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The use of near-infrared as process analytical technology (PAT) during 3D printing tablets at the point-of-care

Research paper

The Use of Near-infrared as Process Analytical Technology (PAT) during 3D Printing Tablets at the Point-of-Care

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A B S T R A C T

Fused deposition modelling (FDM) is one of the most researched 3D printing technologies that holds great potential for low-cost manufacturing of personalised medicine. To achieve real-time release, timely quality control is a major challenge for applying 3D printing technologies as a point-of-care (PoC) manufacturing approach. This work proposes the use of a low-cost and compact near-infrared (NIR) spectroscopy modality as a process analytical technology (PAT) to monitor a critical quality attribute (drug content) during and after FDM 3D printing process. 3D printed caffeine tablets were used to manifest the feasibility of the NIR model as a quantitative analytical procedure and dose verification method. Caffeine tablets (0-40% w/w) were fabricated using polyvinyl alcohol and FDM 3D printing. The predictive performance of the NIR model was demonstrated in linearity (correlation coefficient, R^2) and accuracy (root mean square error of prediction, RMSEP). The actual drug content values were determined using the reference high-performance liquid chromatography (HPLC) method. The model of full-completion caffeine tablets demonstrated linearity (R^2 = 0.985) and accuracy (RMSEP =1.4%), indicated to be an alternative dose quantitation method for 3D printed products. The ability of the models to assess caffeine contents during the 3D printing process could not be accurately achieved using the model built with complete tablets. Instead, by building a predictive model for each completion stage of 20%, 40%, 60% and 80%, the model of different completion caffeine tablets displayed linearity (R^2 of 0.991, 0.99, 0.987, and 0.983) and accuracy (RMSEP of 2.22%, 1.65%, 1.41%, 0.83%), respectively. Overall, this study demonstrated the feasibility of a low NIR model as a non-destructive, low-cost, compact, and rapid analysis dose verification method enabling the real-time release to facilitate 3D printing medicine production in the clinic.

Keywords: personalized medicine, bespoke, additive manufacturing, redistributed manufacturing, real-time release.

1. Introduction

Fused deposition modelling (FDM) 3D printing has been researched as a point-of-care (PoC) manufacturing method for bespoke dosage forms (Quodbach et al., 2021). This technology offers several advantages, including design flexibility and superior reproducibility (Park et al., 2019; Trenfield et al., 2018a). Owing to its low cost and minimal facility requirement, FDM 3D printing could potentially be integrated into clinical settings to produce tailored medicines (Cailleaux et al., 2021; Cerda et al., 2020; Okwuosa et al., 2017).

Manufacturing at the point of care (PoC) is gaining an increasing interest to provide patients with bespoke therapeutic options. In the UK, a tailored framework for the regulation of innovative products manufactured at PoC will be introduced by the regulator (MHRA, 2023). 3D printing of patient-specific products may be applied under such a framework (Panraksa et al., 2022; Trivedi et al., 2018; Xu et al., 2021). One of the major barriers to applying 3D printing in a PoC scenario would be providing timely quality control (QC) of 3D printed products for a real-time release. It would be impractical to undertake such complicate experiments, allocate professional operators and afford costly analytical instruments within a clinical setting for a small number of patients. Conventional quality-by-testing (QbT) techniques are impractical to be carried out on individually customised amounts of patient-specific medicine. In this regard, a contiguous quality certification programme is needed. Quality by design (QbD), a prerequisite for additive manufacturing, is introduced to effectively identify target product profile (TPP) and determine critical quality attributes (CQA) and critical process parameters (CPP) at the early drug development stage (ICH, 2017). Alternatively, non-invasive tablet characterisation methods with process analytical technologies (PAT) could permit a real-time batch release.

Near infrared spectroscopy (NIR) is non-destructive, rapid analysis, low-cost and portable, which enable QC to be imposed in clinical sites (Fonteyne et al., 2014a; M. J. Lee et al., 2011; Wahl et al., 2014). NIR has been extensively used in pharmaceutical industries as a rapid alternative to verify incoming raw materials, monitor CQAs, or quantify final product formulation (Blanco et al., 2006; Chalus et al., 2005; Meza et al., 2006).

To date, research has mainly focused NIR spectroscopy as quantitative QC tools on SLS or inkjet 3D printed products (Blanco et al., 2008; Edinger et al., 2019; Trenfield et al., 2022; Vakili et al., 2017). NIR provided a non-invasive QC method to inspect the dosage of 3D printed at the point of dispensing (Trenfield et al., 2020, 2018b). However, the surface morphology, matrix compositions, and thermal processing of FDM and SLS 3D printing are fundamentally

different. So far, no research has been reported on FDM 3D printed products using NIR for QC.

This work aimed to develop a NIR model as a PAT method for content quantification in FDM 3D printed tablets. First, we created the PLS model for caffeine PVA-based tablets to display the feasibility of NIR as a quantitative analytical method for FDM pharmaceutics. To demonstrate the applicability of the NIR model to measure the content changes during the printing process, NIR models were established with a series of partially 3D printed tablets of increasing 3D printing percentages.

2. Materials and methods

2.1 Material

Caffeine USP/BP grade (Acros Organics, UK) was used as a model drug. Parteck® MXP (PVA) and sorbitol (Parteck® SI 150) were donated by Merck (Darmstadt, Germany). Sodium phosphate dibasic dihydrate ($(HNa_2PO_4.2H_2O)$, MW: 177.99 g/mol) and methanol HPLC grade were purchased from Sigma-Aldrich (Poole, UK).

2.2 Filament preparation and FDM 3D printing process

The filaments were prepared from powder mixtures *via* heat-melt extrusion (HME) using a counter flow conical twin-screws extruder, Thermo-Fisher Scientific HAAKE MiniCTW (Karlsruhe, Germany). Extrusion was carried out through a 1.5-mm diameter cylindrical die nozzle with a torque control of 0.6 Nm. The extrusion of filament was operated at 170 °C and produced a filament of 1.75-mm diameter. The filaments were stored in sealed plastic bags at room temperature prior to FDM 3D printing.

The design of the tablets was carried out using Autodesk® 3ds Max Design 2021 software version 18.0 (Autodesk, Inc., USA) and exported in a stereolithography (.stl) file format. The tablets were printed using MakerBot Replicator 2X Experimental 3D Printer (MakerBot Industries, USA) with MakerWare Software Version 2.4.0.17 (Makerbot Industries, USA) at the specific printing setting. The compositions of caffeine tablets (0 - 40% w/w) are detailed in Supplementary data, Table S1. The cylinder was designed to be 10 mm in diameter with a 2-mm height. The FDM 3D printing parameters were set at extruder speed = 90 mm/s, infill density =95%, layer height = 200 μm, and an extruder temperature = 180 °C. To mimic the in-process characterization of the printed tablets, the 3D printing process was interrupted to achieve a process completion of 20%, 40%, 60%, or 80%, corresponding to 3D tablets of 2, 4, 6, or 8 layers, respectively.

2.3 NIR data acquisition

NIR reflectance spectra were measured using a portable DLP® NIRscan™ Nano spectrometer (Texas Instruments, USA) (Fig. 1B), equipped with the EVM (evaluation module) incorporates the DLP2010NIR DMD (digital micromirror device), a diffraction grating, a single-element extended InGaAs detector for the wavelength range between 900-1700 nm. Following background collection, each 3D printed tablet was placed on black stage and analysed at three different points and the final spectrum was the average of the spectra recorded.

2.4 PLS model development

a. Chemometric model

Seven tablet concentrations (n =3) were selected for calibration model development (0%, 5%, 7.5%, 15%, 25%, 35%, and 40% w/w). Spectral pre-processing, first and second derivatives, SNV standard normal variate (SNV), and Sativzky-Golay (SG) (Savitzky and Golay, 1964) was applied. It was executed using Matlab® software version R2021a (The MathWorks, Inc. USA) to minimise variability and strengthen spectral effects attributed to chemical composition. Partial least squares (PLS) regression was performed using Minitab® software version 19.2020.1 (Minitab, LLC. USA) on the datasets to build the calibration models, and leave-one-out was applied to internally cross-validate the quantitative calibration models. For each model, the correlation coefficient of the calibration curve (R^2 Cal) and the standard error of the calibration curve (RMSEC) were calculated to determine the fitness degree of the model. The correlation coefficient of the cross-validation (R^2 Pred) and standard error of the cross-validation (RMSECV) determined the predictive ability of the model. The most optimal model was defined as the model with the highest linearity (e.g. R^2 Pred as close to 1 as possible) and a relatively low RMSECV value.

b. External validation of NIR quantitative analytical procedure

In addition to linearity (expressed as correlation coefficient, R^2), further validation of the model was performed according to International Conference on Harmonization (ICH) guidance Q2(R1) and other regulatory guidance from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), includes specificity, linearity, accuracy (expressed as RMSEP), and repeatability (expressed as relative standard deviation (RSD)). To assess the accuracy performance of the model and to validate precision, three additional concentrations (10%, 20%, and 30% w/w) within the model range were selected as the external validation sets for caffeine concentration. The precision of an analytical procedure exhibits the closeness of agreement (degree of scatter) between a series of measurements acquired from multiple sampling of the

same homogeneous sample under the prescribed condition.

2.5 HPLC analysis of drug content

Following NIR analysis, each tablet was quantitatively analysed for drug content using HPLC. Agilent 1260 Infinity HPLC system (Agilent Technologies, UK), equipped with a pump and an autosampler, was used to make chromatographic separation and ultraviolet detection. OpenLab CDS ChemStation software (version A.02.02) was used for data processing. Nine individual tablets of each concentration were dissolved in 50 mL of 1:4 v/v methanol: Type I water mixture. The samples were sonicated for 10 min, stirred with a magnetic stirrer over four hours, and filtered with 0.45 µm sterile (Fisher Scientific., Ireland). Caffeine concentration was determined using HPLC. A 50:50 v/v mixture of methanol: Na_2HPO_4 solution (20 mM) was used as a mobile phase through Platinum C8-EPS 5 µm column, 250 x 4.6 mm (Dr Maisch HPLC GmbH, Ammerbuch, Germany) maintained at 40 °C. The analysis was carried out at a detection wavelength of 273 nm, a flow rate of 1 mL/min, an injection volume of 5 µL, and a 6.5-min run time. The retention time for caffeine elusion was 4 min. The analytical method for caffeine content was built using a concentration range from 50 to 1000 mg/L and with a correlation coefficient (R^2 >0.999).

2.6 Scanning electronic microscopy (SEM)

The morphology and cross-section of the Multilayer I and II and Unimatrix polypills were assessed using a JCM-6000 plus NeoScope™ microscope (Jeol, Tokyo, Japan) at 10 kV. All samples were gold-coated using a JFC-1200 Fine Coater (Jeol, Tokyo, Japan). The images were collected using ImageJ software version 1.2.0. (Tokyo, Japan).

2.7 X-ray diffractometry (XRD)

XRD analysis was performed on raw materials, blank filaments, drug-loaded filaments, and 3D printed tablets to evaluate the model drugs' crystalline structure. Samples were measured using a silica low-background sample holder and an X-ray diffractometer, X-ray diffractometer, Miniflex 600 (Rigaku Corporation, Japan). Samples were detected between 2Theta = 5° to 50° using a 0.01° step width and a 1.25 sec time count. The divergence slit was 1 mm, and the scatter slit was 0.6 mm. The wavelength of the X-ray was 0.154 nm using a copper source and a voltage of 30 kV. Filament emission was 10 mA using a scan type coupled with a theta/theta scintillation counter over 60 min.

2.8 Statistical analysis

Statistical analysis of the results was done using paired *t*-test in Excel (version 2016).

Differences in the results below the probability level of $p < 0.05$ were considered significant.

3. Results and Discussion

3.1 Characteristics of 3D printed caffeine tablets

The design and final caffeine FDM 3D printed tablets for constructing NIR models are demonstrated in Figs. 1C1-C4. A regular cylindric shape was selected to simplify the scanning on the upper surface of the design. XRD patterns (Fig. 2A) showed that caffeine has intensity peaks at 2Theta = 12.05° and 26.5° (Sóti et al., 2015). The blank tablet showed two intensity peaks at 2Theta = 19.5° corresponding to the semicrystalline polymer in blank respectively (Fig. 2B). The absence of intensity peaks for sorbitol indicates that plasticiser was soluble in the PVA matrix. The inclusion of caffeine into the PVA matrix showed increasing intensity peaks of 2Theta = 12.05° and 26.5° and hence indicated that caffeine presented in crystalline form within the tablet matrix.

3.2 NIR model validation outcome for QC of completed tablets

Spectra pre-treatments are commonly used to improve the accuracy of quantification by increasing spectral information, decreasing baseline drift, and minimising error caused by light scattering effects (Rinnan et al., 2009).To create a reliable multivariate calibration model, the evaluation of different spectral pre-processing methods was needed to extract the relevant physical attributes information. In this study, a total of ten PLS models were developed.

The model selected was Model 9 (Table 1), with a second derivative plus the SG method. The calibration model covered a total of 63 samples over the caffeine concentration range of 0 - 40% w/w. The developed calibration model demonstrated ideal prediction linearity ($R^2 = 0.985$) (Fig. 4), confirming that the NIR test results were indicative of caffeine concentration in the stated range. The linearity could have been improved by tight control of some variables such as humidity level, and precise positioning of the unit during NIR spectroscopy scan.

a. Specificity

For the model to be fit for purpose, it must have the ability to identify the analyte in the presence of the other ingredients (i.e. PVA and sorbitol). Specificity was evaluated by comparing the second derivative plus SG loadings spectra, and the model manifested caffeine spectral range between 1170 and 1400 nm (Laasonen et al., 2003)(Fig. 3). Unprocessed and pre-processed spectra of the raw materials and the scanned caffeine tablets (0–40% w/w) have been provided in Supplementary data Figs. S1.

The accuracy of the calibration model can be expressed as the closeness of agreement between the observed values and the reference values. A minimum of nine determinations over a

minimum of three concentration levels to assess accuracy is recommended in ICH Q2 (R2) guideline (ICH, 2005). Nine tablets (n = 3 x 3) from three concentration levels (10%, 20%, and 30% w/w) were scanned. Table 2 shows the difference between NIR-predicted and HPLC-determined caffeine concentrations. Paired *t*-test results showed that there were no significant differences between the HPLC and NIR methods ($p > 0.05$) across all three concentrations, confirming that NIR is a suitable quantification method for FDM 3D printed tablets. Accuracy was also confirmed by having a low error value (RMSEP of 1.4%) and a low prediction bias of -0.03%. Additionally, per cent recoveries of 20% and 30% w/w caffeine samples achieved 98%, which lies within the usually accepted limits of 98-102%.

b. Precision

ICH Q2 guidance recommends one approach for repeatability assessment is using a minimum of nine determinations encompassing the stated range e.g. 3 concentrations with 3 replicates each. Therefore, precision was evaluated by scanning 10%, 20%, and 30% w/w tablets in triplicate at the same time while using the same equipment (Supplementary data, Table S2). Table 4 shows the results of repeatability, compared with the reference HPLC method. The model displayed acceptable precision performance while an RSD of 30% and 20% w/w caffeine tablets were below the usual accepted RSD of 2%. However, tablets at 10% showed a relatively high RSD% on NIR compared to the reference HPLC method, this might indicate the reduced sensitivity of NIR for lower caffeine concentration. The higher concentration of caffeine in Table S2 could be attributed to potential operator error during the manufacturing of the test batch.

3.3 In-process control by NIR using different completion caffeine tablets

To extend the application of the NIR model as a PAT method to be integrated into the 3D printing process to monitor content changes. The predictivity performance of the NIR model was carried out by applying caffeine tablets with a series of completion percentages (ranging from 20%, 40%, 60%, and 80% completion) to present different printing stages. The photographs and SEM images of the tablets displayed the difference between individual samples (Figs. 5 and 6).

Initially, the NIR model built from 100% completion tablets (with linearity R^2 of 0.985, RMSEP of 1.4%) was used to predict the content of tablets at different completion stages. However, the mean predicted content values of caffeine tablets across different completion percentages were overfitted to the actual value determined by HPLC (Supplementary data, Table S3). It was

especially evident at low caffeine loading; for example, a significant discrepancy occurred between the predicted and true values of 5% or 7.5% concentration. The results of the predicted content value of individual tablets are supplied in Supplementary Data, Table S4. Hence, it was concluded that the original model was not expedient for measuring table content at different printing stages.

FDM 3D printing uses thermoplastic polymers in a path-line of 400 μm, which has a significant impact on the surface morphology of the 3D printed tablets. Additionally, the multiple stacked layers of 3D printed caplets with inter-layer seem lines result in variability in spectrometer detection. The limited ability of the model bases on complete tablets to deduce drug content concentration during 3D printing might be directly related to the differences in surface morphology of the infill pattern (during tablet completion) and that of the outer shell (of completed tablets). Such differences in surface morphology might influence NIR diffuse reflectance spectra. A similar effect of surface dimension and morphology has been previously used to predict particle size or shape (Y.-Y. Lee et al., 2011; Pasikatan et al., 2001; Stojanovska Pecova et al., 2021).

Due to the unfavourable prediction outcomes from the previous experiment, PLS models for individual completion percentages were developed. In this case, the calibration model covered a total of 21 samples for each completion, respectively. The optimal models selected for each completion percentage are summarised in Table 3. The results of each pre-treatment model of four different completion samples are provided in Supplementary Data, Table S5.

The correlation between NIR predicted values and the reference HPLC concentrations of the developed calibration models is shown in Fig. 7. The model linearity (R^2 pred) of four different completion percentages was higher than the original model (from 100%-completed 3D printed tablets).

Tablets (n = 3) of three concentration levels (10%, 20%, and 30% w/w) were selected as the validation set to examine the accuracy. The predicted value from the original and individual models of 30% w/w caffeine samples with four different completion percentages are demonstrated in Supplementary Data, Table S6. Notably, when separate prediction models were applied (Supplementary Data, Table S7), the retrieved drug loading value between NIR and HPLC method became no statistically significant difference (p>0.05) with RMSEP of 2.22%, 1.65%, 1.41% and 0.83%, respectively. It indicated that the individual PLS models were fit to measure tablet content at different printing stages.

Nevertheless, the results of this study illustrated that the validated NIR model for content quantification is not inferior to previous studies carried out with tablets based on compressed powder (Harms et al., 2019) or SLS 3D printing (Trenfield et al., 2022). It has also demonstrated that a low-cost and compactable NIR modality could achieve a reliable predictability of drug contents. This holds the promise to function as an accessible tool and can be integrated within the 3D printer in a point-of-care setup. The variable thickness of tablets of different completion percentages may also affect the depth of penetration of NIR absorbance (M.-J. Lee et al., 2011; Wahl et al., 2019).

Several factors may have contributed to NIR variation, such as sample management, NIR modality limitation and environment control. For instance, the moisture and homogeneity of samples were proposed to be intrinsic factors to affect NIR detection. Residual moisture might cause light scattering and NIR absorption in signal variation(Domokos et al., 2021; Fonteyne et al., 2014b). Therefore, the control of environmental conditions such as temperature and humidity can directly affect tablet moisture content (Patel et al., 2023; Rantanen et al., 2000).

With new NIR instrument designs equipped with improved fibres and miniaturised design (Beć et al., 2020), multiple measuring points can be carried out from a single instrument. Hence, it could tackle the issues of sampling representation that is often solved by multiple scans on a single tablet. Specifically, 3D printers could be equipped with NIR sensors to determine early termination of the printing process (Cogoni et al., 2021; de Leersnyder et al., 2018; Pestieau et al., 2014; Wu and Chen, 2018). Such approach can also be beneficial for optimising process efficiency and expanding production capacity, which promotes the applicability of 3D printing technologies developed in pharmaceutical industries. However, a technical challenge may stem from the difference between 3D printing speed, which may not coincide with NIR scan time. In addition, interruption 3D printing process to 'bracket' a scan will result in a multiple interruption for the 3D printing process and might negatively affect the finishing of the final product. Shortening the scan-time could mitigate this risk with improved equipment as well as narrowing the range of the inspected NIR spectra.

In principle, a 3D printer with an integrated NIR PAT capacity can achieve a real-time quality assurance to ensure the CQAs are continuously monitored during manufacturing process. Such proposed approach can provide a continuous process verification to replace the conventional three-batches validation approach to reflect the quality of small-batch production more efficiently. While the scope of this work focused on controlling a critical quality attribute during the 3D printing process, a comprehensive approach should be applied throughout the preparation process, including powder blend preparation and filament manufacturing.

4. Conclusion

This work demonstrated the predictive performance of a low-cost compact NIR model to detect

caffeine contents as a CQA in FDM 3D printed tablets and established that the model could be post-manufacturing release. The predicted model was affected by the surface morphology of the scanned 3D printed tablets and its percentage of completion. Hence, prior to developing NIR models, the changes in the topography of the scanned surface of the 3D printed tablets should be considered. Future work could potentially cover the use of NIR to monitor the printing process and shape the fidelity of the produced tablets. Integrated as a PAT framework with FDM 3D printer, the NIR model can potentially ensure final product quality in real time. With intensive research ongoing to apply 3D printing technologies in clinical research, such an integrated NIR modality would offer several advantages, including rapid, non-destructive, compactable, and economical, allowing real-time batch release in the clinical site in practice.

List of Figures

List of Tablets

to develop calibration model. D1: first derivative spectra, SNV: standard normal variant, SG: Sativzky-Golay.

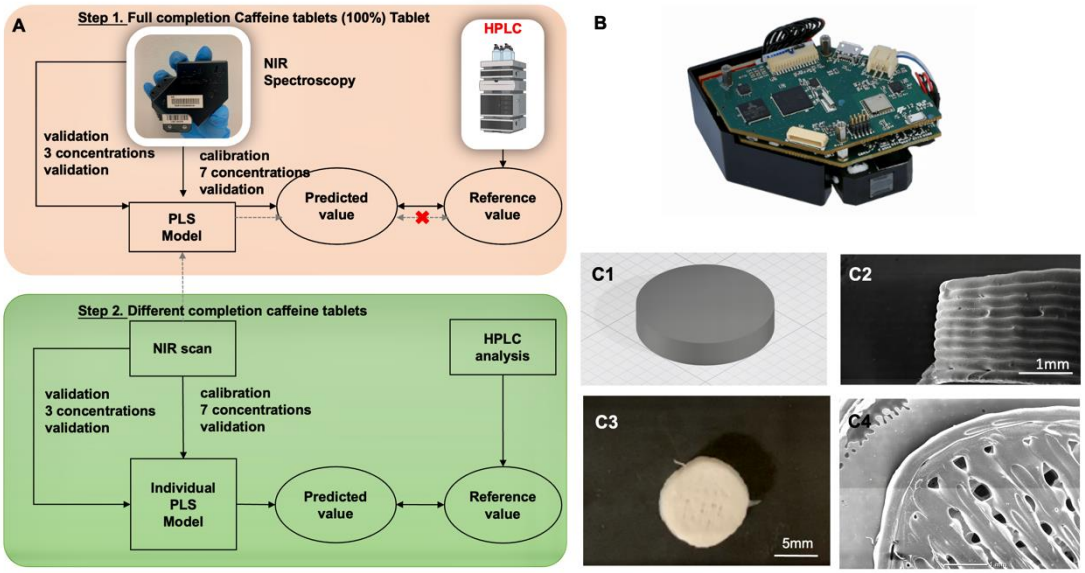

Figure 1. (A) The flow of NIR model development, **(B)** Images of DLP® NIRscan™ (INSTRUMENTS)(INSTRUMENTS)(2), **(C1)** Computer aided design (CAD) of cylinder, **(C2)** SEM images of side view of caffeine tablet, **(C3)** photo and **(C4)** SEM images of top view of 3D printed caffeine tablet.

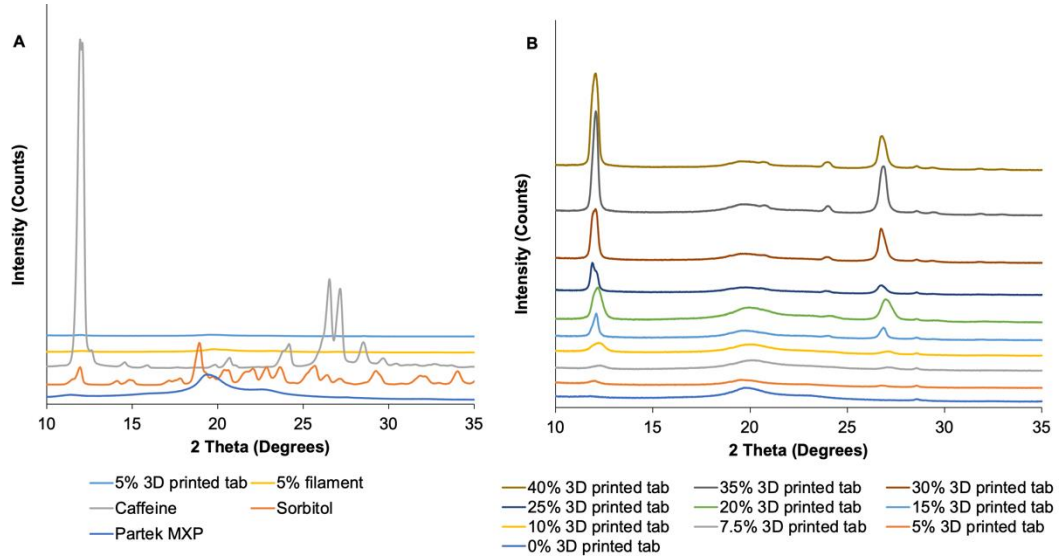

Figure 2. XRD patterns of (**A**) caffeine, Parteck® MXP, sorbitol, 5% caffeine-loaded filaments and 3D printed caffeine tablets, and (**B**) 0-40% caffeine-loaded 3D printed tablets.

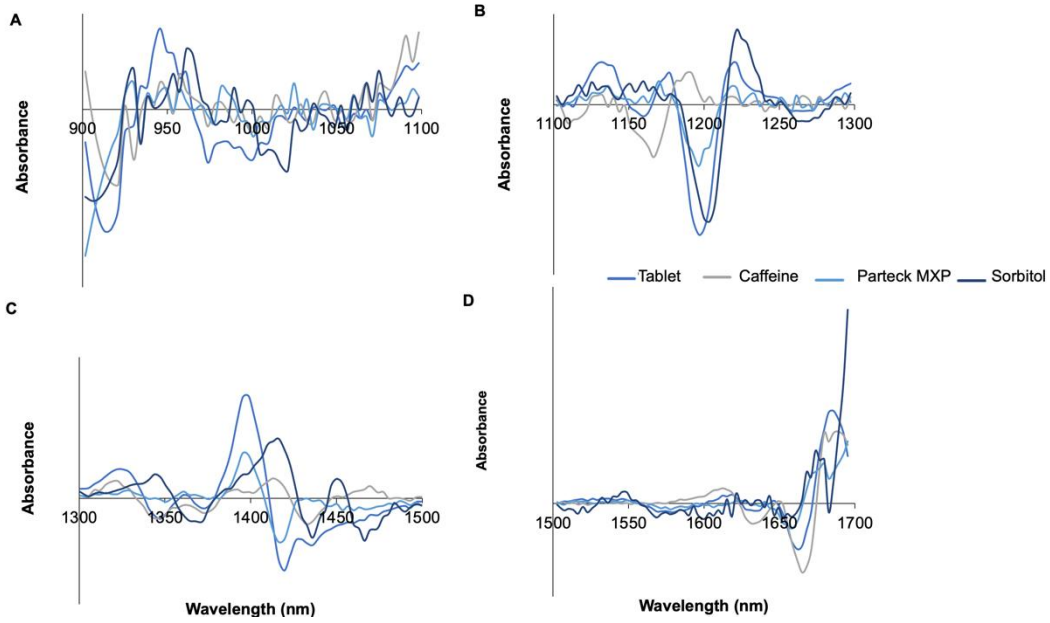

Figure 3. The second derivative plus SG spectra of caffeine tablets, reference caffeine, Parteck® MXP, and Sorbitol. (**A**) 900-1100 nm, (**B**) 1100-1300 nm, (**C**) 1300-1500 nm and (**D**) 1500-1700 nm.

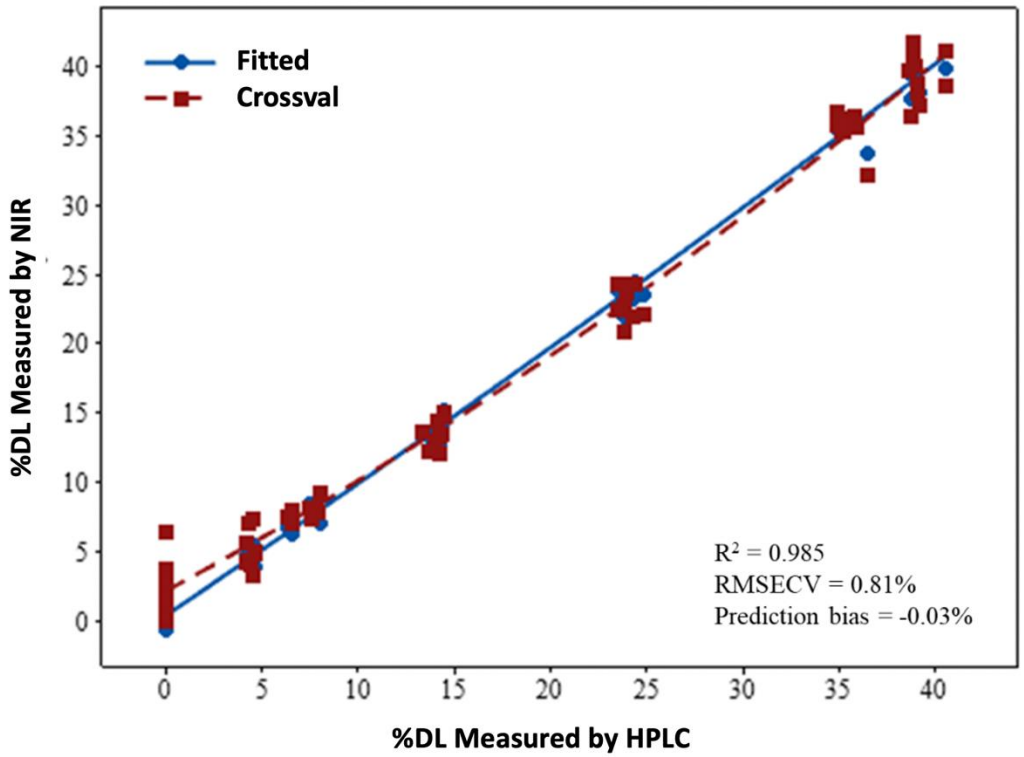

Figure 4. PLS model of NIR predicted vs HPLC measured caffeine content (%drug loading; %DL) of tablets.

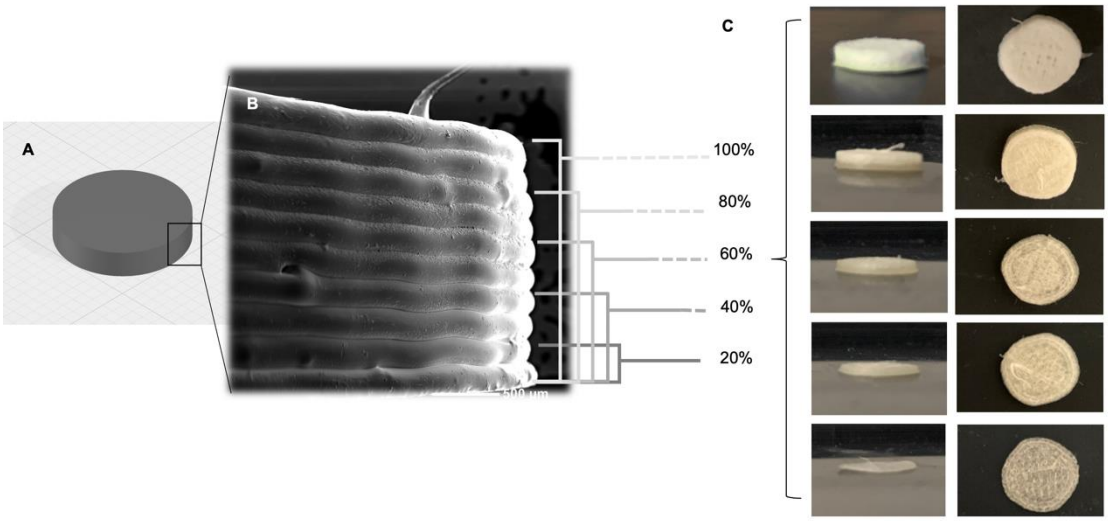

Figure 5. Features of 3D printed caffeine tablet with different completion percentages (**A**) CAD of a cylinder, (**B**) amplified image of the side view (**C**) photos of 20%, 40%, 60%, and 80% completion tablets of top and side view.

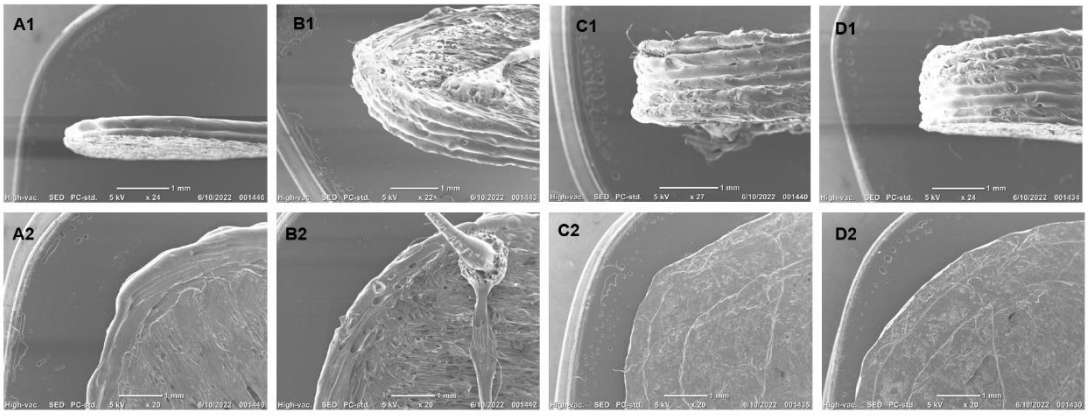

Figure 6. SEM images of 3D-printed caffeine tablets with four different completion percentages. Side view of **(A1)** 20%, **(B1)** 40%, **(C1) 60**%, and **(D1)** 80% completion. Top view of **(A2)** 20%**, (B2)** 40%, **(C2)** 60%, and **(D2)** 80% completion.

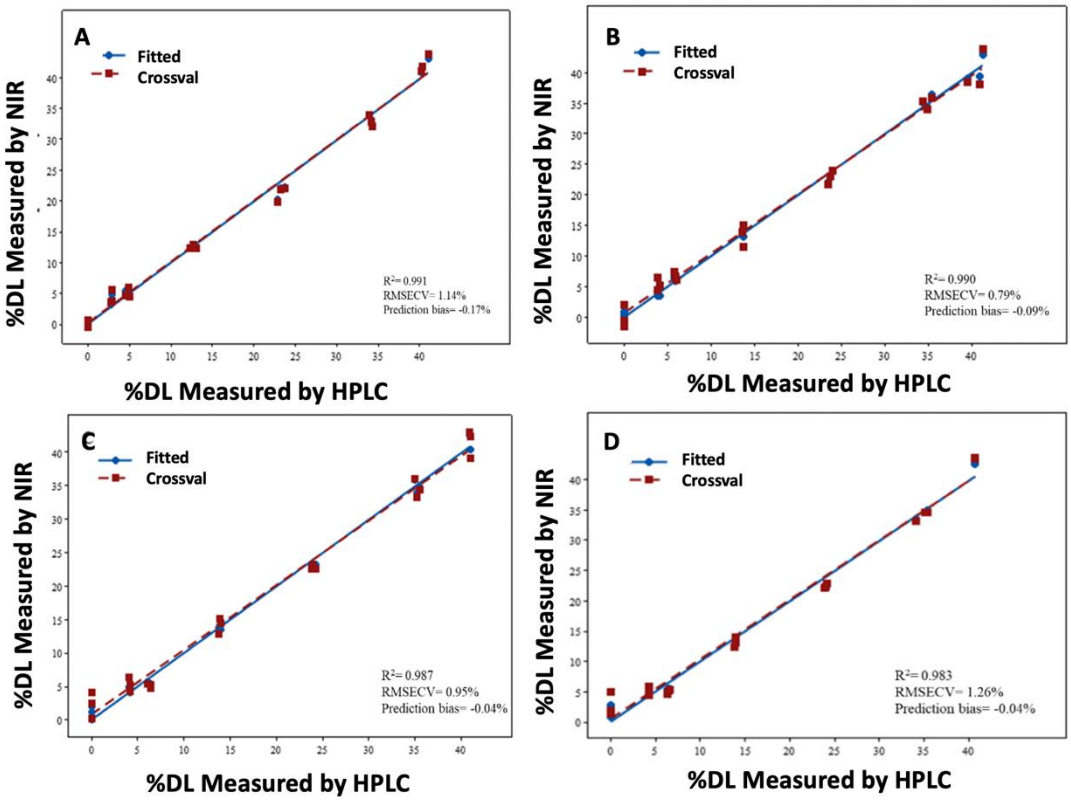

Figure 7. PLS model of NIR predicted vs HPLC measured caffeine content (%drug loading; %DL) of tablets. (**A**) 20% completion percentage, (**B**) 40% completion percentage, (**C**) 60% completion percentage, and (**D**) 80% completion percentage.

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