Journal Pre-proofs

Real-time coating thickness measurement and defect recognition of film coated tablets with machine vision and deep learning

Máté Ficzere, Lilla Alexandra Mészáros, Nikolett Kállai-Szabó, Andrea Kovács, István Antal, Zsombor Kristóf Nagy, Dorián László Galata

PII: S0378-5173(22)00512-9
DOI: https://doi.org/10.1016/j.ijpharm.2022.121957
Reference: IJP 121957

To appear in: *International Journal of Pharmaceutics*

Received Date: 6 April 2022
Revised Date: 20 June 2022
Accepted Date: 21 June 2022

Real-time coating thickness measurement and defect recognition of film coated tablets with machine vision and deep learning

Máté Ficzere[1], Lilla Alexandra Mészáros[1], Nikolett Kállai-Szabó*[2], Andrea Kovács[2], István Antal[2], Zsombor Kristóf Nagy**[1], Dorián László Galata[1]

1 Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1111 Budapest, Műegyetem rakpart 3

2 Department of Pharmaceutics, Semmelweis University, H-1092 Budapest, Hőgyes Endre street 7-9

* Correspondence: kallai.nikolett@pharma.semmelweis-univ.hu; Tel.: +36 1 459 1500

** Correspondence: zsknagy@oct.bme.hu; Tel.: +36 1 463 4129

Abstract

This paper presents a system, where images acquired with a digital camera are coupled with image analysis and deep learning to identify and categorize film coating defects and to measure the film coating thickness of tablets. There were 5 different classes of defective tablets, and the YOLOv5 algorithm was utilized to recognize defects, the accuracy of the classification was 98.2%. In order to characterize coating thickness, the diameter of the tablets in pixels was measured, which was used to measure the coating thickness of the tablets. The proposed system can be easily scaled up to match the production capability of continuous film coaters. With the developed technique, the complete screening of the produced tablets can be achieved in real-time resulting in the improvement of quality control.

Keywords

Film coating, Deep learning, YOLOv5, Process Analytical Technology, Machine vision, Object recognition, Coating thickness measurement

1. Introduction

In the pharmaceutical industry, a paradigm shift is underway from traditional batch to continuous technologies, which can increase flexibility and efficiency, while lowering both capital and operating expenses (O'Connor and Lee, 2017; Rantanen and Khinast, 2015). Continuous manufacturing also requires an in depth understanding of the processes and improved non-destructive analytical sensors, capable of highly accurate, in-line real-time measurements (Mészáros et al., 2020; Pauli et al., 2019). By publishing their guidelines, the regulatory authorities also support this direction in innovation and development (Food and Drug Administration, 2004). Therefore, the pharmaceutical industry is increasingly focusing on Process Analytical Technology (PAT) and Quality by Design approaches to assure the quality of the materials and products at all stages during the manufacturing processes (Casian et al., 2019; Pramod et al., 2016).

PAT is a particularly fitting approach for complex pharmaceutical technological operations, such as the film coating of tablets, where small deviations of critical process parameters (CPP) can significantly alter the quality of the final product (Korasa and Vrečer, 2018; Simon et al., 2015). Solid oral dosage forms are film coated to improve patient compliance by masking unpleasant odours and taste, to protect the tablets from environmental factors, to improve their visual appearance with colours or to modify the kinetics of the drug release (Felton, 2013). The two widespread film coating technologies in the industry, fluid bed coating and pan coating are currently implemented mostly as batch processes (Seo et al., 2020). Continuous film coating is gaining popularity, thanks to its increased throughput and significantly reduced residence time at stressful conditions (Porter, 2021; Zaid, 2020). The most important quality attributes (QA) of film coated products are the thickness and the distribution of the coating (Dreu et al., 2012). They should be visually screened, as malfunctions during the coating operations can result in tablets with damaged or partially missing coating which can ruin both their functionality and appearance (Podrekar et al., 2018). Considering the PAT-initiative, several real-time methods emerged to replace the traditional, cumbersome off-line measurements (Ficzere et al., 2021) of weighing, optical and scanning electron microscopy. The candidates for PAT sensors are near infrared or Raman spectroscopy (De Beer et al., 2011; Paudel et al., 2015), optical coherence tomography (OCT) (Lin et al., 2017) and terahertz pulsed imaging (TPI) (Ho et al., 2007; Lin et al., 2015; Zhong et al., 2011). OCT is based on the phenomenon that a portion of incident light is reflected when it encounters a surface where the refractive index (Lin et al., 2018). In the case of coated tablets, a fraction of the light is reflected when it reaches the surface of the tablet, while the remaining photons penetrate the coating and are reflected when they arrive at the interface between the coating and the core of the tablet. By measuring the reflected light, an image can be obtained where areas with different refractive index can be distinguished, this yields a great opportunity to measure the thickness of the film coating. TPI also exploits changes in the refractive index, however this time pulses of terahertz waveforms are applied (Alves-Lima et al., 2020). These pulses can also be reflected when the refractive index changes, thus measuring the reflected waves can be used to infer the thickness of layers with different refractive indices. Both OCT and TPI have been used for off-line and in-line analysis of coated tablets. Due to the wavelength of the applied light, OCT is better for measuring thin coatings (10-60 μm), while TPI is recommended for coating thicknesses above 40 μm, basically in cases where a weight gain of 4-5% is achieved. Both of these techniques yield a plethora of information about the coating process, however they require expensive hardware, and the analysis of the acquired data can be challenging. Therefore, it is of interest to test other techniques, which can realize similar measurements with less sophisticated equipment and data processing. Image analysis is an excellent candidate for this, because the quality of the product can be characterized by an increase in size and changes in colour during or after the film coating process (Galata et al., 2021). A handful off-line and in-line cases have been reported, where image analysis was used to track the process during either fluid bed coating (Kadunc et al., 2014; Nikowitz et al., 2014) or pan coating (García-Muñoz and Carmody, 2010; Toschkoff et al., 2016) by investigating the tablets inside the coaters.

It is just as important to monitor the tablets after they have been discharged from the coater. Nowadays it is part of the recommended quality assurance standard to inspect each tablet before packaging, which is usually done visually either by humans or machines (Derganc et al., 2003; Petersen et al., 2021). Many companies produce and market various automated visual tablet inspection systems, which are robust and flexible enough to be able to inspect a large variety of tablets and defects. This comes at the expense of low sensitivity, a lower detection rate of smaller errors and suboptimal performance for more complicated tablet designs, such as tablets with imprints or textures. Furthermore, they cannot be used to measure certain critical properties of the tablets, such as their diameter. Možina et al. (Možina et al., 2013) used a statistical appearance evaluation method based solely on rotation information to detect imprint errors on film coated tablets. They found that they could reduce the required computing complexity by half and the method was proven to be more effective in the evaluation of real images compared to their previous, principal component analysis (PCA) based model.

To analyse the data gathered from different PAT sensors, various data processing methods have been implemented, particularly PCA and partial least squares (PLS) (Borsos et al., 2017; Simon et al., 2010). These have already been used for the multivariate image analysis of the coating uniformity of tablets (García-Muñoz and Gierer, 2010). However, with the increasing complexity of the input data, these processes might not be powerful enough to find the underlying patterns.

Convolutional neural network (CNN) methods can provide possibilities for handling complex datasets with different inputs (Hirschberg et al., 2020). Thanks to the major breakthroughs in the field of CNNs within the recent years, their increased inference speed and accuracy makes real-time object detection and recognition possible. There are several pre-trained CNNs that can be fine-tuned for a variety of tasks, showing good performance metrics and being computationally inexpensive (Almadhoun and Abu-Naser, 2021; Kasper-Eulaers et al., 2021).

YOLO (You Only Look Once) algorithms use the entire image as an input for the network, and directly predict the position and the category of the bounding box of objects based on the characteristics of the whole image (Yao et al., 2021; Zhao et al., 2021). YOLOv5, which is part of the YOLO family, was pre-trained on the extensive COCO (Common Objects in Context) dataset, which contains 80 different classes and over 200,000 labelled images. YOLOv5 has significantly improved training and processing times and showed that it can outperform other object recognition algorithms (Darma et al., 2021; Zhou et al., 2021).

There are several cases in the pharmaceutical industry, where deep learning methods have been applied to improve established data processing methods (Ekins, 2016). Deep learning methods have also been implemented for the inspection of the properties of tablets. Ma et al. (Ma et al., 2020) developed an analysis program with an integrated CNN to fully automate the X-ray computed tomography image analysis of tablets. They achieved an average accuracy of 94% for internal crack detection and significantly reduced the measurement time compared to manual user analysis. CNNs have also been utilized in the analysis of OCT images by Wolfgang et al. (Wolfgang et al., 2020), it was shown that they are highly accurate in the segmentation of the coating layer. The application of recurrent neural networks has been demonstrated in the case waveform selection during TPI by Li et al. (Li et al., 2022). Hirschberg et al. (Hirschberg et al., 2020) used images acquired from a conventional office scanner to classify more than 2000 film coated tablets based on their level of coating. They found that the PLS method was faster than the CNN one, however its success of classification was 97.6% compared to the 99.6 % achieved by the neural network. Up to this point, no cases have been published, where a system was set up to observe the diameter and coating integrity of tablets as a real-time PAT tool.

The purpose of this study was the development of a system, which can be used as an in-line tool for accurate tablet diameter measurement and the identification of coating defects in the case of tablets moving on a conveyor. The recently developed YOLOv5 algorithm is utilized for the recognition of typical coating defects, while the diameter of the tablets is determined using classical image analysis techniques. The proposed measurement technique has great potential in the in-line monitoring of continuous film coating, as it can be performed with a lower investment and operational cost compared to already existing solutions.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC; Avicel© PH-302) was obtained from FMC Corp. (Philadelphia, Pennsylvania, USA) and magnesium stearate was purchased from Molar Chemicals (Budapest, Hungary). The low viscosity Opadry®QX, a kind gift of Colorcon Inc. (Dartford, UK), was used for coating process.

2.2. Methods

2.2.1. Preparation of tablets

The 200 mg (set weight) tablets consisted of 99.00 %, w/w Avicel PH 302, and 1.00 % w/w of Mg-stearate as a lubricant. The homogeneous blend was directly compressed on a single punch tablet press (Fette Exacta 1, Fette Compacting GmbH, Schwarzenbek, Germany) fitted with round, biconvex without break line punches. The diameters of punches and die were 8 mm. During the process, set compression force was adjusted so that the wear loss of the tablets was minimal and the hardness was adequate for the next step of coating.

2.2.2. Coating of tablets

Coating of tablets (batch size: 300 g) was performed in a lab-scale pan coater (ProCepT 4M8Trix, Zelzate, Belgium) equipped with a standard (3 mm) perforated drum, which was mounted with wing-like baffles to help the adequate tablet bed mixing and even coating processes. The Schlick nozzle (diameter: 0.8 mm) with Anti Bearding Cap technology was integrated into the set-up, which generated an elliptical spray pattern. The tablet bed was prewarmed to 40 °C before spraying the 30% Opadry®QX coating dispersion, which was prepared by mixing 210 g water with 90 g Opadry®QX powder for 30 minutes. The parameters set during spraying are shown in *Table 1*. After spraying each 20 g of coating material, a sample of about 1.6-2.0 g (8-10 pieces) was taken. The process was discontinued at a total weight of 140 g of coating liquid sprayed onto the surface of tablets, followed by drying for 5 minutes. To produce tablets for the purpose of testing the coating thickness measurement method, a second batch of tablets was film coated until 64 g of coating liquid was applied (tablets were sampled after each 16 g of coating material), while other process parameters were kept at the same settings.

Table 1. Process conditions for film coating.

Process Parameters	Units	Value
Inlet air flow	m^3/min	0.40
Inlet air temperature	°C	60.0±5.0
Product temperature	°C	35.0±5.0
Air out temperature	°C	35.0±5.0
Drum speed	rpm	30.0
Underpressure cabinet	mbar	4.1±0.3
Liquid pump speed	%	10.0
Airflow atomising nozzle	L/min	19.4±0.1

Atomising air pressure	bar	1.0
Pattern airflow	L/min	22.5±0.1
Pattern air pressure	bar	1.3
Total dosed liquid weight	g	140.0

2.2.3. Creation of defective tablets

Seven types of defective tablets were created for the investigation of film coated tablet defect recognition. Uncoated tablets were sampled from the batch of tablet cores. To produce tablets with edge defects, the edges of tablets were grated using a rasp. Dotted defects were created by marking the tablets with a felt pen. Surface defect tablets were created in three different ways. The first type was manufactured by scratching the surface with a metal spatula, the second type was produced by sticking two intact tablets together using a drop of water and pulling them apart by hand after 20 minutes. The third set of these tablets was created by dripping a concentrated suspension made of OpadryQX and water onto the tablets and letting them dry. Lastly, twin tablets were manufactured by sticking together the sides of tablets by a drop of water. *Fig.1.* presents the type of tablets used during the experiments.

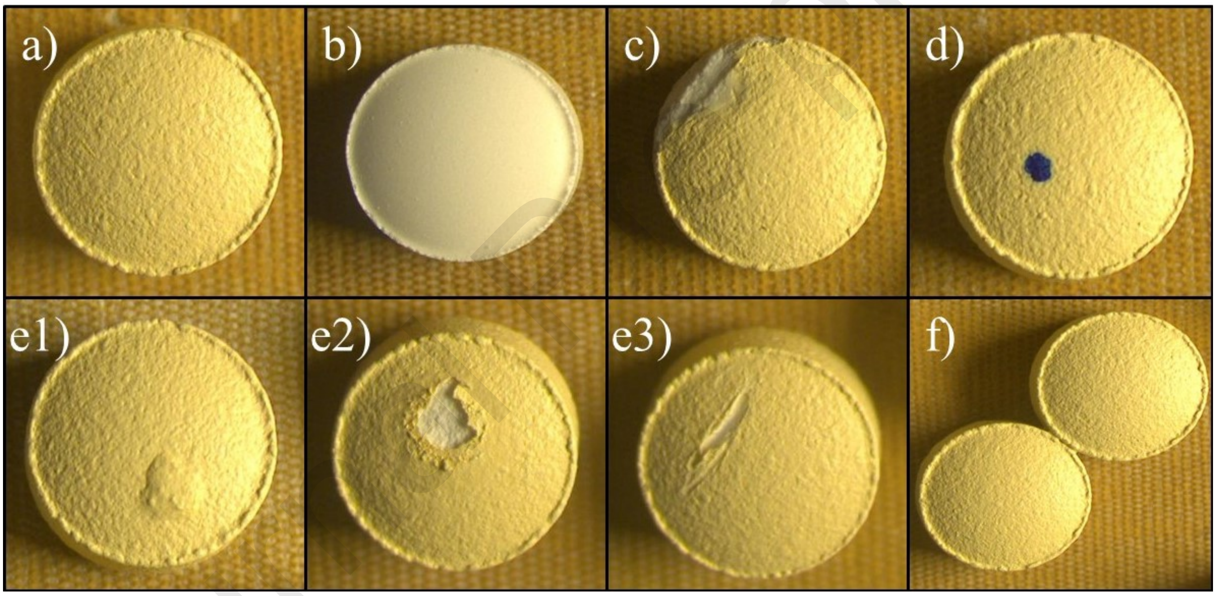


Fig. 1. Types of created defective tablets. (a) Intact tablet, (b) Uncoated tablet, (c) Edge defect tablet, (d) Dotted defect tablet, (e1) Uneven surface tablet produced by dripping film coating solution, (e2) Uneven surface tablet created by sticking two intact tablets together, (e3) Uneven surface tablet created with a metal spatula, (f) Twin tablets.

2.2.4. Real-time imaging

During the classification experiments, the film coated tablets were distributed on a conveyor belt (Brabender Technologie, Duisburg, Germany), which was operated at a speed of 0.083 m/s. A Basler acA4112-30uc (Basler, Germany) area scan, 12-megapixel RGB camera equipped with a Basler MEGA TS1214-MP objective (Basler, Ahrensburg, Germany) was used for image acquisition. The communication between the camera and the computer was carried out via an USB 3.0 port. A 12W LED panel providing evenly distributed light (Mentavill, Székesfehérvár, Hungary) was stationed on an in-house built stand to illuminate the tablets from an angle of

75°. 4096 by 3000 pixels images were obtained with a rate of 15 frames per second, while the exposure time was set to 3 ms. The setup can be viewed on *Fig. 2a*.

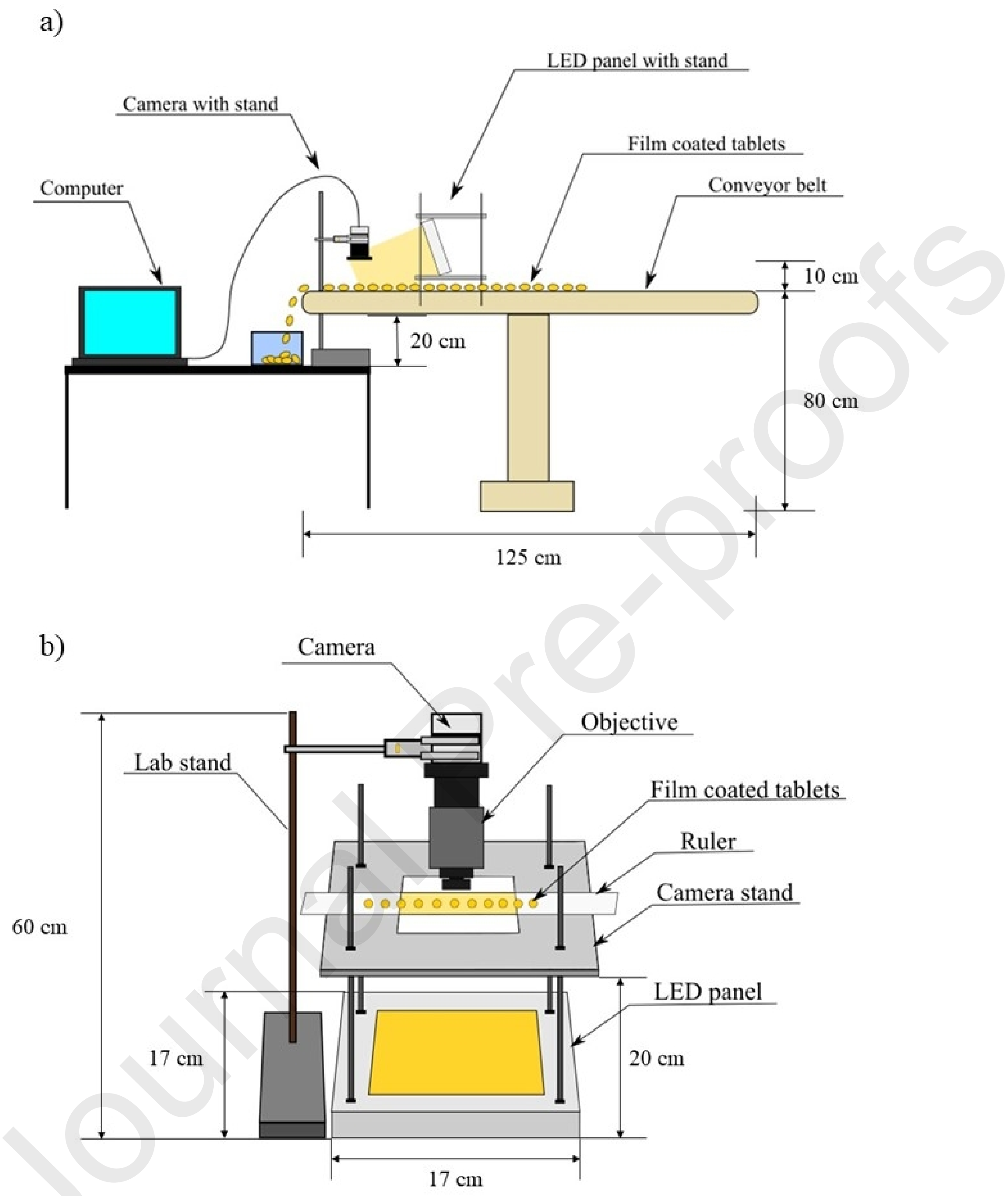


Fig. 2. a) Real-time imaging setup for the classification of film coated tablets. b) Setup for the measurement of film coating thickness.

The setup applied for film coating thickness measurement was using the same camera. The camera was equipped with a Mitutoyo 375-036-2 objective (Mitutoyo Corporation, Japan) with a telescope. The tablets were placed on a translucent surface and were illuminated from below with the LED-panel. The size of the images was also 4096 by 3000 pixels, with an exposure time of 3 ms. The setup is presented on *Fig. 2b*.

2.2.5. Training the YOLOv5 algorithm for tablet classification

The YOLOv5 model's yolov5s version (Ultralytics, 2021) was trained using Google Colab, with the following 5 classes: uneven surface, edge defect, dotted defect, uncoated tablet, and twinning tablets, while the tablets where no defects were detected were considered as intact tablets. For the training of the algorithm, the tablets were photographed in multiple groups by classes. Each group consisted of approximately 20 tablets and was photographed once. A total of 44 images was split into training and validation datasets, and they were annotated manually using bounding boxes for the defects (*Table 2*). The model was trained for 200 epochs, with an input image size of 2500 by 2500 pixels and with a confidence of 0.25. The training adjusted the pre-trained publicly available YOLOv5 model, as a result the weight values of the new model were acquired. This was used for the real-time defect detection experiments.

Table 2. Number of images used for training, validation and testing of the YOLOv5 algorithm.

	Number of images
Training	32
Validation	12
Testing	176

2.2.6. Measuring the diameter of tablets with image analysis

The acquired images were analysed with Matlab 9.8.0.1721703 (Mathworks, Natick, MA, USA). The analysis was performed using a custom-made Matlab algorithm (*Fig. 3*). For the first step, the background had to be separated from the pixels of the tablet. For this, the image was converted to the CIELAB colour space, where a threshold was set for the L* (perceptual lightness) values, if it was higher than 20, then the pixel was considered a part of the background. After this, the minimal and maximal Feret-diameter of the tablets were calculated, their mean resulted in the tablet's average Feret-diameter.

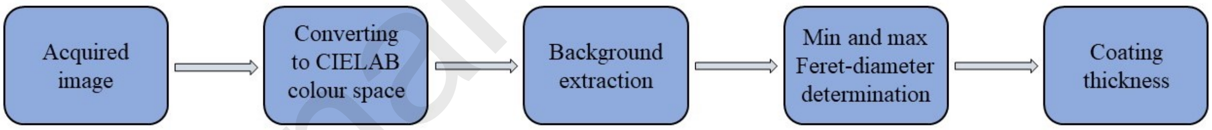


Fig. 3. The structure of the developed Matlab algorithm for coating thickness measurement.

In accordance with the current pharmaceutical practice, we intended to characterize the coating thickness of tablets by their weight gain, therefore their individual weight was recorded on an analytical scale. After this, a first order polynomial was fitted for the coating thickness measured by image analysis (it was calculated by subtracting the average diameter of the uncoated tablets from each measured tablet's diameter) and the weight increase values of the 140 tablets from the first batch. The 64 tablets from the second batch were used for validation. To evaluate the method's ability to accurately predict the weight gain of tablets, the root mean squared error of prediction (RMSEP) was calculated using the following formula (Eq. (1)):

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n}\left(y_{predicted} - y_{measured}\right)^2}{n}} \#(1)$$

where n is the number of samples, $y_{predicted}$ is the weight increase value obtained using the first order polynomial and image analysis and $y_{measured}$ is the weight gain measured with the scale.

3. Results and discussion

3.1. Physical characterization of uncoated and coated tablets

For the studies, the tablets were randomly selected from the batch and the values given in the table give the mean and standard deviation. The individual mass (n=20; Sartorius LA 230S, Sartorius AG, Goettingen, Germany), tensile strength (n=10; TBH 200 TD, Erweka instrument GmbH, Germany) and friability (Erweka single drum friability tester; Offenbach/Main, Germany) of uncoated tablets and coated tablets from the first batch were measured. *Table 3.* summarizes the results of the physical examinations. Based on the examination of mass uniformity and friability, it can be concluded that the uncoated tablet properties are acceptable by Ph. Eur. criteria (European Pharmacopoeia Commission, 2019b). As expected, the tablets became harder as a result of the coating process, and their friability value (European Pharmacopoeia Commission, 2019a) was further improved.

Table 3. Physical characteristics of uncoated and coated tablets from the first batch, where SD is the standard deviation and RSD is the relative standard deviation of mass.

	Individual mass (mg) (n=20; mean ± SD)	**RSD (%)**	**Tensile strength (N)** (n=10; mean ± SD)	**Friability (%)**
Uncoated tablet	206.77 ± 1.023	0.49	131.0 ± 4.10	0.29
Coated tablet	220.70 ± 1.023	0.46	166.1 ± 5.43	0.08

It can be observed that the applied film coating is very evenly distributed on the tablets, given that the 0.49% RSD did not change significantly during the coating process. Therefore, weight measurement can be used as a reference method to track the coating level of tablets.

3.2. Tablet defect classification

The trained YOLOv5 model was used for the categorization of defective tablets on images acquired real-time. For this, 284 tablets were mixed together and distributed randomly along the conveyor belt, with their defective sides up (if there was any). Approximately five tablets were placed in one row, with roughly half a tablet distance from each other in all directions. Then, the conveyor belt was started, and a serial image sequence was captured with the camera. The 176 taken images were evaluated with the trained YOLOv5 model. The program drew the predicted bounding boxes onto the images, two of them are presented on *Fig. 4*. Furthermore, a video was compiled from the captured images, which can be viewed in the supplementary (*Svid*).

Fig. 4. Two images with classified tablets. Bounding box colouring: yellow: uncoated tablet; light orange: dotted defect; dark orange: twinning tablets; red: uneven surface; pink: edge defect.

To evaluate the accuracy of the YOLOv5 model's prediction, we investigated every appearance of every tablet on the images. Each tablet was usually present on 15 continuous images. If a tablet was correctly categorized on more than one occasion, it was considered well-recognized. Out of the acquired data, a confusion chart was constructed, presented on *Fig. 5*.

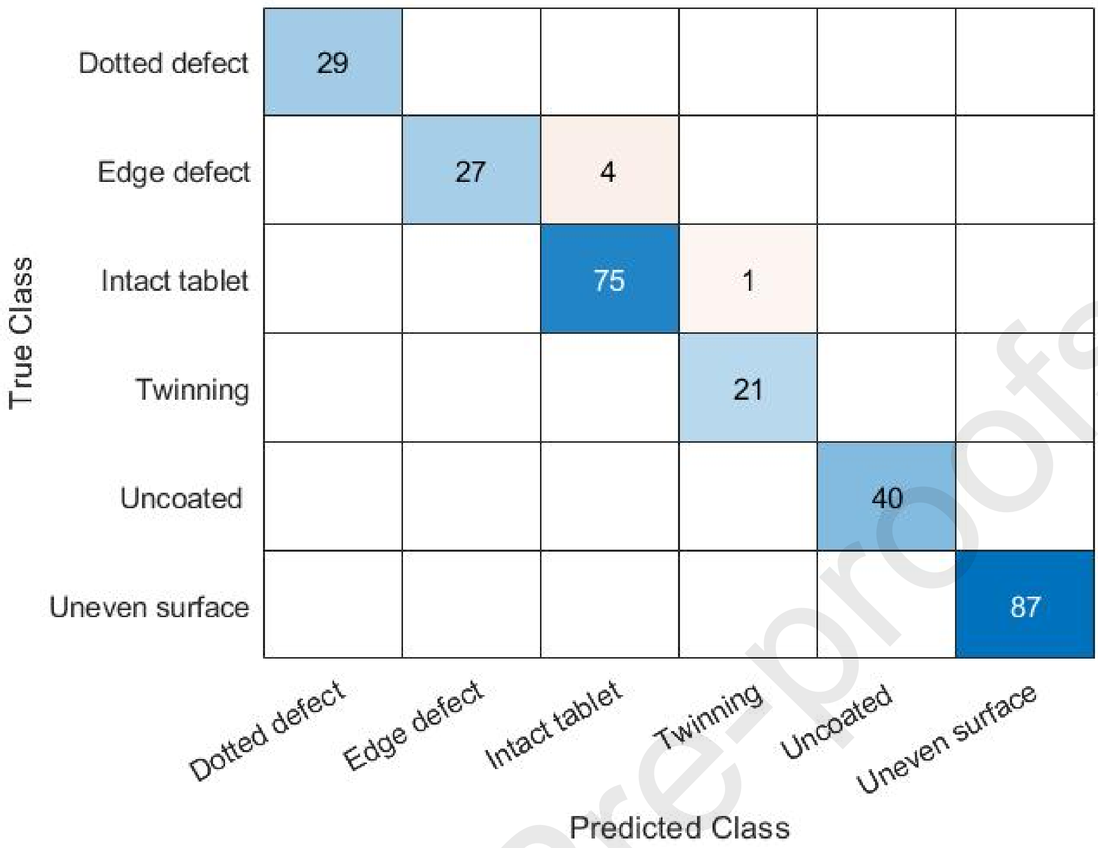


Fig. 5. The confusion chart of the classification.

As it can be observed, there were only a few mix-ups and in all but one of those cases an edge defect was not recognised and was considered as an intact tablet. Furthermore, as it can be observed on *Fig. 4.*, some defects have multiple bounding boxes drawn around them. However, it does not cause interference, because the goal was to identify each defect at least once. Generally, defects with a size of at least 1 mm can be reliably recognized. The model could accurately predict the class of the tablets 98.24% of the time. The sensitivity of the method (the ratio of correctly found defective tablets and the total number of defective tablets) is 98.07% (204 defective tablets were found from a total of 208), while the sensitivity (the ratio of tablets correctly found to be intact and the total number of intact tablets) is 98.68% (75 out of 76 intact tablets were correctly found intact).

When compared to previously published defect recognition algorithms which are based on classical image analysis (Duong et al., 2014; Rani et al., 2015), one would assume that the computational cost favors the classical methods. Using the Tesla K80 GPU (this model was released in 2014) provided by the free version of Google Colab, on average 0.21 s was needed to process an image, this is processing speed a bit less than 5 fps. However, the performance of the utilized GPU is modest in comparison with the currently available top models, which can be up to 5 times faster. Consequently, a processing speed of at least 20 fps should be feasible with newer hardware, which should be enough for this kind of application. The accuracy reported by Rani et al. (Rani et al., 2015) is similar to our results, thus the performance of the methods is similarly good. A possible advantage of deep learning-based defect recognition is that it does not require arbitrarily defined features (which are sometimes very complex) for each kind of defect, instead only a few annotated images are required. The CNN is then able to learn the features belonging to each class on its own, therefore it might find features which would never occur to a human. This can lead to more robust defect detection, where small changes in the environment or illumination does not severely impact the applicability of the method. Another advantage is that the training of the YOLO algorithm can be performed with tablets of different shapes and colours imaged. When the training dataset is diverse enough, the defect recognition method could be applicable in a large variety of scenarios. A well-trained YOLO algorithm can be used for detection in different types of environments without additional training or modifications. Liu el al. (Liu et al., 2021) used YOLOv5 to detect railway signals on a dataset consisting of images taken from subways above ground at day and night as well as in underground tunnels and compared its effectiveness to other methods. They found that the YOLOv5 model had an accuracy of 97.2% with a processing speed of 100 frames per second, surpassing the other methods in effectiveness at all types of backgrounds. Considering the capability of recent object detection techniques, it can be assumed that if our current dataset would be augmented with tablets of different color, shape and embossings, it would be possible to create a model that can recognize the defects on basically all tablet types. However, this assumption must be examined with further experiments, based on the current results it cannot be expected that without said augmentations our model would work accurately with different tablet types. In order to create a reliable measurement setup, lighting and the speed of the conveyor must be optimized. The lighting should be strong enough to enable a low exposure time and thus a fast conveyor speed without blurring. On the other hand, if it is too strong, then the whole surface of the tablets would become too bright, making it harder to distinguish between intact tablet surface and defects.

3.3. Measurement of film coating thickness

The current quality control process for the tracking of continuous film coating is sampling and weighing 100 tablets at given timepoints and examining whether they have the correct amount of weight gain. However, with this approach, only a small number of tablets are inspected. Furthermore, this method does not account for individual tablets, and even if 100 tablets have the correct average weight, there might be outliers with unacceptably low coating thickness. This is especially problematic in the case of a functional coating, where the release kinetics of the drug is impacted by the quality of the coating. These tablets with a thin coating might visually appear to be intact, therefore it is very unlikely that they are found during the traditional inspection procedure. To solve this issue, we found that the experimental setup used for tablet defect detection can be easily augmented in a way, that the diameter of the tablets becomes measurable. This augmentation requires an objective with a higher resolution and a conveyor with a translucent surface, below which an illumination device is placed. From the diameter, the thickness of the coating can be calculated, which should correlate with the weight of tablets. For the determination of coating thickness, we used the reference point of average diameter of the uncoated tablets measured with the camera. The weight increase of tablets was obtained using the average weight of the uncoated tablets as reference. *Fig. 6.* presents the images and properties of three tablets from different samples from the first batch. *Fig. 7.* shows the first order polynomial fitted to the coating thickness measured using image analysis and the weight gain of the tablets of the first batch.

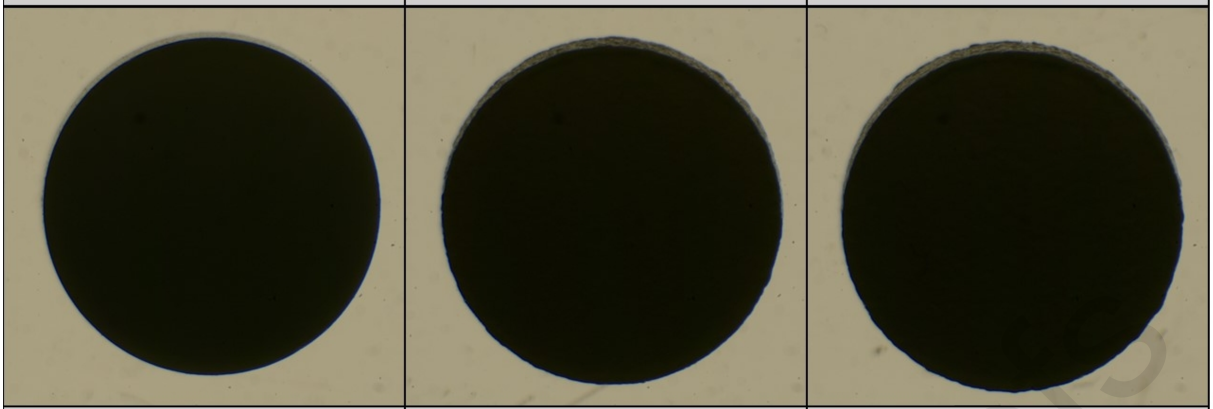
Uncoated	Moderately coated	Fully coated
		
D_{ia}=8.026 mm m=207.8 mg m_p=206.3 mg	D_{ia}=8.115 mm m=214.5 mg m_p=216.1 mg	D_{ia}=8.167 mm m=224.5 mg m_p=222.5 mg

Fig. 6. The images, the measured and predicted properties of three tablets from different samples. D_{ia}: diameter measured with image analysis, m: weight of tablet, m_p=weight predicted using D_{ia}.

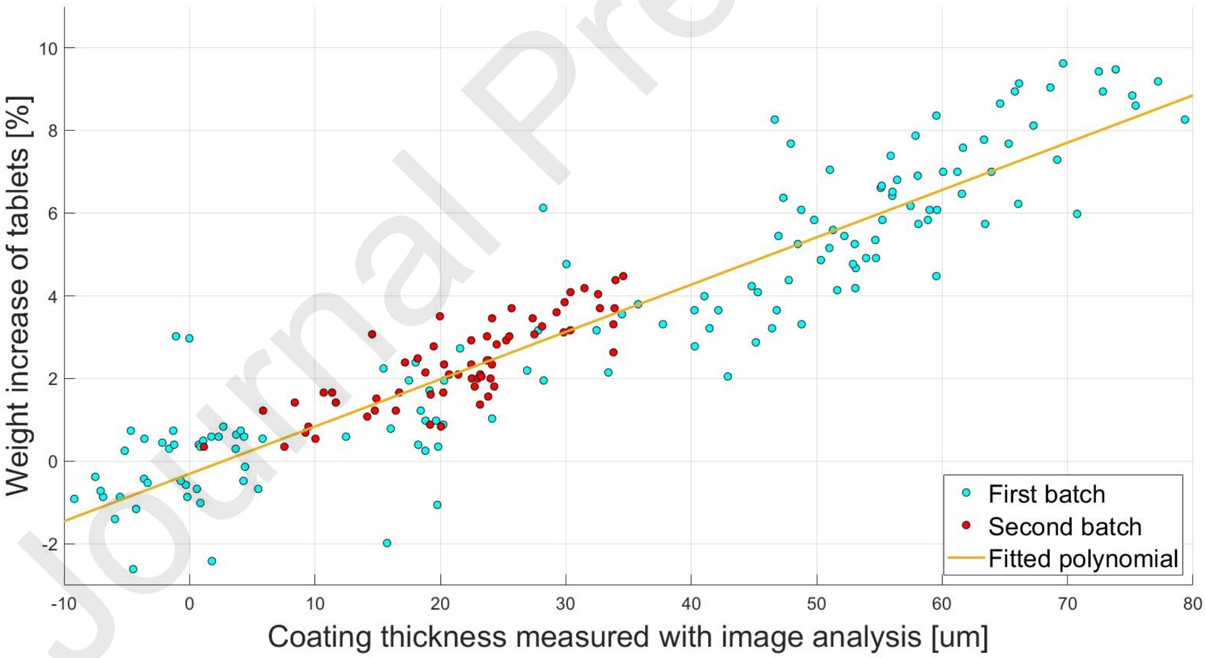


Fig. 7. The weight increase of the tablets as a function of their coating thickness measured with image analysis.

The second batch was used for validation, resulting in an RMSEP of 0.62% weight gain. If the target weight gain is 5%, which is common in the case of functional coatings, this results in a relative error of 12.5%. This means that the technique can accurately determine the weight gain of each tablet. Furthermore, the proposed system is able to inspect all the manufactured film coated tablets, resulting in 100% screening. This could be used to monitor the continuous film coating process, to set the process parameters to the optimal values and to discover individual tablets with thinner coating than desired.

3.4. Throughput of the analytic method

It is important to determine the throughput of the proposed defect recognition and classification system to compare it to the productivity of industrial scale continuous film coaters.

The conveyor belt was operated at its maximum speed of 0.083 m/s = 83 mm/s. If the space left out between tablets is equal to the length of a half tablet (a tablet is 8 mm long), then a tablet and the space behind it takes up 12 mm. During the experiment, the tablets were organized into 5 rows on the conveyor belt, therefore the following equation (Eq. (2)) could be used to calculate the tablet throughput per hour:

$$T = \frac{v \, * \, n}{l} = \frac{83 \frac{mm}{s} \, * \, 5 \, n_r}{12 \, mm} * 3600 \frac{s}{h} = 124{,}500 \frac{n_r}{h} \#(2)$$

where v is the speed of the conveyor belt [mm/s], n_r is the number of rows [n_r], l is the length of a tablet and the space behind it combined [mm], T is the throughput of the system [tablet/hour].

In the case of film coating thickness measurement, a similar setup was used, however there was only a single row of tablets, therefore it can be calculated that the system could inspect a total of 24,900 tablets per hour.

These amounts are already serviceable, however with utilizing state of the art equipment, they could be easily increased. The first opportunity is raising the speed of the conveyor belt. However, by increasing the speed while the exposure time is fixed, above a certain threshold the images will become blurry. We conducted in-house experiments and found that clear images can be captured of a tablet moving at the speed of 200 mm/s with an exposure time of 1 ms. This alone would increase the throughput by 241%, resulting in 300,000 tablets processed in an hour in the case of defect recognition. This is a shorter exposure time compared to the 3 ms that was applied during our experiments, but with a change in the lights and their setup, it can be achieved without image quality loss. With more advanced lighting the exposure time can be lowered further, making higher conveyor speeds and throughputs possible.

The second opportunity is increasing the number of rows of tablets. This is a self-evident advantage of conveyor belts capable of higher speeds, as they tend to be wider as well. By implementing the changes presented in the previous paragraph and increasing the number of rows from 5 to 10 the system could analyse up to 600,000 tablets per hour, with still further room left for improvement. This amount matches the production rate of tablet presses and continuous film coaters.

This novel method of film coated tablet inspection is easy to install, has a low investment cost, requires a small amount of space and its capacity is easily expandable. The line could also be coupled with an ejection system, to discharge the identified defective tablets. Furthermore, this inexpensive method can determine the thickness of the film coated tablets fast and accurately, which is a great advantage compared to currently widespread appliances.

4. Conclusions

This work presented a novel PAT system, in which machine vision was combined with deep learning and image analysis to classify tablet coating defects and determine the coating thickness of film coated tablets. A YOLOv5 model was trained for defect recognition, and it showed that it is a capable tool for real-time defect detection and classification with great accuracy. We demonstrated that it is possible to precisely measure the weight gain of a film coated tablet by determining its diameter using image analysis. The theoretical scale-up showed that the proposed system could comfortably handle the throughput of a fully continuous manufacturing line.

The developed method can possibly be used for the measurement of tablets with different shapes, colours and sizes. The deep learning model could be augmented with other types of tablet defects, resulting in a more complete analysis of the product. This would result in a more compact, flexible and low-cost alternative to the already existing industrial tablet inspection machines. By also measuring the coating thickness in real-time, it would be possible to monitor the trends of the process enabling the appropriate setting of parameters, resulting in the improvement of quality control during production. Furthermore, the acquired data can also be used for the feedback control of the continuous film coating process.

Acknowledgements

This work was supported by OTKA grant FK-132133. The research reported in this paper and carried out at BME has been supported by the National Laboratory of Artificial Intelligence funded by the NRDIO under the auspices of the Ministry for Innovation and Technology.

References

Almadhoun, H.R., Abu-Naser, S.S., 2021. Classification of Alzheimer's Disease Using Traditional Classifiers with Pre-Trained CNN. 5.

Alves-Lima, D., Song, J., Li, X., Portieri, A., Shen, Y., Zeitler, J.A., Lin, H., 2020. Review of terahertz pulsed imaging for pharmaceutical film coating analysis. 20, 1441.

Borsos, Á., Szilagyi, B., Agachi, P.S.e., Nagy, Z.K., 2017. Real-time image processing based online feedback control system for cooling batch crystallization. 21, 511-519.

Casian, T., Farkas, A., Ilyés, K., Démuth, B., Borbás, E., Madarász, L., Rapi, Z., Farkas, B., Balogh, A., Domokos, A., 2019. Data fusion strategies for performance improvement of a Process Analytical Technology platform consisting of four instruments: An electrospinning case study. 567, 118473.

Darma, I.W.A.S., Suciati, N., Siahaan, D., 2021. A Performance Comparison of Balinese Carving Motif Detection and Recognition using YOLOv5 and Mask R-CNN, 2021 5th International Conference on Informatics and Computational Sciences (ICICoS). IEEE, pp. 52-57.

De Beer, T., Burggraeve, A., Fonteyne, M., Saerens, L., Remon, J.P., Vervaet, C., 2011. Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. 417, 32-47.

Derganc, J., Likar, B., Tomaževič, D., Pernuš, F., 2003. Real-time automated visual inspection of color tablets in pharmaceutical blisters. 9, 113-124.

Dreu, R., Luštrik, M., Perpar, M., Žun, I., Srčič, S., 2012. Fluid-bed coater modifications and study of their influence on the coating process of pellets. 38, 501-511.

Duong, N., Chew, M.-T., Demidenko, S., Pham, Q.H., Pham, D.K., Ooi, M.-L., Kuang, Y.C., 2014. Vision inspection system for pharmaceuticals, 2014 IEEE Sensors Applications Symposium (SAS). IEEE, pp. 201-206.

Ekins, S., 2016. The next era: deep learning in pharmaceutical research. 33, 2594-2603.

European Pharmacopoeia Commission, 2019a. Friability of uncoated tablets (2.9.7.), In European Pharmacopoeia 10th Edition, pp. 336-337.

European Pharmacopoeia Commission, 2019b. Uniformity of mass of single-dose preparations (2.9.5.), In European Pharmacopoeia 10th Edition, pp. 335-336.

Felton, L.A., 2013. Film coating of oral solid dosage forms, Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition. CRC Press, pp. 1585-1600.

Ficzere, M., Mészáros, L.A., Madarász, L., Novák, M., Nagy, Z.K., Galata, D.L., 2021. Indirect monitoring of ultralow dose API content in continuous wet granulation and tableting by machine vision. 607, 121008.

Food and Drug Administration, 2004. Guidance for industry, PAT-A framework for innovative pharmaceutical development, manufacturing and quality assurance.

Galata, D.L., Mészáros, L.A., Kállai-Szabó, N., Szabó, E., Pataki, H., Marosi, G., Nagy, Z.K., 2021. Applications of machine vision in pharmaceutical technology: a review. 105717.

García-Muñoz, S., Carmody, A., 2010. Multivariate wavelet texture analysis for pharmaceutical solid product characterization. 398, 97-106.

García-Muñoz, S., Gierer, D.S., 2010. Coating uniformity assessment for colored immediate release tablets using multivariate image analysis. 395, 104-113.

Hirschberg, C., Edinger, M., Holmfred, E., Rantanen, J., Boetker, J., 2020. Image-Based Artificial Intelligence Methods for Product Control of Tablet Coating Quality. 12, 877.

Ho, L., Müller, R., Römer, M., Gordon, K., Heinämäki, J., Kleinebudde, P., Pepper, M., Rades, T., Shen, Y., Strachan, C., 2007. Analysis of sustained-release tablet film coats using terahertz pulsed imaging. 119, 253-261.

Kadunc, N.O., Likar, B., Tomaževič, D., 2014. In-line monitoring of pellet coating thickness growth by means of visual imaging. 470, 8-14.

Kasper-Eulaers, M., Hahn, N., Berger, S., Sebulonsen, T., Myrland, Ø., Kummervold, P.E., 2021. Detecting Heavy Goods Vehicles in Rest Areas in Winter Conditions Using YOLOv5. 14, 114.

Korasa, K., Vrečer, F., 2018. Overview of PAT process analysers applicable in monitoring of film coating unit operations for manufacturing of solid oral dosage forms. 111, 278-292.

Li, X., Williams, B., May, R.K., Zhong, S., Evans, M., Gladden, L., Shen, Y., Zeitler, A., Lin, H., 2022. Optimising Terahertz Waveform Selection of a Pharmaceutical Film Coating Process Using Recurrent Network.

Lin, H., Dong, Y., Markl, D., Williams, B.M., Zheng, Y., Shen, Y., Zeitler, J.A., 2017. Measurement of the intertablet coating uniformity of a pharmaceutical pan coating process with combined terahertz and optical coherence tomography in-line sensing. 106, 1075-1084.

Lin, H., May, R.K., Evans, M.J., Zhong, S., Gladden, L.F., Shen, Y., Zeitler, J.A., 2015. Impact of processing conditions on inter-tablet coating thickness variations measured by terahertz in-line sensing. 104, 2513-2522.

Lin, H., Zhang, Z., Markl, D., Zeitler, J.A., Shen, Y., 2018. A review of the applications of OCT for analysing pharmaceutical film coatings. 8, 2700.

Liu, W., Wang, Z., Zhou, B., Yang, S., Gong, Z., 2021. Real-time signal light detection based on yolov5 for railway, IOP Conference Series: Earth and Environmental Science. IOP Publishing, p. 042069.

Ma, X., Kittikunakorn, N., Sorman, B., Xi, H., Chen, A., Marsh, M., Mongeau, A., Piché, N., Williams III, R.O., Skomski, D., 2020. Application of deep learning convolutional neural networks for internal tablet defect detection: high accuracy, throughput, and adaptability. 109, 1547-1557.

Mészáros, L.A., Galata, D.L., Madarász, L., Köte, Á., Csorba, K., Dávid, Á.Z., Domokos, A., Szabó, E., Nagy, B., Marosi, G., 2020. Digital UV/VIS imaging: A rapid PAT tool for crushing strength, drug content and particle size distribution determination in tablets. 578, 119174.

Možina, M., Tomaževič, D., Pernuš, F., Likar, B., 2013. Automated visual inspection of imprint quality of pharmaceutical tablets. 24, 63-73.

Nikowitz, K., Folttmann, F., Wirges, M., Knop, K., Pintye-Hódi, K., Regdon Jr, G., Kleinebudde, P., 2014. Development of a Raman method to follow the evolution of coating thickness of pellets. 40, 1005-1010.

O'Connor, T., Lee, S., 2017. Emerging technology for modernizing pharmaceutical production: Continuous manufacturing, Developing solid oral dosage forms. Elsevier, pp. 1031-1046.

Paudel, A., Raijada, D., Rantanen, J., 2015. Raman spectroscopy in pharmaceutical product design. 89, 3-20.

Pauli, V., Roggo, Y., Pellegatti, L., Trung, N.Q.N., Elbaz, F., Ensslin, S., Kleinebudde, P., Krumme, M., 2019. Process analytical technology for continuous manufacturing tableting processing: A case study. 162, 101-111.

Petersen, C.R., Rajagopalan, N., Markos, C., Israelsen, N.M., Rodrigo, P.J., Woyessa, G., Tidemand-Lichtenberg, P., Pedersen, C., Weinell, C.E., Kiil, S., 2021. Non-Destructive Subsurface Inspection of Marine and Protective Coatings Using Near-and Mid-Infrared Optical Coherence Tomography. 11, 877.

Podrekar, G., Kitak, D., Mehle, A., Lavrič, Z., Likar, B., Tomaževič, D., 2018. In-line film coating thickness estimation of minitablets in a fluid-bed coating equipment. 19, 3440-3453.

Porter, S.C., 2021. Coating of pharmaceutical dosage forms, Remington. Elsevier, pp. 551-564.

Pramod, K., Tahir, M.A., Charoo, N.A., Ansari, S.H., Ali, J., 2016. Pharmaceutical product development: A quality by design approach. 6, 129.

Rani, N.S., Nithusha, V., Roshna, T., 2015. Automatic recognition and verification of defective tablet blisters using entropy based filtering and histogram processing. 10, 13155-13167.

Rantanen, J., Khinast, J., 2015. The future of pharmaceutical manufacturing sciences. 104, 3612-3638.

Seo, K.-S., Bajracharya, R., Lee, S.H., Han, H.-K., 2020. Pharmaceutical application of tablet film coating. 12, 853.

Simon, L.L., Oucherif, K.A., Nagy, Z.K., Hungerbuhler, K., 2010. Bulk video imaging based multivariate image analysis, process control chart and acoustic signal assisted nucleation detection. 65, 4983-4995.

Simon, L.L., Pataki, H., Marosi, G.r., Meemken, F., Hungerbühler, K., Baiker, A., Tummala, S., Glennon, B., Kuentz, M., Steele, G., 2015. Assessment of recent process analytical technology (PAT) trends: a multiauthor review. 19, 3-62.

Toschkoff, G., Funke, A., Altmeyer, A., Knop, K., Khinast, J., Kleinebudde, P., 2016. Evaluation of the tablets' surface flow velocities in pan coaters. 106, 97-106.

2021. YOLOv5. https://github.com/ultralytics/yolov5 (accessed 2021.11.16.).

Wolfgang, M., Weißensteiner, M., Clarke, P., Hsiao, W.-K., Khinast, J.G., 2020. Deep convolutional neural networks: Outperforming established algorithms in the evaluation of industrial optical coherence tomography (OCT) images of pharmaceutical coatings. 2, 100058.

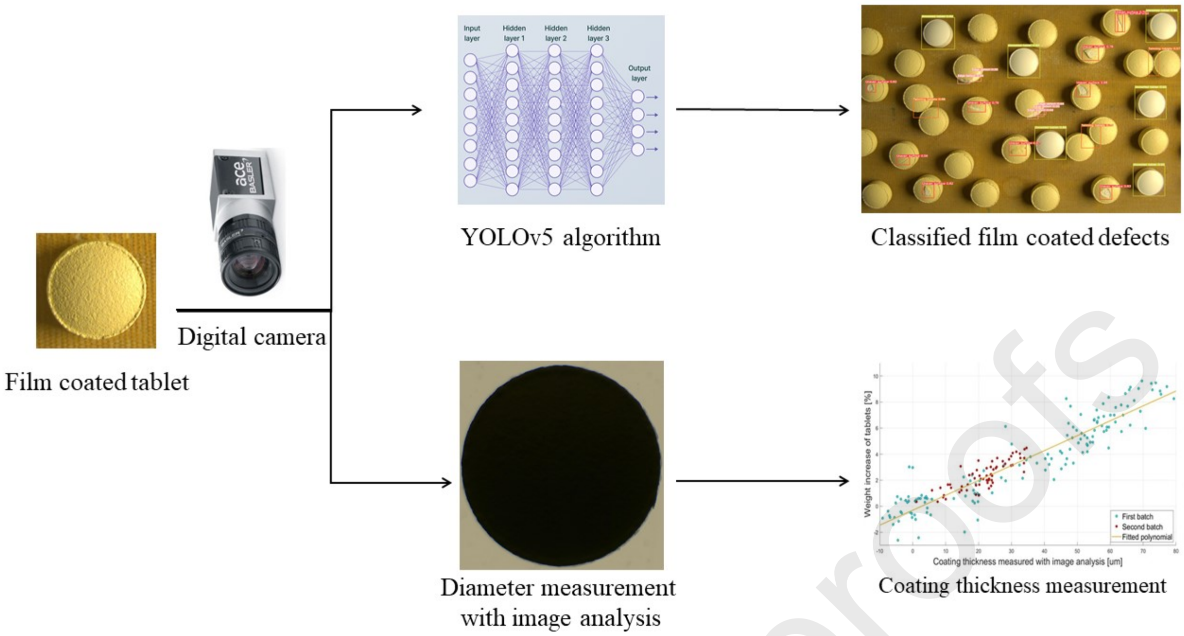
Yao, J., Qi, J., Zhang, J., Shao, H., Yang, J., Li, X., 2021. A real-time detection algorithm for Kiwifruit defects based on YOLOv5. 10, 1711.

Zaid, A.N., 2020. A comprehensive review on pharmaceutical film coating: past, present, and future. 14, 4613.

Zhao, J., Zhang, X., Yan, J., Qiu, X., Yao, X., Tian, Y., Zhu, Y., Cao, W., 2021. A wheat spike detection method in UAV images based on improved YOLOv5. 13, 3095.

Zhong, S., Shen, Y.-C., Ho, L., May, R.K., Zeitler, J.A., Evans, M., Taday, P.F., Pepper, M., Rades, T., Gordon, K.C., 2011. Non-destructive quantification of pharmaceutical tablet coatings using terahertz pulsed imaging and optical coherence tomography. 49, 361-365.

Zhou, F., Zhao, H., Nie, Z., 2021. Safety helmet detection based on YOLOv5, 2021 IEEE International Conference on Power Electronics, Computer Applications (ICPECA). IEEE, pp. 6-11.


Input layer
Hidden layer 1
Hidden layer 2
Hidden layer 3
Output layer
YOLOv5 algorithm
Classified film coated defects
Digital camera
Film coated tablet
Diameter measurement
with image analysis
Weight increase of tablets [%]
Coating thickness measured with image analysis [um]
First batch
Second batch
Fitted polynomial
Coating thickness measurement

Máté Ficzere: investigation, data curation, writing – original draft; **Lilla Alexandra Mészáros:** investigation, data curation; **Nikolett Kállai-Szabó:** investigation, resources; **Andrea Kovács:** investigation; **István Antal:** supervision; **Zsombor Kristóf Nagy:** supervision, conceptualization, writing – review & editing; **Dorián László Galata:** investigation, methodology, conceptualization, writing – review & editing

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: