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Beyond Organic Synthesis: Impurity, Oxidative, and Solid-State Challenges in Pharmacopoeial-Grade Droperidol API Development

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Abstract

The development of robust manufacturing processes for active pharmaceutical ingredients (APIs) requires considerably more than the successful execution of the target organic synthesis. In practice, reaction selectivity, competing transformation pathways, impurity formation, product isolation, and solid-state behavior are often tightly interconnected, ultimately determining whether pharmacopoeial-quality material can be consistently obtained. Despite their critical importance, these relationships are rarely discussed in the open literature because industrial process development is typically protected by proprietary know-how.

Droperidol represents an instructive model system for studying these challenges. Although its molecular structure appears synthetically straightforward, the preparation of pharmacopoeial-grade API is complicated by a series of coupled process phenomena, including competitive reagent consumption,

structurally related impurities affecting downstream isolation, oxidative degradation during processing, and the influence of solvent selection on the final solid form.

In this work, these process vulnerabilities are examined through representative reaction pathways, while the corresponding pharmacopoeial impurities (Imp-C, Imp-D, and Imp-E) are prepared in analytically pure form to serve as mechanistic models and reference standards. Their structures were confirmed by NMR spectroscopy, mass spectrometry, HPLC, and LC–MS. Rather than presenting impurity synthesis as an isolated objective, the study demonstrates how the controlled preparation and characterization of representative impurities can support mechanistic understanding and impurity-control strategies during pharmaceutical process development.

Using droperidol as a case study, the work highlights how reaction chemistry, impurity formation, isolation, and solid-state considerations jointly influence the consistent manufacture of pharmacopoeial-grade API material.

Keywords Pharmaceutical process development · API manufacturing · Process-related impurities · Impurity control · Solid-state behavior · Case study · Reference standards · Droperidol

1. Introduction

The development of robust pharmaceutical manufacturing processes often becomes challenging even for structurally simple APIs because reaction chemistry, impurity formation, isolation, and solid-state behavior are tightly interconnected. As a result, successful pharmaceutical development under Quality-by-Design (QbD) principles requires more than optimizing the synthetic transformation itself [1, 2]. It also demands a mechanistic understanding of impurity formation, degradation pathways, and solid-state properties that ultimately define critical quality attributes.

Droperidol is a well-established butyrophenone drug substance used in antiemetic and neuroleptanalgesic formulations [3]. Since its introduction by Janssen Pharmaceutica in the early 1960s

[4, 5], droperidol has become an important pharmaceutical substance, with its physicochemical properties, pharmacological activity, and synthetic routes being extensively investigated [6]. Despite its simple molecular architecture and long history of clinical use [7], several aspects of its pharmaceutical process chemistry remain insufficiently described in the open literature.

Although the molecular structure of droperidol appears relatively simple, its pharmaceutical development poses several challenges. In addition to impurity control, robust API manufacture requires careful management of competing reaction pathways, product isolation, oxidative stability, and solid-state behavior (Figure 1). These aspects are of particular interest because they are frequently encountered during industrial process development but are rarely discussed together in the open literature.

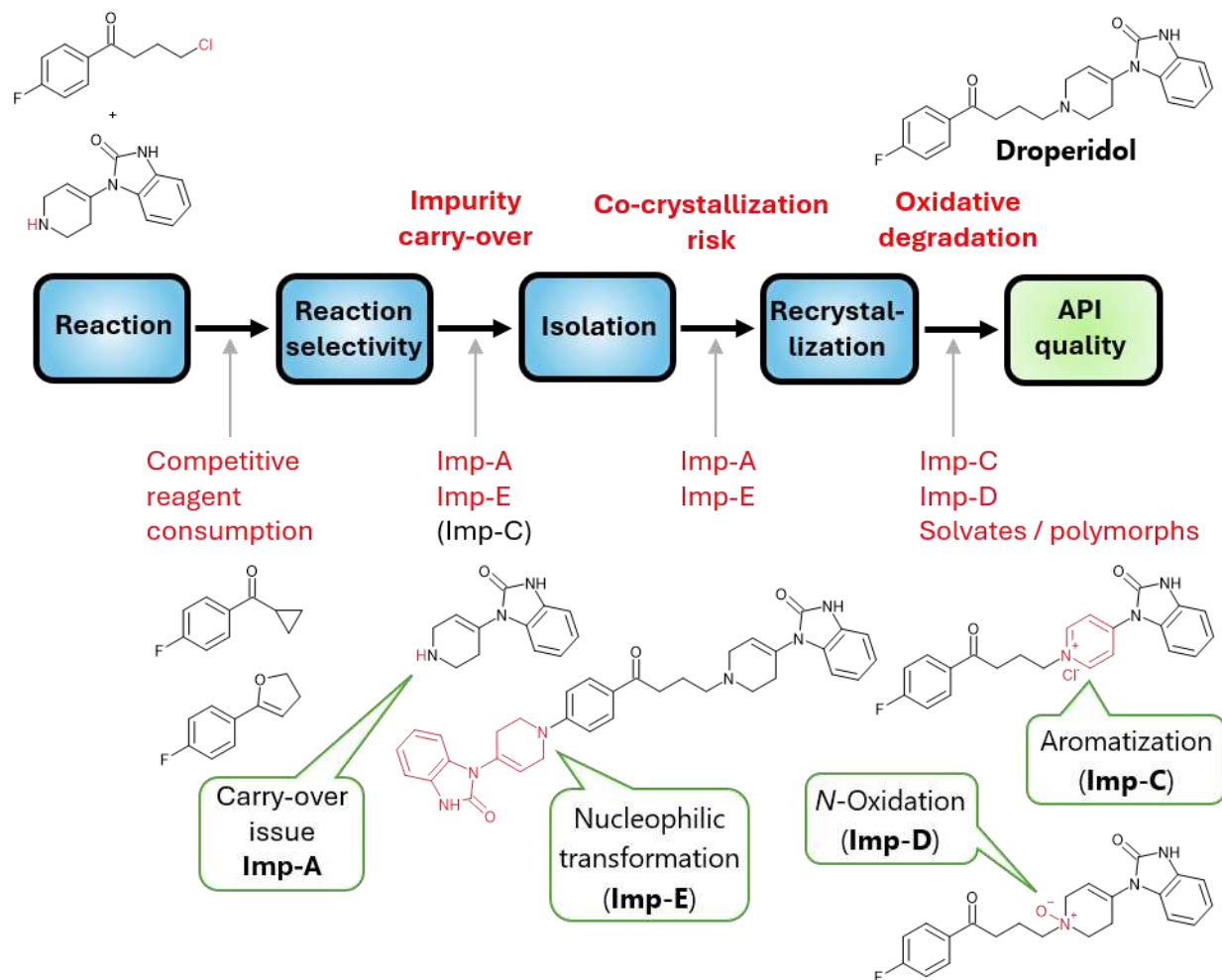


Figure 1. Interrelationship between reaction chemistry, impurity formation, solid-state behavior, and pharmaceutical process development during the manufacture of pharmacopoeial-grade droperidol API.

Several structurally related compounds are recognized in the European Pharmacopoeia as specified impurities of droperidol (Imp-A–E) [8]. These impurities arise from distinct process-related pathways, including residual synthetic intermediates, competitive side reactions, oxidative degradation, and nucleophilic transformation reactions. Consequently, their reliable identification and characterization are important not only for regulatory compliance, but also for understanding pharmaceutical process development. Beyond serving as analytical reference materials, well-characterized impurities can function as mechanistic models that facilitate the investigation of impurity formation pathways, process robustness, and downstream manufacturability.

During pharmaceutical process development, it became evident that structurally related impurities may exhibit a tendency to co-crystallize with droperidol, making their removal by conventional purification procedures considerably more difficult than expected. Consequently, minimizing impurity formation rather than relying solely on downstream purification represents a key aspect of robust droperidol API manufacturing. In addition to impurity carry-over and co-crystallization phenomena, recent investigations have demonstrated that droperidol exhibits complex solid-state behavior and forms numerous polymorphic and solvated crystal structures, further emphasizing the critical role of solvent selection during pharmaceutical development. These observations indicate that crystallization is not merely an isolation step but an integral component of process design [9, 10].

Taken together, these considerations position droperidol as an instructive pharmaceutical process development case study that illustrates how reaction chemistry, impurity control, isolation strategy, and solid-state behavior collectively determine API quality. The present work therefore examines representative pharmacopoeial impurities not as isolated analytical entities, but as mechanistic models that facilitate understanding of the interconnected process phenomena governing the manufacture of pharmacopoeial-grade droperidol API.

Accordingly, the objective of the present study was to investigate the interrelationship between reaction chemistry, impurity formation, downstream isolation, and solid-state behavior during droperidol API development through the controlled preparation and comprehensive characterization of representative pharmacopoeial impurities. The work is intended as a pharmaceutical process-development case study rather than a comprehensive characterization of all degradation and solid-state pathways of droperidol.

2. Materials and Methods

Reagents and solvents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. TLC analyses were performed on Merck TLC Silica gel 60 F₂₅₄ plates

using UV light visualization. The HPLC and LC-MS measurements were performed with an Agilent 1200 liquid chromatography system, coupled with a 6130-quadrupole mass spectrometer, equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA).

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS). Signal assignments were made based on ^1H and ^{13}C NMR spectra and supported by literature data for droperidol-related structures.

Infrared spectra were recorded on a Shimadzu IRAFFINITY-1S FTIR instrument using the KBr pellet method.

Melting points were determined using a Franz Küstner KG HMK 69/2458 melting-point apparatus. Comprehensive experimental details, including synthetic procedures, analytical methodologies, and characterization data, are available in the Supplementary Information (SI).

3. Results and discussion

3.1. Competitive reaction pathways and their impact on API manufacturability

The original Janssen patents established practical synthetic access to droperidol and related benzimidazolinone derivatives and laid the foundation for subsequent manufacturing approaches [4, 5]. However, the primary objective of these disclosures was the preparation and pharmacological evaluation of biologically active compounds rather than the development of pharmaceutical manufacturing processes. Consequently, aspects such as effective reagent utilization, competing reaction pathways, impurity control, and downstream isolation were not discussed in detail. Furthermore, the reported reaction conditions frequently involve prolonged reaction times and, in several examples, repeated addition of the butyrophenone reagent, suggesting that reaction efficiency may be an important consideration during process development. These observations are consistent with our findings and highlight the distinction between establishing synthetic accessibility and developing a robust process suitable for the manufacture of pharmacopoeial-grade API.

The reaction between the tetrahydropyridyl benzimidazolone intermediate and γ -chloro-4-fluorobutyrophenone appears deceptively straightforward. However, examination of the underlying reaction chemistry reveals several plausible competing pathways that may consume the butyrophenone reagent without contributing to API formation (Figure 2).

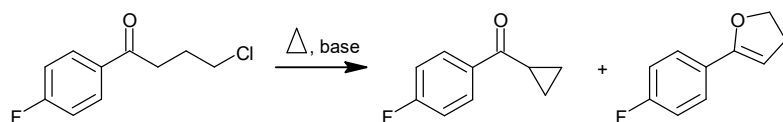


Figure 2. Competing reaction pathways affecting effective reagent utilization during droperidol synthesis.

Examination of the published reaction chemistry suggests that effective reagent utilization may represent an important consideration during process development. From an API manufacturing perspective, achieving high conversion is particularly important because residual process-related impurities may compromise subsequent isolation and purification steps. In the case of droperidol, the tendency of structurally related compounds to complicate crystallization-based purification implies that even relatively small amounts of residual Imp-A may become problematic during crystallization. Consequently, reaction conditions must be selected not only to minimize competing reaction pathways but also to achieve sufficiently high conversion to support the isolation of pharmacopoeial-grade material. The process conditions ultimately required for the preparation of pharmacopoeial-grade API therefore differ substantially from those reported in the early patent literature, reflecting the additional constraints imposed by impurity control, isolation efficiency, and final product quality requirements.

3.2. Conversion is not enough: impurity control during API isolation

From a synthetic perspective, reaction conversion is often regarded as a primary measure of process performance. In pharmaceutical manufacturing, however, conversion alone may provide a misleading picture of process suitability. Residual process-related impurities can significantly complicate downstream isolation, particularly when their physicochemical properties resemble those of the API.

Under such circumstances, even minor impurity levels may become disproportionately important because their removal during crystallization can be considerably more difficult than their suppression during reaction development.

In the case of droperidol, particular attention must be paid to Imp-A and Imp-E, both of which are structurally related to the API and therefore represent potential challenges during purification and isolation.

3.2.1. Consecutive nucleophilic transformation and formation of Imp-E

One particularly illustrative example of the limitations of conversion-based process evaluation is represented by Imp-E, a process-related impurity formed through a consecutive S_NAr transformation.

Although the electron-withdrawing ketone substituent only moderately activates the aromatic ring toward nucleophilic aromatic substitution [11–14], formation of Imp-E remains chemically plausible under the reaction conditions employed for droperidol synthesis.

To better understand the consequences of this pathway for pharmaceutical development, Imp-E was prepared as a representative model impurity and isolated in a form suitable for structural and analytical characterization. Among the evaluated conditions, dimethyl sulfoxide and diisopropylamine provided the most suitable balance between conversion and by-product formation for the preparative synthesis of the impurity (Figure 3).

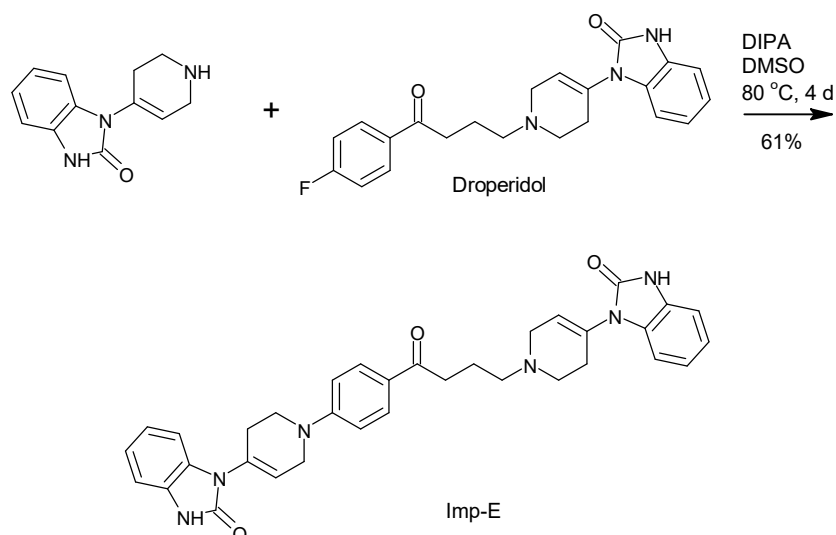


Figure 3. Preparation of Imp-E

Although the reaction proceeded slowly and required an extended reaction time, the formation of secondary by-products remained at an acceptable level. Following methanol-induced precipitation and subsequent trituration with dichloromethane, the crude material was isolated in 61% yield and 84.9% HPLC purity. Recrystallization from ethanol afforded material of 95.8% purity, which proved sufficient for complete spectroscopic characterization and analytical reference use. The structure of Imp-E was unambiguously confirmed by the complete disappearance of the fluorine signals and the emergence of the symmetric AA'BB' splitting pattern of the newly formed para-disubstituted phenylene linker in the aromatic region of the ^1H NMR spectrum (δ 7.89 ppm, 2H), consistent with the diagnostic molecular ion peak of $[\text{M}+\text{H}]^+$ at m/z 575.40 in the mass spectrum (see SI-S2.3).

Analysis of the Imp-E formation pathway further indicates that process time may represent a critical development parameter. Because Imp-E is formed through a consecutive reaction pathway, its formation is inherently promoted by prolonged reaction exposure. This observation suggests that minimization of process time should be regarded as an important impurity-control strategy. In contrast, the early patent literature frequently employs reaction times extending over several days, underlining that the objective of

these disclosures was the preparation of the target compound rather than the development of a manufacturing process capable of consistently delivering pharmacopoeial-grade API.

Despite additional recrystallization, the purity of isolated Imp-E remained lower than that obtained for Imp-C and Imp-D. This observation illustrates the practical difficulties associated with separating structurally related compounds possessing highly similar physicochemical properties. The limited effectiveness of repeated purification steps is consistent with the tendency of such compounds to complicate crystallization-based purification and further highlights why impurity prevention is often more efficient than impurity removal.

The limited effectiveness of repeated purification steps is consistent with a strong tendency toward co-crystallization and further highlights why impurity prevention is often more efficient than impurity removal. Under such circumstances, the key process question is no longer whether the desired API can be formed, but whether it can be isolated in pharmacopoeial quality.

3.3. Oxidative process vulnerabilities

Oxidative degradation represents a particularly challenging aspect of pharmaceutical process development because impurity generation is not necessarily limited to the synthetic transformation itself [15-19]. In many cases, oxidative processes may continue during isolation, crystallization, storage, or drying, creating a direct link between upstream reaction chemistry and downstream process operations.

Consequently, obtaining material of acceptable quality at the end of the reaction does not automatically guarantee that the same quality will be retained throughout subsequent processing.

Solvent selection is particularly important in this context because certain process solvents may promote oxidative degradation through peroxide formation or related oxygen-transfer processes [20, 21]. Such effects become increasingly relevant during isolation and drying, where residual solvent is distributed over large surface areas and remains in prolonged contact with the API.

3.3.1. Aromatization pathway (Imp-C)

The aromatization pathway was investigated through preparation of Imp-C as a representative oxidative degradation product.

The photosensitivity of droperidol is reflected in the formation of Imp-C under oxidative conditions. Initial experiments demonstrated that direct UV exposure in air was capable of producing the impurity; however, the transformation proceeded too slowly to provide material suitable for practical characterization. While this approach was unsuitable for preparative synthesis, it nevertheless provided an important process-development insight. The ability of droperidol to undergo gradual oxidative aromatization under ambient oxygen exposure suggests that impurity formation is not necessarily restricted to the synthetic reaction itself but may continue during downstream operations. Consequently, control of oxygen exposure becomes relevant not only during manufacturing but also throughout isolation and drying, where product quality may be compromised even after successful synthesis of the desired API.

To investigate this pathway under preparative conditions, several aromatization strategies were evaluated. Because oxidation of the tetrahydropyridine moiety is intrinsically accompanied by the risk of competing N-oxidation, selective formation of Imp-C required careful control of the reaction pathway.

Among the conditions examined, the most effective approach involved the treatment of droperidol hydrochloride in DMF in the presence of cobalt(II) chloride and AIBN under a continuous stream of air (Figure 4) [22–24].

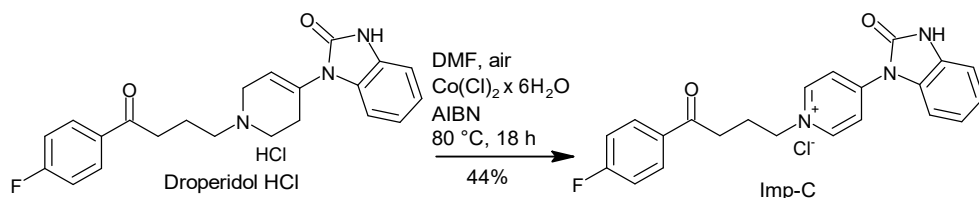


Figure 4. Preparation of Imp-C

The reaction proceeded with good selectivity and achieved conversion exceeding 90%, while LC analysis indicated only minor secondary products. Following crystallization induced by acetone addition, Imp-C was isolated in 44% yield and 98.3% HPLC purity. Structural assignment was confirmed by NMR, FTIR, and mass spectrometric data, including the characteristic pyridinium resonances observed at δ 9.18 and 8.47 ppm (see SI-S2.1).

The formation of Imp-C demonstrates that oxidative degradation may proceed beyond simple impurity generation and can lead to significant structural modification of the heterocyclic core of the API.

From a pharmaceutical manufacturing perspective, this pathway highlights the importance of controlling oxygen exposure not only during reaction processing but also throughout isolation and drying operations, where prolonged contact with air may promote oxidative degradation.

3.3.2. *N*-Oxidation pathway (Imp-D)

In contrast to aromatization, *N*-oxidation does not require substantial structural reorganization and therefore may occur under comparatively mild oxidative conditions [25–30].

To investigate this vulnerability, Imp-D was prepared as a representative model of peroxide-mediated oxidation. *N*-Oxides are most commonly generated using peroxide-containing oxidants, particularly peracids, although a variety of aerobic and metal-catalyzed oxidation systems have also been reported in the literature. Owing to the well-established reactivity of tertiary amines toward peroxide-mediated oxidation, mCPBA was selected as a convenient model oxidant for preparative studies. Under these

conditions, oxidation of droperidol proceeded rapidly and was essentially complete within one hour at room temperature (Figure 5).

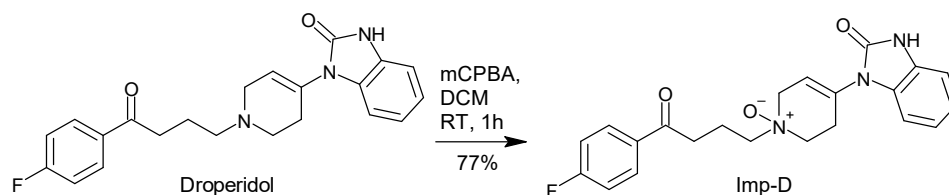


Figure 5. Preparation of Imp-D

Following quenching with aqueous sodium bicarbonate, Imp-D was isolated as a crystalline solid in 77% yield and 99.1% HPLC purity. Structural assignment was confirmed by NMR, FTIR, and mass spectrometric analyses. In particular, formation of the N-oxide functionality was evidenced by the characteristic diastereotopic splitting of the adjacent tetrahydropyridine protons (δ 4.18 and 3.79 ppm) together with the appearance of the diagnostic N $\rightarrow$ O stretching vibration at 1336 cm^{-1} (see SI-S2.2).

The ease of Imp-D formation highlights the susceptibility of droperidol to peroxide-mediated oxidation and reinforces the need for oxidative control beyond the reaction stage.

In contrast to the aromatization pathway represented by Imp-C, the formation of Imp-D does not require extensive structural reorganization of the molecule and can therefore occur under comparatively mild oxidative conditions. Notably, the preparation of Imp-C required continuous exposure to molecular oxygen under catalytic oxidation conditions, whereas Imp-D was readily generated in the presence of peroxide-containing oxidants. This distinction is particularly relevant from a pharmaceutical process-development perspective because both pathways may become accessible during downstream processing. In the presence of oxygen, residual process solvents can participate in oxidative processes and, in some cases, may even act as local oxygen-transfer media through peroxide formation. Consequently, product isolation and drying represent potentially critical stages where both aromatization and N-oxidation

pathways may be promoted. Particular attention must therefore be paid to the selection of process solvents, since peroxide-forming solvents may increase the risk of oxidative impurity generation.

These observations demonstrate that oxidative impurity control cannot be considered independently of downstream processing operations. Even when reaction chemistry is appropriately controlled, isolation and drying conditions may significantly influence the final impurity profile of the API.

Consequently, solvent selection must be evaluated not only from the perspective of process efficiency but also with respect to oxidative stability and solid-state behavior.

3.4. Solid-State Behavior as a Critical Process Parameter

In pharmaceutical manufacturing, solvent selection is often constrained by regulatory requirements related to residual solvents. However, the final isolation of droperidol is further complicated by its pronounced tendency to form multiple solid-state forms. Consequently, solvent selection must satisfy not only regulatory and process considerations but also the requirements imposed by crystallization behavior and the final solid-state properties of the API.

Recent crystallographic investigations have demonstrated that droperidol exhibits a remarkably complex solid-form landscape, including multiple polymorphs, numerous solvent-containing crystal forms, and hydrated phases. These findings indicate that crystallization cannot be regarded merely as a product isolation step but must instead be considered an integral component of process design.

Particularly noteworthy is the pronounced tendency of droperidol to form solvates with a broad range of organic solvents, as well as both mono- and dihydrated crystal forms. As a consequence, the solid phase obtained after crystallization may differ substantially depending on solvent selection and drying conditions. From a pharmaceutical manufacturing perspective, solvent systems that appear favorable for impurity rejection or process efficiency may be unsuitable for final API isolation if they favor the formation of solvated or hydrated crystal forms. This interplay between crystallization behavior and oxidative stability

illustrates the importance of evaluating solvent selection within the context of the overall manufacturing process rather than as an isolated operation.

Formation of such phases may directly affect critical quality attributes because the incorporation of solvent or water into the crystal lattice alters the composition of the isolated material and may result in apparent discrepancies in assay, elemental composition, and pharmaceutical specification compliance.

These observations are consistent with the practical challenges encountered during droperidol isolation and indicate that the critical issue is not merely obtaining crystalline material, but obtaining a solid form compatible with pharmaceutical quality requirements.

Consequently, not all isolated solid forms are equally suitable for pharmaceutical manufacture. In practice, only a limited subset of the known solid-state forms provides the combination of stability and processability required for API production. Attempts to avoid crystalline solvates through generation of amorphous material may introduce additional challenges, including hygroscopicity and limited physical stability.

These observations demonstrate that solid-state behavior constitutes a critical quality attribute of the final API rather than a purely physicochemical property of the final API. For droperidol, successful manufacture of pharmacopoeial-grade material depends not only on reaction chemistry and impurity control but also on the ability to reproducibly obtain an appropriate solid form while avoiding undesired solvates, hydrates, and unstable amorphous phases. Consequently, crystallization serves simultaneously as an isolation, purification, and solid-state control operation within the overall manufacturing process.

The synthesized compounds were comprehensively characterized by MS, ^1H and ^{13}C NMR spectroscopy, confirming the expected structures of the corresponding pharmacopoeial impurities. Because all transformations originated from droperidol through well-defined oxidative or nucleophilic pathways, structural assignment was straightforward and unambiguous.

4. Conclusions

This study demonstrates that robust pharmaceutical process development extends beyond the successful execution of the target organic synthesis. Using droperidol as a representative case study, the results show that impurity control, isolation strategy, oxidative stability, and solid-state considerations must be addressed together to achieve consistent pharmacopoeial-grade API quality.

Analysis of the reaction chemistry revealed that competitive reaction pathways may significantly influence effective reagent utilization and ultimately affect downstream impurity control. The investigation of Imp-E highlighted how seemingly minor process-related impurities can become critical during isolation due to their structural similarity to the API and their tendency to complicate purification processes. These observations emphasize that high reaction conversion alone is not a sufficient indicator of process suitability; the decisive criterion is whether the resulting material can be isolated in pharmacopoeial quality.

The preparation of Imp-C and Imp-D further demonstrated that oxidative degradation pathways may remain active beyond the reaction stage itself. In particular, solvent selection, oxygen exposure, and drying conditions may substantially influence the final impurity profile, illustrating that product quality can be compromised even after successful synthesis of the desired API.

The study also highlights the critical importance of solid-state behavior in pharmaceutical development. The pronounced tendency of droperidol to form solvated, hydrated, or otherwise undesired solid forms demonstrates that crystallization must be regarded not merely as an isolation step, but as a central process operation that simultaneously influences purity, stability, and final API quality.

Although demonstrated using droperidol, the challenges described here are not unique to this molecule and are relevant to pharmaceutical process development more broadly. In this context, the preparation and characterization of representative pharmacopoeial impurities served not only to generate analytical reference standards, but also as mechanistic tools for understanding the factors governing API manufacturability.

Declarations

Data Availability

All data supporting the study's findings are included in this published article and its supplementary information files.

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Conflict of Interest

The authors declare no competing financial interests.

Authors' Contributions

J.S.: Conceptualization, methodology, investigation, writing – original draft. Á.Sz.: Investigation, writing – review and editing. F.M.: writing – review and editing, formal analysis, validation, data curation. Cs.M.: writing – review and editing, formal analysis. I.K.: conceptualization, project administration, supervision, writing – review and editing.

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