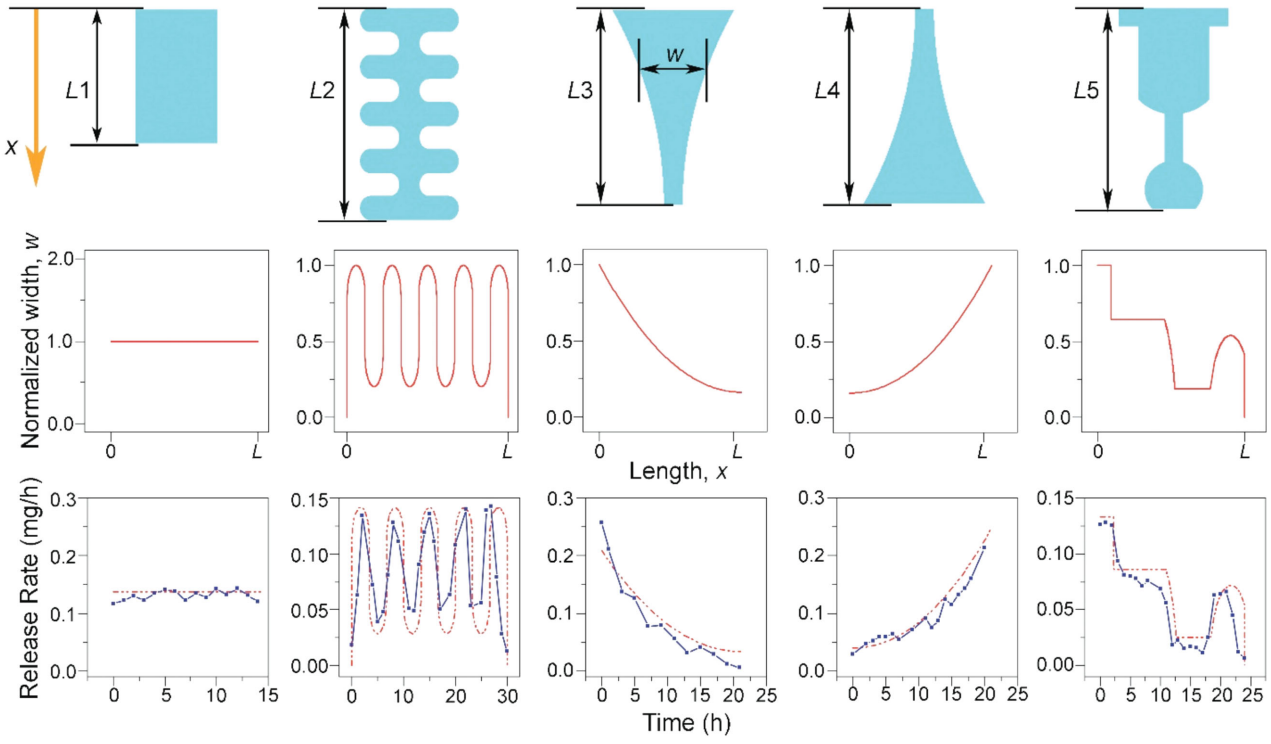

Figure 3. The expected and the experimentally determined rates of release of dye from the tablets. Top row: five tablets with different shapes were used. w represents the width of the dye-containing polymer at any point in the x-axis (i.e., the direction of degradation of the tablet). The lengths of the tablets were $L_1 = 5.5$ mm, $L_2 = 9.0$ mm, $L_3 = L_4 = 8$ mm, and $L_5 = 8.2$ mm. Middle row: the plots of w against the x-axis. w is normalized by dividing it by the maximum w of each shape. w can be translated into the expected rate of release as shown by the red dotted lines in the plots in the bottom row. Experimental results from a representative run of each tablet (blue lines) show that the rates of release of dye are in good agreement with the expected rates calculated based on the shapes of the tablets (red dotted lines).

polymer, we calculated the expected rate of release of the dye (see Supporting Information, Section 5, for the method of calculating the expected rate of release). Experimental results show close agreement between the expected rates and the actual rates of release determined experimentally for each shape of the dye-containing polymer (Figure 3, bottom row, shows the data obtained from a representative run for each type of tablet). The ratio of the cross-linkers used to fabricate the surface-eroding polymer in this set of experiments was PETMP:EGDT = 3.

In addition, the release profiles can also be customized such that the entire duration of the release can be tuned to a desired amount of time. Essentially, the rate of erosion of the polymer can be changed by varying the ratio of the cross-linkers used; that is, PETMP versus EGDT.[30] Because PETMP is capable of a higher degree of cross-link than EGDT, a polymer that contains a higher percentage of PETMP versus EGDT will be harder to degrade; in other words, the rate of erosion will be slower. As a demonstration, we compared the cases when the ratio of PETMP:EGDT = 3, and when PETMP:EGDT = 9 (**Figure 4**). The comparison was done for two types of release profiles: an increasing release profile and a profile with five pulses. Results show that while the entire duration of release is around 20–30 h for the case of PETMP:EGDT = 3, the release is around 50–80 h for PETMP:EGDT = 9. Therefore, the duration of release is customizable and can be changed as desired. Importantly, the profile of the release is preserved regardless of the different durations of release.

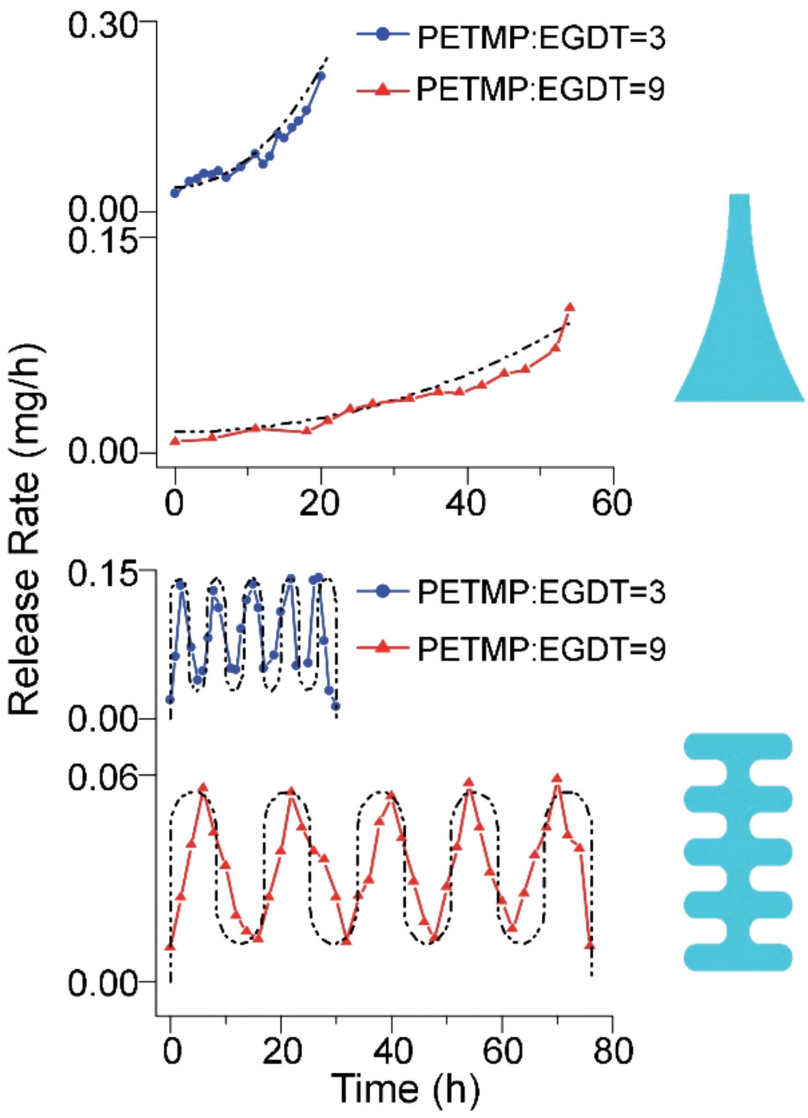

Figure 4. Tuning the duration of release of the dye. The duration can be varied by changing the ratio of the amount of the two cross-linkers (i.e., PETMP and EGDT) used. When a higher ratio of the cross-linker, PETMP, is used, the duration of release is longer. Experiments were performed for the cases of an increasing profile (top), and five pulses of release (bottom). Black dotted lines indicate the release profiles as predicted by the shape of the dye-containing polymer.

In drug delivery, it is often important for more than one type of drug to be administered into the human body simultaneously in order to treat a particular illness.[33–35] The general procedure described in this study (i.e., in Figure 2) can be modified to include multiple types of drugs loaded in the same tablet—importantly, each type of drug can be customized to release its own unique profile. Here, we demonstrated the case in which two drugs were packed together in the same tablet (**Figure 5**). First, we made two molds; the thickness of each mold was half of that described in the original procedure. One of them had a decreasing profile and the other had an increasing profile. In a separate step, we prepared two prepolymer mixtures. In addition to the chemicals that were necessary for polymerizing the surface-eroding polymer, we mixed an orange dye (Orange G) in one of the mixtures and a blue dye (Brilliant Blue G) in the other mixture. The two prepolymer mixtures were poured into each mold separately and were then cured using a UV light. After extracting the polymers from the molds, they were stacked together and inserted into the PLA container. The void spaces in the container were again filled with another prepolymer mixture that did not contain any dye. After exposing the mixture to UV light, the fabrication of the tablet was completed. We then immersed the tablet in a PBS solution (pH = 7.4) and determined the rates of release of the dyes. Experimental results show that one of the dyes released according to an increasing profile and the other dye released according to a decreasing profile as expected. We repeated the experiment for the case in which both the shapes of the drug-containing polymers consisted of five long segments separated by short segments. In order to make the release profiles out of phase from each other, the two pieces of polymers were inserted at different heights away from the bottom of the container manually. Alternatively, it is possible to fabricate one of the shapes with a thicker base.

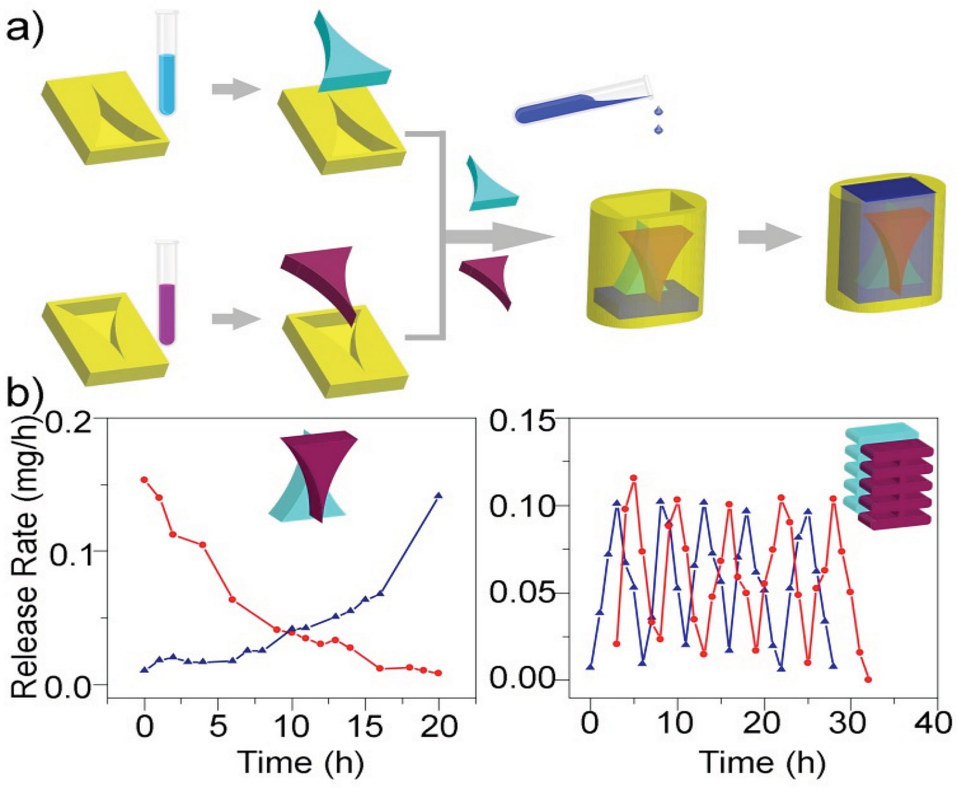

Figure 5. Releasing more than one drug simultaneously. a) The procedure for fabricating a tablet that releases one dye with an increasing profile, and another dye with a decreasing profile. First, two PDMS molds with the desired shapes were fabricated. These molds were used to prepare the surface-eroding dye-containing polymers of their specific shapes. These polymers were stacked together and inserted into the container printed by the 3D printer. The rest of the container was filled up with the polymer that did not contain any dye. b) The plot on the left shows the experiment in which one dye released according to an increasing profile, while the other dye released according to a decreasing profile. The plot on the right shows the case in which both dyes released with five pulses; however, the pulses were out of phase.

After immersing this tablet in the PBS solution, the release profiles of the two dyes were again as expected—both profiles consisted of five pulses that were out of phase.

To conclude, we are introducing a general method for fabricating customizable tablets using a commercially available 3D printer. To the best of our knowledge, this study is the first to propose a common method that allows the fabrication of tablets to be fully customizable in order to release drugs with any desirable profiles. Previous methods have only demonstrated the capability of releasing drugs with a few types of profiles. One of these methods includes the use of a custom-made 3D printer in which drugs are printed directly by the printer for fabricating the tablets. This method is not fully customizable, and has a number of disadvantages.[27] In our approach, the way we customize the tablet is fundamentally and conceptually different from those that use a custom-made 3D printer. Furthermore, through using a commercially available 3D printer, the fabrication of the tablets is relatively simple and inexpensive to implement. Another key feature is that the shape of the template printed by the 3D printer corresponds directly to the release profile; hence, the translation from shape to the release profile does not require any complex mathematical or computational operations.

In general, because it is relatively simple and inexpensive to implement, we believe that this approach can potentially be applied in a clinical setting. For example, after a physician prescribes a drug with a unique release profile to a patient, it is possible to use this method to produce the customized tablet on the spot for the individual—hence, the concept of "personalized medicine" can be realized. This method may also be used for mass production of drug tablets with different customized shapes, since the templates (printed by the 3D printer) and molds are structurally durable and can be used repetitively for the fabrication of the tablets. Besides delivering drugs, this approach can be used to deliver chemicals in general. Potential fields of applications can include foods, cosmetics, pesticides, and the agricultural industries (e.g., for delivering fertilizers to plants with the desired release profiles).[36]

Further work will be needed to explore the right combination of materials (e.g., the type of surface-eroding polymer and the 3D printed coating) used in this method for the specific type of drug and the illness of interest. For fine control of the release, this method is ultimately limited by the resolution of the 3D printer. However, the relatively inexpensive 3D printer that we used can print features down to a minimum size of around 600 μm; this size can be sufficient for many purposes as we have demonstrated. In addition, these commercialized 3D printers are fast gaining widespread popularity. This popularity may encourage manufacturers to further optimize the system (e.g., to increase its resolution) and to drive the cost even lower.

Thus, it seems to be a timely moment to make use of commercially available 3D printers to make customizable drug tablets.

Supporting Information

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

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