INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

ARTIFICIAL INTELLIGENCE (AI)-BASED DETECTION OF TABLET DEFECTS

Sayli D. Shelke*, Tanvi S. Deshmukh, Rutuja B. Kharde, Mr. A. D. Savkare, Mr. S. B. Khatale
MVP Samaj college of Pharmacy, Nashik 422002, Maharashtra, India.

ARTICLE INFO

Article history
Received 04.02.2025
Available online: 11.03.2025

Keywords
Artificial Intelligence,
Tomography,
Terahertz,
Tablet defect.

ABSTRACT

Artificial Intelligence (AI) based formulation development is a promising tool for streamlining the drug product development process. AI is a versatile approach that contains multiple algorithms that can be applied in different circumstances. Critical material attributes (CMAs) and processing parameters (CPPs) can have an impact on a variety of product attributes during the product development process, including dissolution rate, particle size distribution, physical and chemical stabilities, and the dry powder aerosol performance. There are different types of tablet defects such as capping, lamination. Mottling, chipping, cracking, sticking, picking, double impression, etc., these defects can be detected with AI tools such as Terahertz Pulsed Imaging (TPI), Time resolved microtomography images, Acoustic microscopy, convolutional neural network, Automated visual inspection, UV/ Vis imaging based PAT tool, Multivariate image analysis, etc. However, the conventional trial and error approach for product development is inefficacious, laborious and time consuming therefore we can use the AI tools to overcome problems associated with pharmaceutical dosage forms. This review gives the following visions: (1) a general introduction of AI in the pharmaceutical science and principle guidance from the regulatory agencies, (2) To detect tablet defect (3) data preparation and processing, (4) insights on applications and case studies of AI as applied to solid dosage forms. In addition, the innovative technique known as deep learning based image analytics will be covered along with its pharmaceutical applications. By using emerging AI technology, scientists and researchers can better understand and analyse the properties of drug formulations to promote more efficient drug product development processes.

Corresponding author
Sayli D. Shelke
MVP Samaj college of Pharmacy, Nashik 422002, Maharashtra, India.

*Please cite this article in press as **Sayli D. Shelke** et al. Artificial Intelligence (AI)-Based Detection of Tablet Defects. Indo American Journal of Pharmaceutical Research.2025:15(02).*

Introduction

Active pharmaceutical ingredients (APIs) are mainly formulated into different dosage forms and subsequently delivered to patients through various routes of administration, e.g. (Oral, IV, IM, Topical, Rectal, etc.,) Among various drug products in the market, solid dosage forms provide the most convenient administration method. Solid dosage forms consist of one or more APIs and suitable excipients, consisting binders, stabilizers, antioxidants, disintegrants, granulating agents, etc. The development of solid dosage forms is usually complex process and it requires a deep information about physicochemical properties of drug and pharmacokinetic/pharmacodynamic modelling (PK/PD).(1) During the development of formulation a large number of factors must be considered, such as excipient compatibility, polymorph, stability, solubility, dissolution, manufacturing, and scale-up. To address the challenges faced during formulation development, scientists must perform various experiments to fill the knowledge gap. These experiments are both costly and time-consuming. In recent years, Artificial intelligence becomes the most powerful and flexible tool to provide a solution to these problems because it is an efficient and novel approach. Artificial intelligence (AI) is a process that promote human intelligence using computers. This concept was first developed in 1956 during a conference lead by Marvin Minsky and John McCarthy.

The AI workflow involves four main steps:

1. Obtaining and preparing data 3. Testing
2. AI modelling simulation 4. deployment.

A subcategory of AI is machine learning that is referred as the process of using algorithms and recognizing patterns from the data to promote decision-making. As a subfield of machine learning, deep learning is the typically represented as layered structure algorithms and is also known as artificial neural networks (ANN).(2) ANNs, which were stimulated by the biological neuron structure in human brains, exhibit more insights in computational and predictive capability as compared to conventional machine learning algorithm. As well deep learning has been widely used for various applications such as image classification, image segmentation, object detection, medical image analysis and natural language processing.(2)

AI TOOLS USED IN DETECTION OF TABLET DEFECTS:

1. Terahertz Pulsed Imaging (TPI)

In the pharmaceutical industries, tablet coating is frequently managed by using computations on tablet weight gain to regulate the quantity of coating solution applied during the coating procedures. On the other hand, coating uniformity is not disclosed by increased weight determination. (3) Although they can be applied in on-line analysis, other methods such as laser induced breakdown spectroscopy, conventional optical microscopy, and scanning electron microscopy are destructive analysis. (4)

While film coating properties can be obtained through non-destructive characterization of film coatings under environmental conditions thanks to recent advancements in scanning electron microscopy, information on coating layer thickness cannot be obtained without destroying samples. To date, phase transition monitoring, hydrates recognition and polymorph identification and quantification have all been demonstrated to benefit from the use of terahertz radiation in pharmaceutical applications. (5)

The application of terahertz pulsed imaging in the pharmaceutical sciences was only investigated in chemical mapping and tablet coat imaging, as different techniques for terahertz pulsed imaging (TPI) were only recently pioneered. Because TPI can pass through the majority of pharmaceutical excipients while also resolving internal structure by detecting minute changes in refractive index, this initial work demonstrated the utility of this technique for coating thickness analysis and the non-destructive nature of TPI.

Measurements of refractive index (RI) and Terahertz pulsed spectroscopy (TPS) TPS was used to calculate the tablet coat's terahertz RI. Since the thickness of the coating layer was determined by this terahertz RI, accuracy was crucial for TPI coating quality analysis.

To summarise, the method involved three stages:

(a) scanning the first tablet surface

(b) centre band, and second tablet surface

(c) in order to cover all of the tablet's surfaces.

The subsequent terahertz scan and the creation of a three-dimensional terahertz image are based on this surface model. The RI value of the tablet coat is crucial for an accurate calculation of the coat layer thickness because the coating thickness (coat) is calculated as,

$$2dcoat = \frac{\Delta tc}{n}$$

Where,

n is the refractive index of the material the terahertz pulse is propagating through,

c is the speed of light

Δt is the delay time between the surface reflection and the reflection from the coating layer interface.

The weight percentage and the RI of each component in the coating composition were used to estimate the RI of the coat before the actual RI was determined.(6)

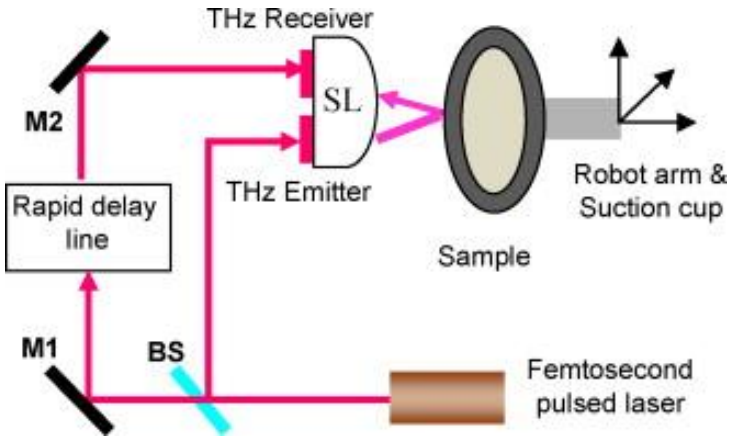

Fig.1: Terahertz pulsed imaging

Fig.1: Terahertz pulsed imaging

2. Time resolved microtomography imaging

The disintegration of pharmaceutical tablets is a complex process influenced by multiple formulation components. Traditional methods to study disintegration include force measurements, imaging techniques like micro-CT, terahertz spectroscopy, high-speed video, and MRI. However, these approaches often provide indirect or isolated insights. Time-resolved X-ray micro-CT offers high-resolution imaging to directly visualize tablet disintegration over time. It enables the study of internal structural changes, helping researchers better understand swelling and erosion mechanisms. Image quality varies based on tablet composition and movement, with faster disintegration leading to lower image clarity. Automated image analysis using machine learning shows promise in evaluating tablet disintegration.(7) A Python script was used to extract quantitative data, while experts provided subjective ratings of erosion and swelling. Despite challenges with image artifacts, this approach offers valuable insights into pharmaceutical tablet performance. (8)(9)

The top, front, and side views of the tablet as it breaks up are provided by the three planes, which are all cross-sections across the volumetric image centre. The subjective formulation performance scores from the live recordings were gathered by qualitative data analysis. The movies showing each formulation's disintegration behaviour were assessed by two human pharmaceutical technology specialists. On a scale of 1 to 10, they were asked to score the degree of erosion and swelling associated with each formulation independently. 1 represents not very characteristic behaviour, not extensive, 10 represents extremely characteristic behaviour, substantial swelling/erosion. This rating scale combines the degree to which the disintegration is visually driven by erosion or swelling. (10)

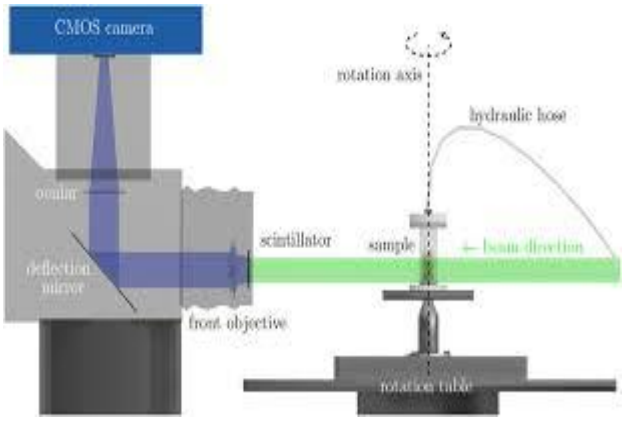

Fig.2: Time resolved microtomography imaging

3. Acoustic microscopy and infrared diffuse reflectance spectroscopy

Various analytical methods, including (terahertz pulse imaging) TPI spectroscopy, spectroscopic and microscopy techniques, have shown promise in assessing coating quality. A selective (inductively coupled plasma-atomic emission spectroscopy) ICP-AES method was developed for quantifying titanium-containing coatings, while NIR spectrometry was used to determine coating amounts on individual tablets.(11)

As an efficient technique for coating analysis, FTIR spectroscopy was used in conjunction with other techniques. A newly developed optical method for creating depth profiles of three-dimensional objects is optical coherence tomography (OCT). It is a non-destructive interferometric technique that can penetrate a few millimetres and responds to changes in the sample's refractive index. Because OCT uses near infrared (NIR) light, it establishes a connection between terahertz (THZ) measurements, which are frequently used to describe tablets. Chemical imaging and in vitro tomography were also employed as efficient methods to gauge the coating thickness. For examination of sustained-release coated pellets, terahertz pulsed imaging (TPI) was used to measure the film coating thickness and terahertz electric field peak strength (TEFPS). Confocal laser scanning microscopy (CLSM) is a new method for imaging the film-core interface and surface flaws of film-coated tablets was presented and investigated.(12)

4. X-ray microcomputed tomography (XRCT)

The three-dimensional (3D) non-destructive imaging technique known as X-ray microcomputed tomography (XRCT) has been extensively employed in a variety of fields to describe the density distribution of powder compacts. The porosity of granules, the structure of solid dispersions made by hot melt extrusion, tablet coating and its thickness in relation to the tablet core, and other dosage forms with varying densities between adjacent regions are all frequently identified and analysed in the field of pharmaceutical sciences using XRCT.(13) Because internal tablet cracks and tablet matrices have different densities, XRCT is ideally suited to identify these internal tablet flaws in non-destructive manner.

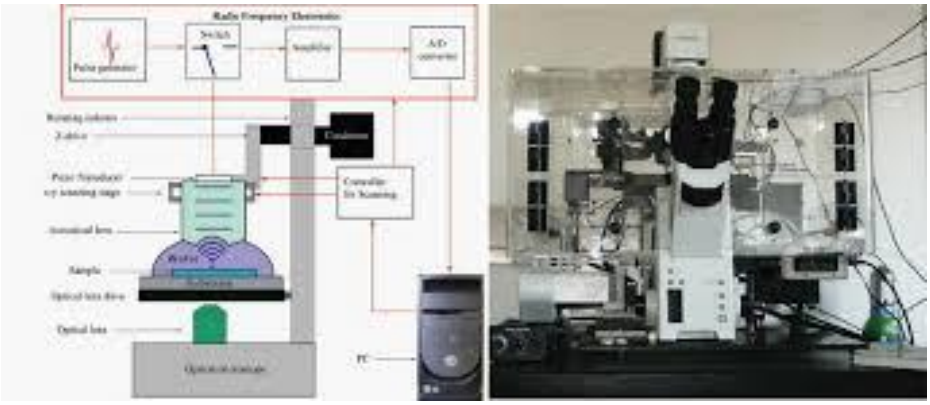

Fig.3: Acoustic microscopy reflectance

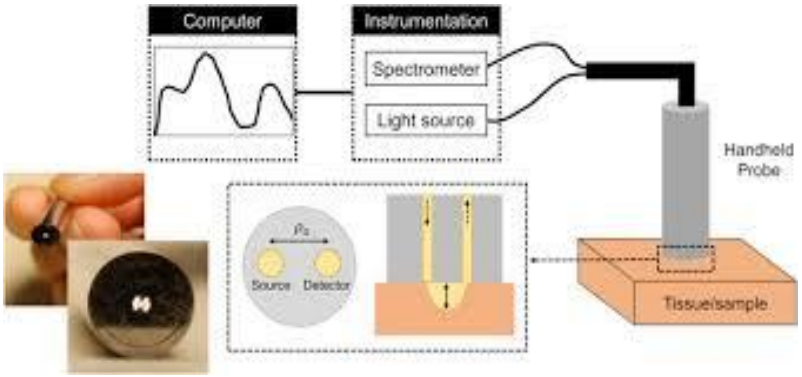

Fig.4: Infrared diffuse spectroscopy

These XRCT images are typically analysed manually using qualitative or semiquantitative methods, which can be biased by the analyst and lead to inconsistent results and poor statistical representation. The use of XRCT for automated analysis of internal tablet defects and attempts to address manufacturing issues for quality control of final products in an industrial setting have been hampered by the inability to accurately and quantitatively identify and characterize internal tablet cracks.

Convolutional neural networks (CNNs) for deep learning data analytics have emerged as a promising field of study in recent years, with applications in appearance testing and visual inspection. The applications of CNNs in many different fields have expanded rapidly due to a combination of advancements in computer hardware, mathematical algorithm improvements, and growing volumes of digital data. This can greatly increase the accuracy and efficiency of industrial analytics processes. CNNs have the potential to revolutionize real-world applications that depend on precise visual analysis and can occasionally match or even exceed human performance.

In order for companies to swiftly extend these techniques into the production line, CNN based deep learning image analytics must be able to be readily converted to a new product and not be limited by large scale in scope. CNNs have the ability to replace manually created feature based learning programs with automated processes because they can directly learn features from complicated structures and can be tailored to a new product. Deep learning CNNs have also been widely used in several fields for automatic inspection and flaw detection. CNN techniques are widely used because they have been demonstrated to achieve high throughput quality control during the manufacturing of steel surfaces and metallic rails.

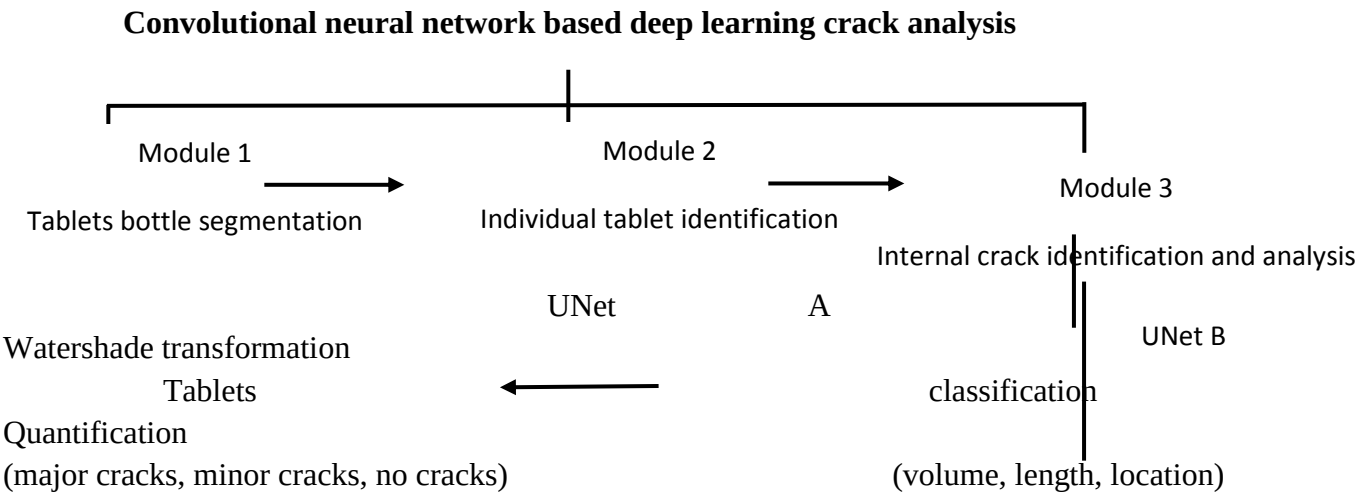

Fig.5: An overview of convolutional neural network based deep learning crack analysis

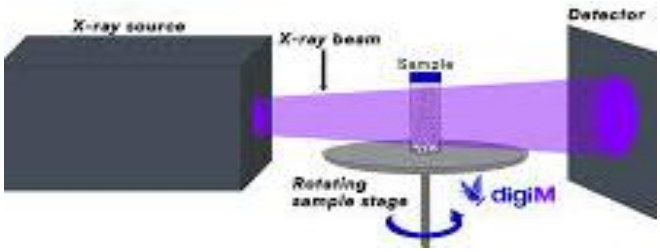

Fig.6: X ray microcomputed tomography

1. Real-time automated visual inspection

Automated visual inspection can be done using roughly two basic approaches 1. template matching and 2. design-rule verification. Every pixel in the examined image is compared to its corresponding pixel in the reference image that is, an image of objects free of flaws or an artificially created image using template matching. For comparisons, original or segmented photos might be used. The design rule verification method looks for instances when a set of general rules are broken. This method compares features from a segmented image of an object that is free of defects with a segmented image of the object that was inspected, while accounting for pre-determined feature tolerances. Because it can be used to a wide range of different inspection tasks, the template matching approach is quite popular in automatic visual inspection. Nevertheless, it necessitates extremely accurate alignment of the reference and inspected images, which is not simple, particularly when inspecting moving objects. On the other hand, the design rule verification approach demands accurate, robust, and quick segmentation rather than highly precise alignment which lowers the final inspection's quality.(14)

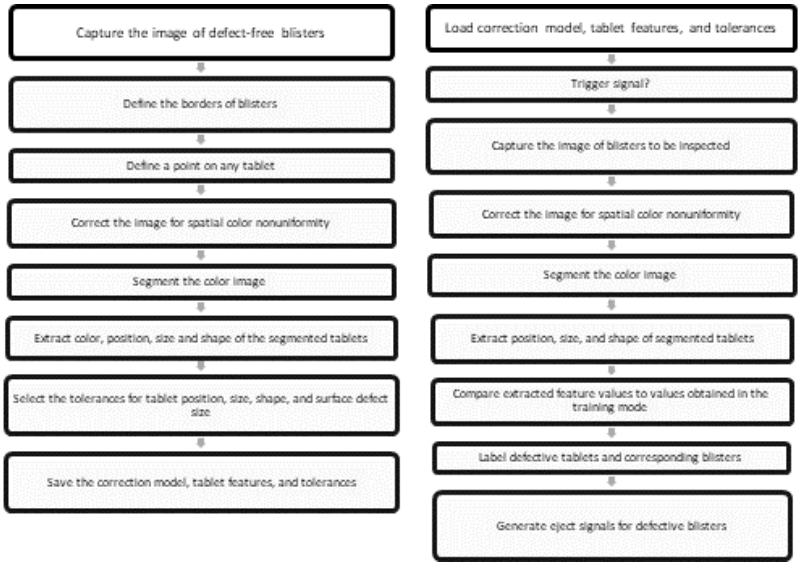

Fig.7: Schematic diagram of the automated visual inspection system

Colour image segmentation is becoming more and more popular since colour photographs typically offer more information than grayscale ones. There are two challenges that characterize colour image segmentation: (a) the segmentation technique and (b) the colour features that were utilized to code the colour information. RGB (red, green, blue) colour characteristics are most frequently used to quantitatively specify colour in colour photographs captured by electronic imaging systems. A 3CCD (3-charge coupled device) colour camera, lighting unit and industrial PC with an I/O card and frame grabber make up the machine vision system. Diffusive glass in front of white neon tubes creates diffuse front lighting, which lights up the scene. There are two modes of operation for the system: "training" and "inspection".

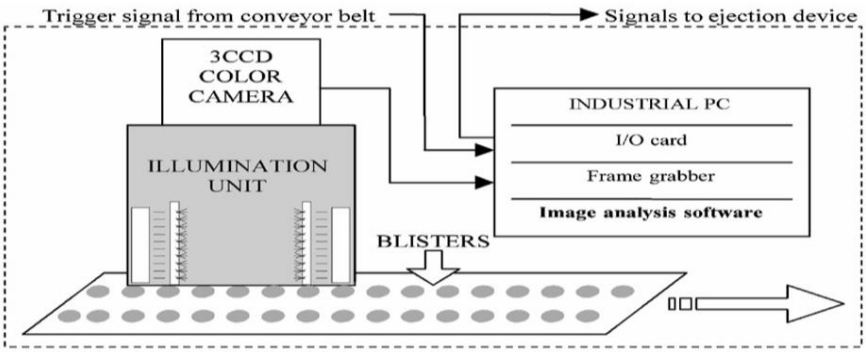

Fig.8: Flowchart of operations in the training (left) and inspection (right) mode

1. Noncontact Photo-Acoustic Defect Detection

For the goal of process monitoring, several techniques have been introduced. For instance, because of their non-invasive and affordable characteristics, non-invasive passive techniques like acoustic emission (AE) have been used extensively in the pharmaceutical sector for granular material monitoring. Many of the events that take place during the powder compaction of pharmaceutical goods, including granular rearrangement, fragmentation and Visco-plastic deformation of grains or granules, can be identified by monitoring AE. During roller compaction of maize starch and microcrystal line cellulose, acoustic relaxation emissions are identified and used.(15)

Drug bioavailability is significantly influenced by tablet coatings and core integrity. Therefore, a key concern for quality assurance is the mechanical integrity and homogeneity of coating layers and cores.

The goal of the current study was to create a technological platform that would allow for the development of quick, noncontact methods for checking and assessing medication tablets for mechanical flaws like internal cracks, irregularities in the coating layer and delamination using a laser-acoustic technique for particular uses. A pulsed laser is used as an acoustic field source in the testing platform to provide noncontact mechanical excitations and interferometric detection of transient vibrations from the medication tablets is used for sensing.(16,17)

Two innovative techniques are created and used to stimulate vibration medication tablets: (I) pulsed laser-induced plasma shockwaves and (ii) a vibration plate stimulated by a pulsed laser. The laser interferometer measures nanometre scale transient surface displacement of the medication tablet in the kHz range to identify changes in stiffness caused by coating, core abnormalities and/or damage. These brief displacement responses are then subjected to signal processing techniques in order to distinguish between the tablets that are defective and those that are not. (18)

2. UV/Vis imaging-based PAT tool for drug particle size inspection in intact tablets

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. 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(19).

Industrial companies have been interested in using PAT tools to characterize a particulate system in the last ten years. Several techniques have been used to determine PSDs of powders or granules, including sieve analysis (International Council for Harmonization), microscopic measurements, sedimentation, spectroscopic methods, and image analysis. However, only a small number of publications evaluate particle sizes and distributions in intact tablets.(20)

Fig.9: UV and vis image processing algorithms for classification and particle size analysis.

In order to analyse the particle size of the manufactured tablets, two algorithms were created for UV and VIS images. The acquired particle size distributions matched the outcomes of the laser diffraction based reference method, according to the statistical tests that were used. A new non-destructive, quick, in-line method for analysing tablet particle size can be created by combining digital UV/VIS imaging with multivariate data analysis.(1,21)

Acknowledgement

We sincerely thank Mr. A. D. Savkare and Mr. S. B. Khatale for his valuable guidance and support throughout this work. We extend our heartfelt thanks to our friends for their constant motivation and support, as well as to everyone who directly or indirectly contributed to the successful completion of this review paper. Your encouragement and assistance have been greatly appreciated.

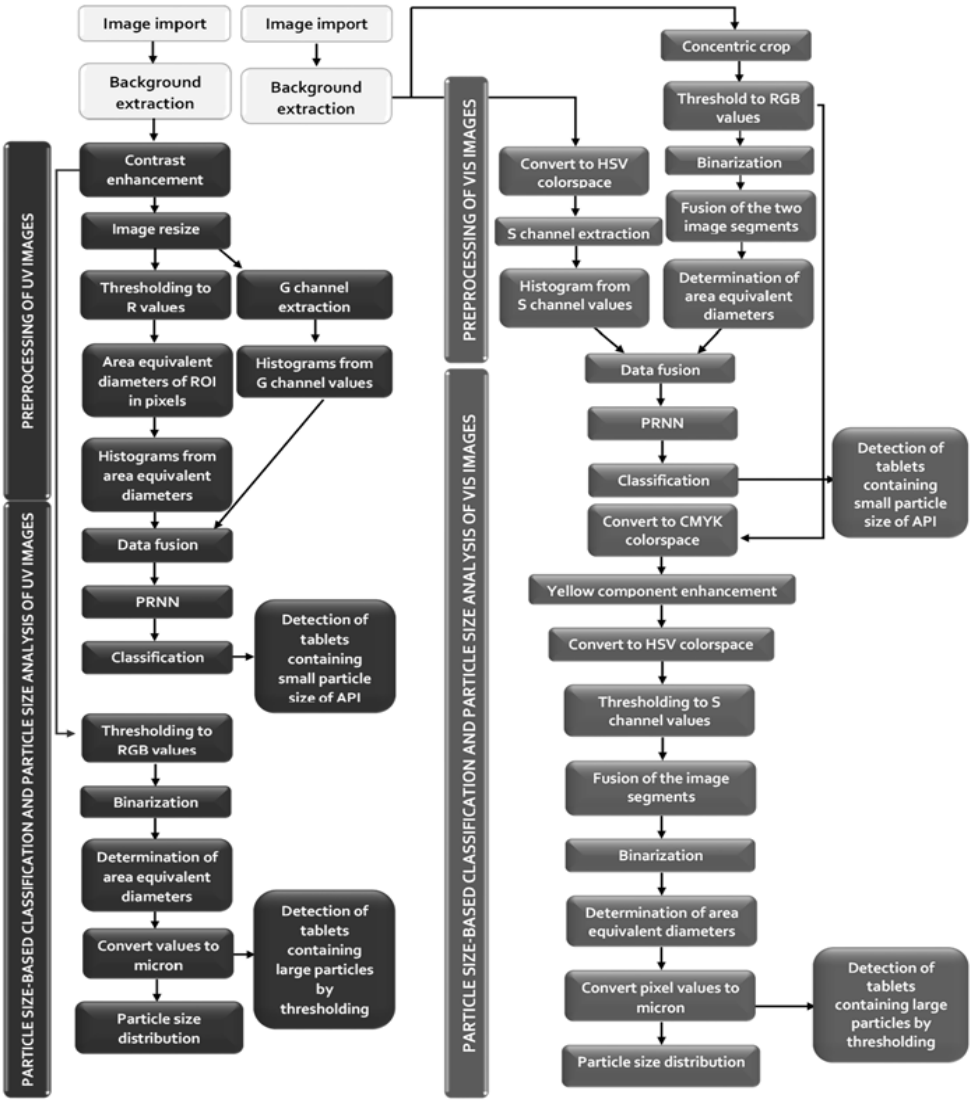

Fig.9: UV and vis image processing algorithms for classification and particle size analysis.

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