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Original Article

Physical Stability of Drugs: Linking Quality-By-Design (QbD) And Process Analytical Technology (PAT)

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ABSTRACT

A key component of pharmaceutical quality is the physical stability of drug ingredients and products. Physical instability can have a negative impact on efficacy, safety, manufacturability, and shelf life. This includes mechanical degradation, moisture-induced changes, polymorphic transformation, crystallization of amorphous forms, and solid-state phase transitions. Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs) are identified, along with a design space, as part of Quality-by-Design (QbD), a methodical, risk-based framework for designing robust products and processes that guarantee physical stability. During development and manufacturing, Process Analytical Technology (PAT) provides real-time, in-line, and online tools to monitor and control those attributes. This review connects the QbD risk-based approach, PAT-enabled monitoring and control strategies, and the scientific mechanisms behind physical instability. Discussion topics include case studies, modeling techniques, regulatory context, real-world PAT tools and examples, and future prospects (such as AI/ML-enabled PAT and continuous manufacturing). To protect physical stability, suggestions are given for putting an integrated QbD–PAT strategy into practice.

Keywords: Physical Stability, Quality-by-Design (QbD), Process Analytical Technology (PAT), Polymorphism, Amorphous Stability, Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), Real-time Monitoring, Modeling and Predictive Approaches

INTRODUCTION

The ability of a pharmaceutical product to function as intended over the course of its shelf life is what defines its quality. Physical stability—alterations in the solid-state form, morphology, moisture content, particle size, or mechanical integrity—is just as important as chemical stability, which has long been the focus (e.g., degradation). Physical alterations have resulted in product recalls and can change dissolution, bioavailability, content uniformity, and manufacturability. [1,2]

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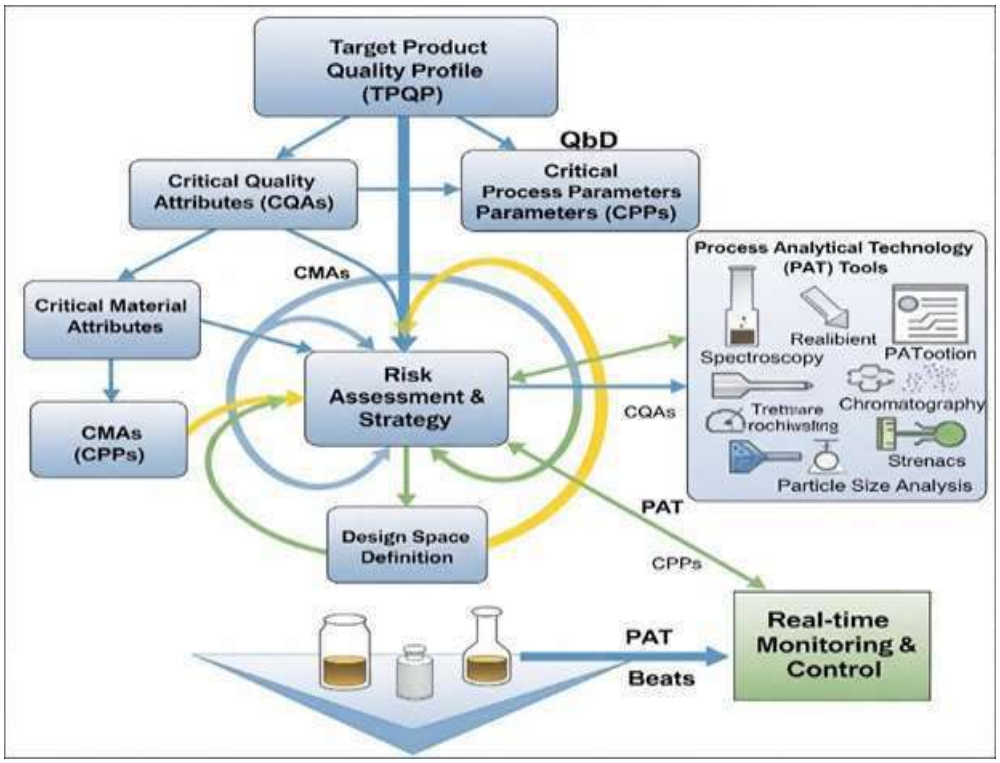

Figure 1: Integrated QbD-PAT Framework

A comprehensive, risk- and science-based approach to product development and lifecycle management is promoted by contemporary regulatory frameworks (ICH Q8–Q10; FDA PAT guidance). [3-5] PAT provides the tools for real-time monitoring and comprehension, while QbD defines quality in terms of CQAs and how to control them. Physical instability can be prevented and lessened proactively by combining QbD and PAT. [6] In terms of quantifiable Critical Quality Attributes (CQAs), how those are impacted by Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), and how a scientifically supported design space can guarantee consistent performance, QbD offers an organized approach to defining quality. By offering real-time, in-process measurements that enable the monitoring and control of physical attributes as they change during manufacturing, PAT, on the other hand, enhances QbD. Because of this synergy, stability management is no longer dependent on end-product testing but rather is a knowledge-driven, ongoing process. As a result, proactive quality assurance techniques that incorporate stability into the design and manufacturing process itself have replaced reactive quality testing of finished goods in the pharmaceutical industry. ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and 010 (Pharmaceutical ↓ Quality System) are examples of regulatory frameworks. [7] In this review, we examine how QbD principles can be used to systematically protect the physical stability of drug substances and drug products, while PAT tools can be used to monitor their stability. We begin by discussing the mechanisms underlying physical instability, then map how QbD frameworks address these risks, followed by detailed coverage of PAT technologies that enable real-time control. An integrated roadmap for guaranteeing physical stability throughout the product lifecycle is highlighted by the presentation of case studies, modeling techniques, regulatory viewpoints, and future directions.

Mechanisms and Manifestations of Physical Instability

Understanding mechanisms is prerequisite to design controls.

1. Polymorphism and pseudo-polymorphism

The mechanical properties, solubilities, and lattice energies of polymorphs vary. Humidity, temperature, solvent traces, compression, and seeding can all cause polymorphic changes, including those between hydrates and solvates. These conversions could alter the compressibility of tablets or decrease their solubility. [8-10]

2. Amorphous–crystalline transformation

Although amorphous forms are thermodynamically metastable and have the potential to recrystallize during processing or storage, they frequently increase apparent solubility. The kinetics of crystallization are controlled by molecular mobility, residual moisture, Tg (glass transition temperature), and excipient interactions. [11,12]

3. Moisture interactions

Hygroscopic compounds, deliquescence, hydrate formation, plasticization of amorphous phases (reducing Tg), and solid-state reaction catalysis are all impacted by water uptake. Two important descriptors are critical relative humidities and sorption isotherms. [13]

4. Mechanical degradation and compaction-induced changes

Milling, blending, and tableting exert mechanical energy that can induce amorphization, polymorphic transitions, or particle breakage altering surface area and dissolution.

5. Temperature- and light-induced transitions

Phase transitions can be accelerated by thermal exposure; photostability is important for light-sensitive APIs or excipients that cause degradation or appearance changes.

Quality-By-Design (Qbd) Framework Applied to Physical Stability

Instead of depending only on end-product testing, QbD stresses incorporating quality into the product through design.

1. Define Target Product Quality Profile (TPQP)

Clinical performance, release and shelf-life requirements, and important physical characteristics (such as dissolution, content homogeneity, particle size distribution, and polymorphic form) are all outlined in the TPQP. [14]

2. Identify Critical Quality Attributes (CQAs)

Crystalline form, percentage of amorphous content, moisture content, particle size and shape, density, porosity, and tablet hardness/disintegration time are examples of physical CQAs.

3. Map Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)

CMAs: physical form, moisture content, particle size, polymorphic purity, and excipient characteristics (polymer Tg, hygroscopicity) of the API. CPPs include compression force, spray-drying parameters, coating conditions, drying temperature and duration, and milling conditions. Targeted control is made possible by knowing which CMAs/CPPs have an impact on CQAs.CPPs: Process parameters that control the conversion of raw materials into final dosage forms. Spray-drying or hot-melt extrusion parameters (feed rate, temperature, and shear rate) that affect the formation of amorphous solid dispersions; compression force, dwell time, and turret speed that affect polymorphic conversion and mechanical robustness; coating spray rate, atomization pressure, and inlet air humidity that determine coating integrity and moisture protection; and milling speed, duration, and energy input that influence amorphization and particle size. Connecting CMAs, CPPs, and CQAs: The contribution of each material or process factor to physical CQAs is highlighted in this mapping exercise. For example, a high humidity granulation step (CPP) in conjunction with a hygroscopic polymer (CMA) may increase residual moisture (CQA), which speeds up the recrystallization of an amorphous API. Similarly, a metastable polymorph (CMA) may undergo conversion to a more stable form, changing the dissolution profile (CQA), if an excessive compression force (CPP) is applied. Therefore, integration of stability studies, process knowledge, and material characterization data is necessary for effective mapping. Contemporary methods strengthen design space justification by connecting real-time CPP measurements to anticipated CQA results through multivariate analysis and PAT feedback. [15]

4. Risk assessment and design of experiments (DoE)

High-risk variables are identified using structured tools (FMEA, Ishikawa); DoE investigates the

process space to measure factor–response relationships for physical stability endpoints (e.g., crystallinity, dissolution). Creating statistical models aids in creating a solid design space. [16]

5. Design space, control strategy, and lifecycle management

Flexible manufacturing is supported by a QbD design space that takes physical stability (processing windows, excipient selection) into consideration. Release testing, stability surveillance, and in-process monitoring (PAT) should all be a part of a control strategy.

Pat Tools for Monitoring Physical Stability — Capabilities and Applications

Spectroscopic, diffractive, thermal, and imaging methods used in-line, on-line, or at-line are all included in PAT. The attribute to be monitored determines the selection.

Table 1: Physical Instability Mechanisms and Corresponding Analysis Tools [17-20]

Physical Instability Mechanism	Description	Key Analysis Tools (PAT)
Polymorphic Transformation	Transform ion polymorphism changing a drug's solubility, rate of dissolution, and bioavailability by transforming it from one crystalline form to another. A distinct fingerprint of the crystalline structure is provided by powder X-ray diffraction (PXRD). Raman Spectroscopy: Identifies variations in molecular vibrations among polymorphs. Heat flow related to phase transitions is measured by differential scanning calorimetry (DSC).	A distinct fingerprint of the crystalline structure is provided by powder X-ray diffraction (PXRD). Raman spectroscopy: Identifies variations in polymorphs' molecular vibrations. Heat flow related to phase transitions is measured by differential scanning calorimetry (DSC).
Amorphous-Crystalline Conversion	The transformation of a non-crystalline, amorphous solid back into a more stable crystalline form. A considerable reduction in solubility and dissolution may result from this.	Powder X-Ray Diffract Ion (PXRD): Identifies the emergence and development of crystalline peaks. Raman spectroscopy: Assesses how spectral characteristics alter as a material gets more ordered. The glass transition temperature (Tg) and the heat of crystallization are measured by Differential Scanning Colorimetry (DSC).
Moisture-Induced Changes (Hydration/Dehydration)	Water loss or absorption by the solid-state material, which can alter its physical characteristics or crystal structure (hydrate formation).	Extremely sensitive to variations in water content is near-infrared (NIR) spectroscopy. The Dynamic Vapor Sorption (DVS) gauges how much water a sample absorbs when the relative humidity fluctuates.
Particle Size and Shape Changes	Agglomeration, mechanical deterioration, or crystal growth that impacts the final product's flow, compressibility, and rate of dissolution.	The particle size distribution is measured by the laser diffract ion. Real-time data on particle chord length and number is provided by Focused Beam Reflectance Measurement (FBRM).

1. Spectroscopic tools (NIR, Raman, FTIR) [21-23]

Rapid, non-destructive measurements of solid-state form, moisture content, and blend uniformity can be obtained using near-infrared (NIR) and Raman spectroscopy. Spectral features are correlated with the water content, assay, or crystalline fraction by chemometric models (PLS, PCA).

2. X-ray based techniques (PXRD, X-ray scattering) [24,25]

The gold standard for phase identification is powder X-ray diffraction (PXRD). During procedures like spray drying or crystallization, polymorphic form and crystallinity can be observed using X-ray scattering and in-line or at-line PXRD systems.

3. Thermal techniques (DSC, TGA) [26,27]

Tg and melting events are detected by differential scanning calorimetry (DSC); sensitivity is increased by modulated DSC and micro-DSC variants. Thermogravimetric analysis (TGA) measures mass loss, such as that caused by water or solvent. In process development, hyphenated or micro-scale methods can be modified for PAT-like monitoring.

4. Imaging and particle analysis (microscopy, laser diffraction, focused beam reflectance measurement) [28]

Dissolution and content homogeneity are influenced by particle size and shape. Particle size distribution and agglomeration are monitored by focused beam reflectance measurement (FBRM), image analysis, and laser diffraction (both in-line and off-line).

5. Terahertz and solid-state NMR [29]

Tablet coating quality and polymorphic variations can be found using terahertz spectroscopy. Deep structural insight is provided by solid-state NMR, which is primarily offline but extremely useful in development.

6. Moisture sensors and humidity monitoring [30]

During drying and storage, critical water levels are maintained with the aid of in-line moisture meters, dynamic vapor sorption (DVS), and gravimetric moisture analyzers.

7. Hyphenated and model-based PAT [31]

Long-term stability can be predicted from short-term in-process signals by combining PAT data streams and applying chemometrics or mechanistic models.

Linking Pat Measurements to QbD Elements: Monitoring CQAs And Controlling CPPs

A validated model must map measured PAT variables to CQAs. Examples of mappings

- NIR/Raman → crystallinity, moisture content (CQA)
- FBRM/laser diffraction → particle size (CQA)
- Inline PXRD → polymorphic form (CQA) Control loops (feedback/ feedforward) can adjust drying temperature, spray rate, or compression force to keep CQAs within the design space, thereby preventing instability manifestations (e.g., recrystallization).

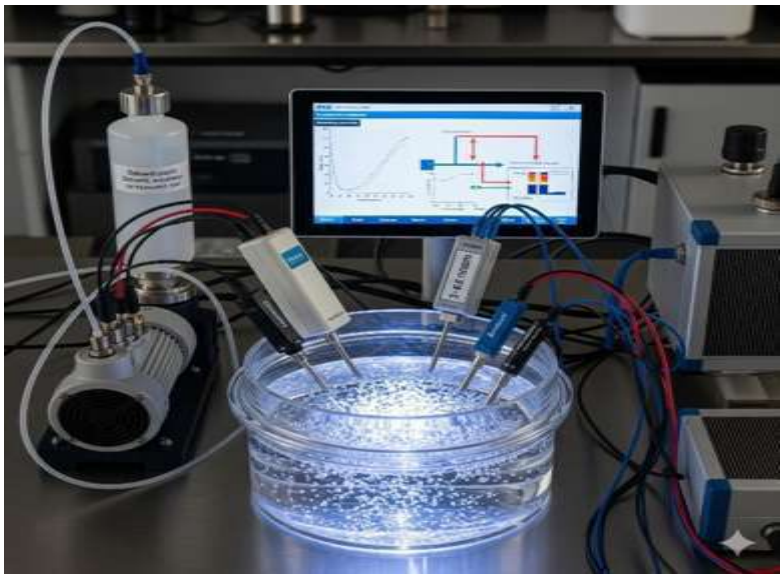

Figure 2: Example of PAT-enabled Control Loop

Case Studies and Applied Examples [32-34]

1. Spray-dried amorphous dispersions

Together with DoE, PAT tools (inlet/outlet gas analysis, NIR, and particle size) assisted in defining spray-drying windows that reduce solvent residue and avoid early crystallization; excipient selection (polymer Tg and interaction) further stabilizes the amorphous state.

2. Crystallization control in API manufacture

Real-time detection of nucleation and polymorphic form was made possible by inline Raman and ATR-FTIR monitoring of crystallization. This allowed process modifications (cooling rate, antisolvent addition) to favor the desired polymorph.

3. Tablet compression and polymorphic transition

Compaction-induced solid-state changes were identified by real-time NIR monitoring during compression; undesired transitions were avoided by adjusting tablet formulation and controlling compression force.

Modelling and Predictive Approaches for Physical Stability

Physical stability is predicted by mechanistic and data-driven models, such as isothermal kinetic models for crystallization, models that relate recrystallization propensity to molecular mobility (relaxation times), and machine learning models trained on PAT spectra to predict long-term stability. Prediction reliability is increased by combining PAT-derived features with accelerated stability data.

Regulatory Perspectives and Documentation

Implementing QbD and PAT is encouraged by the FDA PAT guidance and the ICH Q8–Q10 guidelines. When modifications stay within the validated design space, post-approval flexibility is supported when regulatory submissions show connections between CQAs, CMAs, CPPs, PAT measurements, and control strategies. Regulations require strong model validation, lifecycle management, and change control. [35]

CHALLENGES AND LIMITATIONS [36,37]

- **Model robustness and transferability:** Model maintenance and calibration-transfer strategies are crucial because chemometric and machine learning models can be sensitive to variations in raw materials and instrumentation.
- **Analytical sensitivity:** For low levels of crystalline content, some PAT tools might not be sensitive enough; in these cases, combining orthogonal techniques is frequently required.
- **Regulatory and operational barriers:** Validated workflows and cross-functional expertise are necessary for PAT and continuous control implementation. Practical difficulties include maintaining data integrity and managing massive data volumes.
- **Understanding complex excipient–API interactions:** It is still difficult and frequently empirical to predict how excipients will affect amorphous stability.

FUTURE DIRECTIONS

- **AI/ML-enabled PAT and digital twins** for predictive stability and closed-loop control.
- **Miniaturized, low-cost PAT sensors** embedded in continuous lines enabling broader adoption.
- **Advanced multiscale modelling** linking molecular mobility to macroscopic instability.
- **Stronger integration with continuous manufacturing** to reduce residence-time variability that can trigger instability.

Practical Recommendations for Implementation

1. Identify physical CQAs early on and begin QbD by explicitly including physical stability in the TPQP.
2. Prioritize CMAs and CPPs that impact physical stability using risk assessment (FMEA).
3. Use DoE to create a design space that regulates physical results and measure factor effects.

4. During crucial process stages (drying, crystallization, compaction, and coating), use orthogonal PAT tools.
5. Create and verify chemometric and mechanistic models that relate PAT signals to stability endpoints over the long term.
6. In regulatory submissions, make plans for model maintenance, calibration transfer, and LCM (lifecycle management).

CONCLUSION

Drug quality depends on physical stability, which needs to be incorporated into development and production using QbD principles. The sensing and control required to continuously monitor and maintain physical CQAs are provided by PAT. QbD and PAT work together to improve product robustness, patient safety, and regulatory flexibility by facilitating the transition from reactive testing to proactive design and control. This integration will be strengthened by ongoing developments in data science, modeling, sensors, and optics.

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