



Process analytical technology based quality assurance of API concentration and fiber diameter of electrospun amorphous solid dispersions

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ABSTRACT

In this study, a novel quality assurance system was developed utilizing Process analytical technology (PAT) tools and artificial intelligence (AI). Our goal was to monitor the critical quality attributes (CQAs) like drug concentration, morphology and fiber diameter of electrospun amorphous solid dispersion (ASD) formulations with fast at-line techniques. Doxycycline-hyclate (DOX), a tetracycline-type antibiotic was used as a model drug with 2-hydroxypropyl- β -cyclodextrin (HP- β -CD) as the matrix excipient. The water-based formulations were electrospun with high-speed electrospinning (HSES). Raman and NIR sensors and machine vision-based color measurement techniques were employed to accurately determine the drug concentration. Given that morphology can influence the solubility of the drug, a convolutional neural network (CNN)-based AI model was developed to examine this property and detect manufacturing defects. Additionally, the diameter of electrospun fibrous samples was measured using camera images and a trained AI model, enabling rapid analysis of fiber diameter with results similar to that of scanning electron microscopy (SEM). These methods and models demonstrate potential in-line analytical tools, offering rapid, cheap and non-destructive analysis of ASD formulations.

1. Introduction

In the biotechnology field, there is an increased need for stable solid forms that maintain the living organism's viability during manufacturing and storage [1]. Freeze-drying is the typical formulation technique used in the biopharmaceutical industry. Even though it is a highly energy and money-consuming technique that works with long processing time, it is still the most widespread method to formulate living organisms [2,3]. The biggest issue with lyophilization is that numerous drugs, especially proteins, liposomes, and other sensitive small molecule active pharmaceutical ingredients (APIs) can be degraded during freeze-drying. Electrospinning is a promising alternative of lyophilization because it allows the gentle formulation of bioactive ingredients without causing the degradation of their structure, function, or stability while enabling the production of API containing fibers with a diameter ranging from nano- to micrometer. [4–6]. The simplest electrospinning setup is the single-needle apparatus which results in the continuous formation of nanomaterials in an electric field from a single capillary that contains the polymer solution [7]. The porosity, morphology, and fiber/particle diameter can be customized based on the application [8]. The tunable characteristics of the

electrospun samples enable versatile application across medical, environmental, and food industries. With the single-needle electrospinning (SNES) setup, the productivity is low, it typically ranges between 0.01–1 g/h which highly limits its industrial usage. Therefore, a high throughput high-speed electrospinning method (HSES) has been developed to increase the productivity up to 100–500 g solid electrospun fibers per hour. The HSES requires high voltage just like SNES but also applies fast rotation (40.000 rpm) that helps in the Taylor cone formation, hence the solvent evaporation is more efficient [9–12]. Although this technique has a great reputation in the academic and industrial field there is still no data in the literature that provides information about the quality of the samples during the electrospinning process. Quality control and quality assurance are crucial in the production of pharmaceutical products and other areas of the pharmaceutical industry [13]. Traditionally, information about a sample's quality is acquired through time-consuming, off-line, and often destructive analytical methods [14]. In the pharmaceutical industry, a variety of such analytical methods are available, however high-performance liquid chromatography (HPLC) is the most commonly used analytical tool for measuring the API content [15,16]. Although it is a reliable technique, its biggest disadvantage is that the sample preparation is time-consuming and requires the

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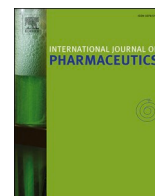
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Review

The current state-of-the art in pharmaceutical continuous film coating – A review

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ABSTRACT

In this decade, one of the major trends in the pharmaceutical industry is the adoption of continuous manufacturing. This requires the development of continuous equivalents of essential pharmaceutical processes such as film coating. The process of film coating is the last step of the processing of solid dosage forms and is critical because it determines the visual appearance of the end product, along with ensuring its stability and possibly even defining the rate of drug release. Several manufacturers advertise continuous solutions for film coating, these include semi-continuous and fully continuous appliances. State-of-the-art continuous coaters can match the throughput of continuous manufacturing lines, because largest appliances have a capacity of 1200–1500 kg/h. The paper also describes the main challenges related to continuous film coating including waste production at the beginning and end of the process and the problem caused by elastic recovery of the tablets when film coating is performed immediately after tablet compression. Lastly, we give an overview of the in-line sensors that can be used to monitor the quality of the film coated tablets, enabling real-time quality control of the process. Near-infrared and Raman spectroscopy can measure the mass gain of the tablets, while terahertz pulsed imaging and optical coherence tomography enable coating thickness measurement of individual tablets and even the characterization of intra-tablet coating thickness variability. UV imaging and machine vision can also measure coating thickness, and they are also excellent for detecting tablets with defective coating.

1. Introduction

Most manufacturing processes used in the modern industry can be separated into two major categories: batch and continuous technologies. In a batch technology, the product is manufactured in portions of predetermined size. Therefore, if multiple processing steps are required, the portion obtained in the previous step is used as input in the next step (Burcham et al., 2018). Typically, the material must be transferred and stored between steps, adding significant expenses to the cost of manufacturing (Helal et al., 2019). The appliances used in batch technologies must be large enough to accommodate the whole mass of one batch (Salawi, 2022). Companies relying on batch technologies find it more difficult to react to short-term changes in demand, since it is usually not possible to manufacture smaller amounts than one whole batch. This is because the processes are designed for a predetermined mass, and quality might change if the recipe is applied to different amounts of material (Kapoor et al., 2021). Continuous technologies

operate with a constant stream of input and output (Teżyk et al., 2016; Yang et al., 2022). Because of this, appliances are designed with a relatively small internal volume (O'Connor and Lee, 2017). Large amounts of material are processed by operating the same machine for a longer time, not by using a larger machine. This enables more flexibility in terms of production volume, as manufacturing 50 % less or 20 % more than usual can be easily achieved by running the process for a shorter or longer period. Continuous manufacturing eliminates the need for intermediate product storage and reduces processing times (Fisher et al., 2022). Due to their more compact size, it is feasible to connect several continuous appliances to each other and the resulting manufacturing line will still require a relatively small space (Gutmann et al., 2015). This way, all steps from raw materials to end product can be performed consecutively, resulting in much faster manufacturing. However, most continuous processes have a start-up and shut-down at the beginning and end of the manufacturing run, respectively. During these periods, the quality of the product will deviate from the standards, resulting in

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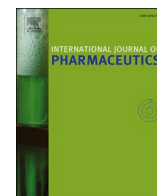
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Automated tablet defect detection and the prediction of disintegration time and crushing strength with deep learning based on tablet surface images

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ABSTRACT

This paper presents novel measurement methods, where deep learning was used to detect tableting defects and determine the crushing strength and disintegration time of tablets on images captured by machine vision. Five different classes of defects were used and the accuracy of the real-time defect recognition performed with the deep learning algorithm YOLOv5 was 99.2 %. The system can already match the production capability of tablet presses, with still further room left for improvement. The YOLOv5 algorithm was also used to determine the disintegration time and crushing strength of tablets produced at different compression force settings based on their surface texture. With these accurate, low-cost methods, the 100 % screening of the produced tablets could be carried out, resulting in the improvement of quality control and effectiveness of pharmaceutical production.

1. Introduction

Tablets are the most popular pharmaceutical dosage form thanks to their high throughput, low cost and high-precision dosing (Mohan, 2012). The traditional quality analysis of tablets is usually carried out with at-line and off-line testing after a random sampling. Methods such as crushing strength, disintegration time and dissolution are essential part of most Pharmacopoeias. However, these traditional methods are time and resource consuming, destructive, and labour-intensive, therefore focus has shifted to the development of new real-time methods (Zeng et al., 2022). By utilizing different types of spectral techniques, several properties of tablets can be determined with faster and non-destructive analysis, compliant with the Process Analytical Technology (PAT) directive (FDA, 2004). Near-infrared (NIR) spectroscopy has been used to determine disintegration time, tablet hardness and porosity (Gavan et al., 2022; Pestieau et al., 2014; Trenfield et al., 2023), while Raman spectroscopy has also been applied for tablet hardness and porosity measurement (Peeters et al., 2016; Shah et al., 2007). These methods also have disadvantages, mainly the difficult interpretability of the gathered spectral data and the high investment cost of the equipment, furthermore they are not capable of yielding high-resolution spatial information of larger areas such as the whole surface of a tablet.

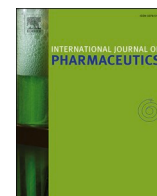
Digital cameras can also be used to gather information from tablets. Machine vision systems are easy to set up, and can scan large areas quickly to acquire sharp images of the desired objects. A tablet's surface contains the most information regarding its quality and properties, therefore by analysing surface images captured with appropriate lighting, essential quality attributes of the tablets, like active pharmaceutical ingredient (API) content and crushing strength can be determined (Galata et al., 2021). Mészáros et al. (Mészáros et al., 2020) used wavelet analysis for compression force and crushing strength prediction. They found that the obtained results were comparable with NIR spectroscopy-based techniques, but their measurements were much faster and cost-effective.

Image analysis can also be implemented for tablet defect detection, which is usually carried out via a visual inspection by an operator. This task can be completed more efficiently and without the typical issues associated with human labour by an automated system. Barimani et al. (Barimani et al., 2022) carried out an off-line, 100 % inspection of film coated tablets manufactured on a continuous production line with the Sensum SPINE instrument (Sensum d.o.o., Ljubljana, Slovenia) which uses image analysis for defect detection. They found that the main types of defects present were the insufficient amount of coating and the chipping of tablet edges. Many other companies manufacture and

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Simultaneous prediction of the API concentration and mass gain of film coated tablets using Near-Infrared and Raman spectroscopy and data fusion

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ABSTRACT

This study investigates the simultaneous prediction of active pharmaceutical ingredient (API) concentration and mass gain in film-coated tablets using Partial Least Squares (PLS) regression combined with three data fusion (DF) techniques: Low-Level (LLDF), Mid-Level (MLDF), and High-Level (HLDF). Near-Infrared (NIR) and Raman spectroscopy were utilized in both reflection and transmission modes, providing four types of spectral data per tablet. Transmission models proved more effective for API prediction by capturing data from the entire tablet, while reflection models excelled in assessing mass gain by focusing on the surface layer. Among the DF strategies, MLDF with Principal Component Analysis (PCA) offered the most significant improvements in predictive accuracy by filtering out irrelevant information. Variable selection methods further enhanced model performance by reducing the number of latent variables required. Overall, the integration of multiple spectral datasets and DF techniques resulted in models that gave predictions for evaluation samples with lower errors, demonstrating their potential to optimize quality control in pharmaceutical manufacturing.

1. Introduction

Orally administered solid dosage forms are the simplest and most commonly used formulations in the pharmaceutical industry, providing numerous advantages, including relatively easy manufacturing, cost-effectiveness, and high patient compliance. Tablets are the most important and widely used members of this group (Augsburger and Hoag, 2016; Zaid, 2020). In recent decades, it also became common to utilize film coatings to enhance certain properties of the tablets (Sastry et al., 2000).

Film coating typically occurs in the final stages of pharmaceutical manufacturing. During this process, the surface of the products is covered with a continuous and uniform film layer (Kapoor et al., 2020). The purpose of film coating can include modifying the kinetics of drug release (e.g., achieving extended drug release), protecting the drug and product from physical and environmental factors (mechanical damage, light, air, moisture, gastric acid, etc.), improving patient compliance through the enhancement of tablet appearance (e.g., colored coating), masking unpleasant tastes and odors, and making swallowing easier (Felton, 2007).

Film coating methods offer great flexibility, allowing for a wide

range of products to be coated, such as tablets, granules, powders, capsules, and nonpareils. Film coating is typically applied gradually to a moving mass of product, usually using a spray atomization technique. The success of the process can be attributed to various factors (Wang et al., 2012). Firstly, by applying a coating of only 2–3 % of the tablet core weight, the attributes of the product can be significantly altered. Moreover, film coating opens up opportunities for branding and identification, further establishing its significance in the pharmaceutical industry (Porter, 2021; Felton and Porter, 2013). Tablet film coating is a commonly used but critical process that provides various functions to tablets, thereby meeting different clinical needs. The evolution of dosage forms with film coatings is based on the development of coating technology, equipment, analytical techniques, and coating materials (Seo et al., 2020).

Two very important quality attributes of film-coated tablets are their active pharmaceutical ingredient (API) concentration and the mass gain that occurs during the film coating process. The cores must be adequately layered to ensure the product's safety and efficacy (Barimani and Kleinebudde, 2018). Acquiring real-time information during the process helps to enhance the production process and to detect possible problems (Peng et al., 2015; Bakeev, 2010). This can be accomplished

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Journal Pre-proof

Artificial intelligence-aided endoscopic in-line particle size analysis during the pellet layering process

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Artificial intelligence-aided endoscopic in-line particle size analysis during the pellet layering process

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Orsolya Péterfi: Investigation, Methodology, Formal analysis, Visualization, Writing – original draft. **Nikolett Kállai-Szabó:** Supervision, Methodology, Resources, Writing – review & editing. **Kincső Renáta Demeter:** Investigation, Formal analysis, Data curation. **Ádám Tibor Barna:** Investigation. **István Antal:** Resources. **Edina Szabó:** Investigation. **Emese Sipos:** Supervision, Writing – review & editing. **Zsombor Kristóf Nagy:** Conceptualization, Supervision, Resources, Writing – review & editing. **Dorián László Galata:** Supervision, Investigation, Methodology, Writing – review & editing.

Artificial intelligence-aided endoscopic in-line particle size analysis during the pellet layering process

Abstract

In this study, an artificial intelligence-based machine vision system was developed for in-line particle size analysis during the pellet layering process. Drug-layered pellets were produced by coating microcrystalline cellulose cores with an ibuprofen-containing layering liquid until the target drug content was achieved. Drug content increases with pellet size; therefore, particle size monitoring can ensure product safety and quality. The direct imaging system, consisting of a rigid endoscope, a light source, and a high-speed camera, provides real-time information about pellet size and layer uniformity, enabling timely intervention in the case of out-of-spec products. A convolutional neural network-based instance segmentation algorithm was employed to detect particles in focus, ensuring that pellet size could be accurately determined despite the dense flow of the particles. After training the model, the performance of the developed system was assessed by analysing the particle size distribution of pellet cores with variable sizes within the 250–850 μm size range. The endoscopic system was tested in-line at a larger scale during the drug layering of inert pellet cores. The particle size data acquired in real time with the endoscopic imaging system corresponded with the reference methods, demonstrating the feasibility of the proposed machine vision-based method as a process analytical technology tool for in-line process monitoring.

Keywords

Machine vision, Convolutional neural networks, In-line monitoring, Endoscope, Particle size distribution, Pellet layering, Process analytical technology

1. Introduction

Pellets are small free-flowing agglomerates with a near spherical or cylindrical shape, utilised across various industries due to their narrow particle size distribution and uniform shape, which provide advantages during processing and handling. Applications include animal feeds, fertilizers, catalyst carriers, iron ores, plastics and pharmaceuticals [1]. In the pharmaceutical industry, pellets are spherical particles with a diameter between 0.2 to 2.0 mm, commonly used in the production of oral dosage forms such as capsules and tablets [2]. Pellets offer several advantages, including enhanced flowability, reduced particle segregation, mitigation of excessive dust, improved distribution within the gastrointestinal tract, reduced risk of dose dumping of modified release dosage forms, and enabling the simultaneous administration of incompatible substances [3,4]. Pharmaceutical pellets are manufactured by various techniques, such as extrusion-spheronization, layering, cryopelletization, freeze pelletization, and hot-melt extrusion [5,6]. Drug-layered pellets are produced by layering of inert pellet cores with active pharmaceutical ingredient (API) until the desired dosage content is achieved. The API content in these pellets is determined by particle size, with variations in drug load corresponding to changes in layer thickness. The fluid bed apparatus is widely utilised in the pharmaceutical industry for drug layering, as it efficiently integrates multiple process steps—preheating, spraying-layering, and drying—into a single piece of equipment[1,7,8]. This technique is also suitable for coating the pellets with rate-controlling film forming polymers to achieve modified-release (MR) profiles [2,9,10].



Real-time component-based particle size measurement and dissolution prediction during continuous powder feeding using machine vision and artificial intelligence-based object detection

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ABSTRACT

This work presents a system, in which machine vision combined with artificial intelligence-based image analysis was used to determine the component-based particle size distribution of pharmaceutical powder blends. The blends consisted of acetylsalicylic acid (ASA) and calcium hydrogen phosphate (CHP). Images of powders were recorded with a digital camera in-line during feeding from a continuous feeder. The component-based particle size distributions determined with the system correlated well with those measured using a microscope as a reference method. This novel method proved to be effective in the real-time determination of particle size distribution of different components in the same blend. It was also possible to predict the in vitro dissolution profile of capsules filled with this blend by using the measured particle size distribution of ASA as input in a population balance model. The method could provide valuable information on the blends used in the pharmaceutical industry and could play a key role in the development of pharmaceutical quality control.

1. Introduction

Powder blends are integral to many areas of the pharmaceutical industry. Tablets represent up to 70 % of all drugs on the market. Powder blends are the main intermediate products of tablets. Therefore, knowing and controlling their properties is of utmost importance. It's particularly important considering that the malfunctions of the equipment used in the manufacturing of tablets are mainly tied to powder behaviour (Brubaker and Moghtadernejad, 2024). The pharmaceutical excipients can vary in size from the nanoscale colloidal range to granules of millimetre size in various pharmaceutical formulations. The two most important parameters of pharmaceutical powder particles are their size and shape, since these can have a huge effect on the quality attributes of the powders and a considerable impact on the end product. Particle size can affect content uniformity since the particles of different size and shape can segregate and cause inhomogeneity. Its effect on flow properties should not be overlooked (Goh et al., 2018, Fu et al., 2012). Particle size can also strongly influence dissolution and absorption rates (Shekunov et al., 2007) in the case of BCS II compounds. In contrast, BCS

I/III compounds are not dissolution rate limited and may result in a simplified dissolution method. Given this great impact, particle size is in many pharmaceutical processes considered a Critical Quality Attribute (CQA) (Madarász et al., 2023) typically measured using the distribution of parameters such as equivalent diameter or Feret diameter.

Determining and controlling the component-based particle size distributions is crucial in understanding the segregation of powder blends, where the sticking behaviour is dependent on material properties, such as surface area and crystal morphology (Abdel-Hamid et al., 2011). Although there are as many as 13 mechanisms related to the segregation of ingredients identified in engineering areas (de Silva et al., 1999) only a few are relevant in handling pharmaceutical solids. Amongst those the most relevant ones are sifting, fluidization and rolling. In these three phenomena the varying behaviour of the particles is attributed to the difference in their sizes, rather than the differences in the materials themselves (Jakubowska and Ciepluch, 2021). As a result, particles of the same component but of varying sizes and shapes may exhibit different behaviours, which can lead to further segregation and inhomogeneity. In their research, Péterfi et al. have investigated the

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