A Reactive Prodrug Ink Formulation Strategy for Inkjet 3D Printing of Controlled Release Dosage Forms and Implants

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A strategy for creating tuneable 3D printed drug delivery devices is proposed. 3D printing offers the opportunity for improved compliance and patient treatment outcomes through personalization, but bottlenecks include finding formulations that provide a choice of drug loading and release rate, that are tuneable, and avoid the need for surgical removal. The suggested solution is to exploit 3D inkjet printing freedoms. A reactive prodrug is used that can polymerize into drug-attached macromolecules during 3D printing and by tuning the hydrophilicity, hydrolysis can be facilitated or hindered, which in turn controls drug release. To demonstrate this approach, ibuprofen is attached to 2-hydroxyethyl acrylate through a cleavable ester bond, formulated for inkjet 3D printing, and then printed to produce a solid dosage form. This allows a much higher loading than is usually achievable—in this case up to 58 wt%. Of equal importance, the 3D inkjet printing freedoms mean that the drug delivery device is highly tuneable: by selection of spacer monomers to adjust the hydrophilicity; through geometry; by spatially varying the components. Consequently, hierarchical release systems are created bespoke, from the molecular to macro. This approach represents a new paradigm for the formulation of printable inks for drug-loaded medical devices.

1. Introduction

We propose a prodrug-based strategy to challenges associated with the formulation of multi-material Inkjet-based 3D Printing (IJ3DP) inks for personalized medicine applications.

There are a number of barriers to the creation of personalized viable implants capable of long-term drug release. These include requirements for sustained drug loading with controlled degradation/release, degradation to nontoxic products, and to be cost effective and industrially scalable.[1–3] 3D printing offers promising routes to overcome these, and also offers ways to include significant additional benefits through: first, being able to selectively combine multiple drugs into a single system to help address poor compliance associated with high medication burden, and second, facile personalization through on-demand fabrication.[3–7] 3D printing methods have been successfully exploited for pharmaceutical delivery using techniques as diverse as extrusion,[8–12] stereolithography,[13–15] and binder jetting.[16–18] This latter method is particularly exciting since it has high scalability and has indeed already been used for a commercial product (Aprecia). IJ3DP offers a combination of benefits, placing it within the portfolio of 3D printing techniques that are available for fabricating solid dosage forms and implants. IJ3DP strengths come into play when there is a need for industrial scalability, high resolution, and multi-material manufacture all to be present.[19–21] Its suitability for the production of tablets has already been

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demonstrated in the works of Acosta-Vélez et al.,[22] Kyobula et al.,[4] and Clark et al.,[23] who each developed adaptations of ink jet printing for drug release over the order of a few hours. Extending this to release over several months as required for an implant is a challenge that requires innovation in both process and materials. This is because in order to achieve an effective dose over a sustained period, whilst keeping the implant to a size where we can implant with a cannula, we need a high drug loading, and this is not easy without drug precipitation and increases in viscosity that prevent inkjet printing. Consequently, we need to create new safe materials, and combine them into functional formulations that can host high drug loadings, sustained degrade, and elute over months whilst still retain the ability to process through IJ3DP.

To overcome these issues, we offer a reactive prodrug-based formulation concept not previously used for IJ3DP. There have been a number of studies on attaching a target drug molecule to functional carriers, through temporary decomposable bonds to achieve controlled or targeted release behavior.[24–29] To the best of our knowledge, however, there has not been any attempt to apply such a concept in formulating for IJ3DP to solve its printability challenges and produce controlled-release structures. This approach allows us to design from the molecular scale to give high drug loadings, while retaining the ability to print. Our formulation can be tailored to achieve a range of release profiles through changing the molecular structure, the composition of the formulation, by printing with multiple materials, or through manipulating the geometry. We demonstrate the design of a reactive prodrug using a low viscosity reactive linker which contains two side groups (**Figure 1**a); one of which can form a temporary bond with the target drug molecules, while the other side group is able to polymerize to form solid structures during the IJ3DP process. Formulations based on a reactive prodrug strategy can obtain control over the drug release since the precise design of the polymerized molecular structure determines the rate at which the bonds that link the drug to the reactive prodrug

linker are broken. Through methodical selection of the linker, additives, and printed geometry, this approach can enable hierarchical personalization of the drug release behavior at the synthesis, formulation, and printing stages.

This concept has been tested via an ester-bonded prodrug model for ibuprofen (Figure 1b). The ester bond has been reported to have accelerated decomposition in alkaline environments.[28,29] Previous studies have also demonstrated that drugs grafted to the molecules via ester bonds can detach and release through a hydrolysis reaction.[30–32] Such a concept, however, can also be extended to other kinds of temporary bonding systems, for example, the acetyl bond, which has accelerated decomposition in an acidic environment.[33–35] In our study, the carboxylic acid functionality of ibuprofen and the hydroxyl group of the reactive linker have been induced to undergo an esterification reaction to produce an ester-bonded photo-curable drug molecule. 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, and 2-hydroxyethyl acrylamide were selected as reactive linker candidates, which contain both hydroxyl groups and photopolymerizable groups. This approach would hence be directly applicable to the very many drugs that have a carboxylic acid functionality,[36] and as stated, can readily be adapted to other chemical moieties.

Our approach has a number of elements that provide advantages over commonly used formulating strategies: First, we are able to achieve ink formulations that can hold up 58 w/w% drug loading and are amenable to IJ3DP processing; second, through the tuning of the ink formulation we have also demonstrated that manipulation of the release profile of the printed product is possible; third, as the drug is released, the polymer backbone structure dissolves avoiding the necessity for surgical removal. Finally, the ability to use IJ3DP offers a macroscopic control over release and personalization, since it enables the bespoke fabrication of complex geometries to meet the need of individuals, while the multi-material facet of IJ3DP allows for tailoring of the material spatial distribution at the voxel level. Our approach will,
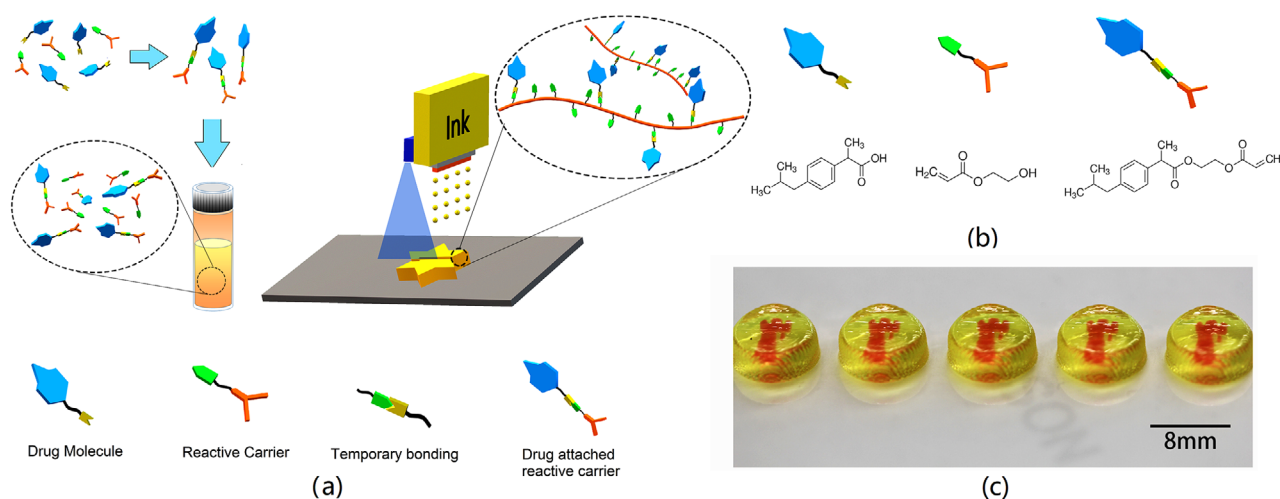
Figure 1. Schematic of the approach used to prepare a reactive prodrug for ink formulation development. a) The selected drug candidate was grafted to a reactive monomer by a degradable covalent bond and prepared into inkjet printable formulations by mixing with additives that can tune the release speed;[37,38] The developed formulation was inkjet-printed and polymerized in situ by UV photo-polymerization to form a solid 3D structure; b) Molecular structures of ibuprofen, hydroxyethyl acrylate, and synthesized reactive prodrug; c) Bespoke tablets with a spatially varying drug distribution fabricated with multi-material IJ3DP.

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therefore, potentially enable the "programming" of the drug delivery device's active pharmaceutical ingredient distribution and hence its release profile through a number of levers. Figure 1c is an image of a showcase tablet structure printed with IJ3DP.

2. Results and Discussion

Our general approach was to combine ibuprofen attached reactive prodrugs with reactive diluents at various ratios (Table S1, Supporting Information), in order to obtain a range of formulations with different drug release behavior as well as having an optimal composition for printability. Three different ibuprofen attached reactive prodrugs were synthesized through an esterification reaction to produce IJ3DP printed tablets (or implants; in the context of this paper these terms are interchangeable with the rate of drug release required, being the only major difference). Controlled release was achieved by mixing the synthesized reactive prodrug with different mole ratios of hydrophilic co-monomers. During printing and exposure to UV radiation, these formulations produced co-polymerized products with different hydrophilicity, and thus different release rates.

Preliminary printability of all the formulations was screened by assessing their miscibility, viscosity, and printability (Table S1, Supporting Information). The ink formulations with physical properties recognized as indicating they could be jetted were placed into a Dimatix 10 pL Cartridge ready for tablet production. All the samples were printed onto a coverslip and exposed to a UV dose after each swathe of ink deposition. Inks for IJ3DP process were chosen for those having reliable droplet formation and able to cure within a short period of UV exposure in order that the droplets pin to the deposited location and able to support any subsequent ink layers placed upon it during the formation of 3D structures.

To minimize oxygen inhibition,[39,40] printing was conducted under a nitrogen-rich environment where the oxygen level was 0.25% ± 0.05%. Different ink formulations showed very dissimilar solidification performance during the printing process. The hydroxyethyl methacrylate (IBHEMA) prodrug monomer mixed with hydroxyethyl methacrylate (HEMA) showed some solid fragments, but no uniform film was achieved. By replacing HEMA with hydroxyethyl acrylate (HEA), increased solidification was observed after the printing and curing process. However, still no well-defined film was observed (Figure S1a, Supporting Information). This trend in the solidification performance matches the general observation that free radical polymerization propagation kinetics are higher with acrylate monomers when compared to methacrylates that contain similar pendant groups.[41,42] Finally, the ink formulation was further improved by replacing IBHEMA with ibuprofen attached hydroxyethyl acrylate (IBHEA), such that an acrylate-based reactive linker was used. The IBHEA-HEA formulations showed sufficient curability to form a defined solid structure through IJ3DP (Figure S1a, Supporting Information).

In order to test how printed materials performed under a range of physiologically relevant conditions, drug release was studied in phosphate-buffered saline (PBS) media under a range of pH covering acidic, neutral, and alkaline environments. The printed samples were placed into different media, during which the drug released into the media after the ester bonds were hydrolyzed.
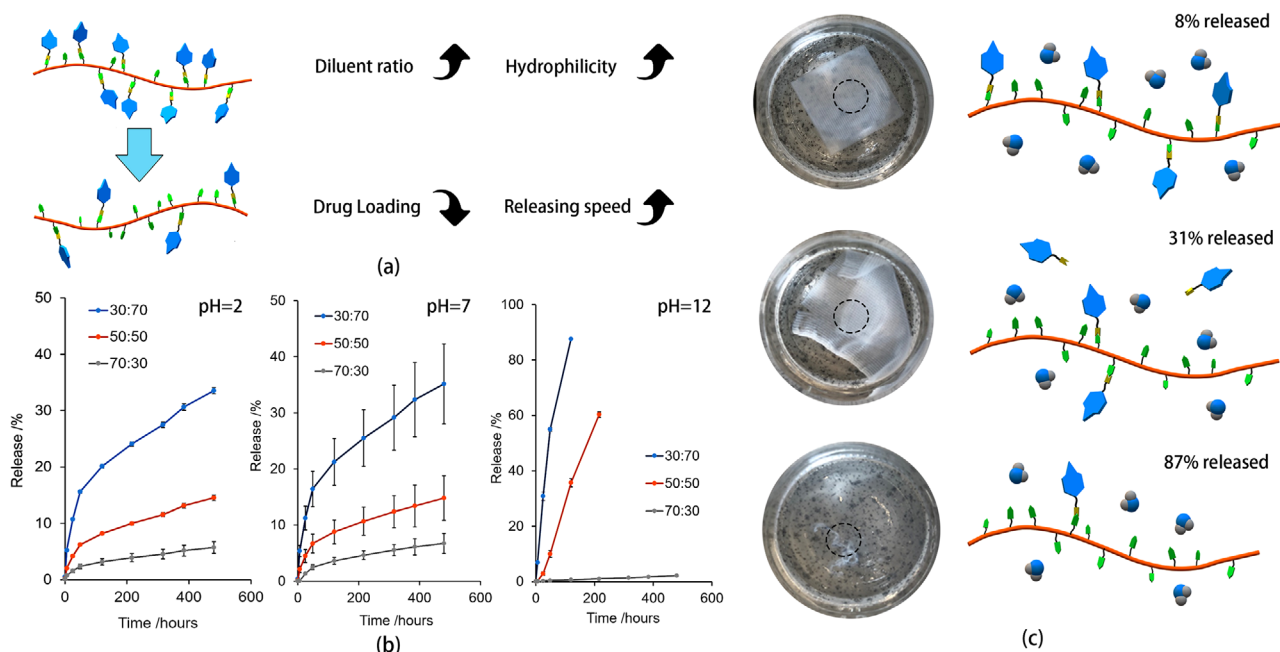
The hydrophilicity of the polymerized molecules was tuned by varying the amount of the HEA monomer (HEA is hydrophilic due to the pendant hydroxyl group, and thus both HEA and poly-HEA are water soluble).[43,44] Conversely, the attachment of ibuprofen on to HEA consumes the hydroxyl and converts it into an ester bond. Thus, the esterification process makes both the ibuprofen (loss of carboxylic acid) and HEA (hydroxyl loss) more hydrophobic.[45,46] Consequently, the synthesized IBHEA acts as a hydrophobic component in the final two component formulations and so varying the ratio of the hydrophobic IBHEA and hydrophilic HEA allows the overall hydrophilicity of the co-polymerized final specimens to be tuned. This, in turn, allows control of the rate of hydrolysis and therefore drug release (**Figure 2**a).

Specimens were manufactured by IJ3DP and the release experiment was carried out in a PBS media under pH 2, 7, and 12 inside an incubator maintained at 37 °C. The ibuprofen release was measured over 20 days (Figure 2b).

Figure 2b shows that under all pH environments, the specimens that contain higher concentrations of HEA exhibited faster ibuprofen release, suggesting that the HEA allowed for greater intimate contact between the ester bonds and the water molecules that drive hydrolysis. In an alkaline environment, the release was considerably increased, indicating a base catalyzed release mechanism. For example, after 120 h, the specimens were printed using a formulation that contained 30 mol% of IBHEA, released 87.6 wt% of the loaded ibuprofen in a pH 12 environment, while the specimens in pH 2 and pH 7 released 20.1 wt% and 21.2 wt%, respectively. Furthermore, in an alkaline environment, the release rate was more sensitive to the overall hydrophilicity (or loading) of the final molecule; for example, when the IBHEA loading reached 70 mol%, release went down to 0.68 wt% after 120 h while in pH 2 and pH 5, the release reached around 3 wt%.

It was found that the release under alkaline conditions was similar to zero order. This suggested that during the test period, the drug was released at a constant rate despite the residual drug concentration. However, by comparing the release profile of the three formulations at pH 12, we see that the release behavior falls into the linear region of Higuchi drug release kinetics. At pH 7 and 2, the release profile fits to a Korsmeyer–Peppas model ($R^2 > 0.98$) with an n value between 0.38 and 0.50, implying that the release behavior is close to quasi-Fickian diffusion. At pH 12, the drug release study of tablets with 70 mol% and 50 mol% of IBHEA were halted at 120 h and 216 h, respectively. Beyond these times the tablets had disintegrated (Figure 2c): during dissolution, the poly-IBHEA-HEA copolymer decomposes to poly-HEA homopolymer (Figure 2c), a water-soluble polymer. Consequently, beyond these time points it was not possible to replace media for the following time point as removing media also removes polymer debris from then on.

Through the IJ3DP process, the geometry and design of the drug delivery device can all be manipulated, providing a further level of control over the release rate of the drug from the device. As a proof of concept, two mesh structures with the same overall dimensions (10 mm×10 mm) but different mesh hole sizes were printed and tested over 5 days at pH 12. The result in **Figure 3**a shows that mesh A (2 mm feature size) which had 7.3% more surface/volume ratio than mesh B (1.2 mm feature size)

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Figure 2. a) Tuning the hydrophilicity of the final polymer chain has a direct impact on the hydrolysis rate for the temporary linkage and therefore influences the drug release rate; b) The printed structure shows different release behaviors in different pH environments, but overall, the more hydrophilic molecules display a faster release speed (mean ± SD, $n = 3$); c) The pictures on the left from top to bottom show the change of the physical state of the specimens after the specified percentage of drug release. The whole device becomes soluble in water and can be washed away after delivery is complete. A schematic of the molecular state is shown on the right.
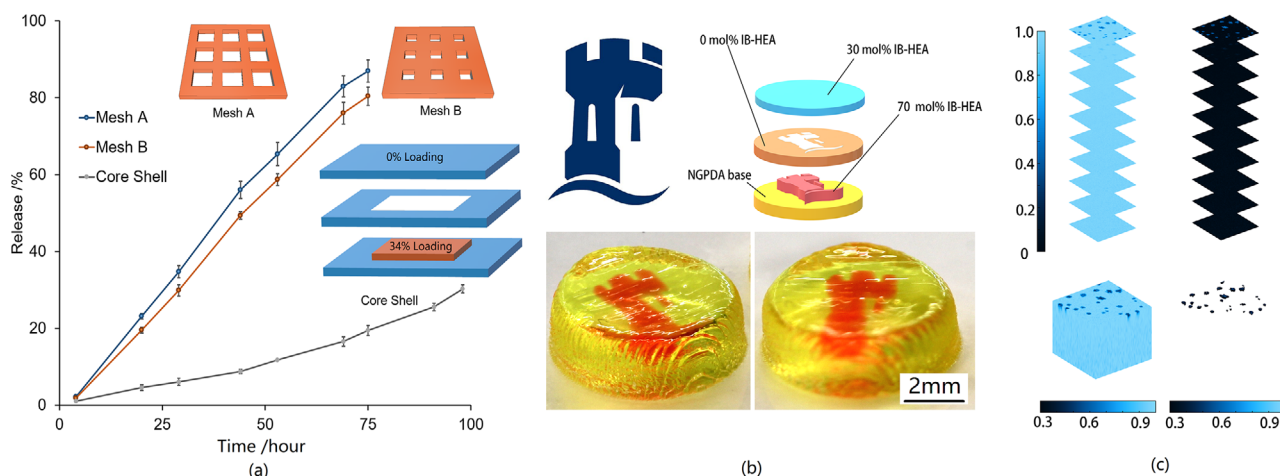
Figure 3. Through multi-material IJ3DP process, a complex drug delivery device was achieved. a) Devices with different geometries and construction were printed and tested under pH 12 within 5 days and the results demonstrated the capability of tuning the drug releasing rate by structural design (mean ± SD, $n = 3$). b) An exemplar of a complex drug delivery device that can be achieved by using IJ3DP, a University of Nottingham logo with 70 mol% of ibuprofen loading was embedded in a tablet; c) Tof-SIMS characterization of a printed 50–50 mol% (IBHEA-HEA) tablet, where the drug molecules were observed to be homogeneously distributed.

exhibited about 10.2% faster releasing speed. A more complex multi-material core shell structure was also printed, in which the same drug loaded ink formulation (30 mol% ibuprofen loading) was embedded into an inkjet printed poly-HEA (0 mol% ibuprofen loading) shell by co-printing both formulations. It showed that the release of ibuprofen was significantly slowed when using a core shell structure. Such a system could therefore enable "programming" of the drug release behavior at the voxel level

(typically of the order of 50 μm) by using a multi-material 3D inkjet printing process, in which the ratio of the two monomers can be controlled spatially to print a 3D device that has different release behavior in different regions of the object. Figure 3b is a concept device produced by IJ3DP showing that with the multi-material capability and exceptional voxel resolution, a more complex tablet design is possible and therefore enables the potential for "dialed up" release profiles.

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To assess the chemical state of the ibuprofen before and after the printing process, Fourier transform infrared spectroscopy (FTIR), Proton nuclear magnetic resonance (H'NMR), and Time-of-flight secondary ion mass spectrometry (ToF-SIMS) analyses were carried out. The FTIR and H'NMR showed that the ibuprofen molecule has been successfully attached to the carrier and was stable after being formulated into inkjet printable formulations (Figures S2 and S3, Supporting Information). The printed samples were examined confirming that the ibuprofen molecules were not degraded or detached from the polymer carrier after the IJ3DP process (Figure S6, Supporting Information). Tof-SIMS (with depth analysis) was introduced to further investigate the state of the ibuprofen drug, in which no chemical or physical changes were observed to the loaded drug molecules through the inkjet print process. Two secondary ions from the Tof-SIMS spectra that are characteristic of the drug covalent linkage: $[M-H]OCH_2CH_2^+$ and $[M-COOH]^+$, where M is the ibuprofen molecule ($C_{13}H_{18}O_2$), were used to map 3D spatial distribution of the covalently-linked drug (Figure 3c, left) and further data were provided in Figure S4, Supporting Information. No ibuprofen precipitation or recrystallization was observed within the analyzed volume apart from the first few nanometers at the surface where island-like features were observed. Such island formation was only observed at the very top surface and shows an intense secondary ion yield only for fragments that are typical of linear, saturated polymers (such as the fragment $C_5H_9^+$) of which 3D distribution is also shown in Figure 3c, right. Therefore, the likely explanation is that minute amounts of low molecular poly-HEA migrate to the surface during the printing process.

Unreacted acrylate monomers are normally not compatible with cells and often pose a risk during therapeutic use. Therefore, the level of residual acrylate group in the final tablets was examined to assess this potential risk. Fourier transform infrared spectroscopy-attenuated total reflection (FTIR-ATR) was used to assess presence of unreacted acrylate groups on the sample surface. For comparison, the uncured ink formulation and inkjet printed tablets were analyzed and compared (Figure S5, Supporting Information). Unreacted acrylate groups contain characteristic peaks at 1636 cm^{-1} (acrylate C=C stretches) and 810 cm^{-1} (=CH$_2$ twisting).[23] It was found that all the characteristic peaks related to unreacted acrylates disappeared in the final product indicating high conversion. As FTIR-ATR is a surface-based technique ($\approx$tens of microns), in order to further track unreacted acrylates through the whole sample, specimens from each formulation were dissolved and characterized by H'NMR (Figure S6, Supporting Information). As no characteristic peak for the acrylate groups in either HEA or IBHEA were observed, it was further confirmed that the printed sample achieved high conversion. A cytotoxicity test (following ISO 10 993) was also carried out with all the inkjet printed specimens where no cytotoxicity was observed on mammalian BJ6 cells over thirty days (Figure S7, Supporting Information). The molar mass of the sample was calculated using MALLS (M_{WMALLS}). The number average molecular weight of the inkjet printed samples reached 5900–9200 g mol^{-1} and the weight average molecular weights were between 90 300 and 118 200 g mol^{-1} (Table S4, Supporting Information). As the proportion of IBHEA increased, the distribution of the molecular weight tends to become broader (Figure S8, Supporting Information).

3. Conclusion

In conclusion, this work has demonstrated that through a strategy of creating a reactive prodrug-based formulation, it is possible to create a range of drug releasing inks that can be used with 3DIJP to produce structures with extended drug loading and controlled release. The loaded drug was shown to be homogeneously distributed throughout both the ink formulation and the printed product without recrystallization or precipitation, indicating physical stability. It was possible to modify the release rate by a number of means; we showed that we could control the release via choice of molecules forming the chain and linker, through variation of the geometry, and through spatially varying the composition of the tablet. The drug-attached molecule chain dissolves completely in an aqueous environment when the drug was fully released and therefore if this approach was to be used for implants the printed device would not need to be removed. Such a formulation system, which is readily adaptable to different small molecular weight drugs, provides a brand new formulation strategy for IJ3DP. Together with the multi-material printing capability for IJ3DP, we propose an important step in enabling the design and production of personalized multi-functionalized drug delivery dosage forms and devices with "programmed" drug loading and release.

Supporting Information

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

Conflict of Interest

The authors declare no conflict of interest.

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