Supporting Information for: Personalized Medicine: A Quality by Design Approach to Printable Tablet Production

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Supporting Information Table of Contents

Methods

Data Analysis. *Linear least squares calibration uncertainty.* As introduced in the text, solution-based calibration curves were created manually by gravimetry and pipetting. API solutions were analyzed by UV-Vis spectroscopy (*i.e.,* peak intensity, *I*) across concentrations (*i.e., c*) in a linear response regime. The resulting curves exhibited the form, $I = mc + b$, for n unweighted data points (c_i, I_i). Linear least squares calibration uncertainty was determined according to Eurachem and NIST guidelines.[37, 38] The unweighted standard uncertainty in p dissolved tablet samples was calculated by $u(c_{pred}, I) = S/m\sqrt{1/p + 1/n + (c_{pred} - \bar{c})^2/S_{xx}}$. Here, variables are represented as, the root mean square error $\left(S = \sqrt{\sum(I_i - \hat{I}_i)^2/(n-2)}\right)$, where I_i is measured intensity and $\hat{I}_i$ is the predicted value of the i^{th} observation, the response curve slope (m), the average concentration of the curve ($\bar{c}$), and the predicted dissolved tablet concentration (c_{pred}). $S_{xx} = \sum(c_i - \bar{c})^2$, with c_i representing the API concentration of the i^{th} point. Relative to the uncertainty in the UV-Vis response, the uncertainty in the reference calibration points was assumed small and disregarded. Therefore, the corresponding standard uncertainty in each tablet dose due to the uncertainty in the calibration point values was estimated by $u(c_{pred}, c_i) \approx u(c_i)/n$.[37, 38]

Supplemental Tables and Figures

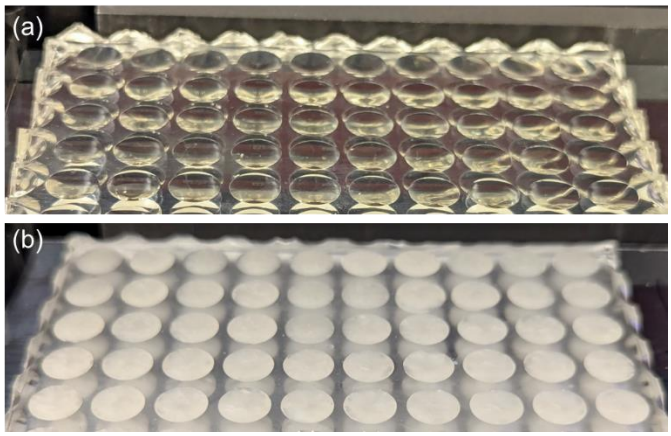

Figure S1. Photographs of (a) liquid and (b) solidified semisolid tablets (Gelucire 48/16) in a PDMS mold. Scale: tablet diameters are approximately 8 mm.

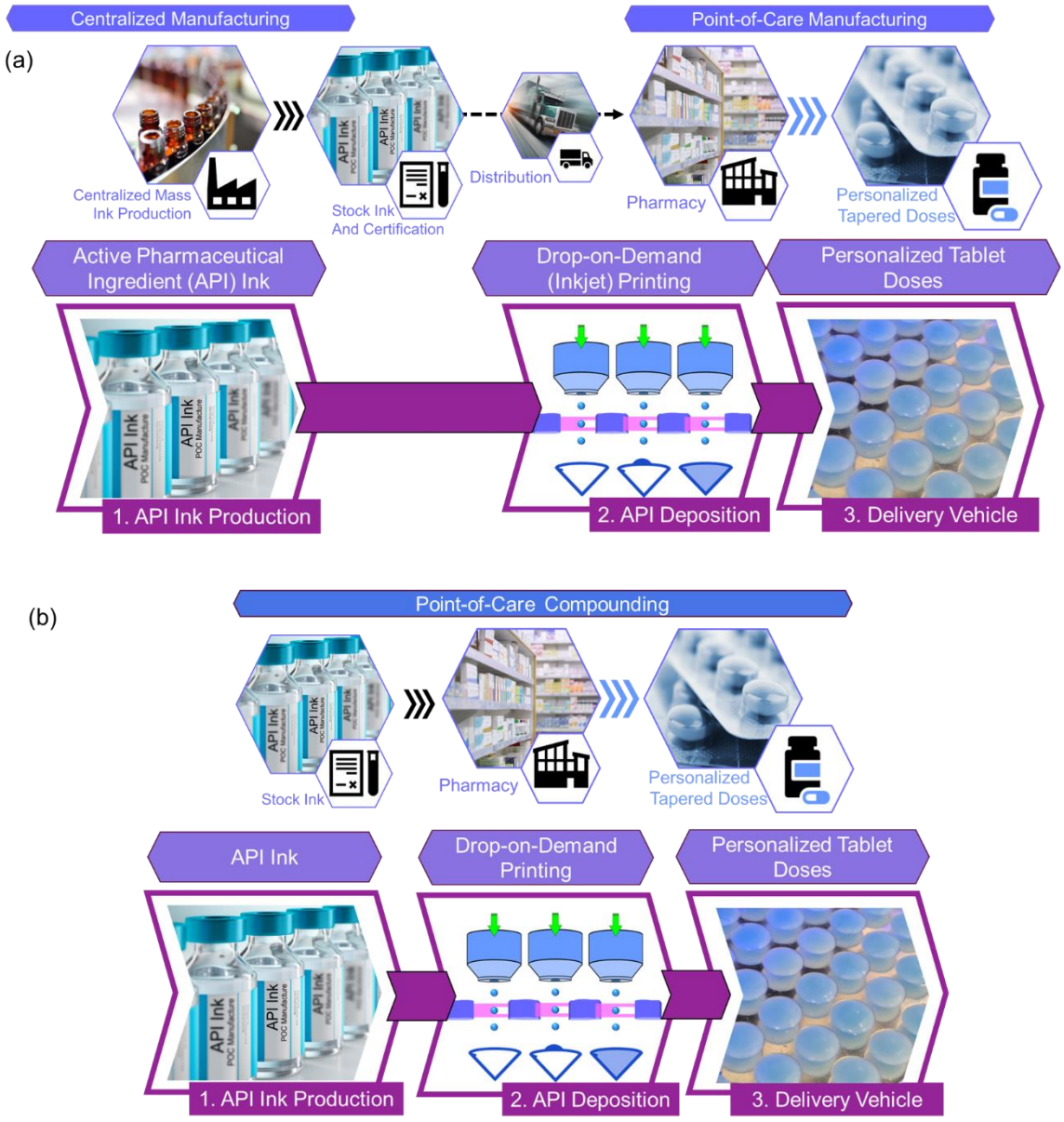

Figure S2. (a) Schematic representation of product flow and processes in a point-of-care pharmaceutical manufacturing workflow. API ink is manufactured at a centralized facility and distributed to point-of-care locations for final production. (b) Schematic representation of the formulation and production at a point-of-care compounding facility (*e.g.*, outsourcing facility). API ink is formulated and final tablet production all on-site.

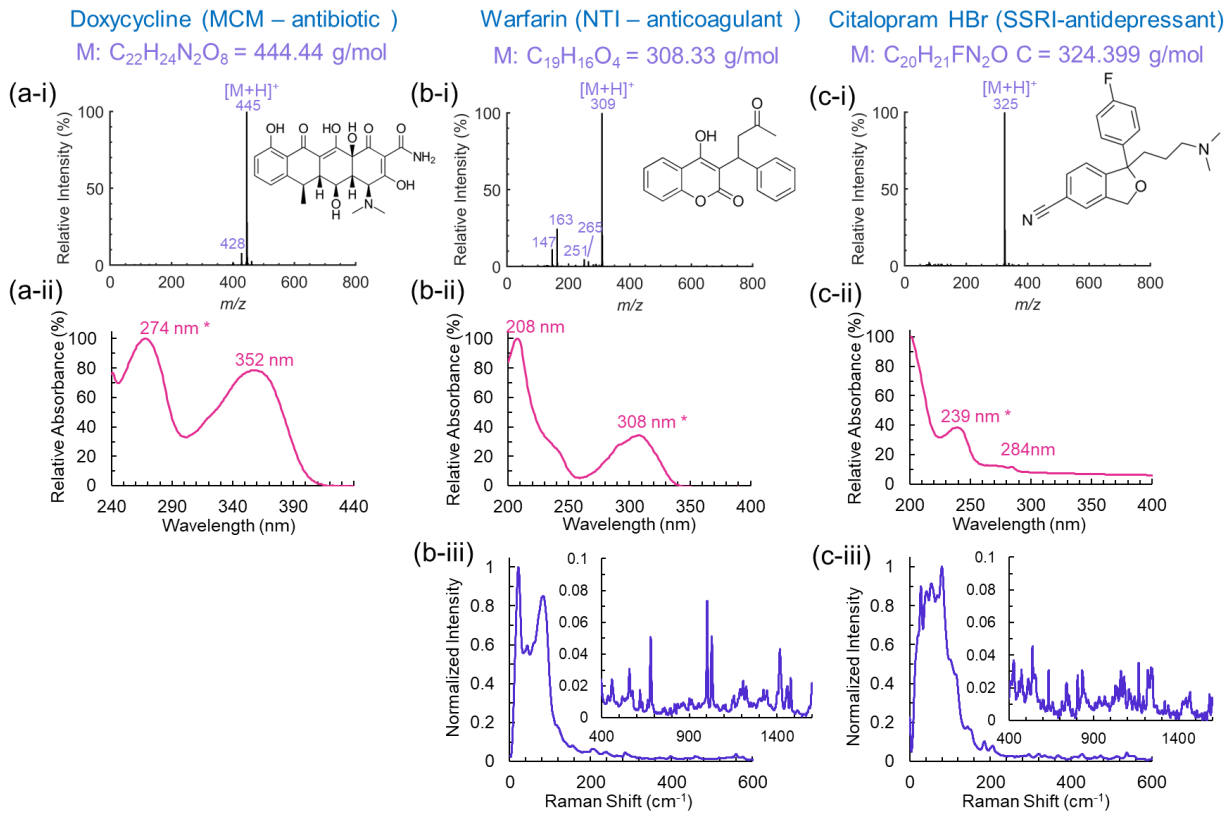

Figure S3. Representative (i) mass spectra, (ii) UV-Vis spectra, and (iii) THz Raman spectra for (a) doxycycline, (b) warfarin, and (c) citalopram API inks. Doxycycline was provided by supplier as DMSO-based solution in amorphous form.

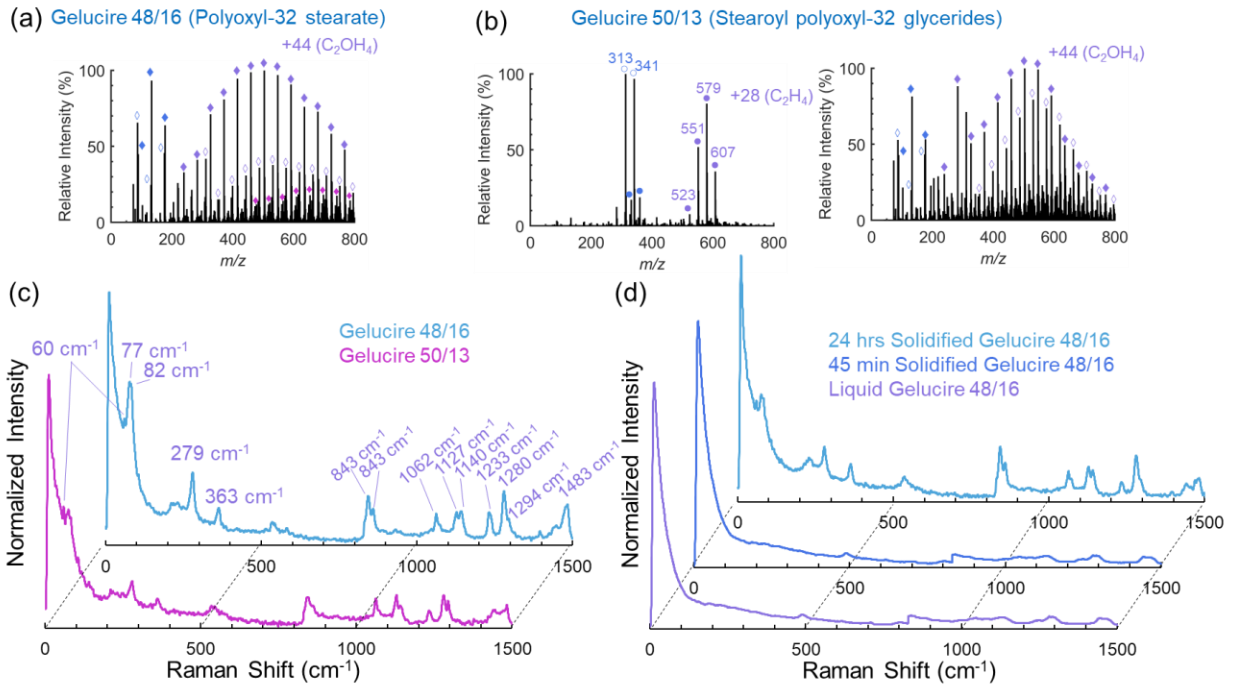

Figure S4. Representative mass spectra of (a) Gelucire 48/16 and (b) Gelucire 50/13 at relatively lower and higher desorption temperatures [DART ion source]. (c) Representative THz Raman spectra of solidified Gelucire 48/16 (blue / back) and Gelucire 50/13 (pink / front). (d) Representative THz Raman spectra of liquid Gelucire 48/16 (purple / front), 45-min solidification time (dark blue / middle), and 24-hr solidification time (light blue / back).

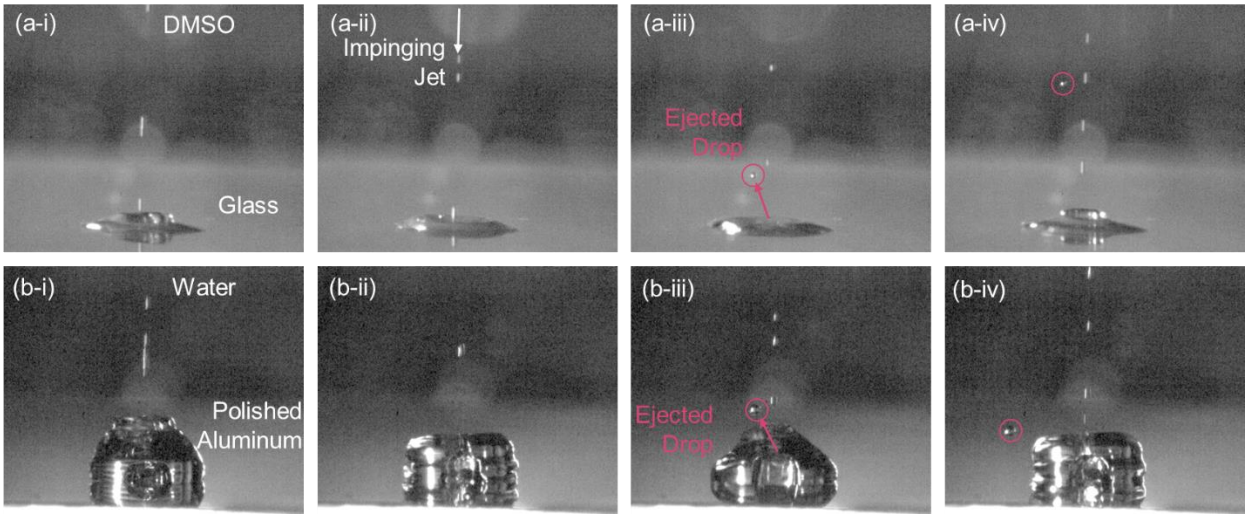

Figure S5. High-speed visualization stills of (a) a DMSO-based ink impinging on a glass slide and (b) a water-based ink impinging on a polished aluminum slide. Images of (1024 × 576) pixels were acquired at 12000 frames/s by a FASTCAM Nova camera and cropped for display.

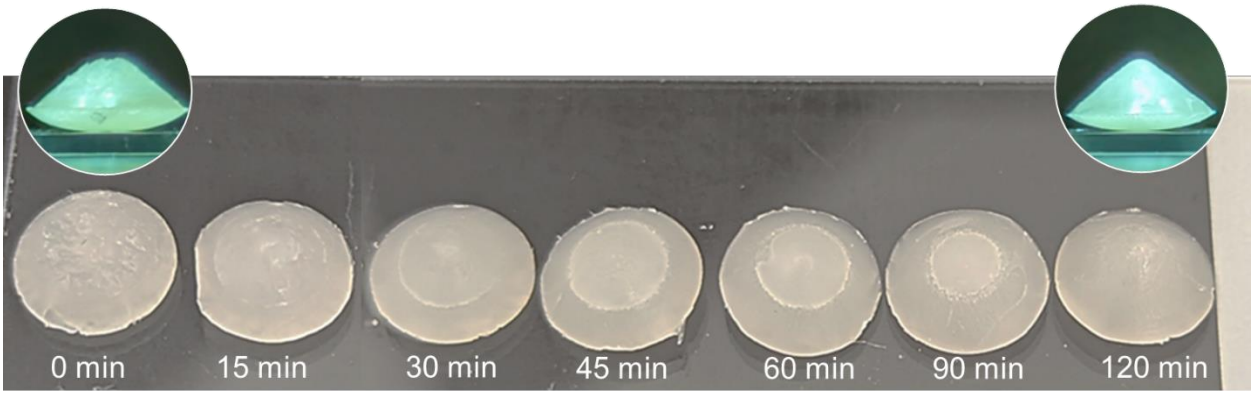

Figure S6. Photograph of tablets (apex up) dosed with 10 µL DMSO and held at 75 °C for the specified time (*i.e.,* the solidification delay). Insets show side view examples of tablets with no solidification delay and 120-minute solidification delay. Scale: tablets are approximately 8 mm in diameter.

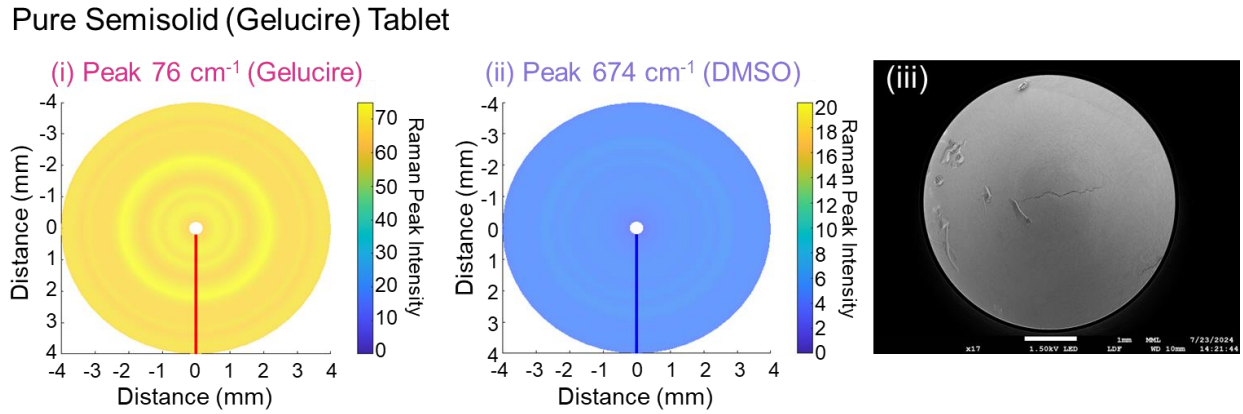

Figure S7. THz Raman spectroscopy rotated line scan results exhibiting the distribution of (i) Gelucire and (ii) DMSO for a pure excipient tablet, with (iii) corresponding SEM images (scale bar: 1 mm).

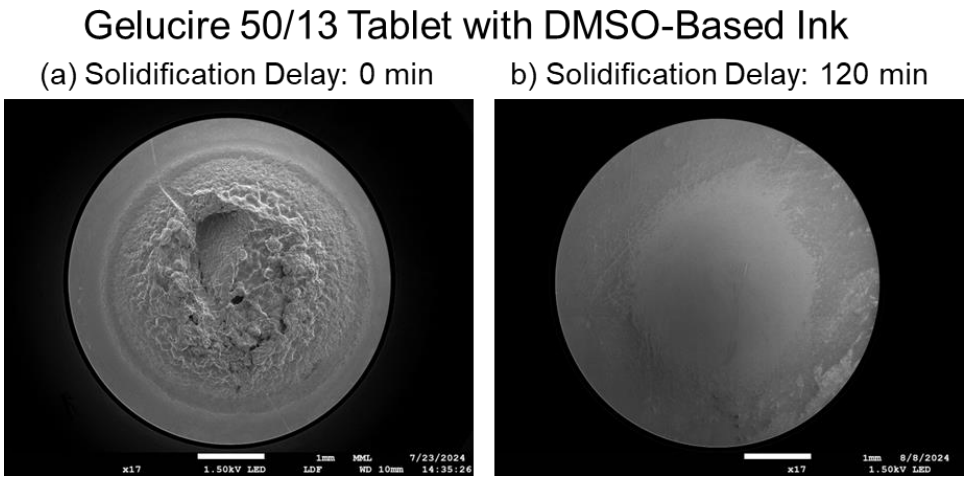

Figure S8. SEM images of Gelucire 50/13 tablets dosed with 10 µL of DMSO ink for (a) 0-minute and (b) 120-minute solidification delays (scale bars: 1 mm).

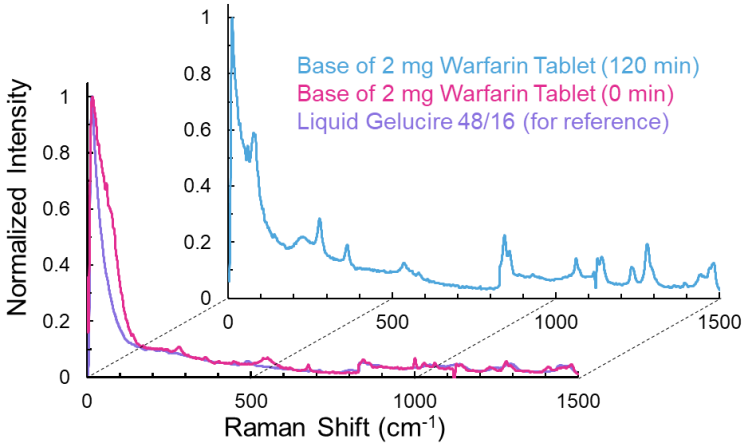

Figure S9. Representative THz Raman spectra from the center of a warfarin tablet allowed to immediately solidify (pink / front) vs delayed for 120 minutes (blue / back). Pure liquid semisolid tablet Raman spectra provided for reference (light purple / front).

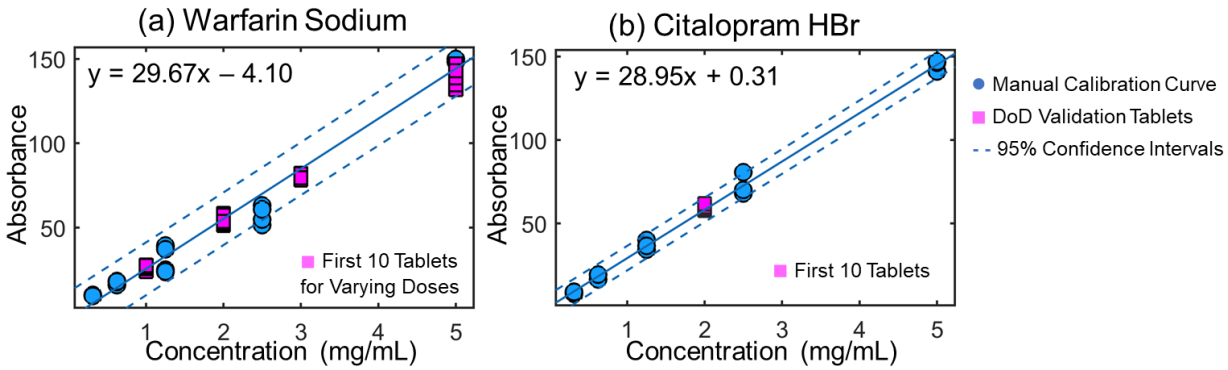

Figure S10. Calibration curves for (a) warfarin and (b) citalopram. Blue circles represent the manually created calibration curves and pink squares represent the drop-on-demand produced tablet samples. Solid and dashed blue lines represent the linear fit and 95 % confidence intervals.

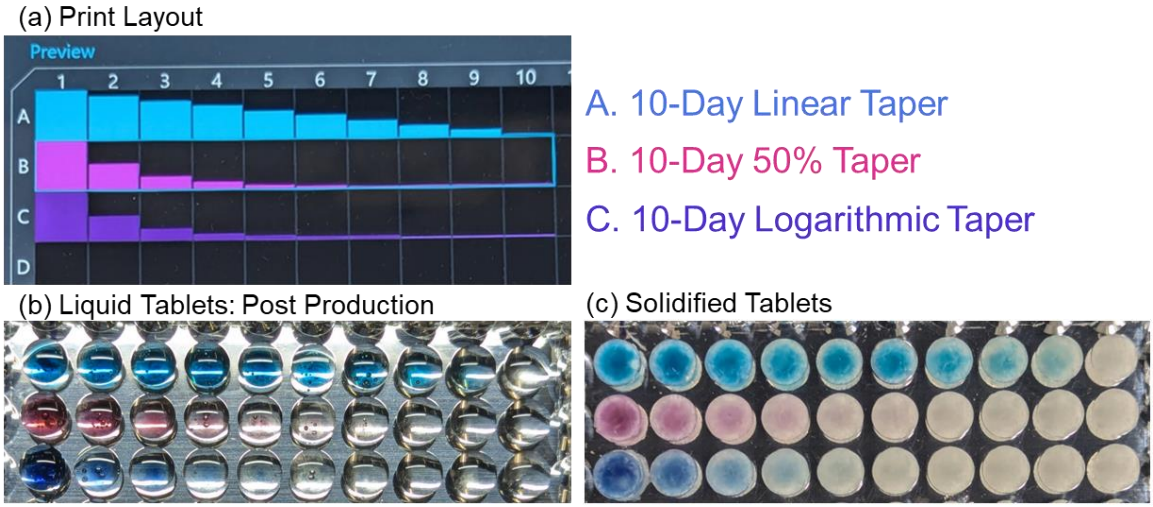

Figure S11. (a) Print layout screen for 10-day linear, halving, and logarithmic taper regimen demonstrations. (b) Image of post print liquid tablets using dyed inks (instead of the Citalopram results presented in article text) for visualization. (c) Image of taper regimens following tablet solidification.