Machine learning-based image analysis of semisolid extrusion (SSE) pharmaceutical tablets on a tapering schedule

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INTRODUCTION

Dose adjustment of pharmaceutical oral dosage forms is often performed to achieve desired doses, such as to fit a tapering schedule. This is traditionally done via methods that lack high accuracy (i.e. tablet splitting or creation of liquid preparations).[1] Semisolid extrusion (SSE), a type of additive manufacturing (AM), has been shown to create desired doses with high accuracy and reproducibility. However, SSE and traditional dose-adjustment methods lack in-line validation, which can lead to dose inaccuracies or errors.[2]

Machine learning (ML) using image analysis (IA) of SSE tablets can provide necessary validation of tablets. This non-destructive method, where images are given to machine learning models (MLMs), can potentially allow for the validation of every tablet produced. An MLM is a model that can find patterns or make decisions on a new dataset based on previously provided data. In this study, newly created MLMs are used to analyze fluoxetine-containing SSE tablets printed on a tapering schedule to contain 5 mg, 3 mg, and 1.8 mg of fluoxetine.

MATERIALS AND METHODS

Materials

Crushed fluoxetine tablets (STADA® 20 mg tablets) were used as feedstock. PVAc-PVP (Kollidon SR®), HPMC (Benecel™ K100 LV PH PRM), and CMC (Avicel® PH-101) served as matrix. Pure fluoxetine hydrochloride (TCI Europe) was used for analytical method development.

Methods

The formulation was prepared based on the results of preliminary studies. It was made with mixing in a mortar and pestle. The obtained mixture was homogeneous, able to be loaded into the printer syringe, and printed well.

Cylindrical tablets all had the same height (2.05 mm) and diameters of 5.33 mm (1.8 mg dose), 7.79 mm (3 mg dose), and 9.84 mm (5 mg dose). A BioX 3D printer (Cellink, Gothenburg, Sweden) was used for printing. Print parameters included: nozzle diameter of 0.41 mm, extrusion rate of 1.7 µL/s, retraction rate of 70 µL/s, print speed of 10 mm/s, and a grid infill pattern with a 99% infill density. After printing, the tablets were dried overnight in a vacuum oven at 40 °C and 400 mbar. Mass and dimensions were determined, as well as drug content and in-vitro drug release.

Top and bottom images of tablets were gathered (Canon 550D, 18-55 mm standard lens). Supervised learning was done with TensorFlow 2.15.0 image analysis package and Keras sequential model.[3] To train the MLMs, images were allocated into different categories: (1) tablet tops and bottoms (i.e. tablet orientation), (2) by drug content, and (3) as mass outliers or non-outliers, according to European Pharmacopoeia specifications, for each drug content. A validation split of 20% of the images was used. Color images were resized to a height and width of 180 pixels. The Adam optimizer was used, data augmentation was done with random rotation, and a dropout of 20% of the output units was applied. To test the model, 10 images of each category were chosen at random and removed from the training and validation set. Training and validation accuracy and loss was examined for each scenario.

RESULTS AND DISCUSSION

Size and Mass Measurements

The tablets dimensions are relatively consistent across all doses (<6% in diameter, <9% in height, Table 1), with average diameters smaller than the designed dimensions. The average tablet height for the 3 mg API target dose tablets was 0.1 mm higher than the other doses. At current, this observation cannot be explained.

Target API Dose (mg)	Avg. Mass ±s.d. (mg)	Diameter ±s.d. (mm)	Height ±s.d. (mm)
1.8	33.7±2.8	5.1±0.3	2.1±0.1
3	63.9±2.6	7.2±0.3	2.2±0.2
5	105.9±7.2	9.3±0.3	2.1±0.1

Table 1. Mass and dimension results, ($\bar{x}$ ± s, n ≥ 70)

Drug Content

The drug content for the tablets was close to the intended value, with 1.81±0.03 mg, 3.05±0.04 mg, and 5.17±0.05 mg.

In-vitro Drug Release

Prolonged release behavior was observed for all tablet sizes. Approximately 80% drug release was

reached in the 1.8 mg tablets in 120 min, the 3 mg tablets in 180 min, and the 5 mg tablets in 210 min. Due to the long half-life of fluoxetine (1-4 days), these profiles are considered to be acceptable pharmacokinetically.

MLM Analysis

For category (1) investigation, a MLM successfully identified tablet top and bottom images correctly for all test images with over 99.87% confidence. The training and validation accuracy, meanwhile, reached over 98% and the training and validation loss were around 2%.

For category (2) investigation, a MLM was then used to identify images of tablets based on drug content. The MLM labelled all test images correctly to the respective dosages with over 99.87% confidence, with a training and validation accuracy close to 100% and a training and validation loss close to 0%.

The category (3) investigation is most critical for establishing MLM-based image analysis as in-line quality control in SSE. The MLM should identify outliers and non-outliers depending of specific dosages that, in our case, adhered to a tapering schedule for fluoxetine. When analyzing the mass uniformity of the target API dose tablets of 1.8 mg, 90% of test images were correctly identified by the MLM. Of the two misidentified images, the one identified with high confidence was 3.1% above the mass range extrema, while the image misidentified with low confidence had a height 8.6% higher than average. Height variations are difficult to identify with only top and bottom images. The training and validation accuracy reached around 90%, while the training and validation loss was around 25%.

The target API dose tablets of 3 mg had 75% of the test images correctly identified by the MLM. This lower percentage is likely due to the greater height variation for these tablets than the other two API doses. Training and validation accuracy reached around 80%, while training and validation loss were 40-45%.

Lastly, the target API dose tablets of 5 mg had results similar to the 1.8 mg tablets, with the MLM correctly identifying 90% of test images. The two misidentified images, as with the 1.8 mg tablets, had one image of a tablet 1.9% above the acceptable mass range and the other had a diameter 5.6% smaller than the average. The training and validation accuracy was 80-85% and the training and validation loss were around 40%.

Overall, the MLMs showed the ability to differentiate between tablets of different orientation (top and bottom), different dose of API, and mass range outliers robustly (example test images in Figure 1).

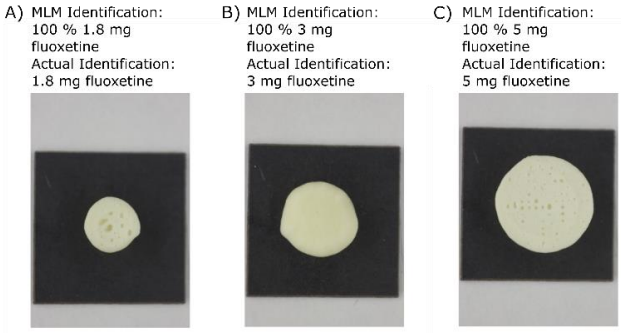

Figure 1. Example test images of tablets

Conclusion

Validation using MLMs for SSE tablet images shows promise when analyzing the three categories (tablet orientation, drug content, and mass range compliance). It is likely that additional visual information, e.g., tablet images from more angles, further improve the accuracy of this method. Still, the MLMs already had a high degree of success in identifying tablets from just two angles (top and bottom). This non-destructive, time- and labor-saving method could allow for validation of every tablet, which, paired with SSE, can provide patients with a more accurate, quality-assured tablet.

References

[1] Johannesson J., Hansson P., Bergström C.A.S., Paulsson M. Manipulations and age-appropriateness of oral medications in pediatric oncology patients in Sweden: Need for personalized dosage forms. Biomedicine & Pharmacotherapy, 146 (2022).

[2] Watson C., Webb E.A., Kerr S., Davies J.H., Stirling H., Batchelor H. How close is the dose? Manipulation of 10 mg hydrocortisone tablets to provide appropriate doses to children. International Journal of Pharmaceutics 545(1-2):57-63 (2018)

[3] Chollet, F. Keras: The Python Deep Learning library. (2018)