Available online on 15.05.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Report

Approaches for Predicting Storage-Induced Reactive Impurities in Pharmaceutical Drugs

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Article Info:

Article History:

Received 10 Feb 2026
Reviewed 30 March 2026
Accepted 24 April 2026
Published 15 May 2026

Cite this article as:

Shende H, Nagpure N, Kuware J , Gupta S , Dhoke V, Rasala T, Approaches for Predicting Storage-Induced Reactive Impurities in Pharmaceutical Drugs, Journal of Drug Delivery and Therapeutics. 2026; 16(5):163-172 *DOI: https://dx.doi.org/10.22270/jddt.v16i5.7758*

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Abstract

Goal: To create a predictive system for the formation of storage-induced impurities in drug formulations through the integration of mechanism-based and risk-based methodologies.

Purpose: The objective of this paper is to explore less-researched aspects of impurity formation, including microenvironment variability, interplay between the drug substance, excipients, and packaging material, as well as the development of new prediction tools based on artificial intelligence, hybrid methods, and digital twinning.

Finding: It can be seen that routine stability testing does not take into account local changes within the microenvironment of the drugs, e.g., pH fluctuations and water content gradients, or conditions during transport that significantly increase impurity generation. Several new factors such as leachates, fluctuating temperatures, and mechanical forces were found to be highly effective in inducing chemical changes. Predictive models have proven to be highly accurate in predicting impurity profiles and pathways of degradation.

Results: The application of predictive analytics in conjunction with QbD and risk assessment techniques such as FMEA ensures that critical risks are identified early and robust control strategies are developed. Real-time monitoring solutions using smart packaging and sensor technology provide additional ways to manage impurity risks during the entire lifetime of the product.

Conclusion: A multi-pronged solution combining knowledge of mechanisms, predictive models, and risk-based controls presents a paradigm shift in the reduction of storage-driven reactive impurities. Using this kind of approach will not only benefit products in terms of stability but also promote regulatory advances towards the adoption of predictive stability guidelines.

Keywords: Predictive stability modeling; Reactive impurities; Heterogeneity of microenvironments; Digital twin; Risk-based control strategies.

1. Introduction

Formation of reactive impurities through various mechanisms during the storage of drugs has been recognized as an important issue. Such impurities are known to form due to various reactions between API, excipients, or other compounds that are present in small amounts. They can adversely affect the effectiveness of drug treatment and cause toxicity problems. While previous research has mainly

considered conventional mechanisms such as oxidation, hydrolysis, and photolysis to study degradation, recent findings suggest that impurity formation is much more complicated and involves several other parameters.[1] Formation of reactive species, presence of trace levels of foreign contaminants and excipient degradation have become increasingly popular areas of research in impurity formation, but they lack proper representation in numerous reviews available in the literature.

Conventional stability tests are usually carried out using various methods based on regulatory standards.[2] Such approaches allow acquiring initial information on degradation rates and reaction pathways. However,

standardization of the process does not account for complexity and variability of the environment where drugs are actually kept after leaving the manufacturer. Variability in temperature, moisture, exposure to light, mechanical stress during transportation, and other factors may go unnoticed during testing. Besides, conventional models presuppose homogeneity of the formulation but pH, moisture content, and molecular mobility can vary significantly. These microdomains can act as "hotspots" for accelerated degradation and reactive impurity formation, representing a critical gap in current stability assessment strategies.[3]

With the increase in complexity of modern pharmaceutical formulations, such as those with amorphous solid dispersions, combination products, and biological sources of excipients, conventional approaches face more difficulties in predicting their performance. Furthermore, interactions among different components, specifically the effect of leachables and the permeability of container-closure systems, may cause additional impurities, which are rarely considered by traditional stability studies.[4] With the increase in complexity of supply chain networks, the effects of actual storage conditions on formulation stability require a greater focus on prediction rather than on static evaluations.

Thus, new technological advances become an urgent necessity, providing solutions that allow incorporating a better understanding of mechanisms of the process into predictive models and risk-based management strategies. The use of innovative technologies, such as artificial intelligence, machine learning, and digital twin concepts, can help evaluate complex processes of degradation and predict impurity formation in a wide range of conditions. With the integration of advanced analytical and monitoring technologies, such as smart packaging and sensors, these solutions will facilitate stability management.[5]

It seeks to fill in these vital gaps through the development of an inclusive and forward-thinking predictive framework for assessing the development of reactive impurities within a storage setting. The proposed framework will incorporate novel elements not previously examined in detail, such as microenvironmental variability, practical challenges faced within supply chains, and cutting-edge digital modeling techniques. Through the synthesis of mechanistic insights with innovative prediction and risk management tools, it hopes to shift the paradigm of current pharmaceutical stability testing practices and lay the groundwork for future advances.[6]

2. Traditional Perspectives on Reactive Impurity Formation During Storage

The occurrence of reactive impurities during the storage period can be explained by the established degradation pathways of oxidation, hydrolysis, photolysis, and thermal decomposition. In oxidative degradation, the process involves the action of reactive oxygen species and trace amounts of peroxides found in excipients, producing reactive intermediates that continue impurity formation. Hydrolysis is greatly affected by moisture content and is highly relevant in cases where the drug contains an ester or an amide group. Photolytic reactions occur when exposed to light, causing structural transformations and free radical formations, while thermolytic reactions increase the rate of reaction.

The role played by excipients in forming impurities is an important but often overlooked factor. While historically, excipients were viewed as inert ingredients, they have been shown to be capable of producing reactive molecules.[7] These include peroxides formed from polyethylene glycols and polysorbates, or reducing sugars that are known to form Maillard reaction products with amino acids in drugs. Furthermore, variation in excipients due to natural differences or during production can result in trace amounts of impurities or metals responsible for catalysis in degradation processes. The presence of environmental variables such as heat, humidity, and light further influences the process, although not in a way considered in traditional study designs.[8]

One area which remains poorly understood is the assumption made about homogeneity in pharmaceutical dosage forms. Recent research shows that there is heterogeneity at the micro-level, where local moisture, pH, and excipients are found to play a critical role in the rate of drug degradation. Moreover, there can be reactions occurring in these microenvironments, which will escape detection using normal analyses. The other underappreciated factor in the formation of impurities is the effect of any temporary reactive species which form and break down quickly and therefore cannot be identified through analysis.

The final underexplored issue concerns the effect of packaging on pharmaceutical stability. Both leachables and permeants from the container-closure systems may contribute towards chemical reactions and thus affect drug stability. Other issues include dynamic conditions such as temperature changes and physical shocks to the formulation which cause impurity formation by promoting certain physical processes.[9] None of these are replicated in the usual studies done to investigate drug formulation and impurity development.

From the above discussion, it can be seen that while the classical view is valid to an extent, it fails to capture some important nuances in drug formation.[10]

3. Microenvironment Inside Dosage Forms (Key Novel Section)

3.1 Concept of Microenvironmental Heterogeneity

Pharmaceutical dosage forms have conventionally been studied as homogenous systems; however, new evidence supports the existence of substantial

microenvironmental heterogeneity within solid and semisolid dosage forms. Uneven distribution of excipients, variations in particle size, compressive forces acting during fabrication, and differential local porosity result in heterogeneous microenvironments within pharmaceutical dosage forms. These microdomains have different physicochemical properties, and therefore degradation reactions are independently affected by the microdomain environment, which results in a highly selective generation of degradation products within the dosage form.[11]

3.2 Localized pH Differences and Water Activity Gradients

A major factor contributing to microenvironmental heterogeneity is localized differences in pH within the formulation. Buffering agents, organic acids, or bases within the formulation can cause microdomains within the formulation to exist in pH levels that differ from those of other microenvironments. These variations in pH level will facilitate or enhance degradation by means of hydrolysis or other reactions.

Localized water activity gradients are another factor that enhances microenvironmental heterogeneity. Hygroscopic formulations may experience non-homogeneous water distribution within the microdomain. Water molecules are highly mobile in regions of high moisture content, and thus the possibility for hydrolysis increases due to enhanced mobility.[12]

3.3 Solid-State Transformations (Amorphous vs. Crystalline Domains)

Solid-state properties significantly contribute to the definition of microenvironments in drug delivery systems. Many drug forms contain domains of both an amorphous state with higher free energy and molecular mobility and crystalline state with a stable structure, and each domain possesses its own stability profile. Amorphous domains are more prone to degradation than crystalline ones due to their higher energy and flexibility.

Phase changes like recrystallization or polymorphic transformations might happen during storage time, changing the physicochemical characteristics of a particular area. This effect will stabilize or destabilize a system, triggering degradation of the compound under certain conditions. The instability of impurities is greatly dependent on internal changes in the structure of the dosage form during storage.[13]

3.4 Impurity Hotspots Formation

The interplay of localized pH and moisture variations and solid-state transformations causes the emergence of impurity hotspots. It is specific zones where degradation reaction occurs with much higher efficiency than in other areas of the dosage form.[14]

Impurity hotspots are especially important to note since it is not possible to observe them using regular bulk analysis techniques. Impurity generation is often overlooked, causing hidden degradation.

3.5 Impact on Stability Prediction Models

Due to microenvironmental heterogeneity, conventional stability prediction models, which operate under an assumption of homogeneity in reaction conditions, may not accurately predict drug stability. To solve this problem, more sophisticated methods, such as Raman mapping, near-infrared (NIR) spectroscopy, and microimaging, are being used for detection of spatial differences inside the dosage form.

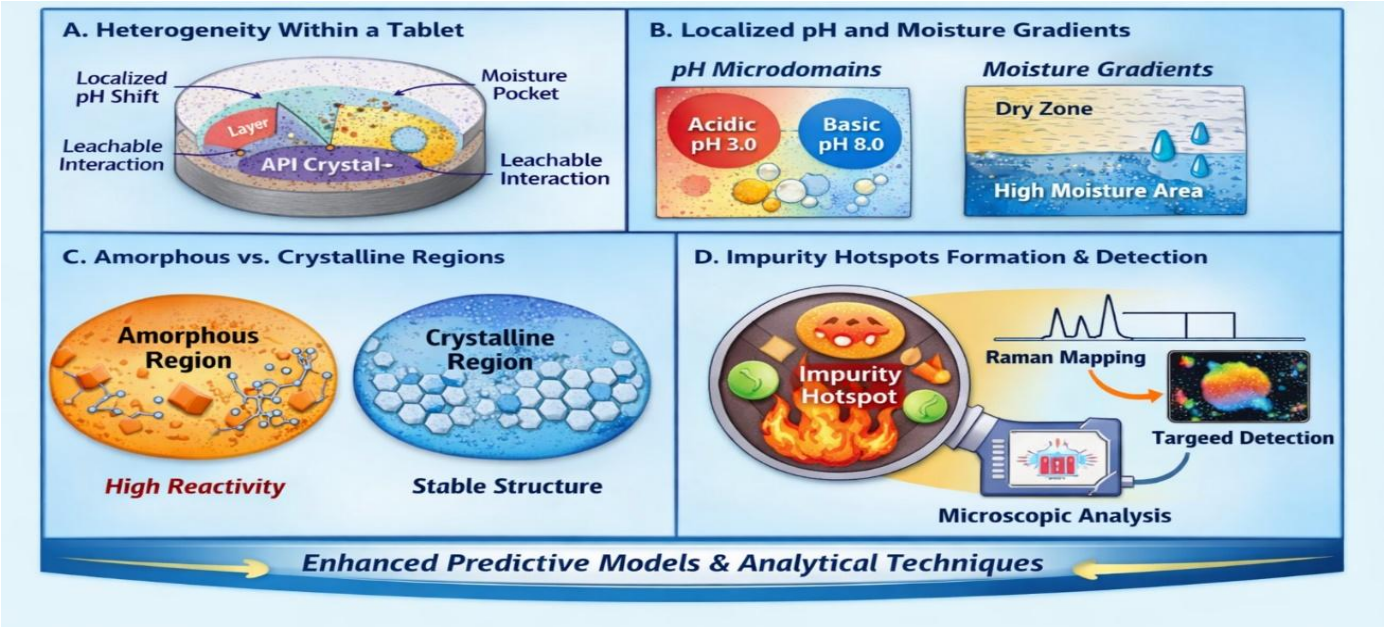

Figure 1: Microenvironmental Heterogeneity in pharmaceutical Dosage forms:

Incorporation of such spatial information into models, both mechanistic and machine-learning based, helps to build a more realistic model of the process of degradation and leads to better predictions of impurity formation and design of optimal formulations and packaging to avoid it. Thus, consideration of microenvironmental variables provides new insights into predicting pharmaceutical stability. [15]

4. Drug–Excipient–Packaging Interaction Network (Emerging Multidimensional Framework)

4.1 Interaction Pathway Complexity

Pharmaceutical product stability is now realized to be a consequence of complex interactions between the drug substance, excipients, and packaging materials rather than a result of isolated binary interactions. The triadic nature of this interaction network opens up multiple dimensions of chemistry, physics, and interfacial interactions happening concurrently. Incompatibilities between drugs and excipients are well known; however, by considering the packaging material as a participant in this interaction, additional interaction pathways to impurity generation have been recognized.

Complex interaction pathways could involve sequential/cascade mechanisms where decomposition reactions of one reactant lead to the formation of other reactive species that go on to react with another reactant in the system. For instance, oxidized excipient molecules can generate peroxides responsible for API decomposition. Furthermore, interactions between packaging and drug substance or excipients could catalyze these reactions or enhance their rates. Another important point of interaction is the interfacial region in which these complex reactions happen, especially with solid dosage forms and suspensions.[16]

4.2 Importance of Leachables and Extractables:

Impurities leached from the packaging and closure systems are another major yet overlooked contributor to reactive impurities. While extractables are substances extracted from the packaging material under stressed conditions, leachables are those that find their way into the product formulation during routine storage conditions.

The recent trend is based on a growing realization that these components are not just passive impurities but rather active participants in various chemical reactions. Plasticizers, antioxidants, and oligomers derived from polymers used in packaging can potentially serve as reactive impurities or catalysts and initiate processes like oxidation or nucleophilic attack. Additionally, there is an interaction between leachables and other excipients that lead to the production of secondary reactive impurities.

Another interesting viewpoint is treating leachables as elements of a “reactive impurity ecosystem.” The amount of leachables, their reactivity, and diffusivity characteristics have a dynamic impact on the impurity profile.[17]

4.3 Permeability of Container–Closure Systems and Its Significance

The extent to which container-closure system permits the passage of various gases such as oxygen or moisture affects the microenvironment of the pharmaceutical product greatly. Depending on their composition, materials like polymers have differential permeability to oxygen, carbon dioxide, and moisture, which could affect the kinetic degradation process.

For instance, the introduction of oxygen in drug formulation leads to oxidative degradation because certain formulations tend to react easily with peroxides or free radicals. Moreover, the introduction of moisture can affect water activity in the dosage form and lead to enhanced hydrolitic reactions. It is worth noting that permeability can change depending on factors such as temperature and age of packaging material among others.

One new phenomenon that is rarely discussed is that of combining permeability effects with micro-environmental heterogeneity. Localized moisture entry could cause degradation of certain portions of the formulation and enhance reaction rates.[18]

Table 1: Case-Based Mechanistic Insights and Emerging Predictive Models for Drug–Excipient–Packaging Interactions

Case Scenario	Key Interaction Components	Mechanistic Pathway	Observed Impact on Impurity Formation	Modeling / Predictive Approach	Key Insight	Ref
Oxidation-sensitive drug in peroxide-generating excipient system	API + peroxide-forming excipients + oxygen-permeable packaging	Peroxide formation → radical generation → API oxidation	Significant increase in oxidative impurities under storage	Kinetic modeling + oxygen diffusion models	Combined role of excipients and packaging accelerates oxidation beyond expected levels	19
Amine-containing drug with aldehyde leachables	API (amine group) + aldehyde-type leachables from packaging	Nucleophilic addition (Schiff base formation) → secondary degradation products	Formation of unexpected impurities not predicted in standard studies	Mechanistic reaction modeling + leachable diffusion simulation	Leachables act as reactive agents, not just contaminants	20
Moisture-sensitive formulation in permeable packaging	API + hygroscopic excipients + moisture-permeable container	Moisture ingress → increased water activity → hydrolysis reactions	Localized and accelerated hydrolytic degradation	Moisture diffusion + water activity modeling	Packaging permeability directly influences internal degradation kinetics	21
Multi-component formulation under real-world storage	API + excipients + packaging + environmental stressors	Cascade reactions involving oxidation, hydrolysis, and secondary interactions	Complex impurity profile with multiple degradation pathways	Systems chemistry + network-based simulation	Real-world conditions create multi-pathway degradation not captured in lab studies	22
Leachable–excipient interaction system	Packaging-derived compounds + reactive excipients	Secondary reaction between leachables and excipients → formation of reactive intermediates	Indirect impurity formation affecting API stability	Integrated AI/ML predictive models	Interaction network extends beyond API to excipient–leachable chemistry	23

5. AI-Based Predictive Modeling and Digital Twinning:

5.1 Machine Learning-Based Predictive Models for Impurity Generation

AI-based predictive modeling is a recent development that can predict impurity generation through stability analysis of massive datasets. Random forest, neural networks, and support vector machine algorithms have proven successful in identifying hidden trends among formulation factors, environmental parameters, and degradation outcomes. In contrast to traditional methods, AI-based predictive models can analyze nonlinear relationships and multivariate interactions, providing a high degree of accuracy for estimating impurity profiles across various storage conditions. Moreover, AI models can learn from past stability experiments, significantly minimizing the necessity for experimentation and speeding up drug formulation.[24]

5.2 Comparative Analysis of Data-Driven vs. Mechanistic Modeling Techniques

Pharmaceutical stability prediction techniques can be broadly categorized into two groups: data-driven and

mechanistic modeling. Data-driven approaches utilize statistical and machine learning algorithms that do not involve any understanding of the underlying chemical processes. Data-driven modeling is flexible, fast, and efficient but lacks transparency.

On the other hand, mechanistic models are founded on chemical principles and kinetics**.**

A modeling strategy that involves both data-driven and mechanistic models has become more desirable.[25]

5.3 The Theory and Applications of Digital Twins in Pharmaceutical Stability

Digital twins are relatively new in the field of pharmaceutical science. They refer to creating an exact copy of a particular pharmaceutical drug that can be used to simulate how it behaves in actual environments. The use of digital twins in stability experiments involves incorporating the formulation and processing methods of a pharmaceutical drug alongside the packaging and storage conditions in predicting the accumulation of impurities in the drug.

Digital twins can help simulate the stability of different drugs in varied storage conditions, such as temperature and humidity variations. These simulations can also be used to perform "what-if" tests on the effects of altering formulations and packaging designs.[26]

5. 4. Integration of Experimental and Computational Data

The accuracy of the AI-driven models is ensured by the seamless integration of experimental and computational data. Information obtained from the study of stability, analysis (e.g., using spectroscopy and chromatography), and physical-chemical characteristics of substances is used to train and verify the models.

Computational methods such as molecular modeling and simulation offer complementary information regarding the reaction mechanisms and molecular interactions. Together, these pieces of information enable the creation of reliable predictive models. Modern data management systems and cloud technologies provide support for data integration and model updating.[27]

6. Strengths of AI-Powered Predictive Modeling and Digital Twin Technology

1. Impurity Production Forecasting: Allows predicting degradation and impurities even when long-term stability studies have not been concluded yet.

2. Saving Time and Money: Reduces the necessity of numerous laboratory tests, thereby reducing costs and time required for developing drugs.

3. Replicating Real World Conditions: Provides precise conditions for temperature and moisture variations, and stress of the supply chain.

4. Better Predictive Accuracy: Takes into account nonlinear associations between formulation parameters and degradation modes.

5. Facilitates Risk-Based Decisions: Recognizes key parameters (CMAs/CPPs) responsible for generation of impurities.

6. Virtually Tests Scenarios: Helps perform "what-if" analyses on various formulations and packaging options.

7. Incorporation of Multiple Types of Information: Merges experimental information with analytical and computer data.

8. Better Understanding of Mechanisms: Correlates data analysis results with the underlying chemical mechanism of degradation.[28]

Table 2: Effects of Real Life Storage and Logistics Stressors on Reactive Impurity Formation:

Stress Factor	Description	Impact on Drug Stability	Typical Lab Limitation	Resulting Risk	Ref
Temperature Excursions & Cyclic Variations	Fluctuations during transport and storage (e.g., day–night changes, delays)	Accelerates degradation kinetics; may trigger new pathways	Lab studies use constant temperatures	Underestimation of impurity formation	29
Mechanical Stress (Transportation)	Vibration, shock, and handling during shipping	Causes particle rearrangement, phase separation, or coating damage	Not simulated in stability chambers	Increased degradation and dose variability	30
Light Exposure Variability	Irregular exposure to UV/visible light during handling and storage	Induces photodegradation and free radical formation	Controlled and limited light exposure in lab	Unexpected photolytic impurities	31
Climate Zone Variability	Differences in temperature and humidity across global	Alters moisture uptake, hydrolysis rate, and stability	ICH zones are generalized and static	Inaccurate prediction for specific regions	32

	regions				
Packaging Interaction Changes	Dynamic permeability changes due to environmental stress	Increased ingress of moisture/oxygen	Packaging tested under fixed conditions	Enhanced oxidative and hydrolytic degradation	33
Handling & Storage Interruptions	Delays, improper storage at pharmacies or during distribution	Exposure to uncontrolled environmental conditions	Ideal storage conditions assumed in studies	Reduced shelf-life reliability	34
Real vs. Lab Conditions Gap	Real-world involves dynamic, multi-factor stress	Synergistic effects increase degradation complexity	Lab isolates single variables	Misleading stability predictions	35

7. Smart Packaging and IoT Stability Monitoring (New Technology)

7.1 Sensor-Embedded Smart Packaging Systems

Smart packaging technology turns ordinary packaging systems into intelligent monitoring systems through embedding tiny sensors inside packaging materials. These sensors are capable of detecting key environmental factors including temperature, humidity, and light exposure. With continuous sensing capabilities, smart packaging systems offer more information about the conditions influencing stability and generation of impurities for drugs.[36]

7.2 Continuous Monitoring of Temperature and Humidity

Continuous monitoring technologies allow for real-time monitoring of environmental conditions during different stages from manufacturing to product distribution to users. Unlike stability studies based on predetermined checkpoints, continuous monitoring captures transient events, like temperature variations or sudden humidity increases, which help assess risks and potential threats to stability more accurately.[37]

7.3 Time–Temperature Indicators with Predictive Models

Time-temperature indicators (TTPs) allow one to visually see how drugs were exposed to varying temperatures over time. Recent advancements in TTPs incorporate sophisticated predictive algorithms that can generate warning signals depending on the risk of impurity generation and other adverse outcomes.[38]

7.4 IoT-Driven Monitoring of Supply Chains

IoT technology incorporation provides for smart packages to send live updates to cloud-based computing platforms. This makes way for constant monitoring, analysis, and remote supervision throughout the entire supply chain. Adaptive and intelligent packaging can provide increased visibility, traceability, and quality assurance, especially in international logistics chains with fluctuating environmental conditions.[39]

7.5 Future Prospects for Adaptive and Intelligent Packaging

Advanced packaging solutions will be heading towards innovative, adaptive, and intelligent technologies able to adapt to changing environments. This can range from smart materials capable of controlling the level of internal moisture or the release of stabilization agents under certain stimuli. Together with artificial intelligence, this can predict deterioration tendencies and regulate environmental conditions accordingly.[40]

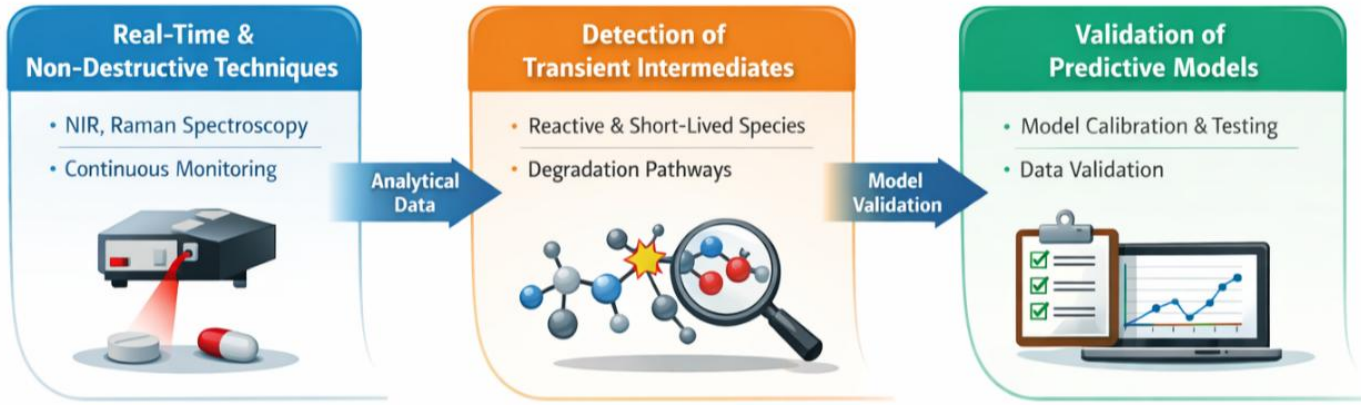

Figure 2: Role of Advanced Analytical tools in Predictive stability assessment.

8. Risk-Based Control Strategies (Next-Generation QbD)

The concept of risk-based control strategies using Quality by Design (QbD) is pivotal for handling storage-induced reactive impurities in pharmaceuticals. As opposed to conventional quality methodologies that depend on testing the final product, QbD focuses on integrating quality in the product from the very beginning through the thorough study of formulation and process-related variables.

One notable innovation in this regard is the use of predictive models alongside QbD approaches. It would be possible to integrate mechanistic models and AI-based models at the design stage to predict how impurities will form depending on varying storage environments.[41] The strategy helps detect possible impurities risks before their onset and facilitates the creation of a reliable design space where product quality will be guaranteed even in case of parameter variation.

The employment of an advanced AI-supported Failure Mode and Effects Analysis (FMEA) tool adds another dimension to risk assessment. While the traditional FMEA considers possible failure modes in terms of severity, probability, and detection, the use of AI technology allows dynamic assessment where risks change continuously in response to new data and predictions.

An equally important element of QbD involves determining and controlling CMAs and CPPs. CMAs such as the quality of excipients, particle size, water content, and polymorphism may play a significant role in impacting the degradation pathway. Understanding their effects on the formation of impurities helps formulation scientists implement appropriate solutions that mitigate potential risks. Likewise, controlling CPPs will ensure consistent product quality and stability during production.[42]

Using a lifecycle-based approach in managing impurity risks also contributes to effective control. The application of QbD in later stages of drug development such as manufacture and commercialization requires continuous analysis of data. Predicting stability risks through real-time analytics and the use of smart packaging during storage and transport is vital to the success of the process.

In summary, the application of predictive modeling techniques, AI-assisted risk assessment, and QbD principles offers a holistic strategy to the control of reactive impurities.

9. Regulatory Gaps and Issues Related to Predictive Stability

Existing regulations concerning stability testing, which rely heavily on ICH guidelines such as Q1A and Q3B, focus on empirical and time-based studies conducted under controlled circumstances. While such guidelines enable consistency, they are characterized by certain shortcomings when it comes to accommodating real-life storage scenarios and degradation behavior. The current guidelines fail to factor in variations in microenvironments and stresses during distribution processes.

There is a need for well-structured regulation that will facilitate the adoption of AI in predicting drug stability. While artificial intelligence and machine learning algorithms significantly improve predictions, regulatory guidance is inadequate in terms of implementation and validation procedures. Such ambiguity discourages the adoption of AI-based systems.[44]

The validation and acceptance of digital twins and other models also constitute another challenge. In order to comply with regulatory requirements, high levels of transparency and accountability must be guaranteed. However, many AI algorithms lack the ability to explain their reasoning process, making them difficult to audit.

However, it is equally critical to ensure global regulatory harmonization in the field.[45] The inconsistency between regional regulatory requirements may affect the application of predictive stability practices, particularly for products available in various climate regions. Such regulations will make it easier for companies to use this approach.

In order to fill the identified gaps, further development of regulatory frameworks is required. In particular, it is important to develop recommendations on the validation of AI models and encourage the development of hybrid approaches as well as apply real-world data. Predictive approaches are going to be adopted by regulators in the future.[46]

10. Future Perspectives:

Pharmaceutical stability analysis is moving towards autonomous predictive systems that learn from data collected in real-time, updating predictive models. The merging of artificial intelligence with cutting-edge analytics and smart packaging technologies ensures that prediction of impurities formed and changes in storage parameters become part of a closed loop, providing real-time quality control instead of quality check.

Predictive tools can be used alongside continuous manufacturing, allowing for process control through real-time monitoring and immediate adjustments, thus ensuring uniform product quality. Personalized medicine, on the other hand, brings about different challenges due to the necessity of producing patient-specific pharmaceuticals and small batch sizes that need individualized stability prediction.

Finally, sustainability is becoming increasingly important, with more and more green approaches emerging in drug development, such as the use of eco-friendly excipients, energy-efficient storage, and minimizing waste with the help of predictive modeling.[47]

11. Conclusion:

The present paper highlights the change from traditional studies on stability to predictive, risk-based,

and technologically advanced approaches in studying the impact of storage on the generation of reactive impurities. Some of the innovations in these approaches include incorporating mechanistic knowledge, using artificial intelligence to predict outcomes, applying digital twins, considering practical storage issues, and employing modern analytical techniques and smart packaging. With the combination of these methods within the QbD framework, a more precise approach in controlling impurity risks may be realized. In addition to enhancing the safety and efficacy of the drug products, these methods also help in closing the gap between laboratory studies and practical applications.

Conflict of Interest: The authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting this paper are available in the cited references.

Ethical approval: Not applicable.

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