Real-time droplet size analysis using laser micrometer as a process analytical technology tool for continuous dripping process

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Abstract
Process analysis and monitoring during the manufacturing of the dripping pills are essential. However, research on developing sensor-based technology or process analytical technology (PAT) tools to analyze and monitor the dripping process is minimal. The purpose of this work is to develop a fast and non-destructive laser detection system for quantitative visualization of droplets, which involves detecting the size of the droplet and calculating the weight of the dripping pills during the dripping process. Several factors influencing the detection performance of the detection system and the detection system capability for quantitation of the pill weight were explored. The laser detection system accurately detects the weight of the dripping pills with the coefficients of determination (R²) higher than 0.99. It was also robust concerning the variation in critical process parameters and critical material attributes. Furthermore, the laser detection system was successfully applied to the production line of *Ginkgo biloba* leaf dripping pills to monitor the dripping pills weight. The proposed laser detection system can analyze and monitor the dripping process in dripping pill manufacturing with stable performance, high accuracy, and high efficiency.

KEYWORDS
dripping process, *Ginkgo biloba* leaf dripping pills, laser detection system, on-line process analysis and monitoring

1 | INTRODUCTION

With the rapid development of information technology (IT) and artificial intelligence (AI), intelligent manufacturing and industry 4.0 manufacturing have become the research focus in many industries [1–4]. The pharmaceutical industry is also on the way to realizing intelligent manufacturing and fostering innovations. The advances in sensor technology, data analytics, and system modeling were described as important innovations to understand, design, and control complex manufacturing processes [5]. The application of various sensors plays an important role in supporting advanced process-control strategies and automated operation in pharmaceutical manufacturing.
Moreover, PAT was introduced by the US Food and Drug Administration (USFDA) and defined as “a system that designs, analyzes, and controls manufacturing by measuring the critical attributes of materials and critical process parameters during the production process, to ensure final product quality” [6, 7]. Accurate on-line measurements of critical process parameters are vital for successful monitoring and process control. Therefore, PAT tools also play a crucial role in pharmaceutical manufacturing [8–10].

The dripping pill is a pharmaceutical oral solid dosage form that can be prepared using solid dispersion technology [11–13]. In recent years, dripping pills have been extensively used for clinical applications due to their excellent bioavailability and pharmacokinetics [14, 15]. The preparation process of dripping pills usually consists of five steps, that is, hot melting, dripping, condensing, washing, and coating [16]. After the hot melting process, the well-blended molten mixture flows out from the drop head as droplets. Then, the droplets fall into the condensing column and are solidified by cold oil to form spherical pills. The pill weight is a critical quality attribute of the dripping pill products which depends on the droplet size. The variation of the pill weight will seriously influence the dosage, and it is a common and important indicator reflecting the size uniformity of dripping pills. Accordingly, the pill weight must be precisely controlled to ensure the quality of dripping pills. The pill weight is influenced by many process parameters, such as the temperature of the dispersing liquid, the drop speed, the drop distance, the temperature of the condensing liquid and so on. In industrial production lines, operators usually sample droplets from a drop head every ten minutes or half an hour and weigh them using an electronic balance to monitor the dripping process. However, there are few studies of sensor technology or PAT tools that can inspect the quality of the dripping pills [17], monitor and control the dripping process [18]. Therefore, more efficient detection systems should be constructed based on sensor technology or PAT tools to better understand, analyze, monitor, and control the preparation process in dripping pills manufacturing.

The laser detection technique is a nondestructive measuring tool based on the theory of laser diffraction or charge-coupled device (CCD) light projection. Laser detection techniques have been used in many industries, such as on-line detection of particle size in pharmaceuticals [19–22], production and detection of parts in manufacturing [23–26], and material determination in medicine [27]. Considering laser detection technique and its wider applications, the present study was conducted to develop an on-line analysis and monitoring system based on a high-detection sensitivity CCD laser micrometer for the quantitative visualization of droplets during the dripping process. As a traditional herbal drug stipulated in the Pharmacopoeia of the People’s Republic of China [16], Ginkgo biloba leaf dripping pills was studied as an example. We analyzed and monitored the dripping process of Ginkgo biloba leaf dripping pills by using the proposed laser detection system. The widths of the droplet in the dripping process were captured and used to further calculate the size of the droplet. Furthermore, a quantitative relation was established between the size of droplets and the weight of the dripping pills. The proposed method provides a novel PAT for on-line analysis and monitoring the dripping process of dripping pills.

2 MATERIALS AND METHODS

2.1 Chemicals, reagents, and instrumentation

Three batches of Ginkgo biloba leaf extracts which were supplied by two raw material suppliers (two batches were supplied by Jiangsu Beisikang Pharmaceutical Co., Ltd., Xuzhou, China; and one batch was supplied by Zhejiang Conba Pharmaceutical Co., Ltd., Hangzhou, China) were used as active pharmaceutical ingredients (API). The polyethylene glycol (PEG) 4000 (supplied by Wanshangde Pharmaceutical Group, Wenling, China) was used as an excipient. The dimethyl silicone oil was used as condensing oil (purchased from Jiangxi Alpha Hi-tech Pharmaceutical Co., Ltd., Pingxiang, China).
The width of the droplets was measured using a laser micrometer (KEYENCE IG-028, Shanghai, China) which is equipped with a sensor amplifier (KEYENCE IG-1000, Shanghai, China). The data acquisition was performed using a data acquisition card (National Instrument cDAQ-9171, Shanghai, China). The homogenous dispersing liquid was prepared using a circulating oil bath (Greatwall Scientific SY-20, Zhengzhou, China) and an electric mixer (Zhengrong instrument ES-60 M, Changzhou, China). The preparation of dripping pills was performed using a dripping device (Anruikang, Beijing, China). The dripping pills were weighed using an electronic balance (Mettler Toledo AE240, Shanghai, China).

2.2 Preparation process of Ginkgo biloba leaf dripping pills

First, PEG 4000 was melted into a liquid at 80°C. Subsequently, the Ginkgo biloba leaf extract was added at a fixed stirring rate until a homogeneous dispersing liquid was formed, which was later transferred to the liquid tank of the dripping device (a double-layer tank in which the outer layer was equipped with a heating unit and filled with conduction oil) (Figure 1). The temperature of the dispersing liquid in the liquid tank was kept between 70°C and 100°C. Next, the dispersing liquid flowed out of the drop head as a shape of droplets, fell into the condensing column, cooled, and shrunk into dripping pills. All dripping pills were produced under the same condensing conditions. The drop distance (the vertical distance between the drop head and the horizontal plane of the condensing oil) was 75 mm. A condensing oil temperature gradient was used, and the temperatures of the upper, middle, and lower layers of the condensing column were kept at 25°C, 15°C, and 10°C, respectively. Next, the pills flowed out of the hose with circulating condensing oil and were collected on the dripping pill plate. Then, the pills were transported to the washing process.

2.3 Construction of the laser detection system

The laser detection system consisted of a laser micrometer, a sensor amplifier, a data acquisition card, and self-designed software based on LabVIEW 2018 (National Instruments, Austin, TX, USA). Figure 2A shows a schematic diagram of the laser detection system. The laser micrometer consists of a laser transmitter and a laser receiver. The laser was produced by the laser transmitter and received by the laser receiver when a droplet passed through the laser micrometer. First, the laser was cut off from the droplet, and the silhouette of the droplet appeared on the high-speed linear CCD of the laser receiver. Then, the widths of the droplet were obtained by calculating the size of the silhouette based on the digital edge-detection processor in the sensor amplifier. The sensor amplifier adjusted the detection mode and parameters. Data acquisition was performed by the data acquisition card and the self-designed software. As shown in Figure 2B, the laser transmitter and the laser receiver were fixed on a mechanical shelf and installed on both sides of the drop head. All data were collected using self-designed software (iDroplet). The software can acquire and save all the width data at a speed of 5000/s.

2.4 Parameters of the laser micrometer

The parameters of the laser micrometer are key influencing factors of the laser detection system. The main features of the laser micrometer include the measurement mode and response time. The laser micrometer has six measurement modes, and the “outer diameter/width measurement mode” was chosen based on the detection requirement. The response time is when the sensor head starts the measuring operation to the point where the output signal is sent. It is an inherent attribute of the laser micrometer. In our study, a droplet goes through the laser micrometer like a free fall during the dripping process, and then the response time should be set as short as possible to capture the widths of a droplet. The response time of the laser micrometer can be selected over a range of 1.96–4031.72 ms. Hence, the shortest response
time 1.96 ms was chosen as the response time in our research.

2.5 Installation location of the laser micrometer

The installation location of the laser micrometer involves two aspects. These include the vertical distance between the laser micrometer and the bottom of the drop head and the horizontal distance between the laser receiver and the drop head. The falling of the droplet was evaluated by the force balance between the gravity force, viscous force, and inertia force and followed a pattern similar to the law of free fall. When the droplet passes through the laser micrometer, the velocity of the droplet increases with the vertical distance between the laser micrometer and the drop head. Therefore, the number of data points of captured widths of a droplet is determined by the velocity of the droplet when the performance of the laser micrometer is constant. Furthermore, there are some differences between the widths captured at different vertical distances between the laser micrometer and the drop head. Therefore, the vertical position of the laser micrometer was investigated in our research. The laser detection system evaluated the influence of vertical distances of 11.4, 16.4, 21.4, 26.4, 31.4, 36.4, and 41.4 mm.

Furthermore, the dispersing liquid may stick to the laser receiver and affect detection when the horizontal distance between the laser micrometer and the drop head is too small. Therefore, to avoid the contamination of the laser micrometer, the horizontal distance between the laser receiver and the drop head was set as 25 mm.

2.6 Data processing method

The droplet size was calculated based on the widths captured by the laser micrometer. Different data processing methods were investigated to study the quantitative relation between the size of the droplets and the weight of the dripping pills in our study. Conceptually, the formation process of a droplet is conveniently divided into two steps. The first step corresponds to the growth of a droplet attached to the drop head, which ends with a broken force balance, and the second step corresponds to the necking, elongation, and breakage of the filament to form a droplet [28, 29]. The dispersing liquid flows out of the drop head and forms a long filament due to its high viscosity. The long filament can be divided into two parts when the main
droplet breaks. One-part blends with the main droplet, and the other retracts to the drop head. Therefore, the filament and droplet widths were captured during the dripping process. Hence, the raw width data could be processed and then applied to evaluate the size of a droplet and quantify the weight of a dripping pill.

To establish a quantitative relation between the size of the droplets and the weight of the dripping pills, different data processing methods were investigated. First, the maximum width of the droplet, the volume sum, and the area sum were extracted and calculated to represent the size of the droplets. Then, the average size of 20 droplets and the average weight of 20 dripping pills were used in each point of the quantitative curves. Moreover, the coefficient of determination ($R^2$) of the quantitative curve was used as the criterion to evaluate the practicability of the pill weight quantitation by the developed detection system.

The volume sum and area sum were calculated according to the formula (1) and (2), respectively.

$$ V = \sum_{i=1}^{m} \frac{\pi \cdot D_i^3}{6} $$

$$ S = \sum_{i=1}^{m} \frac{\pi \cdot D_i^2}{4} $$

where $V$ represents the volume sum; $S$ represents the area sum; $m$ is the number of data points that satisfy the width value is larger than 0.2 mm in a full dripping cycle; $D_i$ is the $i$-th width value of the droplet and filament, which is larger than 0.2 mm.

Furthermore, the subtraction of the retracted filament was also evaluated. The retracted filament’s volume sum and area sum were subtracted from the corresponding volume sum and area sum. The volume sum and area sum of the retracted filament were calculated according to the formula (3) and (4), respectively.

$$ V_f = \sum_{j=1}^{n} \frac{\pi \cdot D_j^3}{6} $$

$$ S_f = \sum_{j=1}^{n} \frac{\pi \cdot D_j^2}{4} $$

where $V_f$ represents the volume sum of the retracted filament; $S_f$ represents the area sum of the retracted filament; $n$ is the number of data points that satisfy the width value is between 0.1 and 0.2 mm in a full dripping cycle; $D_j$ is the $j$-th width value of the retracted filament, where the width is between 0.1 and 0.2 mm.

### 2.7 Evaluation of the laser detection system

The velocity of the droplet is influenced by the critical parameters of the dripping process and the critical attributes of the dispersing liquid. Taking *Ginkgo biloba* leaf dripping pills as an example, the dispersing liquid is a non-Newtonian fluid. The viscosity decreases with increasing temperature and further affects the fluidity of the dispersing liquid. The weight of the dispersing liquid in the tank determines the pressure of vertical mobility and further influences the velocity of the droplet that passes through the laser micrometer. The high temperature and large weight of the dispersing liquid may increase the velocity of the droplet when it passes through the laser micrometer and further decrease the number of width data points. Furthermore, the temperature and the weight of the dispersing liquid also affect the weight of dripping pills. Hence, the temperature and the weight of the dispersing liquid were investigated to evaluate the capability of the detection system for pill weight quantitation.

Due to different resources and preparation processes, batch-to-batch *Ginkgo biloba* leaf extracts may show variation in component and particle size and further cause variations in the dispersing liquid’s viscosity, density, and surface tension. According to fluid dynamic theory, the force balance between gravity, inertia force, and viscous force is the critical element of vertical mobility and determines the dispersing liquid’s fluidity [30, 31]. The dispersing liquid’s fluidity may influence the droplet’s velocity that passes through the laser micrometer, affecting the number of width data points. Hence, three batches of *Ginkgo biloba* leaf extract were also chosen to evaluate the capability of the detection system for pill weight quantitation.

### 3 RESULTS AND DISCUSSION

#### 3.1 Influence of the installation location of the laser micrometer on the performance of the laser detection system

The width profiles captured in 4000 ms (x-axis) at different vertical distances are shown in Figure 3. The captured width profiles become sharper and narrower with increasing vertical distance. This may be because the droplets pass through the laser micrometer at a speed that increases at a large vertical distance and causes a decrease in the detection time of the droplet and the quantity of width. Figure 4 shows the detailed profiles of the widths captured at different vertical distances after aligning the starting point of
FIGURE 3 Profiles of the widths captured at different vertical distances: (A) 11.4 mm; (B) 16.4 mm; (C) 21.4 mm; (D) 26.4 mm; (E) 31.4 mm; (F) 36.4 mm; and (G) 41.4 mm. The temperature of the dispersing liquid was kept at 80°C.

FIGURE 4 Detailed profiles of the widths captured at different vertical distances

the captured widths. As illustrated in Figure 4, the number of data points of captured widths decreases with increasing vertical distance. This is because the widths of the filament induce a progressive decrease and gradually stabilize as the vertical distance increases.

Furthermore, it is evident that when the vertical distance is 11.4 mm, the widths of the filament are much larger than that at other installation positions. This may be because the laser micrometer is too close to the drop head, which detects the thick neck but not the filament of the dispersing liquid. Therefore, the vertical distance between the laser micrometer and the drop head was kept larger than 11.4 mm. However, if the laser micrometer is too close to the condensing column, the laser micrometer may be contaminated with the condensing oil. Therefore, to avoid the contamination of the laser micrometer, the selected vertical distance between the laser micrometer and the drop head was 31.4 mm in this study.

3.2 Selection of the data processing methods

The laser micrometer was installed above the break-up point of the filament, so the captured widths consisted of the widths of the main droplet, the elongated filament, and the retracted filament. The retracted filament was not a part of the final droplet, so theoretically, the captured widths need to be subtracted. Some researchers reported the blow-up of the interfacial curvature and axial velocity values at the pinch-off point due to filament breaks...
3.3 Evaluation of the laser detection system

3.3.1 Temperature of the dispersing liquid

Different temperatures of the dispersing liquid were investigated to evaluate the capability of the laser detection system for pill weight quantitation. The temperatures of the dispersing liquid were kept at 70, 80, 90, and 100°C, respectively. The volume sum was calculated, and the weight of the dripping pills was weighed using an electronic balance. The quantitative relations between the volume sum and the weight of the dripping pills were constructed and are illustrated in Figure 6. The obtained coefficients of determination (R²) were all higher than 0.9985, which demonstrated that the laser detection system provided an excellent quantitative ability under different temperatures of the dispersing liquid.

3.3.2 Weight of the dispersing liquid

The dripping processes were performed with different weights of the dispersing liquid. The temperature of the dispersing liquid was kept at 80°C. The volume sum was calculated, and the weight of the dripping pills was weighed with an electronic balance. A quantitative relation was established between the volumesum and the weight of the dripping pills. As illustrated in Figure 7, it is evident that the weight of the dripping pills decreases with decreasing weight of the dispersing liquid, and the variation trend of the volume sum shows a high similarity with the variation trend of the dripping pill weight. As shown in Figure 7C, the coefficients of determination (R²) was 0.9932, which indicates that the laser detection system still has an excellent quantitative capability for the change of pill weight caused by the weight of the dispersing liquid.

3.3.3 Raw materials

Due to variations in the resource and preparation process, different Ginkgo biloba leaf extracts may show the difference in critical material attributes [32] and further cause the difference in dispersing liquid. In this context, three batches of Ginkgo biloba leaf extract supplied by different companies were chosen to evaluate the capability of the developed laser detection system for pill weight quantitation. The temperature of the dispersing liquid was kept at 80°C. The quantitative relations between the volume sum and the weight of the dripping pills
FIGURE 6  Quantitative relations between the volume sum and the weight of dripping pills under different temperatures of the dispersing liquid. (A) 70°C, (B) 80°C, (C) 90°C, and (D) 100°C. The vertical distance between the laser micrometer and the drop head was 31.4 mm.

FIGURE 7  Variation trend of the dripping pill weight (A), the variation trend of the volume sum (B), and quantitative relationship between the volume sum and the weight of the dripping pills (C). The vertical distance between the laser micrometer and the drop head was 31.4 mm.

were built. As shown in Figure 8, the coefficients of determination ($R^2$) were higher than 0.9985, which showed that the materials had no significant effect on the detection system. Therefore, the laser detection system showed an excellent capability of pill weight quantitation, even though different materials prepared the dispersing liquids.

3.4 Application of the laser detection system to the dripping process of Ginkgo biloba leaf dripping pills

Three batches of Ginkgo biloba leaf dripping pills prepared from the same raw materials were evaluated in our research. The temperatures of the dispersing liquid
FIGURE 8  Quantitative relation between the volume sum and the weight of dripping pills. (A), (B), and (C) indicate three batches of dispersing liquid prepared by three batches of *Ginkgo biloba* leaf extract. The vertical distance between the laser micrometer and the drop head was 31.4 mm.

FIGURE 9  Information on the results of the dripping processes. (A1, A2) 80°C; (B1, B2) 90°C; and (C1, C2) 100°C. The vertical distance between the laser micrometer and the drop head was 31.4 mm.

were kept at 80, 90, and 100°C, respectively. The laser detection system captured all width data during three dripping processes. The predictive weight of the dripping pills was calculated following the quantitative equations illustrated in Section 3.3.1 (Figure 6B–D). The dripping pills were sampled for every 5 min and weighed using an electronic balance. The total sampling time of three batches of dripping processes was different due to the different temperatures. However, as illustrated in Figure 9, the volume sum and the actual weight of the dripping pills showed similar trends as they all decreased with the progress of the dripping process.
Furthermore, the predictive weight of the dripping pills was analyzed and compared with the actual weight of the dripping pills. The results postulated that the variation trend in the predictive and actual weights of the dripping pills showed high consistency. Therefore, the laser detection system is suitable for on-line analysis and monitoring the dripping process of dripping pills. Moreover, the developed laser detection system had advantages over the image processing method [18], showed higher efficiency, and required less storage space.

4 | CONCLUDING REMARKS

The present study proposed a laser detection system for on-line analysis and monitoring the dripping process during dripping pills manufacturing. A method of quantitative visualization of droplets was built during the dripping process. The installation location of the laser micrometer and the data processing method were studied as influencing factors to examine the performance of the detection system. The results indicated that the developed laser detection system could be used to analyze and monitor the dripping process during the preparation of dripping pills in an accurate and non-intrusive manner. The weight of the dripping pills can be quantitated accurately with the coefficient of determination (R²) greater than 0.99 during the dripping process. Furthermore, the high-speed and -accuracy laser micrometer fulfills the required characteristics as a PAT for on-line analysis and monitoring of the dripping process in dripping pill manufacturing. It can further provide the necessary technical support for the next step of controlling dripping pill manufacturing. In the future, the proposed technology could also be tested for other dosage forms or experiments with a similar production process, such as soft gel capsules, personalized-dose medicines prepared by thermal ink-jet printing, etc.

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CONFLICT OF 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.

AUTHOR CONTRIBUTIONS

Xiaoping Wang: Conceptualization, Methodology, Software, Investigation, Formal analysis, Writing- Original draft preparation, Writing- Review and Editing. Ying Tian: Investigation, Validation. Sheng Zhang: Formal analysis, Validation. Haibin Qu: Supervision, Conceptualization, Writing- Review and Editing, Funding acquisition.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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