INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Reducing Sugar Impurities in Pharmaceutical Excipients: Sources, Analytical Characterization and Mitigation Strategies

Prakash Deshinge*[1], Srinivasarao Vaddadi[2], Nandkumar Bhilare[3], Sureshkumar Ramdoss[4], Gautham Shenoy[5], Krishnamurthy Bhat[6]

[1,5,6] Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India
[1,3,4] Lupin Limited, Pune, Maharashtra, India
[2] SPD Analytical, Aurobindo Pharma Ltd. Hyderabad. India.
[6] School of Pharmaceutical Sciences, Manipal University, Jaipur, India.

ARTICLE INFO

Published: 11 Sept 2026
Keywords:
Reducing sugars; Maillard reaction; Drug–excipient incompatibility; Pharmaceutical excipients; Impurity profiling; Quality by Design.
DOI:
10.5281/zenodo.22705349

ABSTRACT

Background and Purpose: Reducing sugars, including glucose, fructose, lactose, and sucrose inversion products, are increasingly recognized as reactive excipient-derived impurities capable of initiating Maillard reactions with amine-containing drug substances. These interactions can compromise product stability, quality, and safety. This review consolidates current knowledge on the origins, analytical characterization, mechanistic pathways, and control strategies associated with reducing sugar impurities in pharmaceutical excipients. Methods: A narrative review of peer-reviewed literature, regulatory guidance documents, pharmacopeial publications, and industry reports was conducted. The retrieved information was critically evaluated and organized into thematic areas encompassing impurity sources, Maillard reaction mechanisms, analytical methodologies, case studies of drug–excipient incompatibility, and Quality-by-Design (QbD)-based mitigation approaches. Results: Reducing sugars may originate from carbohydrate-based excipients, residual saccharides in processed materials, manufacturing-induced degradation, and hydrolytic inversion of sucrose. Their reactions with amine-containing drug substances proceed through Schiff base formation, Amadori rearrangement, and subsequent generation of advanced degradation products. Analytical techniques such as HPLC–RID, HILIC–LC–MS, fluorescence-based detection, and LC–MS/MS provide complementary capabilities for quantification and structural characterization. Reported case studies demonstrate the impact of reducing sugars on impurity formation, discoloration, potency loss, and stability performance. Conclusion: Reducing sugar impurities represent a predictable but

***Corresponding Author:** Prakash Deshinge
Address: *Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka.*
Email ✉: prakashdeshinge@lupin.com,
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

controllable source of drug–excipient incompatibility. Implementation of risk-based analytical monitoring, informed excipient selection, process optimization, and QbD-driven control strategies can minimize Maillard-related degradation and support the development of robust pharmaceutical products with improved quality, safety, and long-term stability.

INTRODUCTION

Reducing sugars such as glucose, fructose, lactose, and hydrolysis products generated from sucrose are increasingly recognized as reactive excipient-derived impurities capable of influencing pharmaceutical product quality, stability, and safety. These carbohydrates may be inherently present in plant- or dairy-derived excipients or formed during manufacturing and storage. Their reactive carbonyl groups readily interact with amino-containing drug substances through Maillard-type reactions, resulting in degradation products that may alter assay, impurity profiles, appearance, and long-term stability.[1-6,37,43-45]

Excipient-derived reducing sugars are established contributors to drug–excipient incompatibility. Increasing evidence demonstrates that pharmaceutical excipients are not always inert and may actively participate in degradation pathways that affect drug quality and stability.[38,40] Reactive saccharides have been reported in widely used pharmaceutical excipients including lactose, cellulose derivatives, and starch-based materials.[1,2,38,41] Among these, lactose is the most extensively investigated because of its widespread use as a filler and carrier in solid dosage forms. The extent of lactose reactivity is influenced by moisture content, crystalline form, particle characteristics, processing conditions, and storage environment.[3,6,17] Manufacturing operations such as milling and compression may further accelerate solid-state Maillard reactions by increasing molecular contact and introducing crystal defects.[3] Regulatory agencies therefore emphasize risk-based evaluation of excipient quality attributes and impurity control throughout the product lifecycle.[8-13]

Reliable detection and quantification of reducing sugars are essential for excipient qualification, compatibility assessment, and impurity control. Classical colorimetric assays such as dinitrosalicylic acid (DNS) and p-hydroxybenzoic acid hydrazide (PAHBAH) provide rapid screening capabilities, whereas chromatographic and mass spectrometric techniques offer improved sensitivity, selectivity, and structural information.[18-27] Advanced approaches including HPLC–RID, HILIC–LC–MS, post-column fluorescence derivatization, and LC–MS/MS support the identification of trace-level reactive sugars and their degradation products, facilitating formulation development and root-cause investigations.[20-27]

The pharmaceutical significance of reducing sugar impurities is demonstrated by several reported cases of Maillard-mediated drug degradation. Lactose-derived adducts have been identified in levothyroxine and liothyronine formulations, requiring detailed analytical characterization and toxicological assessment.[28,29] Similar interactions between lactose and rivaroxaban have been associated with adverse effects on stability and in vitro biological activity.[30] Furthermore, non-reducing sugars such as sucrose may undergo hydrolytic inversion during processing or storage, generating glucose and fructose that subsequently participate in degradation reactions.[35,36]

As pharmaceutical products become increasingly complex, proactive identification and control of reducing sugar impurities are essential. A Quality-by-Design (QbD) approach provides a structured framework for identifying critical material attributes, understanding degradation mechanisms, selecting appropriate analytical

tools, and implementing effective control strategies.[8-15] This review summarizes the sources of reducing sugar impurities, mechanistic pathways of drug–excipient interactions, analytical approaches for their characterization, representative case studies, and QbD-based strategies for mitigating associated risks in pharmaceutical formulations.

2.0 METHODOLOGY

This review was developed through a comprehensive evaluation of published scientific literature, regulatory guidance documents, pharmacopeial references, and industry publications related to reducing sugar impurities in pharmaceutical excipients and their impact on drug product quality, stability, and drug–excipient compatibility. Literature searches were conducted using electronic databases including PubMed, ScienceDirect, and Google Scholar. Search terms included reducing sugars, Maillard reaction, drug–excipient incompatibility, reactive excipient impurities, lactose degradation, impurity profiling, pharmaceutical stability, excipient risk assessment, and Quality-by-Design (QbD).

Peer-reviewed research articles, review papers, case studies, pharmacopeial publications, and regulatory documents published in English were considered. Particular emphasis was placed on publications describing the occurrence and sources of reducing sugars, mechanisms of Maillard-type degradation, analytical approaches for detection and characterization, reported case studies of drug–excipient incompatibility, and strategies for impurity control. Regulatory and industry guidance from the International Council for Harmonisation (ICH), United States Pharmacopeia (USP), and International Pharmaceutical Excipients Council (IPEC) were also reviewed to provide current perspectives on impurity management and risk-based control approaches.[8-12]

The collected information was critically evaluated and organized into thematic sections covering sources of reducing sugar impurities, mechanistic pathways of drug–excipient interactions, analytical characterization techniques, impacts on drug stability, regulatory considerations, and Quality-by-Design (QbD)-based mitigation strategies. The objective of this review was to provide an integrated scientific and regulatory perspective on reducing sugar impurities and their significance in modern pharmaceutical formulation development.

3.0 SOURCES AND TYPES OF REDUCING SUGAR IMPURITIES IN PHARMACEUTICAL EXCIPIENTS

Reducing sugar impurities may originate from multiple sources within pharmaceutical excipients and can arise intrinsically, during processing, or through chemical transformation of non-reducing components. Understanding these sources is essential for predicting Maillard reactivity and establishing appropriate control strategies.[1,2,38]

3.1 Principal Sources of Reducing Sugars

3.1.1 Naturally Occurring Sugars in Raw Materials

Excipients derived from plant- and dairy-based sources inherently contain reducing sugars such as glucose, fructose, and lactose. Among these, lactose is one of the most significant pharmaceutical excipients, with grade-dependent variability influencing Maillard reactivity under thermal and humidity stress conditions.[2,6,17] Other excipients, including microcrystalline cellulose (MCC) and starch derivatives, may contain residual saccharides or degradation fragments

capable of participating in Maillard-type reactions and drug–excipient incompatibilities.[1,38]

Beyond solid oral dosage forms, sugar-containing excipients are widely used in protein and biopharmaceutical formulations, where excipient composition and sugar interactions significantly influence product stability and compatibility.[32]

3.1.2 Processing-Induced Formation During Manufacturing

Manufacturing operations such as drying, wet granulation, milling, compression, and continuous manufacturing processes can increase excipient reactivity or promote the generation of reducing sugars. [3,17,31] Increased surface area, crystal disruption, and localized heat generation may accelerate degradation kinetics, as demonstrated in metoclopramide hydrochloride–lactose systems.[3] Process-induced degradation of cellulose- and starch-derived excipients may also generate low-molecular-weight carbohydrates capable of participating in subsequent degradation pathways.[1,17]

3.1.3 Hydrolytic Generation Through Sucrose Inversion

Although sucrose is a non-reducing disaccharide, it can undergo hydrolysis under acidic, thermal, or high-moisture conditions to yield glucose and fructose, both of which are reducing sugars.35,36 Consequently, sucrose-containing formulations may become indirect sources of reactive carbohydrates during processing and storage. The extent of inversion depends on factors such as pH, temperature, residence time, and water activity.

3.1.4 Trace Impurities in Non-Carbohydrate Excipients

Reducing sugars may also occur as trace impurities in excipients not primarily classified as carbohydrates. Certain polymeric excipients may contain low levels of reducing sugars together with other reactive impurities such as aldehydes and peroxides.[1,2] Such impurities, even at trace concentrations, can contribute to degradation of susceptible amine-containing drug substances and increase the risk of incompatibility reactions.[1,38]

3.2 Practical Implications for Control

The diverse origins of reducing sugar impurities necessitate systematic control throughout pharmaceutical development. Appropriate excipient selection and supplier qualification are particularly important when carbohydrate-containing excipients such as lactose are used. Material specifications should include suitable controls for reducing sugar content and batch-to-batch consistency.[8,10,12]

Process design should also consider the influence of manufacturing operations such as milling, compression, drying, and granulation, since these can increase sugar reactivity and accelerate incompatibility reactions.[1,3] For formulations containing sucrose, the risk of hydrolytic inversion should be evaluated through control of pH, temperature, and moisture exposure during processing and storage.[35,36]

In addition, expanded impurity profiling may be warranted for excipients known to contain reactive impurities. A risk-based approach aligned with Quality by Design (QbD) principles can facilitate identification and mitigation of potential degradation pathways during formulation development.[11,15]

The principal sources of reducing sugar impurities encountered in pharmaceutical excipients and their potential impact on drug product stability are summarized in Table 1. These sources include inherently occurring carbohydrates, processing-

induced degradation products, hydrolytically generated sugars, and trace impurities present in non-carbohydrate excipients. Collectively, they contribute to Maillard reactivity and represent important considerations during excipient selection, compatibility assessment, and formulation development.[1-3,6,17,35,36,38]

Table 1. Sources of reducing sugar impurities and associated risks

Source	Origin/ Mechanism	Representative Examples	Potential Impact on Drug Products	Key References
Naturally occurring sugars	Intrinsic sugars present in carbohydrate-containing excipients	Lactose, glucose, fructose, residual sugars in starch derivatives	Direct participation in Maillard reactions and drug–excipient incompatibility	1, 2, 6, 17, 38
Residual saccharides in excipient raw materials	Incomplete purification of plant- or dairy-derived materials	Microcrystalline cellulose (MCC), starch derivatives	Formation of reactive impurities and reduced formulation stability	1, 2, 38
Processing-induced sugar formation	Mechanical and thermal stress during manufacturing operations	Milling, drying, granulation, compression	Increased excipient reactivity and accelerated degradation kinetics	1, 3, 17
Hydrolytic inversion of non-reducing sugars	Decomposition of sucrose under acidic, thermal, or humid conditions	Sucrose → glucose + fructose	Indirect generation of reducing sugars during processing and storage	35, 36
Trace impurities in non-carbohydrate excipients	Residual reactive species originating from manufacturing processes	Polymeric excipients, processed excipient blends	Initiation of degradation pathways even at trace concentrations	1, 2, 38
Storage-related degradation	Moisture- and temperature-induced degradation of excipients during shelf life	Lactose-containing formulations, starch-based excipients	Increased reducing sugar content and greater Maillard reactivity over time	3, 6, 17
Supplier and grade variability	Differences in excipient manufacturing processes and specifications	Various pharmaceutical lactose grades	Batch-to-batch variation in reactivity and compatibility behaviour	2, 6, 17

4.0 MECHANISTIC PATHWAYS OF REDUCING SUGAR–DRUG INTERACTIONS (MAILLARD CHEMISTRY)

Reducing sugar-induced degradation in pharmaceutical formulations is primarily governed by the Maillard reaction, a series of carbonyl–amine reactions occurring between reducing sugars and amine-containing drug substances. Typical reactants include glucose, fructose, lactose, and reducing sugars generated through sucrose hydrolysis. The reaction progresses through a sequence of condensation, rearrangement, fragmentation, and polymerization events, ultimately producing complex degradation products that may compromise drug quality, stability, and safety.[1-7,37]

4.1 Initiation: Carbonyl–Amine Condensation (Schiff Base Formation)

The reaction begins when the carbonyl group of a reducing sugar reacts with a primary or secondary amine present in the drug molecule, forming a

reversible Schiff base (imine). The rate of this reaction is influenced by factors such as pH, moisture content, water activity, and molecular mobility within the formulation matrix. In solid dosage forms containing lactose or residual saccharides, Schiff base formation often represents the earliest stage of drug–excipient incompatibility.[1,2,17,38]

4.2 Amadori Rearrangement and Formation of Early Intermediates

The initially formed Schiff base subsequently undergoes Amadori rearrangement (or Heyns rearrangement in the case of ketose sugars) to generate relatively stable ketoamine intermediates. These products are generally colorless and may accumulate during storage before undergoing further degradation. The formation and persistence of Amadori products are strongly influenced by temperature, moisture content, excipient composition, and storage conditions.[1,4,6,37]

4.3 Advanced Transformations and Formation of Reactive Intermediates

Amadori intermediates can undergo dehydration, oxidation, enolization, and fragmentation reactions, producing highly reactive species such as dicarbonyl compounds and furfural derivatives. These intermediates can further react with drug substances and excipient components to generate advanced glycation end products (AGEs), colored degradation products, and structurally complex impurities. Such reactions are frequently associated with discoloration, loss of potency, and changes in product appearance during storage.[5-7,35,37]

4.4 Influence of Formulation and Process Variables

Several formulation and manufacturing variables influence the rate and extent of Maillard degradation. Increased temperature, elevated humidity, and extended storage periods generally accelerate reaction kinetics. Mechanical processing operations such as milling and compression can further enhance reactivity by increasing surface contact and introducing crystal defects. This phenomenon has been demonstrated in metoclopramide hydrochloride–lactose systems, where processing significantly increased Maillard reaction rates.3,17

Although sucrose is classified as a non-reducing sugar, it can undergo hydrolytic inversion under acidic, thermal, or high-moisture conditions to form glucose and fructose, thereby becoming an indirect source of reducing sugars.[35-36] In addition, trace reactive impurities present in certain excipients may contribute additional carbonyl species that promote degradation reactions.[1,2]

5.0 ANALYTICAL METHODS FOR DETECTION OF REDUCING SUGAR IMPURITIES

Accurate detection and quantification of reducing sugar impurities are essential for excipient qualification, compatibility assessment, impurity profiling, and implementation of effective control strategies in accordance with ICH and USP expectations. Depending on the required sensitivity, specificity, and structural information, a variety of colorimetric, chromatographic, and mass spectrometric techniques are available for reducing sugar analysis and pharmaceutical impurity management.[9,10,20-27,33]

5.1 Classical Methods

Classical colorimetric assays remain widely used for preliminary screening because of their

simplicity, rapid analysis time, and minimal instrumentation requirements.

The dinitrosalicylic acid (DNS) method is based on reduction of DNS reagent by reducing sugars, producing a colored chromophore that can be measured spectrophotometrically.[18] Similarly, the p-hydroxybenzoic acid hydrazide (PAHBAH) method provides improved sensitivity for reducing sugar determination and is frequently used for routine laboratory analysis.[19] While these methods are suitable for rapid estimation of total reducing sugar content, they lack specificity and cannot distinguish individual carbohydrate species, limiting their utility for detailed impurity characterization.[18-19]

In early-stage compatibility studies, thermal and spectroscopic techniques such as FTIR, DSC, TGA, and XRD, together with forced degradation studies, are often employed to evaluate drug–excipient interactions and identify preliminary evidence of degradation.[14,16,34]

5.2 Chromatographic Methods

5.2.1 High-Performance Liquid Chromatography with Refractive Index Detection (HPLC–RID)

HPLC coupled with refractive index detection (HPLC–RID) is one of the most commonly used techniques for routine carbohydrate analysis. Validated methods enable simultaneous quantification of glucose, fructose, sucrose, and lactose with acceptable precision and accuracy, making this approach suitable for excipient qualification and stability studies.[20]

A limitation of HPLC–RID is its relatively low sensitivity and incompatibility with gradient elution, restricting its application for trace-level impurity analysis.

5.2.2 Specialized Carbohydrate Columns

Ligand-exchange and other carbohydrate-specific stationary phases provide improved separation of mono- and disaccharides through selective carbohydrate–metal interactions. These approaches are commonly employed for pharmaceutical and food-grade sugar analyses and offer superior selectivity compared with conventional chromatographic systems. [20]

5.2.3 Hydrophilic Interaction Chromatography–Mass Spectrometry (HILIC–LC–MS)

Hydrophilic interaction liquid chromatography (HILIC) is particularly suitable for highly polar analytes such as carbohydrates. When coupled with mass spectrometry, HILIC–LC–MS provides excellent sensitivity, selectivity, and structural confirmation. Studies have demonstrated its utility for reliable quantification and profiling of carbohydrates in complex matrices, including pharmaceutical excipients.[21,22]

Because of its high sensitivity and compatibility with trace-level analysis, HILIC–LC–MS is increasingly used for impurity profiling and excipient characterization.

5.3 Fluorescence-Based Detection Methods

Post-column derivatization techniques can significantly improve analytical sensitivity. The fluorometric method developed by Mikami and Ishida uses post-column reaction with arginine to generate fluorescent derivatives of reducing sugars, allowing highly sensitive detection of low-level impurities.[23]

These approaches remain useful when very low concentrations of reducing sugars must be detected and quantified, particularly during excipient screening and degradation studies.

5.4 Industry-Oriented Impurity Profiling Approaches

Modern pharmaceutical development increasingly relies on integrated impurity profiling strategies combining chromatographic, spectroscopic, and mass spectrometric techniques. Such approaches allow simultaneous assessment of reducing sugars and other reactive excipient impurities, including aldehydes, peroxides, and degradation products.[1,2,27]

5.5 Mass Spectrometry for Structural Characterization

When reducing sugars contribute directly to drug degradation, mass spectrometric techniques become indispensable. LC–MS/MS provides molecular-weight information, fragmentation patterns, and structural confirmation of degradation products and drug–excipient adducts.[25-27]

These tools have played a key role in identifying lactose-derived degradation products in pharmaceutical formulations. Advanced LC–MS and HRMS workflows have successfully characterized levothyroxine–lactose adducts and provided insights into the mechanisms of Maillard-type degradation.[24,28,29] More recently, similar strategies have been applied to investigate rivaroxaban–lactose interaction products and other drug–excipient incompatibility systems.[30]

Recent advances in high-resolution mass spectrometry (HRMS) have further enhanced the ability to detect and identify unknown impurities with high confidence, even in highly complex matrices.[24-26]

5.6 Method Selection Considerations

The choice of analytical method should be aligned with the intended application:

Table 2. Selection of analytical techniques based on sensitivity, specificity, and application for reducing sugar impurity analysis

Analytical Need	Recommended Technique	References
Bulk quantification of reducing sugars	DNS, PAHBAH, HPLC–RID	18,19,20
Multi-sugar separation in excipients	Hi-Plex, ligand-exchange chromatography	20
Trace-level detection with high specificity	HILIC–LC–MS	21,22
High-sensitivity screening	Post-column fluorescence (arginine/borate)	23
Structural confirmation of degradants	LC–MS/MS	24-27, 29

For routine quality control, chromatographic techniques are generally preferred, whereas LC–MS and HRMS are more appropriate when structural characterization of unknown impurities or drug–excipient adducts is required. Method selection should ultimately be driven by the analytical objective, required sensitivity, and matrix complexity.[9,20-27]

6.0 IMPACT OF REDUCING SUGAR IMPURITIES ON DRUG STABILITY (CASE STUDIES)

Reducing sugar impurities can significantly affect drug product quality through drug–excipient adduct formation, potency loss, discoloration, and generation of complex impurity profiles that complicate analytical control and regulatory qualification.[1,38,44] The following case studies illustrate the impact of reducing sugar-mediated degradation across different APIs, excipient classes, and processing conditions.

6.1 Levothyroxine and Thyroid Hormone Products: Lactose-Derived Maillard Adducts

Levothyroxine formulations represent one of the most extensively documented examples of Maillard-type drug–excipient incompatibility. Lactose-derived adducts formed between levothyroxine and lactose under thermal stress have been identified and structurally characterized as previously unknown impurities, highlighting the clinical and regulatory significance of excipient-mediated degradation.[24,28,29] These degradants may adversely affect product quality, stability, and potentially patient safety, necessitating detailed analytical and toxicological evaluation.[24,28] In pharmaceutical products, such interactions may manifest as impurity growth, discoloration, and assay reduction, particularly under elevated moisture and temperature conditions or when highly reactive lactose grades are employed.[2,4,6] This case underscores the importance of selecting low-reactivity lactose grades, establishing robust supplier qualification programs, controlling environmental conditions during manufacturing and storage, and considering alternative excipients or less reactive API salt forms when appropriate.[2,4,29]

6.2 Metoclopramide Hydrochloride–Lactose System: Processing-Induced Acceleration

The effect of pharmaceutical processing on Maillard degradation is well illustrated by metoclopramide hydrochloride–lactose formulations, where milling and compression accelerate degradation by increasing surface area, generating crystal defects, and enhancing molecular contact between the API and lactose.[3] These changes facilitate Schiff base formation and subsequent Maillard reaction pathways, leading to increased impurity levels and discoloration compared with storage-induced degradation alone.[3,17] The findings highlight the importance of controlling milling intensity and compression force as critical process parameters, incorporating these variables into the QbD design space, and supporting formulation and process development through stress testing and accelerated stability studies.[3,11,15]

6.3 Amine-Containing APIs Formulated with Carbohydrate-Based Excipients

Primary and secondary amine-containing APIs are particularly susceptible to Maillard reactions when formulated with lactose, starch derivatives, or other carbohydrate-containing excipients.[1,2,38] Such interactions may lead to potency loss, discoloration, and the formation of unknown impurities requiring extensive analytical characterization.[1,14,38] Beyond lactose, residual saccharides present in cellulose- and starch-based excipients can also contribute to degradation, particularly under elevated humidity and storage stress conditions.[1,2] These findings highlight the importance of early API–excipient compatibility screening, evaluation of excipients for trace reducing sugars, and selection of alternative excipients when incompatibility risks are identified.[1,15,38]

6.4 Sucrose-Containing Formulations: Indirect Sources of Reducing Sugars

Although sucrose is a non-reducing sugar, it can undergo hydrolytic inversion to glucose and fructose under acidic, thermal, or high-moisture conditions, thereby generating reactive reducing sugars capable of participating in Maillard degradation.[35,36] Consequently, formulations initially considered at low risk may become susceptible to impurity formation and discoloration during processing or storage.[35] These observations emphasize the importance of controlling pH, temperature, and moisture during manufacturing, assessing the potential for sucrose inversion during stability studies, and employing

stress testing to identify latent degradation pathways.[35,36]

6.6 Summary of Representative Impacts and Controls

Table 3. Representative case studies illustrating the impact of reducing sugar impurities on drug stability and corresponding control strategies.

Case/System	Observed Impact	Primary Driver(s)	Illustrative Controls
Levothyroxine + lactose	Adduct formation, impurity growth, toxicity concerns	Intrinsic lactose sugars; humidity/temperature	Lactose grade selection, moisture control, alternative excipient, salt form [2,4,24,28,29]
Metoclopramide HCl + lactose	Accelerated degradation, discoloration	Milling/compression energy	Process optimization, controlled RH, drying [3,11,15]
Amine APIs + MCC/starch	Potency loss, unknown impurities	Trace sugars; humidity	Excipient screening, alternative materials, salt forms[1,14,15,38]
Sucrose-containing systems	Browning, new impurities	Inversion to glucose/fructose	pH/temperature control, moisture limits [35,36]
Polymeric excipients (PVP/cPVP)	Multi-impurity pathways	Trace sugars + aldehydes/peroxides	Reactive impurity testing, supplier control [1,2,8,12]

7. QBD-BASED MITIGATION AND CONTROL STRATEGIES

A Quality by Design (QbD) framework provides a systematic, science- and risk-based approach for minimizing Maillard-driven degradation by controlling reducing sugar availability, API reactivity, and process and storage conditions. This strategy integrates risk assessment, analytical characterization, design space development, and lifecycle monitoring in alignment with ICH Q3B(R2), ICH Q2(R2), USP <1086>, and IPEC guidance.[8-12]

7.1 QbD Framework and Risk Assessment

Within the QbD paradigm, risks associated with reducing sugar impurities are managed through the interaction of critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs). Relevant CQAs include assay, impurity profile, appearance, color, and potential toxicological burden.[8, 24-29]

Key CMAs include reducing sugar content and speciation, lactose grade variability, residual saccharides in cellulose- and starch-based excipients, moisture content, and the presence of reactive impurities in polymeric excipients. [1,2,28,29,38] Critical process parameters include granulation moisture, drying conditions, milling energy, compression force, dwell time, and packaging barrier performance.[3,8-10]

Major risk indicators include: Presence of primary or secondary amine-containing APIs, Use of lactose, starch derivatives, or sucrose-containing excipients, Elevated temperature and humidity exposure, Historical evidence of discoloration or impurity growth, Use of excipients known to contain reactive impurities.[1-4]

7.2 Material-Level Controls

Effective mitigation begins with excipient selection and qualification. Preference should be given to low-reactivity excipient grades with well-defined specifications and demonstrated lot-to-lot consistency.[2,8,10,12]

For carbohydrate-containing excipients, routine monitoring of reducing sugars using HPLC–RID or HILIC–LC–MS is recommended, particularly when formulating amine-containing APIs.[20-22]

Polymeric excipients such as povidone and copovidone should be evaluated not only for compendial compliance but also for reactive impurities including reducing sugars, aldehydes, and peroxides because of their potential contribution to degradation pathways.[1,2,38]

For sucrose-containing formulations, controls should be established to minimize hydrolytic inversion to glucose and fructose through appropriate management of pH, temperature, and moisture conditions.[35,36]

7.3 Process-Level Controls

Process design plays a critical role in controlling Maillard reactivity. Moisture and temperature are among the most important variables because increased water activity enhances molecular mobility and accelerates reaction kinetics.[3,8-10]

Mechanical processing operations such as milling, compression, and other stress-intensive manufacturing processes can accelerate degradation by increasing surface area, inducing crystal defects, and generating localized heat.[3,42] The metoclopramide hydrochloride–lactose system demonstrates the importance of controlling these variables during development and scale-up.[3]

Accordingly, CPPs such as: Granulation moisture, Drying temperature and time, Milling intensity, Compression force, Dwell time should be incorporated into the design space and evaluated during process development.[3,11,15]

Microenvironmental pH should also be considered since amine ionization can influence nucleophilicity and thus reaction susceptibility.[1,4]

7.4 API-Centered Risk Mitigation

API structural characteristics significantly influence susceptibility to Maillard degradation. APIs containing primary amines, secondary amines, hydrazides, or other nucleophilic functional groups are generally at higher risk.[1,4]

Appropriate salt selection may reduce nucleophilicity by protonating reactive amine groups and thereby suppressing Schiff base formation. Consequently, evaluation of alternative salt forms during preformulation development is recommended for high-risk molecules.[1,4,38]

Binary API–excipient compatibility studies conducted under accelerated conditions should be routinely employed to identify potential incompatibilities before formulation optimization.[1,3,15]

7.5 Analytical Control Strategy

An effective analytical control strategy is essential for implementation of QbD principles.

Initial screening and quantification of reducing sugars may be achieved using: DNS assay, PAHBAH assay, HPLC–RID.[18-20]

For trace-level analysis and impurity profiling, HILIC–LC–MS provides greater sensitivity and specificity.[21,22]

Post-column fluorescence methods offer highly sensitive detection of reducing sugars and are useful for lot-to-lot comparison of excipients.[23]

When degradation products or drug–sugar adducts are formed, LC–MS/MS and HRMS become indispensable for structural characterization and impurity profiling.[24-29]

All analytical procedures should be validated according to ICH Q2(R2) with appropriate evaluation of specificity, accuracy, precision, linearity, and robustness.[9] Impurity limits and

reporting thresholds should remain aligned with ICH Q3B(R2).[8]

7.6 Packaging and Storage Controls

Because Maillard reactions are strongly influenced by moisture, packaging selection is an important component of the overall control strategy. High-barrier packaging systems such as alu–alu blisters or HDPE containers with desiccants help minimize moisture ingress and reduce molecular mobility.[8-10]

Storage conditions should be established based on stability data and should specifically address: Temperature limits, Humidity limits, Moisture-sensitive handling requirements

For formulations susceptible to oxidative degradation, oxygen-control measures such as nitrogen purging or low-oxygen packaging environments may provide additional protection.[28-29]

7.7 Risk-Based Control Matrix

Table 4. Risk-based control matrix linking key drivers of reducing sugar reactivity with mitigation strategies and analytical confirmation approaches.

Risk Driver	Primary Control	Analytical Confirmation	Outcome
Lactose variability	Grade selection, supplier control	HPLC–RID / HILIC–MS	Reduced Maillard risk [2,20-22]
Milling/compression	Limit energy, optimize parameters	Stress testing, LC–MS	Slower impurity growth [3,24-27]
Moisture exposure	Controlled drying, low RH handling	KF, water activity	Reduced reactivity [8-10]
Sucrose inversion	pH/temp control	Sugar assays, HILIC–MS	Prevent hidden sugars [20-22,35,36]
Polymeric impurities	Reactive impurity screening	Fluorescence, HILIC–MS	Controlled trace impurities [1,2,38]
API nucleophilicity	Salt selection, buffering	Compatibility studies	Reduced reaction initiation [1,4,38]

7.8 Current Challenges and Future Perspectives

Although the mechanisms of Maillard-driven degradation are well understood, implementation of consistent control strategies remains challenging. One major limitation is the lack of harmonized pharmacopeial specifications for reducing sugar content in many excipients, leading to variability in supplier qualification and risk assessment approaches.

Another challenge involves characterization of trace-level reactive impurities. Traditional methods provide useful quantitative information but often lack the sensitivity and specificity necessary for identification of individual sugar species and their degradation potential. Consequently, advanced analytical techniques such as HILIC–LC–MS, LC–MS/MS, and HRMS are increasingly required for comprehensive impurity profiling.[21-27]

Future developments are likely to involve increased use of predictive modeling, artificial intelligence, and data-driven risk assessment tools to identify high-risk API–excipient combinations early in development. Integration of such approaches with QbD principles may enhance design-space development, reduce late-stage stability failures, and support more robust pharmaceutical formulations.

In parallel, regulatory expectations are expected to evolve toward more comprehensive characterization and lifecycle monitoring of reactive excipient impurities, particularly for products containing highly reactive amine-functional APIs.

7.10 Summary

A Quality by Design (QbD)-based approach provides a systematic framework for controlling reducing sugar–mediated degradation throughout the pharmaceutical product lifecycle. Effective mitigation relies on the integration of robust excipient selection and qualification practices, process designs that minimize exposure to moisture, heat, and mechanical stress, and API-centered strategies such as salt selection and compatibility assessment. In addition, implementation of fit-for-purpose analytical methods validated in accordance with ICH Q2(R2) and supported by impurity control principles outlined in ICH Q3B(R2) enables reliable monitoring of reducing sugars, degradation products, and drug–excipient interactions. Collectively, these measures reduce the risk of Maillard-driven degradation, minimize the formation of unknown impurities, and support the development of pharmaceutical products with improved quality, safety, and long-term stability.[1-4,8-15,18-30,38]

8. CONCLUSION

Reducing sugar impurities, whether inherently present in excipients, generated during manufacturing processes, or formed through sucrose inversion, represent important contributors to drug–excipient incompatibility and Maillard-driven degradation in pharmaceutical products.[1-6,35-38] These reactions progress through a series of carbonyl–amine transformations, ultimately leading to impurity formation, discoloration, potency loss, and, in certain cases, the generation of toxicologically relevant degradation products. Studies involving levothyroxine and other amine-containing drug substances have demonstrated the practical significance of these pathways and highlighted the need for proactive control of reducing sugar–related risks.[3,24,28-30]

Effective management of reducing sugar impurities requires the application of appropriate analytical techniques for their detection, quantification, and structural characterization. While classical colorimetric and chromatographic methods remain valuable for routine analysis, advanced techniques such as HILIC–LC–MS, LC–MS/MS, and HRMS provide enhanced sensitivity and enable detailed characterization of degradation products and drug–excipient adducts[18-27]

A Quality by Design (QbD)-based approach offers a comprehensive framework for mitigating Maillard-related degradation through informed excipient selection, robust supplier qualification, optimized process design, suitable packaging and storage controls, and implementation of validated analytical procedures. Integration of these strategies with regulatory expectations outlined in ICH Q2(R2), ICH Q3B(R2), USP, and IPEC guidance can significantly reduce the risk of impurity formation while supporting long-term product quality, safety, and stability.[8-12] Ultimately, proactive management of reducing sugar impurities should be considered an essential component of modern pharmaceutical development, particularly for formulations containing amine-functional drug substances.[1,2,11,15,38]

CONFLICT OF INTEREST: The authors have no conflicts of interest regarding this investigation.

ACKNOWLEDGMENTS:

The authors would like to acknowledge Lupin Limited, Pune, for providing the necessary research facilities and support. The authors also thank Manipal Academy of Higher Education, Manipal, for academic guidance and support during the course of this research.

REFERENCES

1. Wu Y, Levons JK, Narang AS, Raghavan K, Rao VM. Reactive impurities in excipients: Profiling, identification and mitigation of drug–excipient incompatibility. AAPS PharmSciTech. 2011;12(4):1248–1263.
2. Wu Y, Levons JK, Narang AS, Raghavan K, Mantri RV. Reactive impurities in excipients. In: Katdare A, Chaubal M, editors. Excipient Applications in Formulation Design and Drug Delivery. New York: Springer; 2015. p. 37–66.
3. Qiu Z, Stowell JG, Morris KR, Hayes D, Chowhan ZT. Effect of milling and compression on the solid-state Maillard reaction between metoclopramide hydrochloride and lactose. J Pharm Sci. 2005;94(11):2568–2580.
4. Chowdhury DK, Sarker H, Schwartz P. Regulatory notes on impact of excipients on drug products and the Maillard reaction. AAPS PharmSciTech. 2018;19(2):965–969.
5. Khoder M, Gbormoi HK Sr, Ryan A, Karam A, Alany RG. Potential use of the Maillard reaction for pharmaceutical applications. Pharmaceutics. 2019;11(2):83.
6. Xiang J, Chen S, Tan S. A comprehensive review of the Maillard reaction in solid pharmaceutical dosage forms: A focus on lactose. Expert Opin Drug Deliv. 2026. doi:10.1080/17425247.2026.2613921.
7. El Hosry L, Elias V, Chamoun V, Halawi M, Cayot P, Nehme A, et al. Maillard reaction: Mechanism, influencing parameters, advantages, disadvantages, and food industrial applications: A review. Foods. 2025;14(11):1881.
8. ICH Q3B(R2). Impurities in New Drug Products. International Council for Harmonisation; 2006.
9. ICH Q2(R2). Validation of Analytical Procedures. International Council for Harmonisation; 2024.
10. United States Pharmacopeia. General Chapter <1086>: Impurities in Drug Substances and Drug Products. USP-NF.
11. Yang S, Hu X, Zhu J, Zheng B, Bi W, Wang X, et al. Aspects and implementation of pharmaceutical Quality by Design from conceptual frameworks to industrial applications. Pharmaceutics. 2025;17(5):623.
12. IPEC Federation. Risk Assessment Guide for Pharmaceutical Excipients. 2025.
13. Mali A, Kuvar V, Bharadwaj S. Bridging the gap: A comparative investigation of pharmaceutical excipient regulations. Ther Innov Regul Sci. 2024;58(2):258–272.
14. Hotha K, Roychowdhury S, Subramanian V. Drug–excipient interactions: Characterization and evaluation. Am J Anal Chem. 2016;7:107–140.
15. Matharu AS, Dhareshwar SS, Cao YJ. A Rapid 3-Day Excipient Screening Methodology and its Application in Identifying Chemical Stabilizers for Solid Formulations with Mixed Mechanisms of Degradation. AAPS PharmSciTech. 2024;25(1):12. doi:10.1208/s12249-023-02730-5.
16. Daware S, Baiwar S, Warokar A, Somani K, Waghmare S, Agrawal S. Structural and functional characterization of drug–excipient compatibility using FTIR, DSC, XRD and TGA. Res J Pharm Technol. 2025.
17. Flemming A, Picker-Freyer KM. Compaction of lactose drug mixtures: quantification of the extent of incompatibility by FT-Raman spectroscopy. Eur J Pharm Biopharm. 2008;68(3):802–810.
18. Miller GL. Use of dinitrosalicylic acid reagent for determination of reducing sugar. Anal Chem. 1959;31:426–428.
19. Lever M. A new reaction for colorimetric determination of carbohydrates. Anal Biochem. 1972;47:273–279.

20. Tiwari M, Mhatre S, Vyas T, Bapna A, Raghavan G. A validated HPLC-RID method for quantification and optimization of total sugars: fructose, glucose, sucrose, and lactose in eggless mayonnaise. Separations. 2023;10(3):199. doi:10.3390/separations10030199.
21. Pismennõi D, Kiritsenko V, Marhivka J, Kütt ML, Vilu R. Development and optimisation of HILIC–LC–MS method for determination of carbohydrates. Molecules. 2021;26(12):3669.
22. Meyer M, Montero L, Meckelmann SW, Schmitz OJ. Comparative study for analysis of carbohydrates in biological samples. Anal Bioanal Chem. 2022;414(6):2117–2130. doi:10.1007/s00216-021-03845-z.
23. Mikami H, Ishida Y. Post-column fluorometric detection of reducing sugars in high performance liquid chromatography using arginine. Bunseki Kagaku. 1983;32(6):E207–E210. doi:10.2116/bunsekikagaku.32.6_E207.
24. Chmelařová H, Catapano MC, Garrigues JC, Švec F, Nováková L. Advancing drug safety and mitigating health concerns: High-resolution mass spectrometry in the levothyroxine case study. J Pharm Anal. 2024;14(9):100970. doi:10.1016/j.jpha.2024.100970.
25. Cai H, Xing X, Su YS, Yang C. Innovative applications and future perspectives of chromatography–mass spectrometry in drug research. Front Pharmacol. 2025;16:1529468. doi:10.3389/fphar.2025.1529468.
26. Kulkarni SV, Panchgalle SP, Deosarkar SD, More VS. Advanced LC-MS/HRMS strategies and relative response factor approaches for impurity profiling of asthma inhalation drugs: A critical review. Asian J Chem. 2026;38(5):1105–1116. doi:10.14233/ajchem.2026.35730.
27. Jahani M, Fazly Bazzaz BS, Akaberi M, Rajabi O, Hadizadeh F. Recent progresses in analytical perspectives of degradation studies and impurity profiling in pharmaceutical development: An updated review. Crit Rev Anal Chem. 2023;53(5):1094–1115.
28. Agarwal A, Asif M, Deshmukh R, Vinchurkar M, Singana SB, Bhondave P. Preclinical toxicological assessment of levothyroxine and liothyronine Maillard impurities. Toxicol Res. 2022;11(5):743–749.
29. Ünlü TB, Halamoğlu Z, Kıvanç B, Uz Gökalp M. Detection and characterization of an unknown impurity in levothyroxine sodium tablets by UHPLC, LC/MS, MS/MS and MS/MS/MS. Glob J Pharm Pharm Sci. 2021;9(3):555763. doi:10.19080/GJPPS.2021.09.555763.
30. Bachchhao K, Goswami A, Patil C, Patil D. Investigation of Maillard-type drug–excipient interaction between rivaroxaban and lactose: Implications for stability and in vitro anticoagulant activity. Fabad J Pharm Sci. 2026;51(1):147–162.
31. Janssen PHM, Fathollahi S, Dickhoff BHJ, Frijlink HW. Critical review on the role of excipient properties in pharmaceutical powder-to-tablet continuous manufacturing. Expert Opin Drug Deliv. 2024;21(7):1069–1079.
32. Muntu CM, Avanti C, Hayun H, Surini S. Impact of excipients blending on sugar-stabilized therapeutic proteins. J Med Chem Sci. 2024;7(6):777–799. doi:10.26655/JMCHEMSCI.2024.6.2.
33. Singh D, Isharani R. A detailed review on analytical methods to manage the impurities in drug substances. Open Access Libr J. 2023;10:e10223. doi:10.4236/oalib.1110223.
34. Blessy M, Patel RD, Prajapati PN, Agrawal YK. Development of forced degradation and stability indicating studies of drugs—A review. J Pharm Anal. 2014;4(3):159–165. doi:10.1016/j.jpha.2013.09.003.
35. Wu QW, Yang CC, Zhang RZ. Inhibition strategies on the formation of Maillard reaction products in food. Front Nutr. 2023;10:1162097.
36. USP. Review of PDG monographs—Sucrose and Lactose Impurity Revisions. United States Pharmacopeia; 2020.
37. Xiang J, Liu F, Wang B, Chen L, Liu W, Tan S. A literature review on Maillard reaction based on milk proteins and carbohydrates in

food and pharmaceutical products: advantages, disadvantages, and avoidance strategies. Foods. 2021;10(9):1998.
38. Bharate SS, Bharate SB, Bajaj AN. Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. J Excipients Food Chem. 2010;1(3):3–26.
39. Dave VS, Haware RV, Sangave NA, Sayles M, Popielarczyk M. Drug–excipient compatibility studies in formulation development: current trends and techniques. AAPS Formulation Design and Development Section Newsletter. 2015:9–15.
40. Silva DA, Davies NM, Löbenberg R. Are excipients inert? Phenytoin pharmaceutical investigations with new incompatibility insights. J Pharm Pharm Sci. 2018;21:414–428.
41. Akers MJ. Excipient–drug interactions in parenteral formulations. J Pharm Sci. 2002;91(11):2283–2300.
42. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar Battu S, et al. Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm. 2007;33(9):909–926.
43. Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of Pharmaceutical Excipients. 9th ed. London: Pharmaceutical Press; 2020.
44. Carstensen JT, Rhodes CT. Drug Stability: Principles and Practices. 3rd ed. New York: Marcel Dekker; 2000.
45. Waterman KC, Adami RC. Accelerated aging: prediction of chemical stability of pharmaceuticals. Int J Pharm. 2005;293(1–2):101–125.

HOW TO CITE: Prakash Deshinge, Srinivasarao Vaddadi, Nandkumar Bhilare, Sureshkumar Ramdoss, Gautham Shenoy, Krishnamurthy Bhat, Reducing Sugar Impurities in Pharmaceutical Excipients: Sources, Analytical Characterization and Mitigation Strategies, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 1274-1289. https://doi.org/10.5281/zenodo.22705349