Characterization of micro-extrusion 3D printing for the production of dose homogeneous paediatrics orodispersibles Printlets™

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INTRODUCTION

The orodispersible tablets combines the advantages of the solid and oral liquid forms [1]. 3D printing technology allows to produce personalized medicine, since active pharmaceutical ingredient (API) dose can be modified by varying the volume of material to be extruded, as well as the final attributes of the dosage form by modifying printing parameters [2]. Hydrochlorothiazide (HCTZ) which is paediatric BCS class IV, was used as model drug due it has several therapeutic indications in the paediatric population [3].

OBJECTIVES

The aim of this study was to characterize micro-extrusion 3D printing as an accurate manufacturing process for the production of hydrochlorothiazide orodispersibles Printlets™ for paediatric use, meeting all the requirements of the European Pharmacopoeia.

MATERIALS AND METHODS

A wet mass were prepared with the following composition: **HCTZ** (40.4 % w/w), paediatric dose of 10.1 mg in 25 mg Printlets™, lactose monohydrate (18.2 % w/w), polyvinyl pyrrolidone 30K (8.1 % w/w), Ac-Di-Sol (30.3 % w/w), banana flavouring essence (3.0 % w/w) and a volume of purified water.

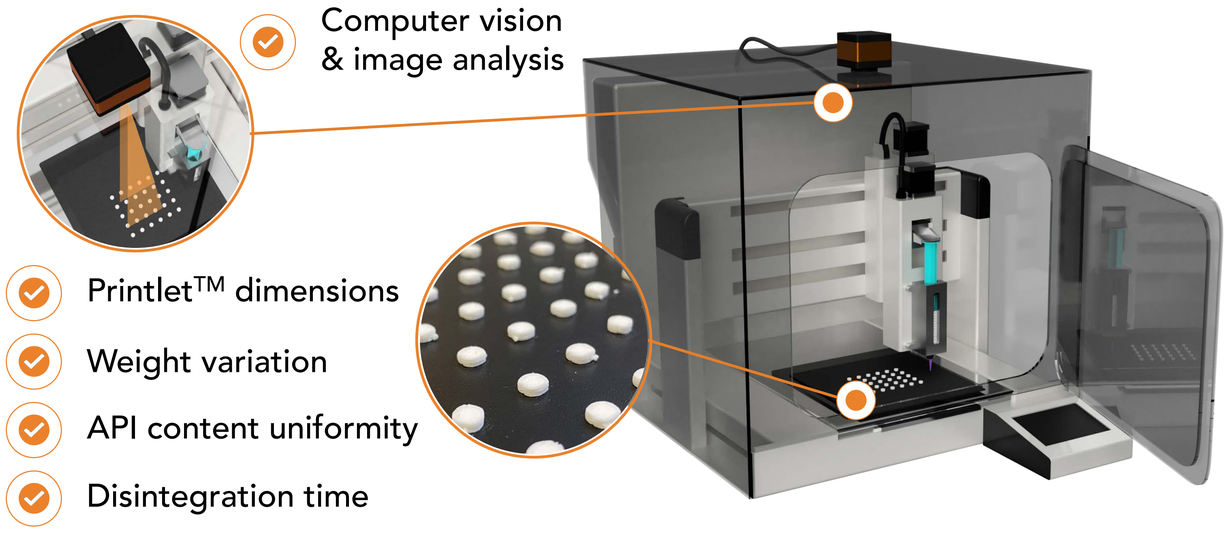

Figure 1. Schematic view of **FabRx M3dimaker** printer equipped with SSE technology. Studied quality attributes and top view camera for image analysis are shown in a detailed view.

RESULTS AND DISCUSSION

In-line quality control

In-line measurements offer the advantage of fast and high frequency data acquisition, it was possible to identify which of them did not meet the predefined quality attributes requirements.

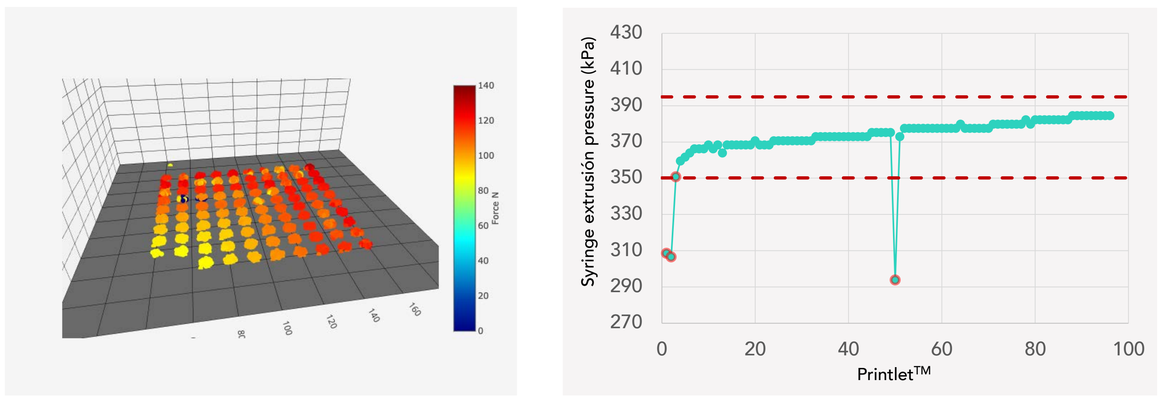

Figure 2. A. Syringe extrusion pressure measurements distributed in 3D space. B. *Shewhart chart* of batch 4. Dashed lines shows control limits (mean ± 6%). A slight increase was observed in the pressure as batch elaboration progressed

Dimensions of the Printlets™

After 6 hours of drying process (t_{6h}) the volume reduction was not homogeneous in all produced batches, obtaining **Printlets™** of **4.62 ± 0.197 mm** in diameter and less than **1.73 mm** thickness.

Weight variation

The **weight variation** remained under control (**SD < 1.0**), no differences were found between batches. Due to the average mass of each batch **(< 25 mg)** was below 40 mg, 2.9.6 assay of Eu. Ph. was required.

Uniformity of content of single-dose preparations

For batch 4 the **average content** was **10.32 ± 0,329 mg** of HCTZ, the average content (%) being inside the limits, and therefore **meeting the requirements** of the 2.9.6 assay of the Eu. Ph. Then, the **API was homogeneously distributed in the extruded wet mass**.

Disintegration time

Disintegration time of the Printlets™ was reduced by decreasing the infill in the gcode generated. For a 70% infill (Batch 4) **less than 180 seconds** was achieved, **meeting the requirements** of the Eu. Ph.

Table 1. Four batches modifying infill density printing parameter were carried out.

Batch	Shells	Solid layers	Infill density	Volume reduction (%)	Disintegration time (s)
1	All (5)	All (4)	All shells	32.54 ± 1.89	208 ± 15.13
2	2	1 & 1	90%	30.74 ± 4.24	175 ± 17.16
3	2	1 & 1	80%	28.49 ± 3.63	142 ± 19.14
4	2	1 & 1	70%	33,60 ± 4.01	128 ± 18.06

Computer vision & image analysis

The equivalent diameter values from the image analysis for initial time (t_{0h}) presented a **high coincidence** (**94.16% - 98.83%**) with the diameter established in the 3D model (6.00 mm x 2.40 mm).
The volume reduction was estimated as the difference between the equivalent diameter (t_{0h} vs t_{6h}), being lower in those produced with filling patterns (Batch 2-4).

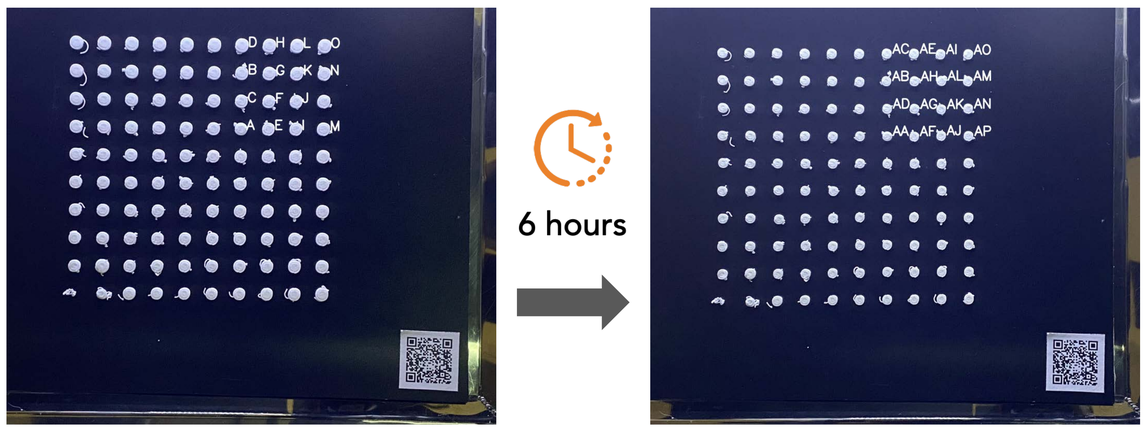

Figure 3. A. Batch 4 (t_{0h}). B. Batch 4 (t_{6h}). Using the Pyhton image analysis algorithm to detect Printlets™ with filament residues or irregular edges.

CONCLUSION

By in-line measurements it is possible to have a strict control of the process and determine which tablets have defects.
By adjusting the infill density, the disintegration time can be reduced without losing the quality attributes of the final tablet.
It is possible to obtain orodispersible Printlet™, of a **very small size (4.62 mm x 1.70 mm), with a high API load (> 40.4 %),** obtaining **high quality** Printlets™, ensuring dosage accuracy.

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