3D printing, automate to individualize: Process validation and quality control

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INTRODUCTION

3D printing (3DP) is a useful tool in the field of **individualized medicines** when a certain active pharmaceutical ingredient (API) it is not commercially available, even more in the case of **paediatrics** where there is a lack of child-friendly medicines. The incorporation of this technology in community pharmacies and hospitals could **improve the treatment** as it is possible to produce printlets with **different doses**, reduce size and change colour, texture, or taste to increase adherence[1]. However, it is frequently that several patients need the same API to be treated, but with different doses strength so, using the same printing cartridge in the same printing platform and at the same time would be useful to **save cost and time**.

MATERIALS AND METHODS

A SSE technology pharma-ink was developed using hydrochlorothiazide (HCTZ) as the API and several excipients. The 3DP platform M3dimaker[1] by FabRx, was used to produce printlets of different doses strengths (2–24 mg.), and the HCTZ content was analyzed using an Acquity UPLC® H-Class system. Variance analysis was performed to evaluate the linear relationship between extruded mass and % DV. In-line measurements (mean pressure, printlet area by image analysis and printlet weight) were used to develop a process control strategy in the QbD approach, and an automatic algorithm was developed in Python to identify printlets that did not meet the **quality target product profile (QTPP)**.

RESULTS AND DISCUSSION

Validation of the print cartridge

A correlation coefficient of 0.994 established a linear relationship between the variables studied. The 2 and 4 mg HCTZ printlets showed high variability and averages outside 100.0±5.0 of %DV, 129.6±46.2% and 79.2±20.3% respectively. Furthermore, although the 6 mg printlets averaged 101.5%, the variability was high (±10.4%) (**Fig. 1**). Thus, the procedure **allowed the production of printlets with doses higher than 8 mg of API** by changing the amount of extruded material, a different strategy to that carried out by other authors who use the increase or decrease of complete layers and not of the total amount[2].

Manufacturing of personalised medicines

The validation of the pharma-ink for producing various dosage strengths was conducted. Subsequently, a simulation was performed to assess the feasibility of printing **three distinct prescriptions (8 mg, 12 mg, and 16 mg)** in a single printing process (**Fig. 2**). The implementation of **process analytical technologies (PAT)** on the 3DP platform, along with the **algorithm built in Python**, enabled the automation of the decision-making process for discarding printlets that do not meet the required quality criteria[3] (**Fig. 3**). . The mean pressure values in printlets A1, A2, and A9 experienced an increase in their standard deviation as a result of the presence of air within the syringe. In contrast, the mean pressure values exhibited an increased trend towards the conclusion of the printing process (G4 and G5), potentially indicating a nozzle obstruction.

CONCLUSIONS

It has been possible to use the same printing cartridge to obtain several individualized medicines from the same API but with different doses, saving money and time, but ensuring quality. The use of QbD and PAT made it possible to determine which printlets did not meet the critical quality attributes required.

OBJECTIVES

The objectives of this work are to validate the use of the same print cartridge to obtain printlets with different API dosages by semi-solid extrusion (SSE) 3D printing using hydrochlorothiazide (HCTZ) as the model API. As well as, applying QbD and PAT to guarantee the final critical quality attributes (CQA) of the dosage forms, printlets.

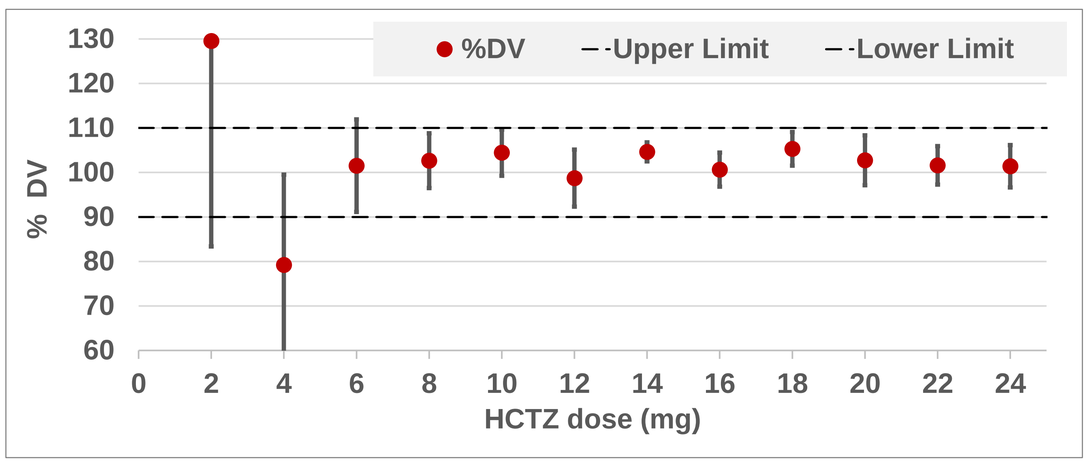

Figure 1. HCTZ % declared value (DV) for each printlet dose strength.

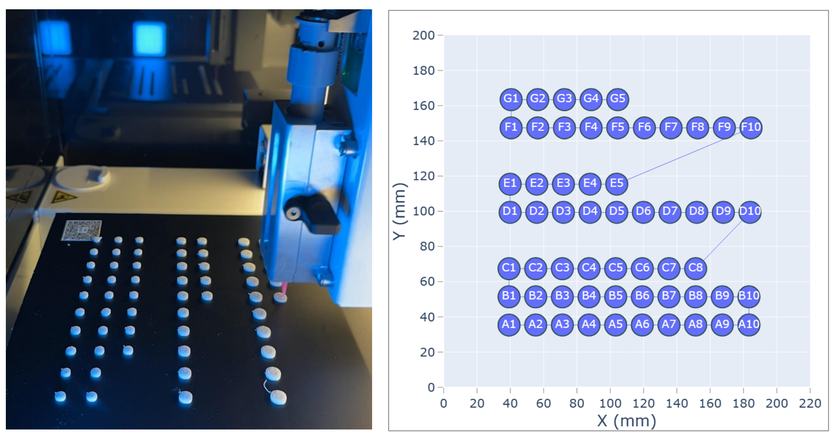

Figure 2. Image of the 3DP job and printlets distribution.

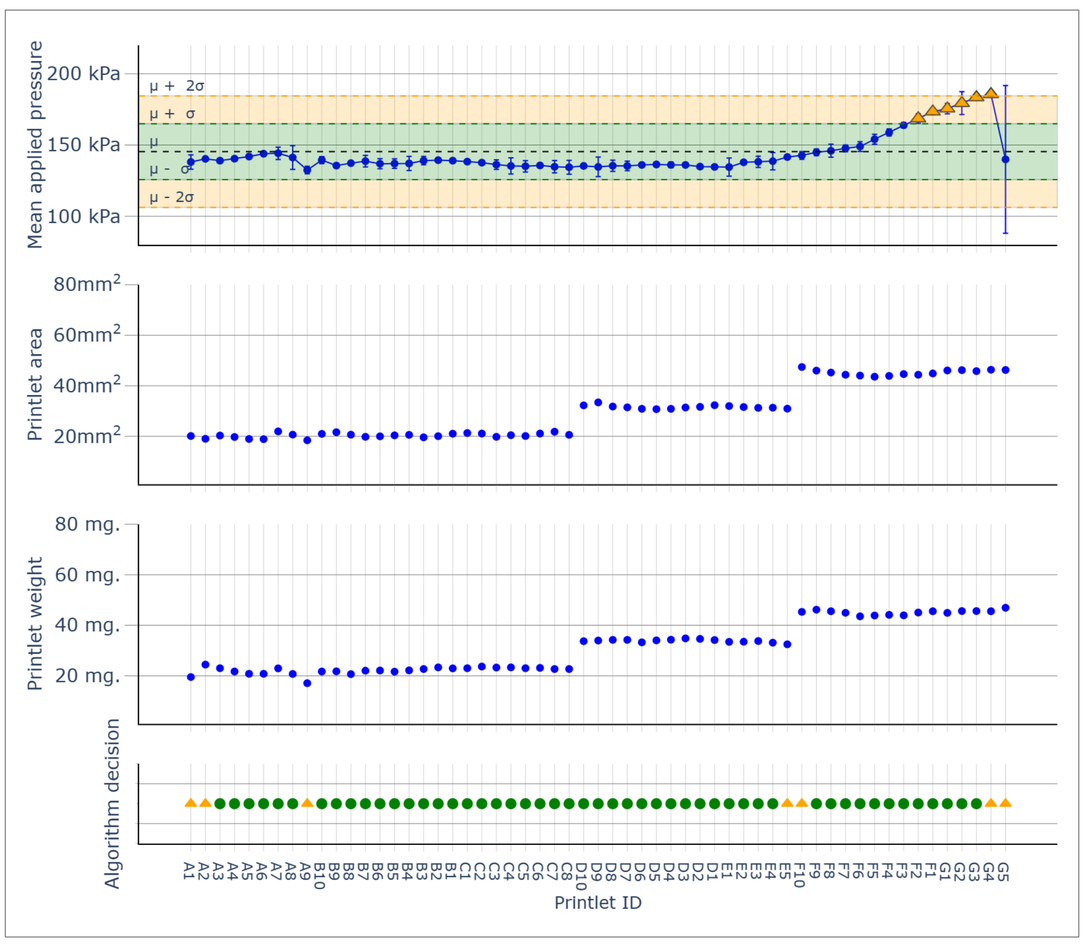

Figure 3. PATs obtained information and decision made by the python algorithm. Discarded printlet (▲) and accepted (●) printlet.

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