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High throughput in-line content uniformity measurement of tablets based on real-time UV imaging

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ABSTRACT

This paper presents a precursor of a novel, high-throughput, in-line system, which utilizes ultraviolet (UV) imaging in order to predict the active pharmaceutical ingredient (API) content of tablets in real-time, non-destructive manner. Pimobendan, cardiovascular drug used in veterinary medicine was chosen as a fluorescent model API. Two experiments were carried out using different measurement setups, where the tablets were moving at different speeds. The blue colour components of the images were used to predict the pimobendan content of the tablets, and as a reference method, traditional UV spectroscopy was used to measure the API content of the dissolved tablets. In the case of the first, slower experiment (with a conveyor belt speed of 83 mm/s), a second order polynomial was fitted to the calibration tablets containing a nominal dose of 1.25, 5 and 10 mg of pimobendan and it was used to predict the API content. The RMSEP obtained was 0.428 mg for the validation tablets with a relative error as low as 7% for the target level. For the second, faster experiment (1000 mm/s) the same polynomial was used to predict the pimobendan concentration of a different set of tablets, achieving a relative error of 2.03%. Finally, the throughput of both systems was calculated to assess their applicability to meet the requirements of a pharmaceutical manufacturing line. The first system could inspect up to 93 375 tablets per hour, while the second was able to process up to 360 000 tablets in an hour, making it suitable for industrial application. By using these developed systems, the API content of all produced tablets could be determined non-destructively, which can greatly improve patient safety.

1. Introduction

Quality-by-testing (QbT) is the currently widespread approach in the pharmaceutical industry as a quality control strategy during manufacturing. During this, a small set of samples undergo slow and destructive off-line testing (Nagy et al., 2022) and if the evaluated parameters (for example their content uniformity) do not meet the desired specifications, the entire batch could be discarded, causing severe financial loss (Rossi, 2022). The process analytical technology (PAT) concept was introduced in order to better understand the pharmaceutical production process and to combat this phenomenon. The initiative is supported by the authorities (Food and Drug Administration, 2004) and over the years has attracted the significant interest of the pharmaceutical manufacturers. These tools can comprehensibly understand the products and processes, and they are also able to rapidly analyze and control any deviations that may occur during production (Casian et al., 2022).

Content uniformity is considered as a high-risk critical quality attribute, and recalls have been initiated regarding it (Food and Drug Administration, 2024). Therefore, several faster methods have been developed to replace the traditional off-line, destructive measurements. Spectroscopic methods, such as near infrared (NIR) and Raman spectroscopy have emerged as PAT tools for the measurement of API content in tablets. NIRS has already been utilized to assess the API content and hardness of tablets (Kandpal et al., 2017) and to predict the API concentration of tablets produced at different levels of compression force (De Man et al., 2023). Transmission Raman spectroscopy has also been used for content uniformity measurement coupled with NIRS (Wang

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et al., 2021) or as a standalone method (Belay et al., 2021). However, despite developments in the speed of Raman spectroscopy, new models could still only inspect up to 100 tablets per hour in transmission mode (Agilent, 2024). Systems using NIRS have been reported with higher speeds up 120 000 tablets/hour (Brouckaert et al., 2022), but this value is still below the productivity of pharmaceutical tablet presses.

Machine vision is an innovative analytical tool in pharmaceutical manufacturing, thanks to its numerous advantages, such as its low investment cost and fast data acquisition. By using colour cameras, the content of various coloured components can be monitored throughout the pharmaceutical manufacturing process (Galata et al., 2021b; Péterfi et al., 2024). Machine vision has already been used to accurately monitor the content of the yellow-coloured API riboflavin during continuous twin-screw wet granulation (Ficzere et al., 2021) and continuous blending (Galata et al., 2021a). Durão et al. found that powder mixtures containing coloured multivitamins could be monitored accurately inside the feed frame of a tablet press as well (Durão et al., 2017). Machine vision could also be used for the investigation of tablets containing coloured components (Wagner et al., 1999). These systems all applied visible illumination, which however cannot be used in the case of colourless APIs for direct concentration measurement.

UV imaging utilizes ultraviolet illumination, creating a non-destructive and fast tablet inspection method. One type of it is multispectral UV imaging, which was successfully used by Wu et al. to visualize glibenclamide in tablets (Wu et al., 2014). This same approach was used for the visualization of pellets in tablets (Novikova et al., 2016) and for the determination of tablet physical properties (Klukkert et al., 2016). However, due to the consecutive process of data acquisition at different wavelengths, in all of these cases the acquisition time was 18 s per multispectral image. This greatly limits the number of samples, making multispectral UV imaging not suitable for an in-line, real-time system.

By exposing a pharmaceutical dosage form to only a single wavelength of UV light, its components can change into different colours thanks to differences in their fluorescence and absorption. This phenomenon if combined with an RGB camera, could be used for API content prediction with high speed and resolution (Mészáros et al., 2022). Mészáros et al. (Mészáros et al., 2020) used single wavelength UV/VIS imaging to determine the drug content, the crushing strength and the dissolution profile of tablets containing meloxicam, a yellow model drug. They used an acquisition time of 1.2 ms, and were able to predict the API content of tablets with RGB and CIELAB colour space-based algorithms with a relative error of 4.9%. In their previous work, the authors (Ficzere et al., 2024) utilized single wavelength UV imaging to determine the content of two colourless APIs in their respective tablets. They used artificial neural networks to predict the amlodipine and valsartan content of the tablets, and have achieved relative errors of 4.41% and 3.98%, respectively. However, there have been no cases reported in the literature, where UV imaging was used an in-line, high-speed tool for the API content determination of tablets in real-time.

The authors have demonstrated in their prior publications that the API content can be determined in tablets through an offline approach. The goal of this study was the development of a precursor of a first of its kind, high-throughput, real-time system which utilizes UV imaging in order to determine the API content of colourless tablets accurately. The authors aimed to create a system that could be utilized for efficient image acquisition in industrial settings, incorporating a concept of a rapid evaluation algorithm. We intend to use pimobendan, as a fluorescent API. The applied excipient matrix also models commercially available formulations. Finally, we also intend to check if the developed system is capable of matching the productivity of the already existing pharmaceutical manufacturing lines.

2. Materials and methods

2.1. Materials

Pimobendan, a cardiovascular drug used in veterinary medicine was chosen as a model API and was obtained from Sigma-Aldrich (St. Louis, Missouri, USA). Lactose monohydrate (EMPROVE® ESSENTIAL) and magnesium stearate were acquired from Merck (Budapest, Hungary). Microcrystalline cellulose (MCC, Vivapur® 200) was purchased from JRS Pharma (Rosenberg, Germany), while cross-linked sodium carboxymethyl cellulose (Ac-Di-Sol® SD-711) was obtained from IFF Inc. (New York, USA).

2.2. Methods

2.2.1. Preparation of tablets

The tablets were manufactured using a Dott Bonapace CPR-6 (Limbiate, Italy) single punch tablet press with flat punches that had a diameter of 8 mm and the compression pressure was set to 14 kN. Tablets with a target weight of 200 mg contained 1.25 mg, 5 mg, 7.5 mg or 10 mg of pimobendan, 40 mg MCC, 40 mg Ac-Di-Sol, 2 mg magnesium stearate and the rest was lactose. The powder mixtures were all blended manually before tableting for 10 min. All in all 42 samples were prepared with the mentioned API content levels. The elements of the calibration and validation set were selected randomly from the 1.25 mg, 5 mg and 10 mg nominal API content levels, with the consideration of maintaining a balanced dataset.

2.2.2. Real-time UV imaging

A Basler acA4112-30uc (Basler AG, Ahrensburg, Germany) 12-megapixel, area scan, RGB camera was used for image acquisition, which was equipped with a Basler MEGA TS1214-MP objective (Basler AG, Ahrensburg, Germany). The communication between the computer and the camera was carried out via a USB 3.0 port. Real-time UV imaging was conducted using two separate setups. Fig. 1 showcases the first setup, providing a side view of its implementation. The combination of the camera and objective specifications provided the opportunity to capture images of multiple rows of samples. Consequently, it should be emphasized that, in the side view, only one row is observable, whereas in the measurement, five rows of samples were positioned manually close to each other on a conveyor belt (Brabender Technologie, Duisburg, Germany). The belt was operated at its maximum speed of 83 mm/s. The speed of the belt was also checked using the acquired images, the diameter of the tablets, and the framerate throughout the experiments. The tablets were illuminated using five 5 W LED lights (VastFire, China), positioned above each tablet row, as illustrated in Fig. 1. Consequently, five illumination sources were placed on both sides of the camera at a slight angle for the appropriate image acquisition. The applied LEDs were emitting in the range of 360–370 nm.

In the second experiment, a developed rotating sample holder-based inspection system with a higher throughput was employed to assess the system's capabilities at increased speeds. Due to that reason, an in-house designed, 3D printed circular apparatus was used as a sample holder, which consisted of a 200 mm diameter plate with one row of hollows on the rim. The samples were placed manually on the apparatus. The rotary motion of the apparatus was provided by an electrical mixer resulting in 1 m/s perpendicular speed. The camera was mounted on the concentric edge of the inspection system. The samples were illuminated from above similarly as illustrated in Fig. 1 with a single 365 nm LED light.

Both the calibration and validation sample sets underwent the same measurement procedure. This consisted of the identical steps in both experimental setups. Subsequent to the manual placement of the samples, the image acquisition was initiated at a frame rate of 30 fps, while simultaneously activating the LED lamps. Following that, the samples were set in motion. Once the images were acquired, the samples were carefully collected in a specific sequence to align them with the

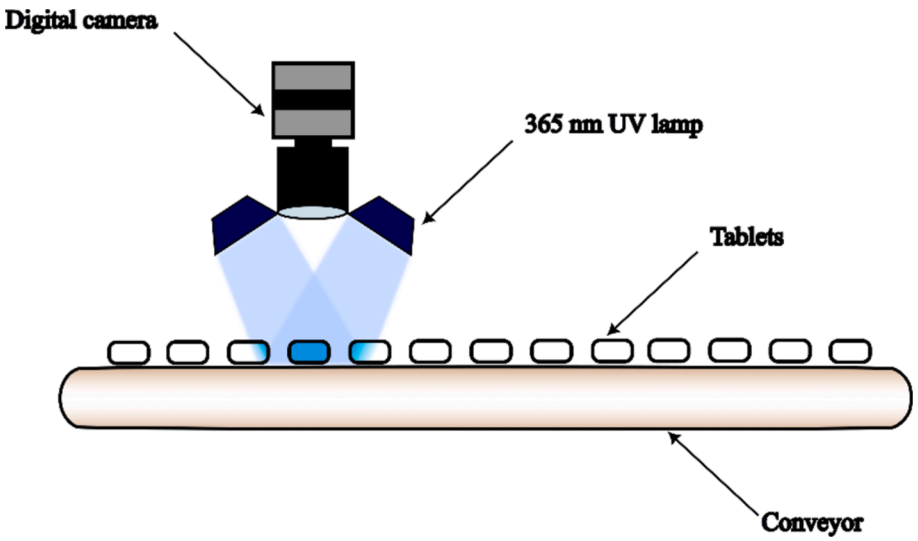

Fig. 1. Schematic side view representation of the real-time UV imaging setup utilized in the first experiment.

corresponding API content measurements.

2.2.3. Analysis of the captured images

The images were analysed with a custom-made algorithm written in Matlab 9.8.0.1538580 (MathWorks, Natick, MA, USA), utilizing Image Processing and Computer Vision Toolbox 11.1. (MathWorks, Natick, MA, USA) and Curve Fitting Toolbox 3.5.11. (MathWorks, Natick, MA, USA).

The first executed step was the extraction of the background, which was done using a threshold of 50 in the case of the blue (B) channels. After that, by using the B values of the pixels, the images were binarized and were used in a Hough-transformation based circle detection with a preset range of radii to detect the tablets. Finally, the average B value of each tablet was calculated by averaging the B values of all of its pixels. The blue colour of the tablets is mainly caused by the fluorescence of the API, therefore the average B values were used to predict the API content of the tablets.

2.2.4. Determination of the pimobendan content of the tablets

To validate the predicted pimobendan content of tablets, traditional UV absorption spectroscopy measurements were carried out using an Agilent 8453 UV/VIS spectrometer (Hewlett-Packard, Palo Alto, CA, USA) with flask method. The determination of the pimobendan content was done by dissolving the tablets in 500 mL volumetric flasks for 30 min in 4.5 pH phosphate buffer. The solutions were then filtered with 1.2 μm syringe filters (Labex Ltd, Budapest, Hungary). The pimobendan content was measured at 266 nm in a 10 mm cuvette. In total, 18 tablets were measured for calibration and 16 and 8 for validation in the first and second experiment, respectively.

3. Results and discussion

3.1. Assessment of tablets under UV illumination

In order to assess the applicability of UV imaging for the determination of the pimobendan content of tablets, three samples with different API contents were investigated, presented on Fig. 2.

It can be observed that tablets containing less amount of pimobendan have a darker blue hue, with the 1.25 mg tablet being the darkest of all three. Meanwhile, the 10 mg tablet has the brightest blue colour due to the fluorescence of pimobendan, therefore it can be possible to predict the drug content of the tablets based on the colour change caused by 365 nm UV illumination. The 1.25 and 5 mg samples exhibit more significant differences in colour, whereas the disparities are less

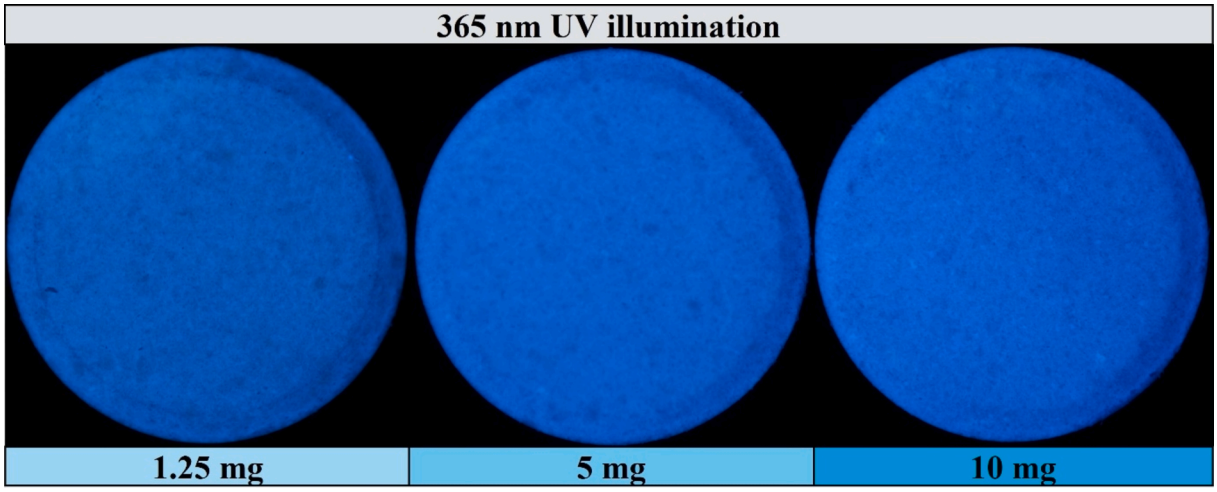

Fig. 2. Tablets containing different amounts of pimobendan under 365 nm UV illumination. The mean blue values of the tablets were 91, 106 and 115 respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pronounced between the 5 and 10 mg samples. As a result, there can be a non-linear correlation between the API content and the colour values. A visual inspection was conducted on the acquired images, revealing no significant colour irregularities. As a result, the samples and acquired images can be utilized to assess the API content.

3.2. Results of the first experiment

Based on these observations, the first experiment was carried out with the conveyor belt setup using 36 tablets, out of them 12 were 1.25 mg, 12 were 5 mg and 12 were 10 mg nominal dose tablets. After the UV imaging, their pimobendan content was measured using UV spectroscopy. The tablets were then split into calibration and validation sets, containing 18 and 16 tablets respectively. Fig. 3 presents the measured pimobendan content of the tablets as a function of their average B values calculated using image analysis.

A second order polynomial was fitted to the calibration data ($R^2 = 0.971$), which was then used to predict the validation points. In order to assess the performance of the method, the root mean squared error of prediction (RMSEP) was calculated by using the following formula (Eq. (1)):

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}} \quad (1)$$

where n is the number of samples, y_i is the pimobendan content value obtained using the model and $\hat{y}_i$ is the pimobendan content measured with UV spectroscopy.

The obtained RMSEP was 0.428 mg, leading to a 7% relative error (relative RMSE) based on the average measured dosage, and the residual distribution was close to uniform. To further evaluate the performance of the obtained model mean absolute error and the mean absolute percentage error were also calculated, which was obtained at 0.372 mg and 9.3%. The mentioned values of the goodness parameters show that the system might be applicable for predicting the pimobendan content of moving tablets. However, the performance of the UV imaging method should also be investigated in the case of tablets moving at higher speeds.

3.3. Results of the second, higher throughput experiment

In order to move the tablets faster, a different measurement setup was used, which could speed the tablets up to 1000 mm/s, which is more than 12 times higher, than the 83 mm/s used in the first experiment. It was also our goal to investigate that could the same calibration that was set in the first experiment be used to determine the pimobendan content of tablets during the second one. For this, 8 tablets with a nominal pimobendan content of 7.5 mg were measured with UV imaging, and their true API content was determined using UV spectrometry. Fig. 4 presents the measured pimobendan content and the average blue values of the tablets.

It can be observed that the second order polynomial that was fitted in the first experiment can be used to predict the points of the second experiment. The RMSEP calculated for these points was 0.152 mg, which is a relative error of 2.03% for the 7.5 mg nominal dose of tablets. This proves that the same calibration could be used for tablets moving at speeds more than a magnitude faster.

3.4. Throughput of the proposed systems

In order to assess the applicability of the developed systems, their throughput should be calculated to compare it to the production capability of rotary tablet presses. The following equations have been used to determine the throughput in the case of the first (*Eq. (2)* and the second measurement system (*Eq. (3)*

$$T = \frac{n^*v}{l} = \frac{5^*83\frac{mm}{s}}{16mm}{}^*3600\frac{s}{h} = \mathbf{93375}\frac{\boldsymbol{tablet}}{\boldsymbol{h}} \quad (2)$$

$$T = \frac{n^*v}{l} = \frac{1^*1000\frac{mm}{s}}{10mm}{}^*3600\frac{s}{h} = \mathbf{360000}\frac{\boldsymbol{tablet}}{\boldsymbol{h}} \quad (3)$$

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

Based on *Eq. (2)*, the throughput of the conveyor belt setup used in the first experiment was 93 375 tablets per hour. This amount is already applicable in the case of some production lines, however there are some lines with higher productivity.

In the case of the second experiment (Eq. (3), there is only a single row of tablets instead of 5, but they are moving at a much higher speed, increasing the throughput up to 360 000 tablets per hour. This could enable the 100% screening of the produced tablets on the majority of the manufacturing lines, therefore increasing the speed and thus the throughput of the system is not required further.

Although a thorough technology transfer was not the aim in the

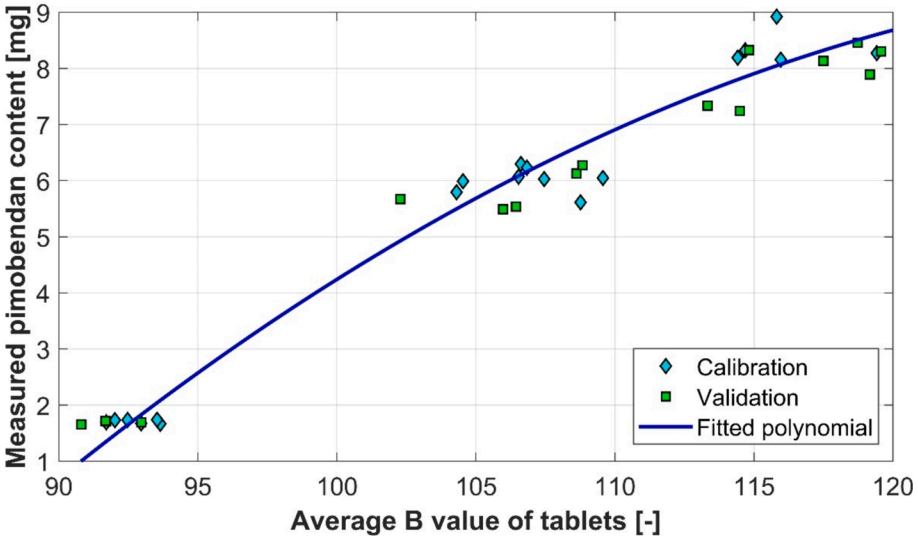

Fig. 3. The measured API content in the function of the average B values of the samples in the first experiment.

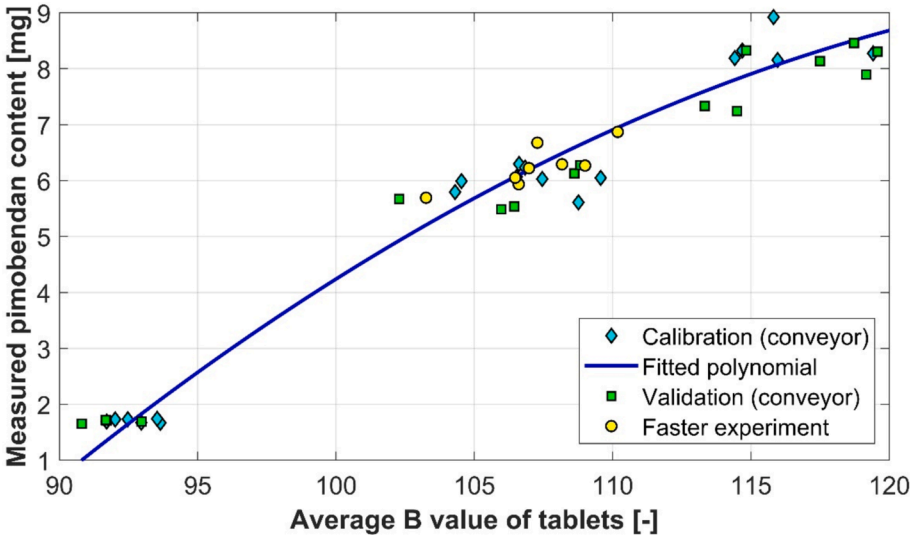

Fig. 4. The measured API content in the function of the average B values of the samples in the first (conveyor) and the second (faster) experiment.

presented study, based on the obtained results there is a crucial improvement towards the application of UV imaging systems in the pharmaceutical industry. By considering the goodness parameters of the model and utilizing data from one side of the samples, comparable results can be obtained in relation to the authors' previous publication (Mészáros et al., 2020) on API content prediction. Important to note that the performance of the model can be improved through the enlargement of the dataset. Furthermore, a comprehensive evaluation of the performance can be achieved through validation using an extended dataset and a wider range of API content in the future.

The performance of the presented system could be augmented by acquiring images from both sides of the samples. This can be accomplished, for instance, by rotating devices positioned on the conveyor belt. The presented UV imaging-based machine vision system was specifically designed for uncoated samples, as a coating on the core surface introduces a masking effect. Within the context of manual sample placement, deflectors or feeders can be considered suitable alternatives.

The choice of camera, objective lens, and illumination source also influences the system's throughput. A comprehensive assessment of the potential impact of the specified hardware is crucial prior to the implementation of such high-speed applications. The wavelength of the illumination source significantly influences results. In the case of samples containing pimobendane, a UV illumination source centred around 365 nm has proven effective. Nevertheless, when diverse APIs and excipients are utilized, the selection of wavelength should be adjusted accordingly. LED panels with comparable specifications to the applied sources are capable of delivering consistent illumination across extensive areas in real-world scenarios. To ensure practical applicability, optimization of the algorithm's execution time using other programming languages may be necessary to enhance performance. Utilizing sophisticated multivariate data analysis methods may improve the evaluation of the samples by incorporating relevant information into the dataset.

The developed non-destructive UV imaging-based method may enable the API content prediction for each individual tablet produced. Therefore, all of the not acceptable tablets could be identified and removed, enabling a higher level of quality control. This could result in a better understanding of the tableting process and simultaneously increase patient safety.

4. Conclusions

This work presented a precursor of novel in-line systems, which utilize UV imaging to non-destructively determine the pimobendan content of tablets. Two different setups were developed, which had tablets moving at different speeds. Tablets have been produced for calibration and validation and after the UV imaging measurements, their true pimobendan content was determined using traditional UV spectrometry. In the case of slower tablet movement, a second-order polynomial was fitted to the measured API content in the function of the average blue values, with RMSEP obtained at 0.428 mg. According to the obtained goodness parameters, further improvements are needed to achieve the predetermined accuracy and precision standards for API content determination outlined in the guidelines. The same polynomial was used to predict the pimobendan concentration in the faster moving experiment, yielding a lower RMSEP of 0.152 mg. Finally, the throughput of both systems was calculated as 93 375 and 360 000 tablets/hour, showcasing that they could serve as a part of an existing pharmaceutical manufacturing line. This novel, UV imaging-based method could be used for tablets with different shapes or containing different APIs. This method could also be coupled with an ejection system, where tablets with insufficient API contents could be removed, thanks to the 100% screening of the produced tablets, which can greatly improve patient safety and decrease the amount of rejected batches.

CRediT authorship contribution statement

Máté Ficzere: Writing – original draft, Visualization, Methodology, Investigation, Data curation. **Anna Diószegi:** Investigation. **Attila Farkas:** Writing – review & editing. **Béla Weiss:** Methodology. **Lilla Alexandra Mészáros:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Zsombor Kristóf Nagy:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

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.

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Data availability

Data will be made available on request.

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