The Application of Computer Vision in Pharmaceutical Manufacturing

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***Abstract*—The study gives a brief introduction to the use-cases of computer vision techniques in the field of pharmaceutical manufacturing. Initially, the paper discusses the overall computer vision field and pharmaceutical domain. Afterwards, the use of computer vision in the domain is explained with high-level use cases and the advantages in doing so. Further, the various computer techniques in the field are discussed concerning each process and how it improves the quality and productivity in various stages. Finally, improvements and future requirements in this domain for the computer vision techniques are discussed in short in the conclusion section.**

Keywords—computer vision; pharmaceutical manufacturing; drug manufacturing; image analysis;

I. Introduction

This paper is aimed at providing a comprehensive overview of the computer vision techniques used in the domain of pharmaceutical manufacturing. Initially, a brief introduction to computer vision and pharmaceutical manufacturing is given. Afterwards, the steps involved in the manufacturing of drugs is listed for which various machine vision techniques proposed and demonstrated by various researchers are discussed. Each use case is presented with its importance, conventional methods used, computer vision method and its advantages. To conclude, the future improvements and scope of computer vision in the pharmaceutical domain are briefly discussed.

II. Introduction to Computer Vision

Computer vision is the field of computer science which deals with the analysis image and videos to derive information. The field has evolved from the ability to do simple extraction to derive primal sketches from 2D images to re-create scenarios in a 3D environment using the concepts of augmented reality and artificial intelligence systems [1]. Dr Larry Roberts is considered as the father of computer vision for his contribution to defining the blocks world context for the field of computer vision[2].

III. Introduction to Pharmaceutical Manufacturing

Pharmaceutical manufacturing which is also known as drug manufacturing is the production of pharmaceutical drugs in the commercial-scale for retail distribution. There are multiple classes of medicines based on the purpose but they are usually manufactured in a single plant to increase efficiency and reusability [3]. The process of pharmaceutical manufacturing consists of multiple stages [4] such as powering, granulation, shaping, coating and packaging which are discussed in detail in applications.

IV. Use of Computer vision in pharmaceutical manufacturing

Historically, the qualitative analysis of the tablet was done manually in an assembly-line manner by random sampling where tablet specimen was taken out from the production line and inspected under microscopes for texture composition[4]. Based on the quality check criteria, the tablet was also put under chemical composition tests[3]. However, the advancements in the computer vision field like automatic recognition of cavities, object tracking in the manufacturing line, etc. have contributed to reducing the manual labour involved and increased quality of the pharmaceutical manufacturing. This section will present various techniques proposed and demonstrated by various authors in this field. The applications will follow an introduction to the process, what is the conventional method to cater to this process requirement, new computer vision-based method can be implemented and finally the advantages of using the computer vision.

A. Cavity detection

The cavities inside a tablet are of utmost importance as it plays a critical role in deciding the solvency of a tablet. Currently, the random samples are broken and inspected for manual inspection under a microscope. Yin et al [5] have demonstrated a machine learning approach in analysing the tablet architecture which can directly indicate the correlation between the tablet composition, molecular structural distribution to the disintegration process when consumed [6]. The method uses X-ray based microcomputed tomographic images (SR-μCT) which are captured in 3D space as shown in Fig 1. These images are then used to derive the morphological architecture of the tablet, which is then used to detect the voids and porosity inside the tablet. Radial and axial dial direction context were created based on the three-dimensional structure of the tablet [7]. The principal component analysis (PCA) was used to do multivariate data analysis to derive correlation factors between disintegration behaviours, cavities morphology, single particles attributes, and the cavities spatial arrangement within the tablets [5]. As a result, two disintegration types were defined for the solvency factor correlation; laminating and splitting tablets. In the laminating

This paper is presented as per the curriculum requirement for the module Artificial Intelligence under the guidance of Dr. Kevin Meehan, Lecturer, LYIT.

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type tablets, the cavities were concentrated towards the centre of the tablets whereas the splitting type tablets had the cavities uniformly distributed. Information like these were not analysed in the conventional methods.

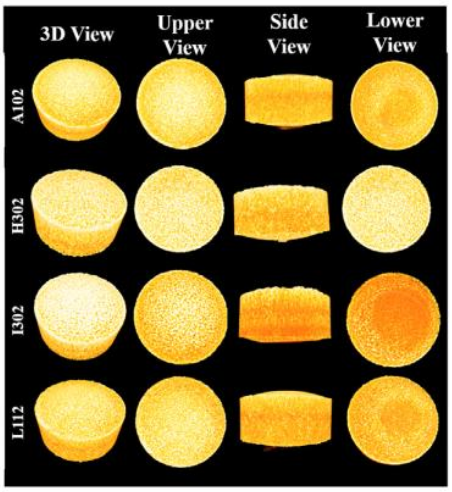

Fig 1. 3D graphics of MCC tablets representing upper, lower and middle layer surfaces of 3D images of tablets [5].

B. *Prevention of capping*

Capping is one of the most common defects which occurs during the process of tablet manufacturing which is caused by inappropriate compression (pressure and speed). Currently, the pressure and speed are manually calibrated accordingly to the run cycle phase of the machine (scheduled maintenance). Xu et al have demonstrated a new method using image analysis of the cross-section of the tablet using a non-destructive ultrasound scan [8]. The scan will be done in various stages as depicted in Fig 2 which is further processed to derive the capping point of the tablet. A strength analysis can be done by studying the chemical composition of the tablet structure. Using this information, the mechanical properties are predicted which in turn can be used to set the pressure and speed of the compression process [9]. The system proposed is an early detection mechanism where live images will be monitored such that the pressure and speed can be set before going to the compression stage thus reducing the capping rate of the tablets. The current study by the team on this early detection [10] will help in solid dosage development and manufacturing process alike. This can help in research phase also to run simulations of the manufacturing process which will also reduce the dry run cost.

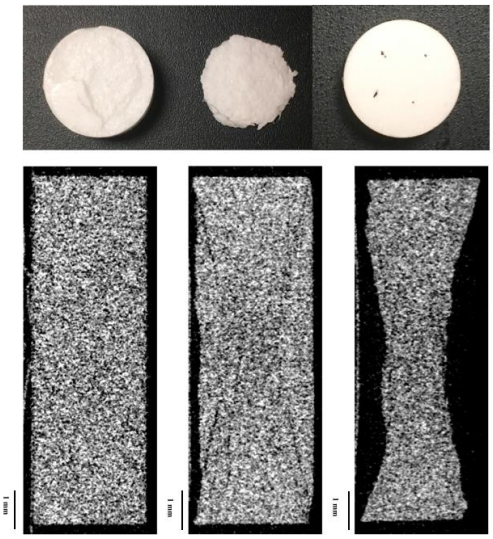

Fig 2. Texture analysis of the tablet surface to check integrity [8]

C. *Polymorph quantification*

Polymorph quantification is a method surface analysis method of a tablet to determine the distribution of the polymorph formations. Currently, manual inspection using a microscope is the only analysis performed to identify issues in this area. Da Silva et al [11] have presented a comparison study between two commonly used polymorph quantification, that is, MCR-ALS ad PLS regression. This study is backed up with the images which are captured doing performing score analysis of the surface scans [12]. The images are captured using a technique called Near-Infrared hyperspectral imaging (HIS-NIR) which is also a non-destructive analysis for surface scanning for minute variations which is combined with the previous algorithms discussed to detect the irregularities on a tablet after manufacturing. In general, the PLC method has a lower RMSEP [11] comparing to the MCCR-ALS predictions. This is based upon the image-analysis of the tablet on the same set of collections in both methods. The reason pointed out by Da Silva et al [11] is that the MBZ polygraph which was used has concentrated on main spectral regions which reduced the effect of minor spectroscopic changes. But the MCR-ALS was advanced in depicting the distribution maps of the polymorphs whereas the PLS was better in the giving a more accurate overall average. Fig 3 depicts the conversion of the distribution maps into the concentration values. In this study, the author concluded that the goal of the analysis determines the superiority of the algorithm performance [11].

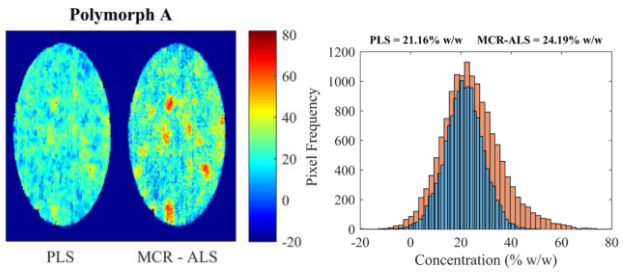

Fig 3. Distribution maps and its frequency histogram for MBZ polymorphs [11]

D. Flow Analysis

Powder flow is a simple but volatile process which can create ramifications in the later stages of the manufacturing process. In a conventional process, the power flow is measured using funnel or orifices where a physical device is added to quantify the flow of material [13]. These measurement techniques are not able to provide with other aspects of the flow such as the density of current flow and other indirect flow measurements due to the in capabilities to read interparticle forces [14]. This is because, in the flow analysis, the macro-level properties are diminished by the micro-level properties. Therefore, Blanco et al [15] have presented a computer vision-based flow analysis method where the video of the flow is processed in real-time by capturing the lumination intensity of the reflection by the powder in the assembly line. The method has been successful in predicting the success rate of the batch by using the machine algorithms. Fig 3 shows the scanning electron micrographs and the derivation of spacing between the polymorph formations in the power while flowing through the assembly line. The experiment was successful in eight variations of the tablet manufacturing process [15]. This method is a good example of how computer vision is used to achieve real-time analysis of a physical process to increase productivity and reduce the failure rate. Another example for improvement of the manufacturing process using computer vision is provided by Madarász et al [16] using high-speed process camera coupled with an image process software As shown in Fig 4, the video capturing is integrated which uses a PAT-tool which completes a continuous quality ensuring-process for drug manufacturing. Fig 5 shows various stages in the image processing and how image-processing is used to detect the flow amount through the funnel.

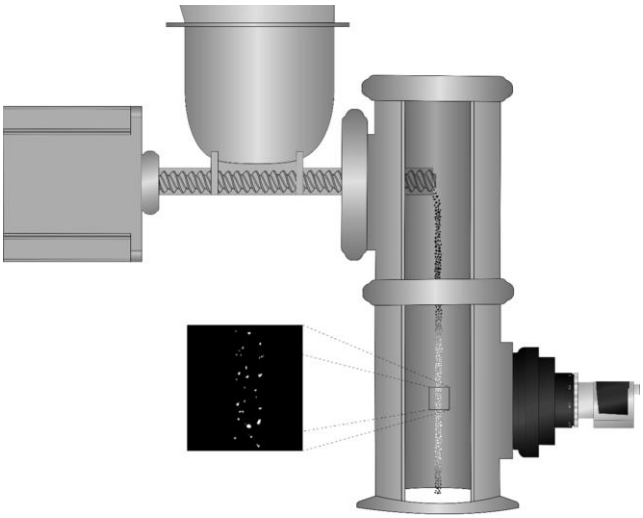

Fig 4. The physical arrangement of the developed videometric system [16].

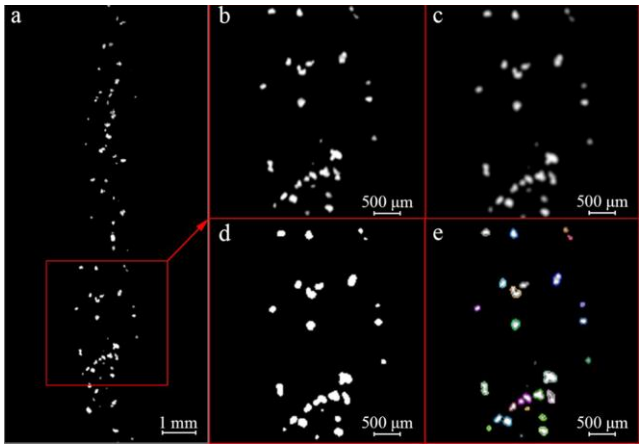

Fig 5 Stages of image processing [16]: (a and b) Raw image, (c) Gaussian blur, (d) Binarization and (e) Contouring.

E. Coating Quality

The tablets coating is a crucial step in the process which ensures the durability of the shelf life of a tablet. The coating is a very delicate process because of which the quality has to be ensured in real-time rather than a post metric analysis. In this process, Optical Coherence Tomography is one of the most commonly used methods which can ensure the coating quality in a non-destructive way [17]. Fig 6 illustrates a general framework of how the OCT systems. This is achieved using the real-time analysis of the cross-sectional images of the tablets which were conventionally an offline-measuring and competitive process which had a significant delay in ensuring the quality. Sacher et al [18] have given evidence in his study about how the real-time coat measurements could be applied with modern computer vision techniques. The study further discusses how the variations in the image analysis method can be optimized to adapt to various sizes of the tablets without creating the framework from scratch. The experiments were conducted on an industrial scale pan coating process where automated layer detection of tablets, qualitative classification and thickness check performed in real-time [19]. One of the other major contributions is that, by implementing real-time image analysis, an increase in coating roughness over time was identified which was not detected in the manual process. The application of machine learning has given wider insights into the manufacturing process.

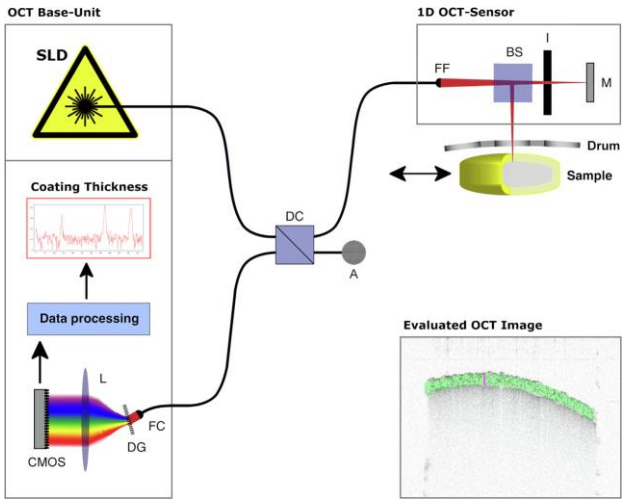

Fig 6. Schematic of the OCT system consisting of a base unit and sensor heads [18].

F. Dissolution Analysis

The dissolution analysis of tablets is a study of how the tablets disintegrate when in contact with various liquids. That is, the dosage release into the body once consumed. Conventionally, this is measured by observing the dissolution process the tablet in various liquids such as water and acid [20] (Simulation of the digestion process). The PI methods for the same are Multivariate Curve Resolution – Alternating Least Squares (MCR-ALS) and Parallel Factor Analysis (PARAFAC and PARAFAC2) which is done on the multi-series hyperspectral imaging. Alexandrino et al have proposed real-time monitoring of the process which could derive insights into the process [21] by applying the techniques into machine vision systems where amorphous-to-crystalline transitions could be analysed using RNN networks to capture the time-sensitive data insights. This study has helped to exhibit the capability of bilinear and multi-way curve resolution approaches to model the hyperspectral images for deriving the solid-state transitions of tablets in solid dosage forms.

G. Visual Inspection Automation

The lyophilized drug products are a special type of tablets which have multiple stages of drying and freezing to produce a solid dosage form. This is done for increasing the shelf life which is mostly done for protein and vitamin tablets [22]. Currently, the inspection to make sure the tablets are contamination-free and packaging is manual labour. Throughout the development of computer vision techniques, the automation of this process has been researched extensively to improve the quality assurance policy. Currently, the liquid-based contamination checks are already automated but the solid-state contamination inspection is not for which Tsay and Li [23] have proposed a new method using computer vision and multi-input deep neural networks to identify the abnormalities in the tablets. Fig 7 describes the architecture to capture images from two cameras and feed to the CNN network. The goal of the method is to use convolutional layers to analyse multi-angle images of the same vial to overcome the issue of the blind spot in the single image analysis. Transfer learning is used to reduce the effects of data inefficiency for the new type of drugs and experimented over a range of industry-grade manufactured samples [24]. The visual inspection of the products cannot be eliminated in the current state of the method; the human skills are still required especially in training the system. But an increase of 80% efficiency is projected based on the manufacturing process analysis.

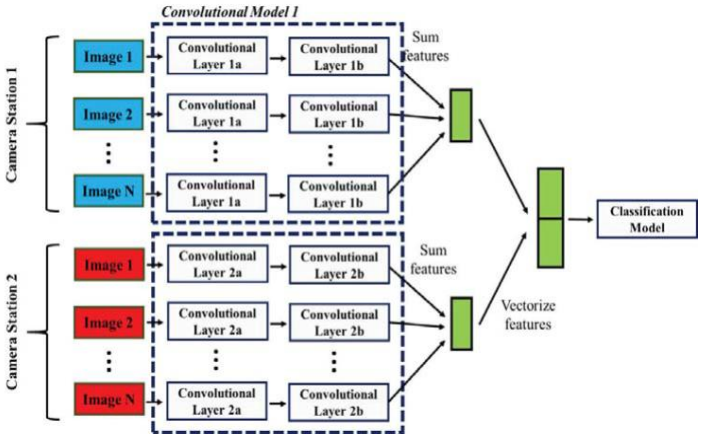

Fig 7. Sample multi-input CNN architecture for processing the images from two cameras si simultaneously [23].

H. Analytical Chemistry

Computer vision-based analytical chemistry (CVAC) is the set of techniques used to identify the pharmaceutical formulations majorly, the iron content. The iron content of a tablet is crucial as it has a decisive role in oxygen transport in the human body [25]. Several methods currently exist for determining iron most of which are based on volumetric, potentiometric, anodic stripping voltammetric, graphite-furnace and flame atomic absorption [26]. In for this process, Solana-Altabella et al [27] have proposed a computer vision-based approach in which software packages like ImageJ and NIH were used to derive numerical values for the intensity of RGB channels. These values are evaluated to create a calibration graph and interpolate the measurements of the sample which outputs the concentration strength. As per the Solana-Altabella et al [27], the method is cheaper than the current US Pharmacopoeia's current method using a spectrophotometer.

I. Bottle Packaging

The bottle packaging of the drugs is one of the final stages in which the quality has to be ensured. Automation in this stage has a very high maturity and scope that the integration of computer vision techniques is easier. Huaiyuan et al [28] have presented a framework for identifying the assembly lines distortion in the bottle packaging belt. The system is based on the machine vision software named HALCON along with some supplementary packages for the support platform. As explained in the flowchart given in Fig 1, a serial combination of a photoelectric sensor is used with CMOS digital camera to process the images in real-time to eliminate the unqualified bottle.

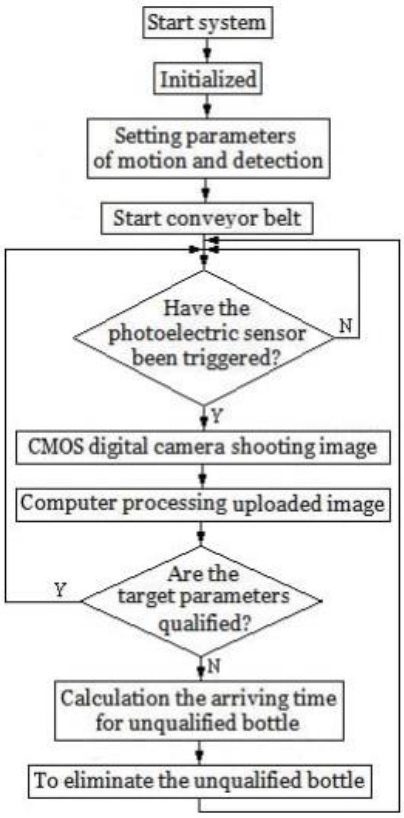

Fig 8. Control flow of the bottle packaging and quality check using video analysis.[28]

This section has presented various use cases in the manufacturing of the drugs and how computer vision techniques can be used to improve the process in various stages.

V. Conclusion and Future Scope

As of now, pharmaceutical manufacturing is in its germinal state where the researchers are still experimenting with the various computer vision techniques. The implemented computer vision systems are not matured end-to-end solutions [29] with some exceptions like Siemens solutions for the chemical processing using their DSC systems for the process industry. Major efforts are directed towards achieving the Good Manufacturing Practice (GMP) using artificial intelligence [28]. New GUI based systems are developed to give live feedback to the manual operator to cross verify the results from computer vision which in turn can improve the credibility and trust of the manufactures in computer vision systems [30]. One other issue is the large variances in the dataset for image analysis but a lack of huge dataset to train for specific cases. Therefore, transfer learning is a key aspect in using the deep neural networks for tablet manufacturing process to develop the pragmatic and economic solutions by reducing the training time for CV systems [31]. To conclude, even though there is large scope of implementing computer vision techniques in the pharmaceutical domain, there are constraints and challenges to overcome. The automation of the drug-creation process has vast potential and will be impossible without computer vision technology.

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