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UV/VIS imaging-based PAT tool for drug particle size inspection in intact tablets supported by pattern recognition neural networks

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ABSTRACT

The potential of machine vision systems has not currently been exploited for pharmaceutical applications, although expected to provide revolutionary solutions for in-process and final product testing. The presented paper aimed to analyze the particle size of meloxicam, a yellow model active pharmaceutical ingredient, in intact tablets by a digital UV/VIS imaging-based machine vision system. Two image processing algorithms were developed and coupled with pattern recognition neural networks for UV and VIS images for particle size-based classification of the prepared tablets. The developed method can identify tablets containing finer or larger particles than the target with more than 97% accuracy. Two algorithms were developed for UV and VIS images for particle size analysis of the prepared tablets. According to the applied statistical tests, the obtained particle size distributions were similar to the results of the laser diffraction-based reference method. Digital UV/VIS imaging combined with multivariate data analysis can provide a new non-destructive, rapid, in-line tool for particle size analysis in tablets.

Keywords: Image analysis Machine vision Tablet inspection Particle size distribution Particle size analysis Pattern recognition neural network

1. Introduction

Tablets represent a significant portion of the pharmaceutical dosage forms, due to their several advantageous properties, for example, convenient administration, stability, portability, and dosing accuracy (Gaikwad and Kshirsagar, 2020; Sayeed, 2015; Skelbæk-Pedersen et al., 2020). In 2015, the U.S Food and Drug Administration (FDA) approved the first commercial product, Orkambi by Vertex, manufactured using continuous technology. Thus, the modern manufacturing of pharmaceutical solid dosage forms has begun (Kensaku et al., 2019). Since then, continuous manufacturing, emerging technologies, modernization, and innovation have been the focus of attention and supported by the regulatory agencies (Yeaton, 2019). The published recommendations, guidelines, and frameworks, including process analytical technology (PAT) and the concept of quality-by-design (QbD), enable

production monitoring and controlling, data collection, and process understanding (U.S. Food and Drug Administration, 2004; U.S. Food and Drug Administration, 2009). The initiative of PAT published by the U.S. FDA reinforces the in-line or on-line data-based process control (am Ende and am Ende, 2019; U.S. Food and Drug Administration, 2004). The development of PAT tools can provide consistent quality throughout the manufacturing by monitoring and controlling process parameters and quality attributes (Scott et al., 1998). In the modernization concept, data-driven solutions can contribute to understanding the processes and controlling the intermittent variability to enable consistent quality in each step of the production. These reserve an essential role in implementing QbD and real-time release testing (RTRT) approaches (Ramadan et al., 2021).

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article sizes and the particle size distributions (PSDs) of the components are vital parameters in the pharmaceutical development and manufacturing phases. These critical material attributes (CMAs) affect critical quality attributes (CQAs) and the critical process parameters (CPPs) considering the systematic concept of QbD (Thakral et al., 2018; Šimek et al., 2014; Razavi et al., 2018). Based on the general quality

target product profile (QTPP) of tablets, the content uniformity, *in vitro* dissolution behavior, and bioavailability of the final dosage form, which are more significant related to poorly water soluble APIs, are among the affected CQAs. The time and the blend uniformity are affected CPPs belonging to the homogenization step of the API with excipients, where the particle size of the API potentially represents a high risk. In the compaction step, the compactibility of the powder blends, the compression force, the tensile strength, and the porosity can be affected

by the mentioned CMAs (Thakral et al., 2018; Šimek et al., 2014; Razavi et al., 2018).

Consequently, particle sizes and PSDs of the components in tablets significantly affect the efficacy, stability, and safety of the final product. During the production of solid dosage forms, operations are performed, affecting the particle size of the applied materials. Therefore, the monitoring and control of these CMAs are crucial in both powders and the final dosage form throughout the manufacturing (Šimek et al., 2014; Thakral et al., 2018). The development of real-time, in-line particle size analysis methods in intact tablets can contribute to getting more information about the processes throughout the manufacturing, including tableting (Thakral et al., 2018).

The characterization of a particulate system by PAT tools has been in the attention of industrial companies in the recent decade (Scott et al., 1998). There are several methods for the determination of PSDs of powders or granules, such as sieve analysis (International Council for Harmonisation, 2009), microscopic measurements (Saravanan et al., 2021), sedimentation (Alexander et al., 2008), spectroscopic methods (Gupta et al., 2004), and image analysis (Thakral et al., 2018). However, only a few publications assess particle sizes and distributions in intact tablets.

Šimek et al. applied hot stage microscopy for

particle size determination of tablets containing meloxicam and tadalafil as APIs. In the

context of the sample preparation methods, destructive mechanical and liquid disintegration was applied (Šimek et al., 2014).

Thakral et al. published a 2-dimensional X-ray diffraction method where the particle size of the API was estimated in intact flat-faced tablets containing lactose-monohydrate and sucrose with different particle sizes. There are a few limitations of this technique, such as the curvature of the surface (Thakral et al., 2018).

Skelbæk-Pedersen et al. investigated the effect of different particle sizes on material fragmentation during the tableting process. They applied diffuse reflectance near-infrared spectroscopic technique and executed a qualitative examination of the particle size of microcrystalline cellulose and calcium hydrogen phosphate dihydrate in tablets using principal component analysis (Skelbæk-Pedersen et al., 2020).

The most important advantage of the mentioned methods is the capability to examine the particle size of the components in tablets. However, the hot stage microscopic technique appears available for offline analysis of PSD because of the instrumentation, the requirements, and the destructive manner of the sample preparation. The 2-dimensional X-ray diffractometry does not require such sample preparation, although it cannot be applied as a PAT tool due to the instrumentation. Both methods have limitations in the context of the examinable sample number. The U.S. FDA approved the application of near-infrared spectroscopy for in-line measurements despite the mentioned publication only qualitatively examining the particle size in intact tablets.

Machine vision is a specific solution in many fields (Zhou et al., 2019; Yu et al., 2021; Smith et al., 2021), which is recently gaining interest in the pharmaceutical industry. It may provide a new, cost-efficient, and rapid way in quality assessment of pharmaceutical products and process control (Galata et al., 2021). A few paper reports on the analysis of the final pharmaceutical products, such as tablets. For instance, these mainly focus on monitoring coating processes (am Ende and am Ende, 2019), defects (Ma et al., 2020), and pellet distribution on the surface of the tablets (Novikova et al., 2016). According to the authors' knowledge, a machine vision system is not applied for particle size analysis in intact tablets.



However, these can assist or supplement other instrumentations and methods in manufacturing and contribute to the process controlling. One of the significant advantages of applying these systems is that all the produced tablets can be examined. The rejected products can be isolated immediately, which reduces the financial loss. The application of artificial intelligence gained ground in the business processes, the drug development in the pharmaceutical industry and also emerged in the manufacturing of pharmaceutical dosage forms (Kalyane et al., 2020; Kulkov, 2021; Mak and Pichika, 2019). Neural

networks are nonlinear computational methods that model the communication of neurons in the human brain (Marini, 2009). These computational methods are popularly used for approximations and pattern recognition (Butts et al., 2003). Pattern recognition neural networks are classifiers and similar in structure to a feed-forward neural network. The difference between them is in the softmax transfer function of the output layer (Mark et al., 2021). The application of pattern recognition neural networks can be found in other industrial sectors (Ghorpade and Koneru, 2020).

This proof-of-concept paper aimed to develop and apply a machine vision system based on digital UV/VIS imaging for qualitative and quantitative particle size assessment of the API in intact tablets. Image processing algorithms were developed, and pattern recognition neural networks were applied for classification based on the different particle sizes of the API. Subsequently, the paper intended to predict the PSD of the API in tablets by combining the classification results and the image processing algorithms. At last, an application example was presented, in which the developed system is introduced for automatic tableting where the tablets included different particle sizes of meloxicam, a yellow model API. The purpose of the final experiment was to determine whether the produced tablets met the criteria for the particle size, thus performing a quality-based selection.

2. Materials and methods

2.1. Materials

Meloxicam (MLX), magnesium stearate (MgSt), sodium hydroxide, hydrochloric acid, ethanol, and acetone were purchased from Sigma Aldrich (St. Louis, MO, USA). Vivapur 200 microcrystalline cellulose (MCC) was purchased from JRS Pharma (Rosenberg, Germany).

2.2. Preparation of different particle size fractions from MLX

Different particle size fractions were produced from the initial MLX using crystallization methods for particle size analysis. The denotation of these groups contained the measured, rounded D50 values in the subscript. If any crystallization process was applied, the solvent was named in the superscript. The denotations and the differences between the particle size groups were summarized in Table 1.

The applied technique for the particle size enlargement of $MLX_{25\mu m}$ was based on the publication of crystallization using a slow cooling method by Bolourchian et al. (Bolourchian et al., 2020). Accordingly, 1 g of $MLX_{25\mu m}$ was placed in a crystallization dish and dissolved in acetone at 50 °C using 100 rpm stirring. The applied $MLX_{25\mu m}$ concentration was 0.45 w/v%. The solution was kept overnight at room temperature to evaporate the applied solvent. The obtained crystals were gathered in a glass sample holder and stored at room temperature. When ethanol solvent was applied, the aforementioned slow cooling method was used and the $MLX_{25\mu m}$ concentration was set to 0.16 w/v%.

Crystallization was also applied to produce a fine particle size fraction from $MLX_{25\mu m}$. Based on the patent of Coppi et al., 1 g of $MLX_{25\mu m}$ was placed in a beaker and dissolved in sodium hydroxide solution (1 equivalent of NaOH with respect to $MLX_{25\mu m}$, water/ $MLX_{25\mu m}$ ratio was set to 30) at 45 °C, using 100 rpm stirring. When a clear solution was

Table 1

The denotations and the attributes of different particle size samples of MLX.

Denotation of the different particle size samples	Applied solvent for crystallization	Measured particle size range	Measured D50 value
MLX^{NaOH}	NaOH/HCl	<10 μm	5.490 μm
$MLX_{25\mu m}$	—	<50 μm	25.048 μm
$MLX^{Acetone}$	Acetone	<440 μm	176.113 μm
MLX^{EtOH}	Ethanol	<472 μm	303.148 μm

5 μm



176 μ m 303 μ m



obtained, the pH was adjusted to 4 with hydrochloric acid. The obtained suspension was kept at 45 °C for 60 min (Coppi et al., 2005). After a cooling step, crystals were filtered, washed with distilled water, and dried. The obtained crystalline fraction was gathered and stored the same as mentioned. The applied crystallization methods were reproduced in both cases to collect sufficient amount of crystalline samples.

2.3. Particle size analysis of the prepared MLX crystals

The PSDs of different particle size samples (Table 1) were determined by laser diffraction-based method executed on Malvern Master-sizer 2000 (Malvern Panalytical Ltd., UK) with Scirocco 2000 (Malvern Panalytical Ltd., UK) sample dispersion unit. The instrumentation allows particle-in-gas particle size analysis.

1 g of crystalline sample was placed on the sample tray of the dispersion unit manually. Due to the vibration of the tray, the sample was fed into a sieve with bearings for controlled sample flow and to break the loose agglomerates. The sample flow and the dispersion were provided by compressed air. The applied standard operation procedure parameters were the followings: vibrational feed rate was set to 40%, dispersive air pressure was set to 1 bar, and measurement time was 30 s. The applied theory of particle size analysis is based on the Mie theory. The measurement range of this instrument takes from 100 nm to 2 mm.

2.4. Preparation of the tablets

In the first experiment, tablets were produced to train, validate, and test the pattern recognition neural network, which executed the particle size-based classification task. These tablets were also crucial in the development phase of the algorithms for particle size analysis using UV/ VIS images, especially identifying the API with different particle sizes. To test the capabilities of the developed system in finer and larger particle size ranges than the target, powder blends from the four different particle size samples (Table 1) and a mixture was prepared from $MLX_{25\mu m}$ and MLX^{NaOH} and used as APIs. The authors determined

the PSD of $MLX_{25\mu m}$ as target.

After weighing the appropriate amount from the

different particle size samples of MLX (Table 1), 10.5 g powder blends with 2.5 m/m% API content were prepared using MCC as excipient (Table 2). The API

content was determined based on the commercially available MLX- containing tablets. In the first experiment, no MgSt addition was to avoid other interfering parameters in the development phase of the particle size analysis methods. The lubrication was provided between the tableting of the different particle size groups.

To maintain the integrity of the different particle size samples and to avoid the breaking of the prepared crystals, the homogenization step was executed by manual blending for 10 min. From each powder mixture, 25 tablets were produced one by one on a Dott Bonapace CPR-6 (Dott Bonapace, Italy) eccentric tablet press, equipped with a single concave punch using 10 kN compression force. Biconvex tablets were obtained with a diameter of 14 mm, the weight of the tablets was 400 mg, and the content of the applied API was 10.5 mg per tablet.

The further experiment aimed to test the capabilities of the developed machine vision system to identify changes in the particle size from $MLX_{25\mu m}$. The tableting was executed in automatic mode on the same instrumentation supplemented with a feed frame. Two blends containing the target and finer or larger particle size fractions ensure the changes in the system. After weighing the components, 22 g of powder blends were prepared using the homogenization method. The compositions of the applied powder blends are presented in Table 3. In this experiment, MgSt was also added to the powder blends to determine its effect on the classification and particle size analysis both in UV and VIS images. After 5.5 g of powder blend containing $MLX_{25\mu m}$ was fed into the feed frame of the tablet press, the tableting process started. Defined amounts of the following blends were layered in a specific order (Table 3) with time shifts to ensure the occurrence of tablets containing the approved particle size of the API.

2.5. Image acquisition

Images were acquired using a Canon 650D (Canon, Japan) DSLR (digital single-lens reflex) camera and Canon EFS 18–55 macro lens (Canon, Japan) mounted with a reversing ring. The camera was connected to a computer with a USB 3.0



interface. UV images were taken using a ring light containing one row of UV light-emitting diodes emitting in the 380–395 nm range (Apokromat Ltd, Hungary), and VIS images were taken using a ring light containing three rows of white, light-

calibration of the system was executed with QPCard

101 v3 millimeter reference scale (Argraph Corp., NJ, USA). After the calibration of the system, the size of a pixel was 4.2 μm . For image resizing, a sophisticated mathematical approach, Lanczos kernel was applied, which provided an opportunity to reduce a pixel size to 2.2 μm .

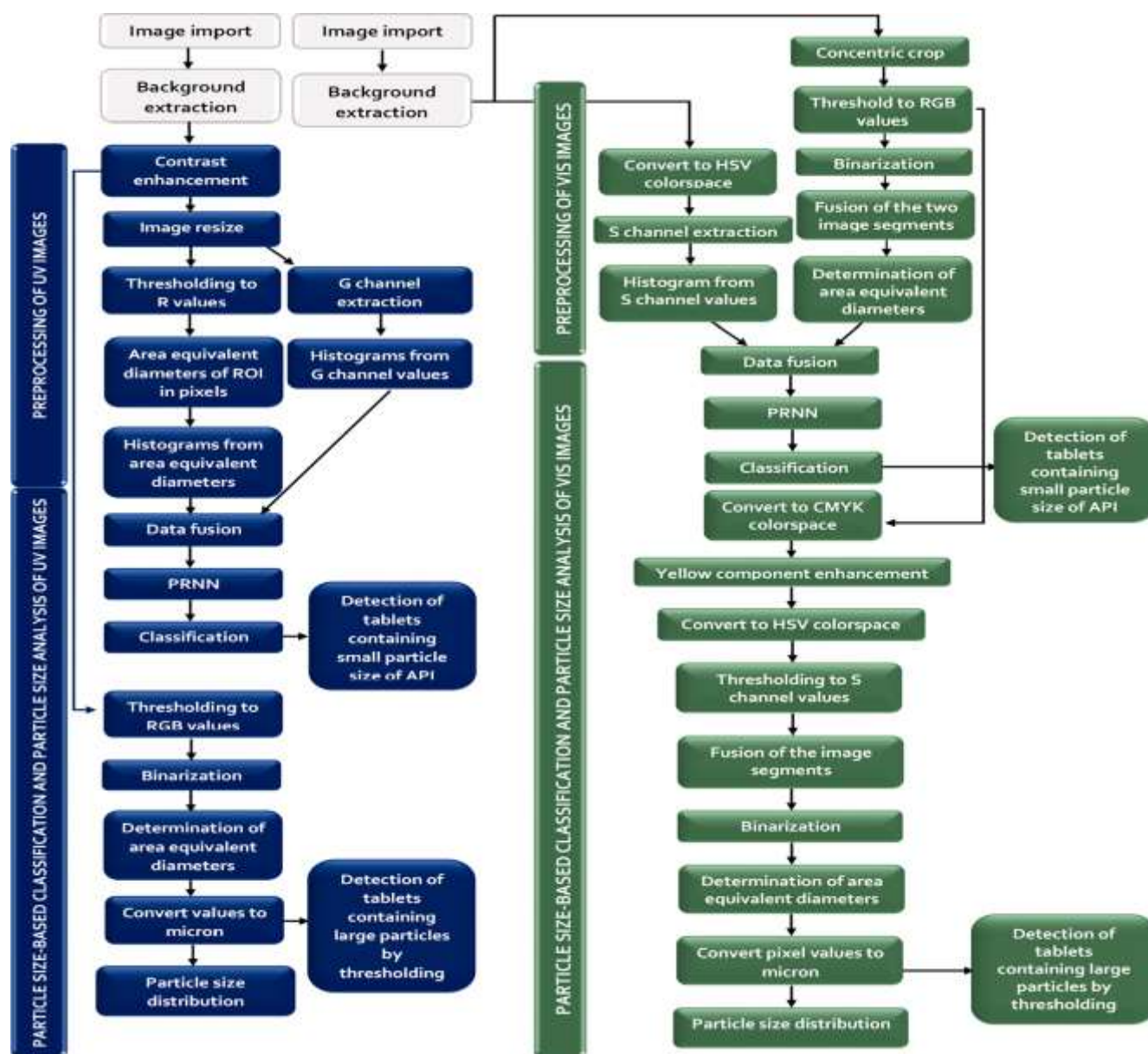


Fig. 1. UV and VIS image processing algorithms for classification and particle size analysis.



2.6. Particle size-based classification and particle size analysis with the developed machine vision system

2.6.1. Particle size-based classification of the prepared tablets

Two image processing algorithms were developed for UV and VIS images (Fig. 1) in Matlab 2020a (Mathworks, Natick, MA, USA). Particle size-based classification tasks were executed using Pattern Recognition Neural Network from Pattern Recognition and Machine Learning Toolbox (Mathworks, Natick, MA, USA).

After the image importing and the background extraction steps, UV images were resized to 20% of the original size. The resizing allowed the reduction of the image processing duration and the time consumption of the classification. For the classification task, the determination of the exact R, G, and B threshold values were not necessary because only the extraction of the distinguishable features and the regions of interest (ROIs) were required. Identifying ROIs was achievable using more permissive thresholds for only one channel from the applied colorspace. After the thresholding step, the obtained logical values were used to generate binary images. Then area equivalent diameters of the ROIs were calculated. Histograms were created from these values and used as input for pattern recognition neural network after normalization.

In the applied network, 50 neurons were applied in one hidden layer with a saturating linear transfer function, and 5 neurons were applied in the output layer with softmax transfer function. The pattern recognition neural network was trained using scaled conjugate gradient back-propagation. The end of the training was determined by reaching the appropriate number of validation checks. The training sample set contained 70%, the validation and the test set

contained 15%-15% of the samples prepared in the first tableting experiment. Classes were determined according to the prepared different particle size samples and

A complex algorithm had to be developed for particle size analysis using VIS images. The first step was the concentric crop of the images. The image segments were converted to CMYK colorspace. In that colorspace, the yellow component corresponds to one channel. Thus, the enhancement of MLX particles can be executed. The image segments were converted to HSV colorspace, and thresholding to S channel values was executed. Binary images were created with the fusion of the pre-processed image segments. The determination of the PSDs and the statistical values were obtained as in the analysis of UV images.

2.7. Statistical comparison of the measured and the predicted particle size distributions

The measured PSDs were compared to the predicted PSDs using the nonparametric, two-sample Kolmogorov-Smirnov test. The null hypothesis of the test was the measured and the predicted PSDs came from the same distribution. The null hypothesis was rejected or approved at 5% significance level. In this work, complex, bimodal PSDs were obtained, thus Wasserstein distance was also calculated for comparison.

3. Results and discussion

Table 4

Cross-entropy and error percentage values of the training, validation, and test set for UV and VIS images taken from both sides of the tablets.

Image preprocessing Image type

Set Percentage of correct classification

Percentage of incorrect classification

Cross-entropy

MSE

Image classes)	resize	(5	V IS	Traini ng	93.53%	6.47%	$3.3 \cdot 10^{-2}$	$4.7 \cdot 10^{-1}$
				Valida tion	90.00%	10.00%	$3.4 \cdot 10^{-2}$	$3.5 \cdot 10^{-1}$
				Test	90.00%	10.00%	$3.6 \cdot 10^{-2}$	$3.7 \cdot 10^{-1}$
Image classes)	resize	(5	U V	Train ing	99.41%	0.	$9.2 \cdot 10^{-1}$	$6.8 \cdot 10^{-1}$
				Valid ation	97.5%	59 %	$4.5 \cdot 10^{-1}$	$7.8 \cdot 10^{-1}$
				Test	100%	50 %	$6.5 \cdot 10^{-1}$	$3.5 \cdot 10^{-1}$
Image classes)	resize	(2	V IS	Train ing	99.41%	0.	$4.5 \cdot 10^{-1}$	$4.7 \cdot 10^{-1}$
				Valid ation	97.50%	59 %	$1.3 \cdot 10^{-1}$	$1.3 \cdot 10^{-1}$
				Test	100%	50 %	$1.8 \cdot 10^{-1}$	$2.1 \cdot 10^{-1}$
Image classes)	resize	(2	U V	Train ing	95.00%	5.00%	$6.2 \cdot 10^{-1}$	$4.2 \cdot 10^{-1}$
				Valid ation	100%	0%	$4.7 \cdot 10^{-1}$	$3.5 \cdot 10^{-1}$
				Test	100%	0%	$6.0 \cdot 10^{-1}$	$2.8 \cdot 10^{-1}$
Image algorithm classes)	processing	(5	V IS	Traini ng	97.06%	2.94%	$5.0 \cdot 10^{-2}$	$1.0 \cdot 10^{-1}$
				Valida tion	100.0%	0.00%	$3.0 \cdot 10^{-2}$	$1.1 \cdot 10^{-1}$
				Test	100.0%	0.00%	$4.1 \cdot 10^{-2}$	$1.0 \cdot 10^{-1}$
Image processing algorithm classes)	(5	U V	V IS	Train ing	99.41%	0.	$2.1 \cdot 10^{-1}$	$1.0 \cdot 10^{-1}$
				Valid ation	100.0%	59 %	$2.0 \cdot 10^{-1}$	$1.0 \cdot 10^{-1}$
				Test	97.50%	50 %	$2.0 \cdot 10^{-2}$	$1.2 \cdot 10^{-1}$
Image algorithm classes)	processing	(2	V IS	Traini ng	97.75%	2.35%	$2.6 \cdot 10^{-2}$	$2.6 \cdot 10^{-1}$
				Valida tion	97.50%	2.50%	$3.4 \cdot 10^{-2}$	$3.9 \cdot 10^{-1}$
				Test	95.00%	5.00%	$1.0 \cdot 10^{-1}$	$5.0 \cdot 10^{-1}$
Image algorithm classes)	processing	(2	U V	Traini ng	100%	0%	$3.46 \cdot 10^{-1}$	$6.34 \cdot 10^{-1}$
				Valida tion	100%	0%	$1.9 \cdot 10^{-1}$	$2.5 \cdot 10^{-1}$
				Test	100%	0%	$1.9 \cdot 10^{-1}$	$2.5 \cdot 10^{-1}$

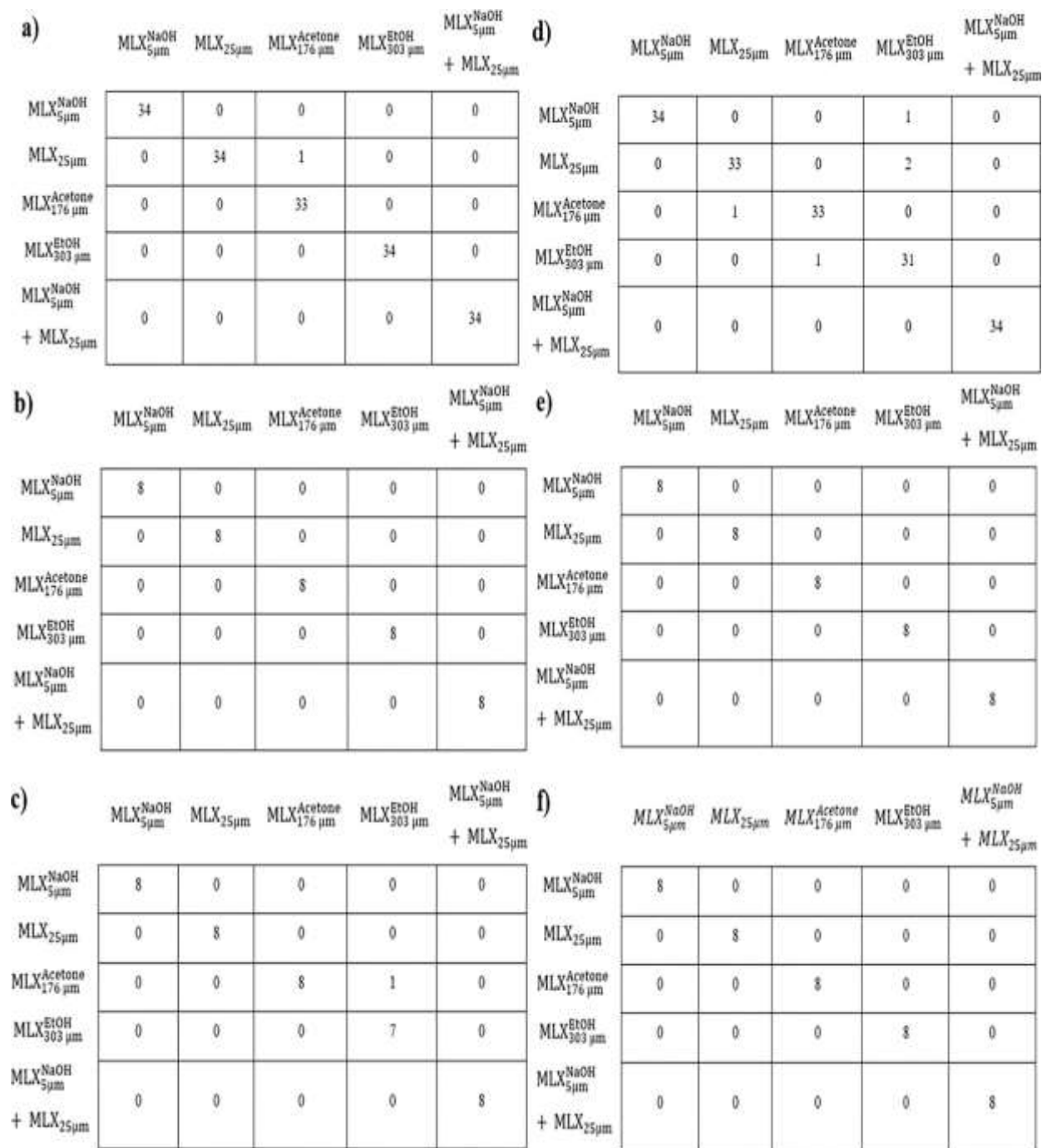


Fig. 5. Confusion matrices of the pattern recognition neural network-based classification using image processing algorithms and five classes (a) training, b) validation, c) test set for UV images, d) training, e) validation and f) test set for VIS images).

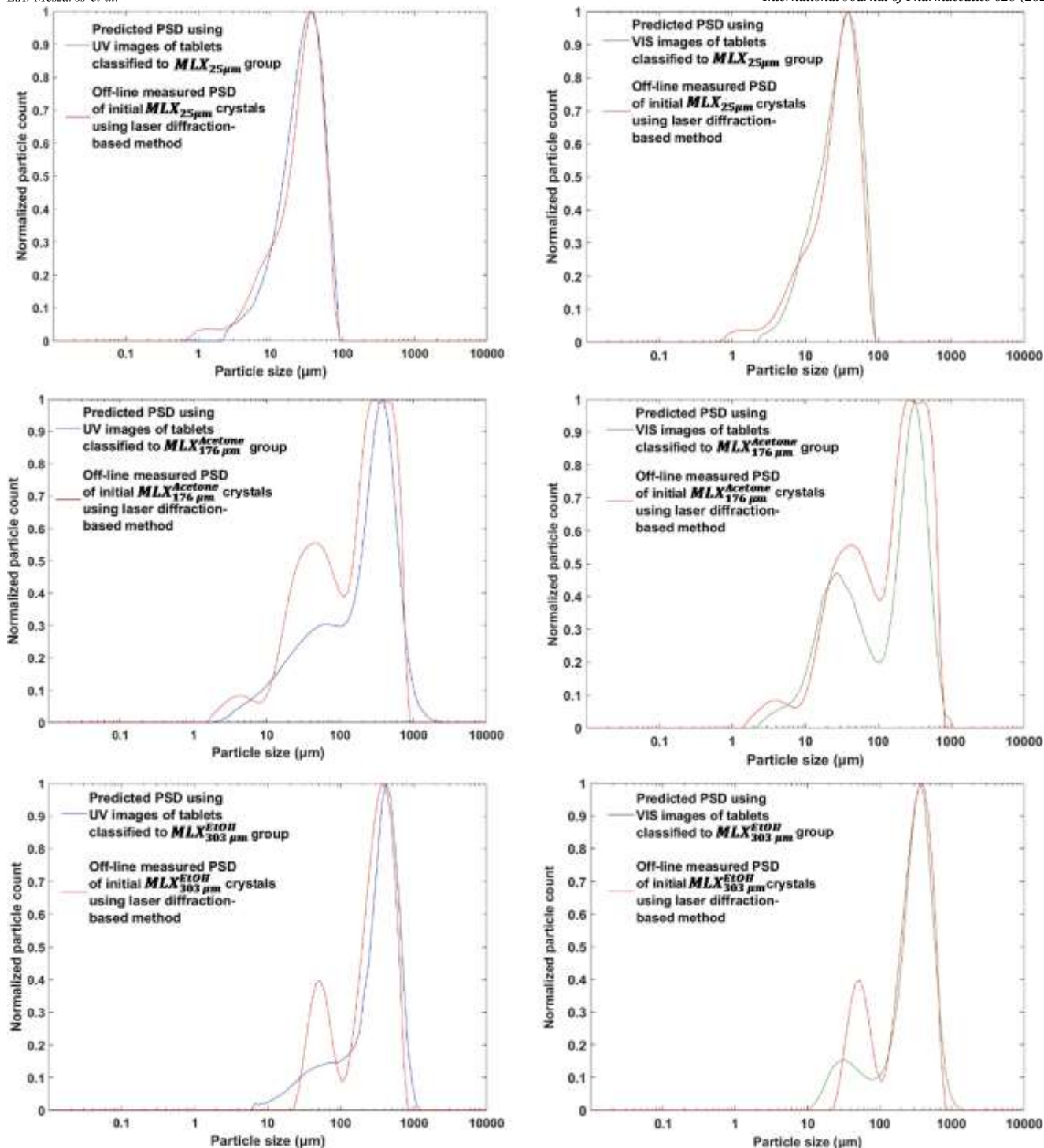


Fig. 6. The measured and the obtained PSDs of MLX tablets supported by digital UV/VIS imaging and image processing coupled with pattern recognition neural network (left column: results based on UV images, right column: results based on VIS images).

In the case of VIS images, five samples were misclassified. The most in Fig. 6. and Table 5. for UV and VIS images. These distributions and

considerable are three samples from the MLX^{EtOH} group. The samples of statistical values were obtained as a summary from all the images taken from the prepared tablets. The reference distributions and statistic the validation and the test sample set were classified correctly.

3.1. Particle size analysis of the prepared tablets containing different particle sizes of MLX

After the prepared tablets were classified, the particle size analysis was executed. The obtained PSDs and the

statistical values were shown

values were obtained from the initial crystals of different particle size samples of MLX using an off-line laser diffraction-based method.

The fine particle size of MLX^{NaOH} made the particle size analysis not feasible because the individual particles were not distinguishable with the applied resolution of the images. In other cases, the calculated distributions were similar to the measured distributions. Between the

can be applied up to the API concentration when the particles are not

303 μm groups. Important to mention that the machine vision system can collect information from every individual tablet, which can monitor

The results of Kolmogorov-Smirnov tests and the Wasserstein distances between the off-line measured PSDs of the initial crystals of the API and the predicted PSDs of all the tablets of different particle size groups using UV and VIS images.

overlapping. Consequently, the developed model should be applied to much higher MLX concentrations without any modifications. Although, when the particles overlap to a large extent, advanced methods should be applied for particle identification.

It is worth mentioning that the developed method needs to be adjusted to the API UV activity and color in VIS, the applied particle size, the API content, the applied excipients and the resolution of the images.

A single tablet image can be enough to determine if the particle size analysis works. Another outstanding feature is that the algorithms do not depend on the camera type.

$MLX_{25\mu m}$	UV	0.6828	0.0145
VIS	0.6828	0.0147	

This work presented the PSD determination and particle size-based classification of the API. The same high-resolution UV and VIS images

	Acetone	
$MLX_{25\mu m}$	0.1930	0.0535
$MLX_{176\mu m}$	0.3499	0.0480
$MLX_{303\mu m}$	0.3499	0.0247
UV	0.5626	0.0233
VIS		

allow the system to examine the particle size of MCC. Because the MCC particles are less defined than the API, an advanced method should be applied to identify the edges. In the case of MgSt, due to the small particle size and weight fraction, the application of the machine vision

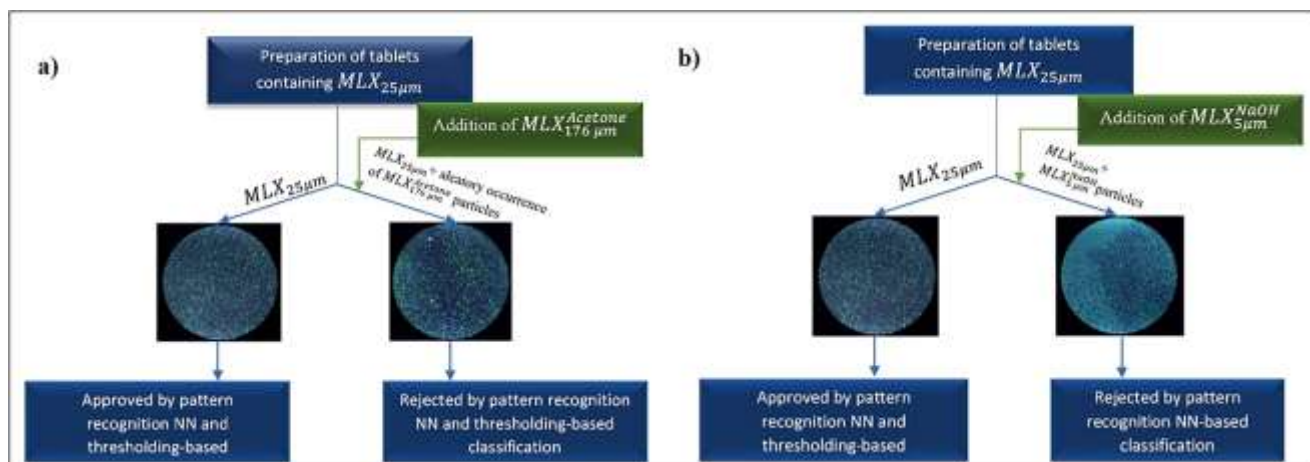


Fig. 7. The two scenarios, which can occur in automatic tableting in the context of batch changes of different particle size fractions, when (a) adding $MLX^{Acetone}$ + $MLX_{25\mu m}$, and b) adding MLX^{NaOH} + $MLX_{25\mu m}$ to the initial $MLX_{25\mu m}$ powder mixture).

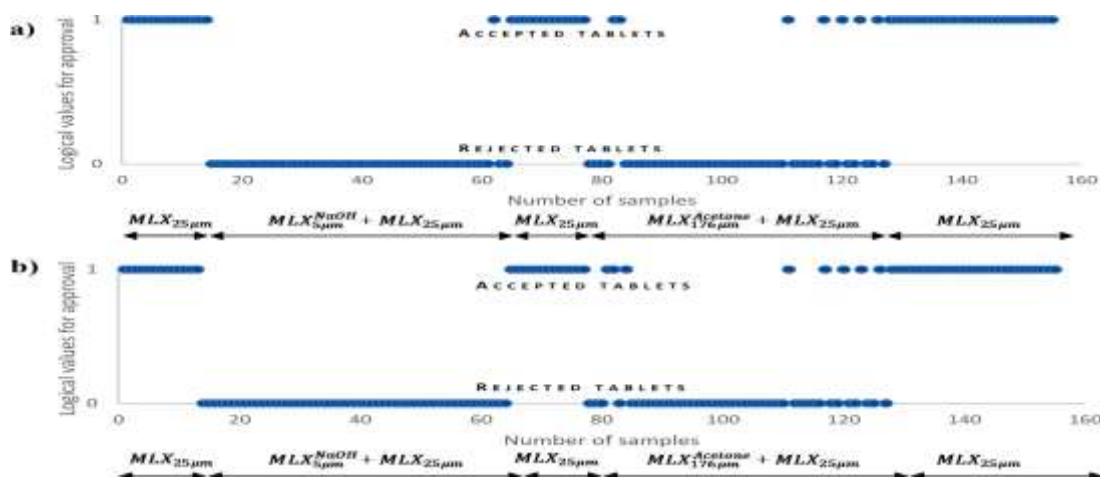


Fig. 8. The summarized approval results of the continuously prepared tablets selected by classification using pattern recognition neural network and thresholding-based algorithms (a) results based on UV images and b) VIS images of the prepared tablets).

system demands a more comprehensive investigation. In the context of MLX, other excipients or different particle sizes of excipients may not require modified algorithms.

4. Conclusion

With the shift towards continuous technologies supported by the regulatory agencies in the pharmaceutical industry, the appropriate sensors, multivariate data analysis, and data-driven methods are becoming more and more valuable. According to that, the newly developed machine vision systems will soon gain more interest in industrial applications. The digital UV/VIS imaging-based particle size classifications supported by the developed image processing algorithms and the applied pattern recognition neural networks were successfully executed with more than 97% accuracy using UV or VIS images. The

developed method was applicable in the case of 2.5 w/w% MLX content, and the application was not restricted to particle size fractions higher or lower than the optimal particle size of the applied API. On the other hand, the particle size analysis based on digital UV and VIS images of the tablets was restricted to those particle size fractions, which D₅₀ value was higher than 5 μm . Although in that case, the defective tablets, which contained fine particles, can be detected, and rejected based on the results of the classification. The particle size analysis of the tablets, when d₅₀ higher than 5 μm was successfully carried out when the mixtures of the API with the target and defected particle size were applied. The presented methods can be feasible for pharmaceutical applications and can open a new perspective for particle size analysis qualitatively and quantitatively based on a single UV or VIS image of an intact tablet.

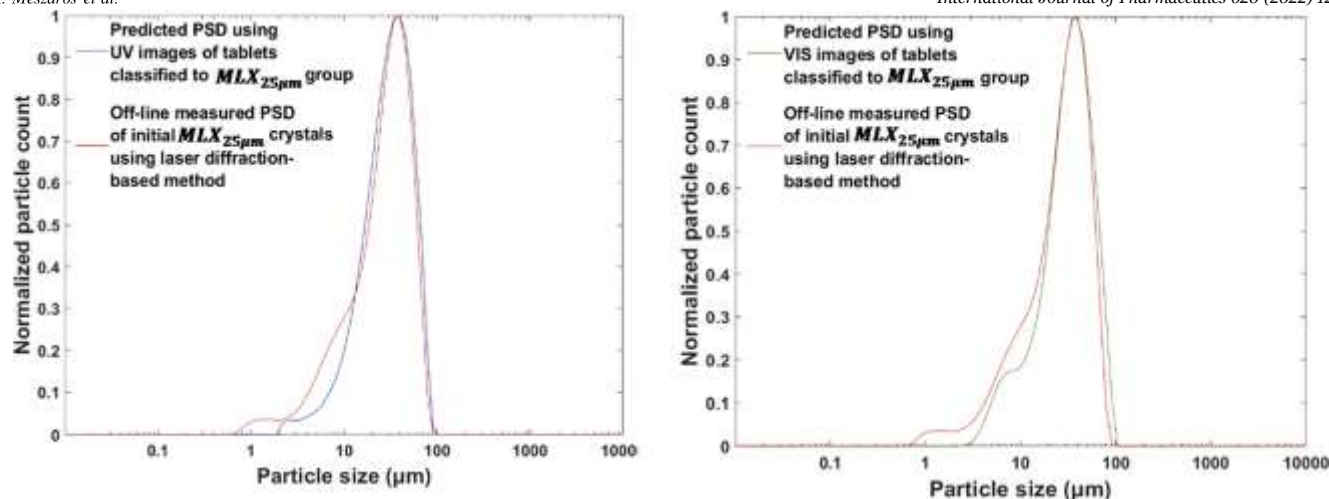


Fig. 9. The off-line measured PSD of initial crystals and the predicted PSDs of all accepted tablets containing MLX_{25μm} supported by digital UV/VIS imaging and image processing (results based on UV images (left), right and results based on VIS images (right)).

Lilla Alexandra Mészáros: Investigation, Methodology, Formal analysis, Visualization, Writing – original draft. **Attila Farkas:** Conceptualization, Supervision, Writing – review & editing. **Lajos Madarász:** Investigation. **Rozália Bicsár:** Formal analysis. **Dorián László Galata:** Investigation. **Brigitta Nagy:** Formal analysis, Investigation. **Zsombor Kristóf Nagy:** Conceptualization, Supervision, Writing – review & editing.

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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