WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 22, 947-976. Review Article ISSN 2277–7105

IN-PROCESS QUALITY ASSURANCE IN TABLET MANUFACTURING: A CRITICAL REVIEW OF PROCESS MONITORING, DEFECT PREVENTION, AND GMP COMPLIANCE

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Article Received on 15 Oct. 2026,
Article Revised on 05 Nov. 2026,
Article Published on 16 Nov. 2026,

https://doi.org/10.5281/zenodo.24300195

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How to cite this Article: Mohd. Abid Khan[1], Suraj Yadav[2*] (2026). In-Process Quality Assurance In Tablet Manufacturing: A Critical Review Of Process Monitoring, Defect Prevention, And Gmp Compliance. World Journal of Pharmaceutical Research, 15(22), 947–976.

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ABSTRACT

In Process Quality Assurance (IPQA) is a crucial element of tablet production that guarantees uniform product quality, adherence to regulations, and safety for patients. This comprehensive review examines the strategic importance of IPQA in over seeing essential process parameters throughout all phases of tablet manufacturing, such as dispensing, blending, granulation, drying, compression, and coating. The assessment emphasizes contemporaryprocess monitoring instruments like Process Analytical Technology (PAT), in-line sensors, and statistical process control for immediate identification of variances. It methodically examines typical tablet issues like capping, lamination, weight discrepancies, hardness failures, and dissolution issues, and explores their prevention via Quality by Design (QbD) and risk management strategies. Particular attention is placed on adherence to current GoodManufacturing Practices (cGMP), integrity of data, and requirements for documentation. Successful application of IPQA not only avoids batch failures and minimizes rework but also enhances overall manufacturing efficiency and GMP adherence in modern tablet production.

KEYWORDS: In-Process Quality Assurance, Tablet Manufacturing, In-Process Quality Control, GMP, Process Monitoring, Tablet Defects, Quality Risk Management.

INTRODUCTION

3.1 Overview of pharmaceutical quality assurance

Pharmaceutical Quality Assurance (PQA) is a preventive, lifecycle-oriented management system that guarantees pharmaceutical products are consistently produced to complywithnecessary quality, safety, and efficacy standards (World Health Organization [WHO], 2007). The WHO defines quality assurance as a comprehensive concept encompassing all factors that individually or collectively affect the quality of a product, suchas development, production, quality control, and distribution.

Contemporary QA is regulated by the ICH Q10 guideline, outlining a thorough pharmaceutical quality system framework that enhances Good Manufacturing Practices and includes monitoring of process performance, Corrective and Preventive Action (CAPA), alongwithcontinuous improvement during the product lifecycle (International Council for Harmonisation [ICH], 2008).[1][2][3]

3.2 Introduction to tablet manufacturing

Tablets represent the most commonly used solid oral dosage form, making up roughly 70% of all ethical pharmaceutical formulations, thanks to benefits like self-administration, precise dosing, stability, and patient adherence. Tablets can be described as solid forms of pharmaceutical dosage that consist of drug substances, with or without appropriate fillers, and created through either compression or molding techniques.[4]

The process of tablet production involves a sequence of unit operations such as weighing, milling, mixing, granulation, drying, compaction, and often coating and packaging. According to the formulation design, three main methods are used: direct compression, dry granulation, and wet granulation.[5] Direct compression is regarded as the most efficient and cost-effective technique due to fewer processing steps, whereas wet granulation entails liquid binder agglomeration, and dry granulation involves compaction through slugging or roller compaction for moisture-sensitive medications.[6][7]

3.3 Concept of in-process quality assurance

In-Process Quality Assurance (IPQA), known as In-Process Quality Control (IPQC) as well, refers to a systematic and organized series of inspections and controls implemented before, throughout, and following the completion of the manufacturing process.[8] The main role of IPQA is to oversee and, when needed, adjust the manufacturing process to guarantee that the

product meets its established specifications, which involves managing equipment, environment, and personnel.

Recent evaluations indicate that IPQA is more than just testing; it serves as a quality assurance process that starts with the receipt of raw materials and continues until the finished product is released.[9] In-process materials undergo testing for identity, strength, quality, and purity, with approval or rejection by the quality control unit throughout production. Rejected in-process materials are recognized and managed through a quarantine system to avoid their utilization in production.[10]

In tablet dosage forms, IPQA testing is closely linked to the quality of the final product, as it allows for early identification and mitigation of mistakes during all phases of production, thus guaranteeing an excellent finished product.[11]

3.4 Importance of IPQA in pharmaceutical industries

In-Process Quality Assurance is essential in the pharmaceutical sector as it guarantees that quality is integrated into the product instead of only evaluated in the finished product. The key significance of IPQA is its capability to avert mistakes and inconsistencies throughout all phases of production, thus minimizing batch failures, rework, and product recalls.[8]

IPQA enables real-time observation of important process parameters like tablet weight variation, hardness, thickness, friability, and disintegration time, which are directly related to the quality of the final product and its therapeutic effectiveness.[11] By identifying non-compliant conditions promptly, it guarantees adherence to current Good Manufacturing Practices (cGMP) and pharmacopoeial requirements.

Moreover, IPQA reduces production expenses, improves process effectiveness, and secures patient safety by confirming product identity, potency, purity, and stability prior to release.[10] Establishing strong IPQA via Standard Operating Procedures (SOPs) and Process Analytical Technology (PAT) is crucial for regulatory compliance and ongoing enhancement within the Pharmaceutical Quality System.[9]

3.5 Difference between IPQA and IPQC

While In-Process Quality Assurance (IPQA) and In-Process Quality Control (IPQC) are frequently considered synonymous, they actually denote two separate elements of the pharmaceutical quality system (World Health Organization, 2007; International Council for

Harmonisation, 2008).

IPQA is a forward-looking, process-focused, and system-centered methodology. It is a broad concept encompassing all factors that individually or collectively affect product quality, such as documentation, validation, change control, and process oversight throughout the product lifecycle (WHO, 2007). The goal of IPQA is to avoid defects by making certain that the correct processes are executed properly.

On the other hand, IPQC is a responsive, product-focused, and testing-driven method. IPQC denotes the inspections and examinations performed during production to oversee and, when needed, adjust the process to meet specifications.[8] It encompasses physical evaluations like weight fluctuation, hardness, thickness, friability, and disintegration carried out during the granulation and compression phases.[11]

- **3.6 Aim and objectives of the review**

This review intends to critically assess the significance of In-Process Quality Assurance (IPQA) in tablet production, focusing on process observation, defect avoidance, and GMP adherence.[8]

Goals:

1. To summarize the idea and significance of IPQA in the manufacturing of tablets.
2. To examine essential IPQC assessments and process oversight instruments such as PAT.
3. To examine frequent tablet flaws and their prevention methods

Overview of Tablet Manufacturing Process

4.1 Raw material dispensing

The initial crucial phase in tablet production is raw material dispensing, where active pharmaceutical ingredients (APIs) and excipients are precisely measured and confirmed according to the authorized Master Formula Record. In contemporary manufacturing, dispensing has evolved beyond just manual weighing; it is connected to material traceability, supplier validation, and instantaneous identification through PAT tools like NIR and Raman spectroscopy to avoid mix-ups and cross-contamination.[12][13][14]

Recent evaluations emphasize that the precision of dispensing directly influences blend uniformity, content uniformity, and the quality of final tablets, particularly in low-dose and continuous direct compression processes where minor fluctuations in API feeding lead to

significant dosage discrepancies.[12] Consequently, dispensing should occur in a regulated, specific zone equipped with calibrated balances, barcode verification, double-checking procedures, and thorough documentation in accordance with cGMP and the ICH Q10 Pharmaceutical Quality System.[13]

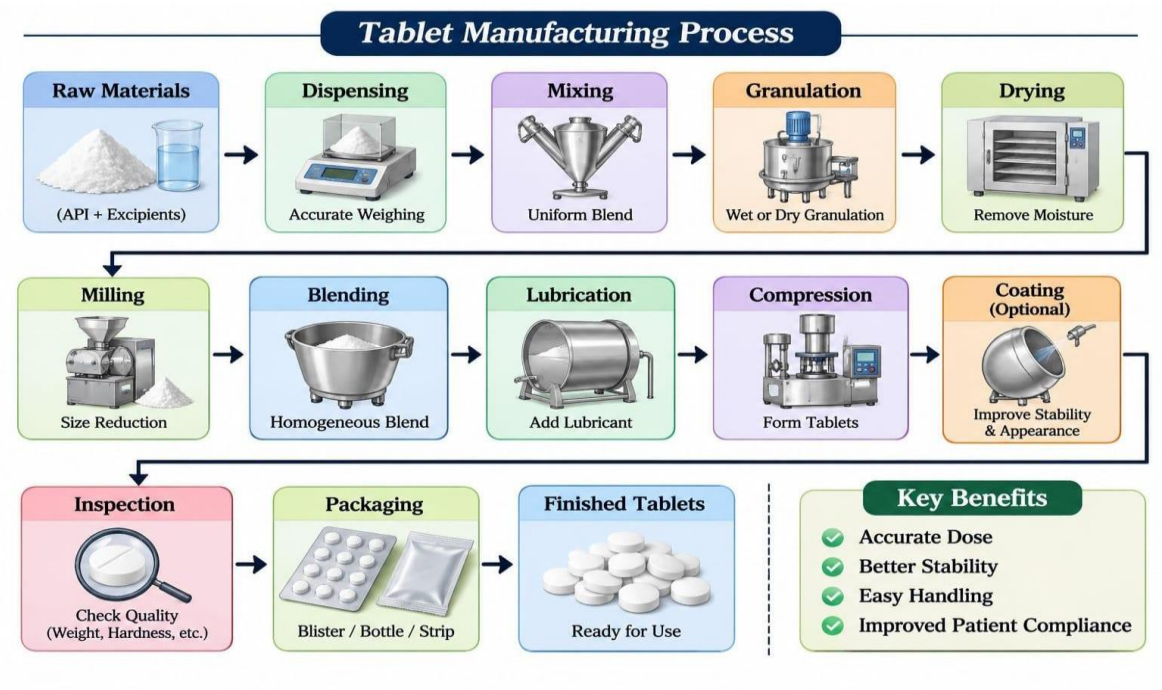


Figure 1: Flowchart of tablet manufacturing process.

4.2 Sifting and screening

Sifting and screening is an essential mechanical process conducted post-dispensing and milling, intended to guarantee consistent particle size distribution while eliminating contaminants, large lumps, and agglomerates.[17]

In the production of tablets, sifting is accomplished through vibro-sifters or mechanical sieves that have particular mesh sizes. The method guarantees the de-agglomeration of cohesive powders, enhances powder flow properties, and avoids segregation during later blending and compression.[14][15] The uniformity of particle size achieved through sifting directly affects content consistency, dissolution speed, and the variation in tablet weight.

Recent analyses highlight that inadequate sifting causes blend segregation, especially sifting and trajectory segregation during the transfer from intermediate bulk[16] containers to tablet press hoppers, ultimately leading to failures in content uniformity.[17] Consequently, sifting is recognized as an essential IPQA control point to reduce rework and guarantee consistency

between batches.[12]

4.3 Granulation

Granulation involves the enlargement of particles through an agglomeration method, transforming fine powders into larger, free-flowing granules to enhance flow characteristics, compressibility, uniformity of content, dissolution rate, and general product stability.[18][14]

Granulation is primarily divided into two categories.

1. Wet Granulation: A solution of liquid binder is mixed with the powder blend to create a moist mass, which is then screened, dried, and sized. Techniques consist of high-shear granulation, fluidized bed granulation, twin-screw wet granulation, and moisture-activated dry granulation.[18] Wet granulation is ideal for low-dose medications and powders that flow poorly, but it is unsuitable for active pharmaceutical ingredients that are sensitive to moisture or heat.
2. Dry Granulation: Powder particles are compressed without the use of liquid through slugging or roller compaction, followed by milling and screening into granules.[18]

4.4 Drying

Drying occurs post-wet granulation to eliminate the granulating fluid and to attain an ideal moisture level in the granules. The fluidized bed dryer is commonly utilized due to its ability to deliver consistent and quick drying.[18] Excessive moisture in granules can result in sticking, picking, and microbial development, while excessive drying may cause inadequate compressibility and capping. Consequently, Loss on Drying (LOD) is tracked as an Essential Quality Attribute in IPQA. Contemporary Process Analytical Technology (PAT) instruments like Near-Infrared (NIR) spectroscopy enable real-time moisture observation while drying.[14]

4.5 Blending and lubrication

Blending is done to achieve a uniform distribution of the active pharmaceutical ingredient (API) and excipients. It is particularly important for low-dose tablets, as even slight inconsistencies can lead to content uniformity issues.[19][17] Following the blending process, lubrication is performed by incorporating a lubricant, typically magnesium stearate, for a brief duration of 2-5 minutes. Lubrication minimizes friction between the tablet and die wall, prevents adhesion, and aids in tablet removal. Nonetheless, extended mixing leads to excessive lubrication, diminishing tensile strength and increasing disintegration duration.[19]

Table 1: Different stages of tablet manufacturing and their IPQA activities.

Manufacturing stage	Key IPQA activity
1. Dispensing	Verify material identity, status and quantity; check balance status.
2. Sifting	Confirm sieve integrity, mesh size and material transfer controls.
3. Blending	Check mixing time, equipment status and blend-sampling results, where specified.
4. Granulation	Monitor binder addition, granulation endpoint and relevant process settings.
5. Drying & milling	Check drying endpoint/moisture and granule size as per approved limits.
6. Lubrication	Verify lubricant quantity and mixing time to avoid over- or under-lubrication.
7. Compression	Monitor tablet weight, appearance, hardness/thickness and machine settings.
8. Coating & packing	Check coating appearance/process conditions, line clearance, coding and reconciliation.

4.6 Tablet compression

Compression is the essential phase where the combined granules are pressed into tablets between the upper and lower punches of a rotary tablet press. Tablet weight, hardness, thickness, and friability are determined by compression force, turret speed, and die-fill depth.[12] Sophisticated in-line technologies like terahertz time-domain spectroscopy and optical coherence tomography are presently utilized to assess tablet porosity, hardness, and mass during compression, facilitating real-time monitoring.[20] IPQA monitors weight fluctuations, hardness, and disintegration periodically to identify defects like capping, lamination, picking, and sticking early on.

4.7 Tablet coating

Coating consists of layering a thin polymer film on compressed tablets to enhance visual appeal, conceal bitter flavors, shield against moisture, and regulate drug release. Film coating is the most frequently utilized method, using polymers like hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA). Current trends feature TiO2-free coatings and continuous film coatings, offering enhanced uniformity and greater eco-friendliness. In IPQA, the monitoring includes coating weight increase, consistency, and flaws like orange-peel effect, bridging, and cracking.[21]

4.8 Packaging

Packaging is the last stage that safeguards tablets from moisture, oxygen, light, and physical damage during their shelf life. PVC, PVDC, and Alu-Alu blister packs, alongside HDPE

bottles, are frequently utilized as primary packaging materials.[22] Choosing an unsuitable packaging material may lead to moisture penetration and deterioration of the drug. Consequently, predictive modeling is currently employed to choose the most appropriate blister material for a particular drug product.[23] IPQA checks seal integrity, conducts leak tests, verifies labeling, batch coding, and expiration information prior to release.

5. Role of IPQA at Different Stages of Tablet Manufacturing In-Process Quality Assurance (IPQA) is a continuous monitoring system used at each phase of tablet production rather than a standalone test. Its primary function is to identify variations at the source, stop defect transmission to the subsequent phase, and guarantee adherence to cGMP (Neugebauer et al., 2024).

5.1 Material dispensing and verification

IPQA verifies that the appropriate API and excipients are provided in the right amounts according to the Master Formula Record. Verification consists of identity verification, batch number, quantity, and expiration of materials. Current dispensing employs barcode validation and Process Analytical Technology tools such as NIR and Raman spectroscopy for identifying materials to avoid mix-ups and cross-contaminations.[24] At this phase, calibrated balances, verification by another individual, and accurate labeling are essential IPQA controls.

5.2 Monitoring of granulation process

During granulation, IPQA monitors binder addition rate, impeller speed, granulation time, and granule characteristics. Granule particle size, bulk density, flow properties, and uniformity are checked to ensure good compressibility.[25] In wet granulation, over-wetting produces hard granules, while under-wetting produces weak and friable granules. In dry granulation, roller compaction force and ribbon density are critical. IPQA prevents defects such as poor flow, segregation, and weight variation by controlling these parameters.

5.3 Monitoring of drying process

IPQA tracks drying temperature, airflow, drying duration, and the final moisture level of granules. Loss on Drying (LOD) is a crucial factor, as too much moisture leads to sticking and degradation, whereas excessive drying results in capping and ineffective binding.[26] In fluidized bed drying, temperatures at the inlet and outlet are continuously monitored. NIR-based PAT enables real-time moisture tracking, minimizing batch failure risks and facilitating

quicker decision-making.

5.4 Blending and lubrication checks

IPQA guarantees consistent integration of API with excipients to maintain content uniformity. Time, blender speed, and load are tracked as Critical Process Parameters.[17] Lubricant is incorporated for a brief, confirmed duration following blending. Excessive blending with magnesium stearate decreases tablet hardness and prolongs disintegration, whereas insufficient lubrication leads to sticking and increased ejection force.[27] Uniform blend samples are gathered from various areas of the blender for examination.

5.5 Compression stage monitoring

Compression is the key stage in IPQA. IPQA conducts evaluations at consistent intervals (every 30 minutes) for variations in tablet weight, hardness, thickness, friability, and disintegration time.[12] Compression force, turret velocity, and die-fill are constantly observed. Contemporary in-line instruments like terahertz spectroscopy and optical coherence tomography enable instantaneous assessment of tablet porosity, mass, and hardness.[28] Timely identification aids in managing flaws such as capping, lamination, picking, sticking, and weight discrepancies.



Figure 2: IPQA monitoring during talet compression.

5.6 Coating stage monitoring

While coating, IPQA observes pan speed, inlet air temperature, spray rate, atomization pressure, and the increase in coating weight. Consistent coating is crucial for aesthetics, flavor masking, and controlled release. Defects like orange-peel effect, bridging, cracking, twinning, and color variation are evaluated visually and through weight gain measurement. Recent developments in continuous film coating and coatings without TiO2 necessitate rigorous IPQA monitoring to ensure coating uniformity and stability.[29]

5.7 Packaging stage monitoring

IPQA during the packaging phase guarantees product safety, identification, and traceability. Inspections consist of seal integrity, leak testing, blister formation, label checks, batch number, manufacturing and expiration dates, and count per strip.[22] Predictive modelling is currently utilized to choose suitable blister materials to avoid moisture penetration and deterioration.[30] Any faulty blisters, printing errors, or broken cartons are discarded. Correct packaging guarantees patient safety and adherence to regulations.

6. Important In-Process Quality Control Tests

In-process quality control (IPQC) tests are performed during tablet manufacturing to confirm that tablets meet predefined specifications before they move to the next stage. These tests prevent large-scale batch rejection and ensure consistent product quality (Arshad et al., 2021).

6.1 Weight variation

The weight variation test guarantees that each tablet has a consistent quantity of the medication. It is influenced by powder flow, particle size, die-fill consistency, and compression rate. IPQA gathers 20 tablets at consistent intervals and weighs each one separately. The variation from the mean weight must stay within pharmacopoeial standards (IP/USP). Significant weight variability signifies inadequate flow, segregation, or incorrect die-fill, potentially causing content uniformity issues.[17]

6.2 Tablet hardness

Hardness, also known as crushing strength, measures the force required to break a tablet. It reflects the mechanical strength and bonding of granules after compression (Arshad et al., 2021). Low hardness causes friability and breakage during handling, while excessive hardness delays disintegration and dissolution. Modern tablet presses use in-line hardness monitoring tools such as optical coherence tomography to predict hardness without

destructive testing.[28]

6.3 Friability

The friability test assesses how likely tablets are to chip, break, or crumble during handling, packaging, and transportation. Tablets are spun in a friabilator at 25 rpm for 4 minutes (100 turns), and the weight loss is measured. According to pharmacopoeia, weight reduction must not surpass 1.0%. High friability results from insufficient compression force, inadequate binding, or excessive drying of granules. IPQA employs this test to enhance compression force and binder concentration.[25]

6.4 Thickness and diameter

A Vernier caliper or micrometer measures thickness and diameter to maintain consistency in the size and appearance of tablets. Thickness is directly connected to die-fill and compression force. Thickness variation impacts packaging, particularly blister packs, and suggests issues with inconsistent die-fill or punching. IPQA measures thickness periodically to ensure uniformity across batches and meet patient satisfaction.[12]

Table 2: In-process quality control tests and their importance.

Test / check	Importance in tablet quality
Appearance	Detects visible defects, contamination or variation in tablet finish.
Average weight / weight variation	Indicates consistency of tablet mass during compression.
Thickness & diameter	Checks dimensional consistency and supports packaging suitability.
Hardness / crushing strength	Assesses resistance to handling and mechanical stress.
Friability	Estimates tendency to chip, cap or lose mass during handling.
Disintegration	Checks whether tablets break up within the specified time.
Dissolution	Measures drug release under defined test conditions.
Moisture content	Helps control moisture-related stability and processing risks.

6.5 Disintegration test

The disintegration test evaluates the duration it takes for a tablet to crumble into smaller pieces in a defined medium. It serves as an initial signal of medication release. According to IP, uncoated tablets must break down in 15 minutes, while film-coated tablets should do so in 30 minutes. Extended disintegration could result from excessive compression, too much lubrication, or an abundance of binder. The type and concentration of lubricant notably influence disintegration time, as demonstrated in recent research involving magnesium

stearate.[19]

6.6 Dissolution test

The dissolution test evaluates how quickly and extensively the drug is released from the tablet into the dissolution medium. It serves as the key indicator of in-vivo bioavailability. Dissolution is influenced by factors such as API particle size, hardness of the tablet, disintegration, and thickness of the coating. Modern PAT instruments seek to substitute traditional dissolution testing with predictive models that consider tablet hardness and porosity, facilitating real-time release.[26,28]

6.7 Moisture content

The moisture level is assessed through Loss on Drying (LOD) or Karl Fischer titration. Granules are inspected prior to compression and also for the completed tablets. Excessive moisture results in sticking, deterioration, and microbial growth, whereas insufficient moisture leads to poor compressibility and capping. NIR-based PAT enables real-time moisture tracking during drying and blending, decreasing batch rejections.[24,26]

6.8 Appearance and visual inspection

A visual examination is carried out to assess tablet color, shape, surface texture, imprinting, and flaws. Typical flaws consist of capping, lamination, picking, sticking, mottling, and chipping. Coated tablets are additionally assessed for orange-peel appearance, bridging, and cracking.[29] Automated vision systems are currently implemented for rapid inspection during compression and packaging, enhancing detection precision and minimizing human mistakes.

7. Critical Process Parameters and Critical Qualit Attributes

7.1 Introduction to CPP

Critical Process Parameters (CPPs) are variables in the process that, when altered within their limits, have a direct impact on the quality of the intermediate or final product. Instances consist of granulation duration, drying temperature, blending velocity, compression pressure, and coating spray rate. If CPPs are unmanaged, they may result in batch failure despite having high-quality raw materials.[26] CPPs are recognized through risk assessment and Design of Experiments (DoE) in the product development phase.

7.2 Introduction to CQA

Critical Quality Attributes (CQAs) are the physical, chemical, biological, or microbiological

properties of a drug product that must remain within a specified limit to ensure desired product quality, safety, and efficacy. For tablets, CQAs include weight variation, hardness, friability, disintegration, dissolution, content uniformity, and moisture content.[12] CQAs are measured through in-process and finished product testing. Failure to meet any CQA means the batch cannot be released.

7.3 Relationship between CPP and CQA

CPPs and CQAs are directly related in a cause-and-effect manner. Any alteration in a CPP results in a quantifiable change in a CQA. For instance, a rise in compression force enhances tablet hardness while reducing the dissolution rate. In a like manner, extending the blending duration with magnesium stearate leads to decreased tensile strength and extended disintegration.[19] The contemporary Quality by Design (QbD) strategy leverages this correlation to create a design space, in which CPPs are maintained within established boundaries to reliably meet intended CQAs.[24]

Table 3: Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs).

Process step	Examples of CPPs	Related CQAs / quality responses
Granulation	Binder quantity; mixing time/speed; granulation endpoint	Granule size distribution; moisture; flow properties
Drying	Inlet temperature; airflow; drying time	Residual moisture / loss on drying; granule properties
Blending	Blend time; blender speed; load level	Blend uniformity; content uniformity
Lubrication	Lubricant level; lubrication time/speed	Tablet strength; disintegration and dissolution performance
Compression	Compression force; turret speed; feeder setting	Weight variation; hardness; thickness; friability; dissolution
Coating	Inlet/product temperature; spray rate; pan speed	Coat uniformity; appearance; weight gain; dissolution, where relevant

7.4 Important parameters during granulation

In granulation, the key CPPs include the rate of binder addition, speeds of the impeller and chopper, duration of granulation, and volume of granulating fluid. These parameters influence the CQAs, including granule size distribution, bulk density, flow characteristics, and compressibility. Over-granulation results in dense, hard granules that dissolve poorly, whereas under-granulation leads to fragile, dusty granules with inadequate flow.[25]

7.5 Important parameters during compression

During compression, the key CPPs are compression force, pre-compression force, turret

speed, die-fill depth, and feeder speed. These parameters control CQAs such as tablet weight, thickness, hardness, friability, porosity, disintegration, and dissolution.High compression force increases hardness but may cause capping and lamination. High turret speed can cause weight variation due to incomplete die filling.

In-line monitoring of porosity and hardness using OCT and terahertz spectroscopy now allows real-time control of compression parameters.[28]

7.6 Important parameters during coating

Key CPPs during the coating process include pan speed, inlet air temperature, spray rate, atomization pressure, and coating suspension concentration. These parameters influence CQAs including coating weight gain, uniformity, appearance, and drug release. A high spray rate paired with a low drying temperature leads to sticking and twinning, whereas a high temperature combined with a low spray rate results in premature drying and a rough coating.[21]

8. Common Tablet Manufacturing Defects and Their Prevention

Tablet defects mainly arise due to faulty formulation, improper process parameters, or worn-out tooling. Early detection through IPQA prevents batch rejection and ensures product quality.[31]

Table 4: Common tablet defects, causes and preventive measures.

Tablet defect	Possible cause(s)	Preventive measure(s)
Capping / lamination	Air entrapment, low binder, excess fines or unsuitable compression	Optimise granule properties and compression settings; maintain suitable pre-compression.
Sticking / picking	Excess moisture, tacky formulation or worn tooling	Control granule moisture; review formulation and lubrication; clean and inspect punches.
Weight variation	Poor flow, segregation or inconsistent die filling	Improve flow and granule uniformity; check feeder and machine settings; monitor weights.
Chipping / breaking	Low tablet strength, dry granules or tooling damage	Optimise binder/moisture and compression; inspect punches and handling systems.
Mottling / colour variation	Uneven colour distribution or non-uniform drying	Improve mixing and colour dispersion; control drying and coating conditions.
Double impression	Punch movement or defective/unsuitable tooling	Inspect and maintain punches; use appropriate anti-turning features where applicable.

8.1 Capping

Capping refers to the partial or total detachment of the upper or lower crown of a tablet from its primary body during ejection or handling. It primarily happens because of air trapped in granules, excessive small particles, overly dry granules, low binder levels, and high compression force.[25,31]

8.2 Lamination

Lamination involves dividing a tablet into two or more separate horizontal layers. It results from air entrapment, excessive lubrication, high compression speed, and weak granule adhesion.[26]

Prevention: Decrease compression force, lower turret speed, employ ideal lubricant concentration, enhance granulation, and utilize tapered dies for gradual decompression.[32]

8.3 Sticking and picking

Sticking refers to the attachment of tablet material to the die wall, whereas picking denotes the attachment of a small quantity of material to the punch face, particularly in engraved letters. Factors include excessive moisture, low melting point components, inadequate lubrication, and a coarse punch surface.

Prevention: Properly dry granules, enhance lubricant, smooth punch surfaces, apply anti-stick agents such as talc, and manage humidity in the compression area.[12,19]

8.4 Mottling

Mottling is uneven colour distribution on tablet surface with light and dark patches. It occurs due to uneven distribution of colourant, dye migration during drying, different colour of API and excipients, and use of large particle size colourant (Rayhan et al., 2025).Prevention: Use finely milled colourant, mix properly, dry granules at low temperature, change binder-solvent system, and use lake colours instead of water-soluble dyes.[21,33]

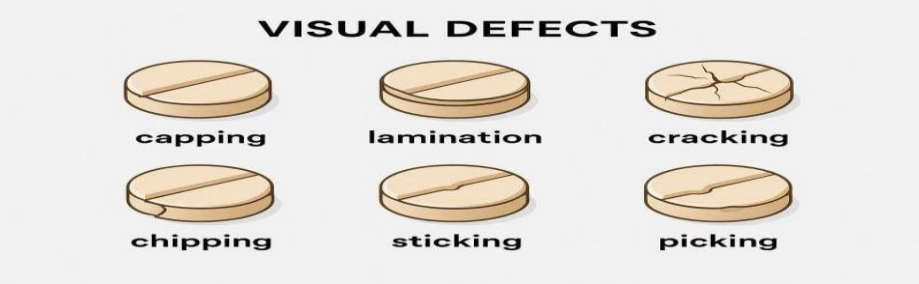


Figure 3. Common talet manufacturing defect.

8.5 Chipping and cracking

Chipping refers to the breaking of tablet edges, whereas cracking involves the development of small cracks on the tablet's surface. Chipping happens because of excessively dry granules, worn tools, and increased ejection force. Cracking happens as a result of swift expansion post-compression, employing deep concave punches, and significant granule size.[31]

Prevention: Ensure optimal moisture levels, minimize compression force, utilize flat punches, steer clear of deep concave tools, and handle tablets gently during coating.[28]

8.6 Double impression

Double impression refers to the creation of two overlapping prints on the surface of a tablet through engraving or monogram. It happens because of the unfettered movement of the lower punch during ejection (Adhikary et al., 2023). **Prevention:** Employ an anti-rotation device or keyed punches, verify punch alignment, and ensure the ejection cam is set correctly. IPQA visual assessment identifies this flaw in the initial phase.[17][34]

8.7 Weight variation

Weight variation refers to the differences in the weight of individual tablets within a batch. The issue arises from inadequate granule flow, uneven granule size, surplus fines, irregular die filling, elevated turret speed, and segregation.[17] **Prevention:** Maintain consistent granule size, incorporate glidant, decrease turret velocity, keep hopper level uniform, utilize force feeder, and manage segregation during transfer.[22,23]

9. Role of IPQA in GMP Compliance

IPQA is the backbone of Good Manufacturing Practice (GMP). It ensures that every batch is manufactured, checked, and documented as per approved procedures, and that no batch is released without Quality Assurance approval.[30]

9.1 Line clearance

Line clearance is the recorded confirmation performed prior to initiating a new batch or product on the same line. IPQA verifies that no materials, labels, or components from the prior batch are present on the line to avoid mix-ups and cross-contamination. IPQA inspects and approves the line clearance checklist for equipment, areas, dies-punches, and packaging supplies. Production cannot commence without IPQA line clearance.[35]

9.2 Area and equipment cleanliness verification

Prior to production, IPQA ensures that the equipment and production area are sanitized according to the approved cleaning procedure. It verifies cleaning status labels, the cleaning logbook, and the visual cleanliness of equipment, punches, dies, and contact components.[36] Additionally, IPQA checks swab and rinse samples for cleaning validation. If the cleaning does not meet standards, IPQA halts production and requests a re-cleaning.

9.3 In-process sampling and inspection

IPQA conducts in-process sampling at specified intervals according to the Batch Manufacturing Record (BMR). Samples are gathered from the blending, compression, coating, and packaging phases for evaluation of weight, hardness, friability, disintegration, and appearance.[30] Sampling follows established plans to guarantee that the samples are representative.

9.4 Batch manufacturing record verification

The Batch Manufacturing Record (BMR) serves as the legal evidence that the batch was produced according to the authorized master formula. IPQA checks each entry in the BMR — included amount, equipment utilized, process parameters, in-process results, yield, and signatures from the operator and checker.[37] Any absence of entries, alterations, or back-dating is considered a breach of data integrity.

Table 5: Role of In-Process Quality Assurance (IPQA) in GMP compliance.

S. No.	IPQA activity	Role in GMP compliance	Typical evidence / record
1	Pre-start-up and line clearance	Checks that the previous product, labels, documents and unwanted materials have been removed before a new operation begins. Confirms the area and equipment are suitable for the next batch.	Line-clearance checklist; area and equipment status labels; documented verification.
2	Verification of material status	Confirms that dispensed materials are correctly identified and carry the required approved/released status before use. Helps prevent material mix-ups and unintended use of rejected or quarantined items.	Material labels; dispensing records; status/reconciliation checks.
3	Monitoring of critical process steps	Verifies that defined in-process checks and critical process parameters are performed at the required stages and remain within approved limits.	BMR entries; in-process test results; process monitoring records.
4	Batch record review during processing	Checks entries for completeness, traceability, contemporaneous recording, corrections and adherence to approved instructions. Raises missing or inconsistent entries for investigation.	Completed and checked batch manufacturing/packaging records.
	Equipment and	Confirms that equipment is clean and appropriately	Equipment logbooks;

5	instrument status checks	identified, and that instruments used for quality-related measurements are within calibration or qualification status.	cleaning records; calibration labels/certificates.
6	Personnel practices and area conditions	Observes gowning, personal hygiene and relevant environmental/housekeeping practices to reduce contamination and mix-up risks.	Gowning checks; area monitoring records; housekeeping observations.
7	Deviation and abnormality escalation	Ensures that process deviations, unusual observations and out-of-limit results are promptly documented and communicated for investigation and impact assessment.	Deviation report; investigation and CAPA records.
8	Packaging and labelling checks	Verifies approved packaging components, coding details, printed particulars and reconciliation controls to reduce the risk of incorrect or mixed labels.	Packaging line-clearance record; specimen labels; component reconciliation.
9	Adherence to validated procedures	Checks that operations are performed using current approved procedures and that changes or interventions are handled through the site change-control system.	Current SOPs; change-control records; validation-related documents.
10	Escalation and batch documentation support	Communicates significant quality concerns to the responsible QA/production functions and ensures that relevant observations are traceable in batch documentation. IPQA monitoring does not replace the authorised batch disposition process.	IPQA observation reports; QA review trail; documented follow-up.

9.5 Documentation and data integrity

Documentation is essential to GMP — "If it's not recorded, it hasn't been accomplished." IPQA guarantees that every record adheres to the ALCOA+ standards — Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available.[38] IPQA verifies audit trails, electronic signatures, and access controls in electronic systems according to 21 CFR Part 11. Sharing passwords, erasing data, and manual transcription without confirmation are not allowed.

9.6 Handling of deviations

Deviation refers to any unexpected divergence from established procedure or specification. IPQA is the initial system to identify and communicate discrepancies in the manufacturing process.[39] Upon detection, IPQA promptly halts the impacted operation, separates the materials, and notifies QA. A deviation report is created containing information on what occurred, when it took place, and what immediate measures were implemented. Root cause analysis utilizes methods such as the 5-Why technique and Fishbone diagram, followed by CAPA — Corrective Action and Preventive Action.[40]

10. Quality risk management in IPQA

10.1 Introduction to quality risk management

Quality Risk Management (QRM) is a structured approach for evaluating, managing, conveying, and reassessing risks to product quality during the entire product lifecycle. It is regulated by ICH Q9(R1), which was updated in 2023 to lessen subjectivity, enhance formality, and encourage risk-based decision-making (International Council for Harmonisation, 2023).

10.2 Identification of manufacturing risks

Risk identification represents the initial phase of QRM, during which all potential hazards in tablet production are recorded — including cross-contamination, mix-ups, incorrect dispensing, inadequate granulation, excessive lubrication, compression issues, and coating problems. Risks are recognized through brainstorming sessions, process mapping, analysis of historical deviation patterns, and examination of past batches.[41]

10.3 Failure Mode and Effects Analysis (FMEA)

FMEA is the most commonly utilized QRM instrument in the pharmaceutical sector. In FMEA, each failure mode is assessed based on Severity (S), Occurrence (O), and Detectability (D), with the Risk Priority Number computed as **RPN = S × O × D** [42]. Failures with high RPN are prioritized for management. For instance, incorrect dispensing carries high severity, mandating barcode verification and a double-check.

10.4 Root cause analysis

Root Cause Analysis (RCA) is performed following a deviation or defect to identify the actual cause rather than merely the symptom. Typical tools include 5-Whys, Fishbone/Ishikawa Diagram, Fault Tree Analysis, and Pareto Analysis.[43] For instance, if capping happens, RCA doesn't conclude at "high compression force" — it investigates why the force was elevated, why granules were dry, and why the binder amount was low. Human error by itself is never regarded as a primary cause; the underlying system failure must be identified.

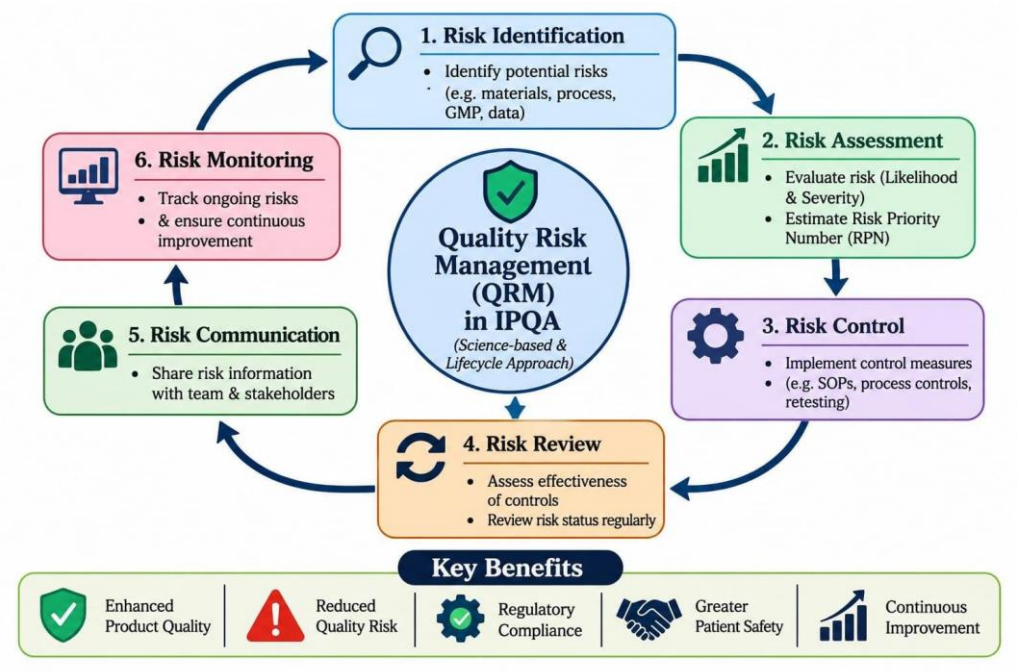


Figure 4: Quality risk management approach in IPQA.

10.5 Corrective and Preventive Actions (CAPA)

CAPA is the measure implemented following RCA. Corrective Action addresses the current issue, whereas Preventive Action stops it from happening again in other products or lines. An effective CAPA should have a defined owner, timeline, and effectiveness assessment. The FDA does not consider retraining alone as sufficient for CAPA. The effectiveness of CAPA is confirmed by tracking the deviation rate, OOS rate, and complaints for six months following implementation.[44]

10.6 Risk-based defect prevention

Risk-based defect prevention involves directing IPQA resources towards high-risk stages rather than distributing them equally across all stages. Steps considered high- risk, such as dispensing, blending, compression, and coating, undergo more frequent inspections, whereas low-risk steps are subject to occasional checks. This strategy minimizes batch rejections, enhances GMP compliance, and guarantees product availability.[45]

11. Challenges in Implementation of IPQA

Despite its importance, implementation of IPQA in tablet manufacturing faces several practical challenges. If these challenges are not addressed, even a well-designed IPQA system can fail to prevent defects.

11.1 Human errors

The most frequent obstacle in IPQA implementation is human error. Mistakes happen in dispensing, weighing, sampling, and documentation because of fatigue, workload, distraction, or misinterpretation of SOP.[46] Manual verification, result transcription, and visual checks greatly rely on the operator's attentiveness.

11.2 Equipment-related problems

Used punches and dies, non-calibrated scales, defective tablet press sensors, and broken coating pans result in variable tablet quality. Numerous small and medium-sized enterprises continue to operate outdated machinery lacking automated controls or in-line sensors. Failure during compression leads to interruptions, changes in weight, and loss of batches.[47]

11.3 Inadequate process monitoring

In numerous plants, IPQA continues to rely on manual, off-line testing rather than real-time monitoring. Outcomes are available after 30-60 minutes, during which a significant number of faulty tablets might have already been manufactured The absence of PAT tools such as NIR, Raman, and in-line hardness testers, along with high automation costs and inadequate sensor integration with tablet presses, complicates real-time management.[48]

11.4 Documentation errors

Errors in documentation—such as absent entries, overwriting, back-dating, application of correction fluid, and incomplete BMR—pose a significant challenge for IPQA. Manual documentation is prone to errors and takes a lot of time. In audits, just one absent signature can result in an FDA 483 observation.[49]

11.5 Training and skill-related challenges

IPQA personnel frequently do not receive adequate training on new technologies, QbD, PAT, and risk management instruments. High turnover, regular job shifts, and absence of ongoing training initiatives diminish the competency of operators and IPQA personnel. Lacking insight into the purpose of a test, employees regard IPQA as a mere formality — solely completing checklists. This results in overlooked flaws and incorrect reporting.[50]

11.6 Maintaining consistent product quality

The greatest long-term challenge is ensuring consistency from batch to batch. Differences in raw material quality, fluctuations in seasonal humidity, changes in suppliers, and scaling up

from pilot to commercial production influence tablet quality. A batch that passes quality control may still be followed by a failing batch due to a slight variation in API particle size or excipient lot.[51]

12. Recent Advances in IPQA

IPQA is rapidly shifting from manual, off-line testing to automated, real-time, and data-driven quality assurance. These advances reduce human error, speed up batch release, and improve GMP compliance (Wang et al., 2024).

12.1 Process Analytical Technology (PAT)

Process Analytical Technology (PAT) is a method for creating, examining, and managing production by promptly measuring essential quality characteristics. PAT instruments such as Near-Infrared (NIR) spectroscopy, Raman spectroscopy, and terahertz spectroscopy assess blend uniformity, moisture levels, and tablet hardness instantaneously without compromising the sample.[52] The FDA launched PAT guidance in 2004 to promote real-time release.

12.2 Real-time process monitoring

Real-time process monitoring employs sensors, virtual sensors, and digital twins to incessantly observe CPPs and CQAs throughout the manufacturing process. For instance, modern tablet presses continuously monitor compression force, ejection force, and tablet weight every second. If any parameter deviates from trend, the system automatically halts the press or diverts defective tablets.[53]

12.3 Electronic batch manufacturing records

Electronic Batch Manufacturing Records (eBMR) substitute traditional paper BMR with electronic documentation. In eBMR, information from balances, tablet presses, and coating pans is automatically recorded, including an audit trail and electronic signature as required by 21 CFR Part 11. eBMR eliminates back-dating, transcription mistakes, and omitted entries. It enables QA to examine the batch from a distance and expedite its release.[54]

12.4 Automated inspection systems

Automated inspection systems utilize high-speed cameras, machine vision, and Artificial Intelligence (AI) to examine all tablets for flaws such as chipping, cracking, color variation, and double impression. These systems operate at speeds of 10,000 tablets per minute, significantly surpassing the pace of manual inspection. Vision systems powered by AI can

identify new defects and minimize false rejections.[55]

12.5 Digitalization in pharmaceutical quality assurance

Digitalization involves integrating all IPQA data—from dispensing to packaging—into a unified digital platform utilizing cloud, IoT, and blockchain technologies. This allows for trend analysis, predictive maintenance, and advance notice of process deviations [56]. Pharma 4.0 and Quality 4.0 efforts leverage big data analytics to forecast which batch is at risk of failure before it actually fails.

13. Future Perspectives

The future of IPQA is moving from "test and reject" to "predict and prevent." With smart technologies, IPQA will soon be able to predict a defect before it happens and automatically correct the process.

13.1 Smart manufacturing and Industry 4.0

Smart manufacturing under Industry 4.0 connects machines, sensors, and quality systems through Internet of Things (IoT) and cloud computing. In a smart tablet plant, the tablet press, coater, blister machine, and IPQA system will communicate with each other in real-time.For example, if granule moisture increases during drying, the system will automatically adjust drying time and inform compression to change compression force. This self-adjusting system reduces human intervention and ensures consistent quality.[57]

13.2 Predictive quality monitoring

Predictive quality monitoring employs Artificial Intelligence (AI) and Machine Learning (ML) models that are developed using historical batch data to forecast the final quality of tablets — including dissolution, hardness, and content uniformity — during the ongoing batch process. Rather than relying on laboratory outcomes, IPQA receives a prediction such as "this batch has a 92% likelihood of passing dissolution." If the likelihood decreases, prompt measures can be implemented.[58]

13.3 Risk-based in-process control

Future IPQA will completely adopt a risk-based approach according to ICH Q9(R1) and ICH Q14. High-risk factors such as blend uniformity and compression force will be continuously monitored, whereas low-risk factors will be assessed periodically. Implementing risk-based control will minimize unnecessary testing, cut costs, and direct resources to areas with the

highest likelihood of failure.[59]

13.4 Integration of digital technologies in IPQA

IPQA in the future will combine PAT, digital twins, blockchain, augmented reality (AR), and robotics into a single platform. A digital twin — a virtual representation of the tablet production line — will replicate the process and forecast the impact of modifications prior to implementation in actual manufacturing. Block chain will provide secure traceability from raw material to the patient, while AR glasses will assist operators during line clearance and inspections.[60]

14. CONCLUSION

In-process quality assurance has evolved from a supplementary checking function to the crucial foundation of contemporary tablet manufacturing. This review clearly demonstrates that product quality cannot be guaranteed solely by end-product testing; it must be integrated into the product at every phase — from dispensing to packaging— by means of ongoing process monitoring, prompt intervention, and rigorous GMP adherence. IPQA is critical at each stage of manufacturing. While dispensing, it avoids mix-ups and cross-contamination by verifying materials. While granulating, drying, and blending, it regulates moisture, particle size, and consistency, which directly influence compressibility and content uniformity. During compression and coating — the stages most susceptible to defects — it identifies capping, lamination, sticking, picking, weight discrepancies, and coating flaws at their source, averting significant batch rejection. In the packaging process, it guarantees seal integrity, accurate labelling, and traceability, thus safeguarding the patient. The evaluation further emphasizes that the connection between Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) forms the scientific basis of IPQA. When CPPs like compression force, blending duration, drying temperature, and spray rate are regulated within the approved design parameters, CQAs such as hardness, friability, disintegration, dissolution, and content uniformity are reliably obtained. Quality Risk Management tools such as FMEA, Root Cause Analysis, and CAPA transition IPQA from responsive corrections to proactive defect prevention

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