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Beyond Poor Solubility: A Critical Narrative Review of Solid-State, Excipient Chemistry, and Dissolution Risks in Eltrombopag Olamine Tablet Development

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ABSTRACT

Eltrombopag olamine presents an interconnected development challenge in which very low aqueous solubility, solid-state diversity, particle attributes, excipient chemistry, process-created microstructure and dissolution-method design may influence one another. This critical narrative review synthesises publicly available regulatory assessments, prescribing information, peer-reviewed studies, international quality guidance, pharmacopeial materials, and patent disclosures identified through 31 July 2026. The available evidence establishes that eltrombopag olamine is practically insoluble in aqueous buffers across pH 1-7.4 and that systemic exposure is highly sensitive to polyvalent cations. A high-calcium meal markedly reduces exposure, whereas the higher fasting exposure reported for the powder for oral suspension compared with the tablet is consistent with dosage-form-dependent availability but does not isolate microstructure as the sole causal factor. Regulatory assessments repeatedly examine solid form and particle-size distribution; however, particle-size criticality is conditional and may be moderated by morphology, agglomeration, wetting, excipient distribution, process history, and the dissolution environment. Qualitative similarity to the reference excipient system is informative but cannot replace understanding of grade, supplier, moisture, elemental profile, reactive-impurity burden, and functional performance. Overall, the evidence supports an integrated, product-specific development framework linking salt and solid-state control, particle and excipient attributes, process-created microstructure, discriminatory dissolution, stability, packaging, and strength bridging. Patents are treated as hypothesis-generating sources rather than evidence of regulatory acceptance or product superiority. No original experimental data were generated or analysed.

Keywords: Eltrombopag Olamine; Critical Narrative Review; Solid State; Particle-Size Distribution; Excipient Compatibility; Chelation; Dissolution; Generic Development; Quality by Design

Graphical Abstract

(Figure 1).

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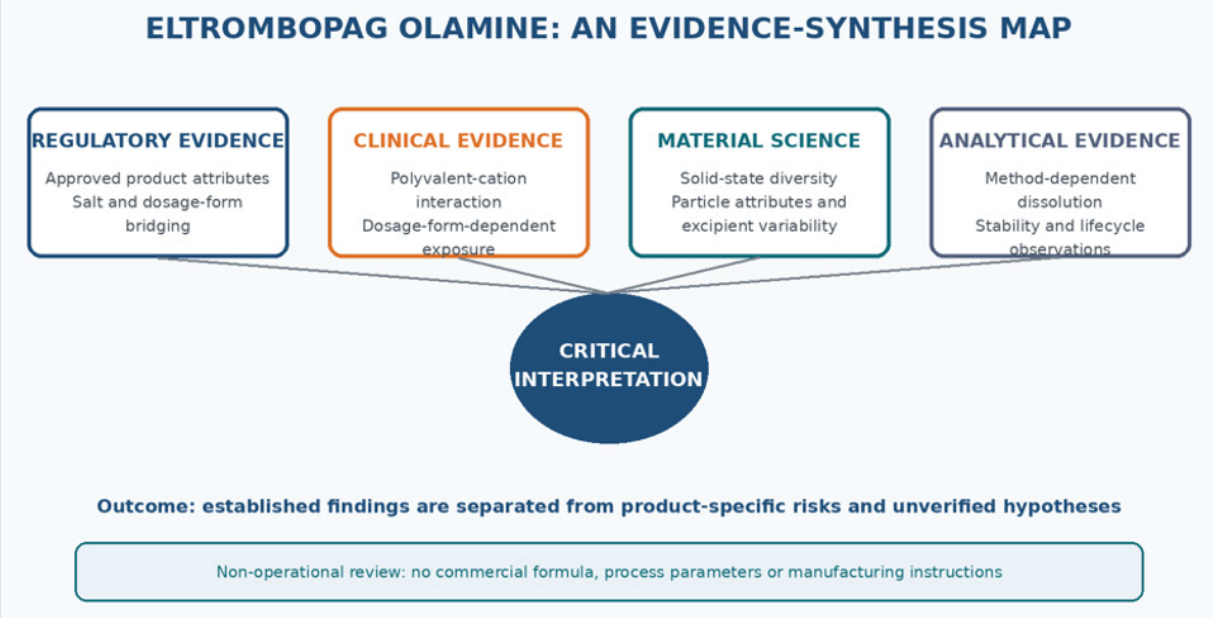

Figure 1: Evidence-synthesis map separating regulatory, clinical, materials-science and analytical findings from product-specific risks and unverified hypotheses.

Introduction

Immediate-release generic development is often described as a sequence of familiar tasks: select an active-substance specification, approximate the reference excipient system, choose a scalable process and demonstrate comparable dissolution and bioequivalence. Eltrombopag olamine challenges this linear model. Its low aqueous solubility, multiple solid-state possibilities, sensitivity to polyvalent cations and dosage-form-dependent exposure create a network in which a change intended to improve one attribute may adversely affect another. A finer active substance may increase apparent dissolution while worsening flow, segregation or lubricant sensitivity; a highly solubilising medium may produce complete release while concealing meaningful product differences; and an excipient that is pharmacopeially compliant may still differ in metal, moisture or peroxide profile. The central scientific question is therefore not whether a single formulation variable is intrinsically "critical", but under which material-process-medium combinations its effect becomes relevant. This distinction is central to formulation science because apparently conflicting regulatory or experimental observations may reflect differences in the surrounding formulation, process, and analytical context. The objective of this review is to integrate those findings and to distinguish established evidence from product-specific observations and hypotheses requiring experimental confirmation.

Methods

Search Strategy and Eligibility Criteria

A structured critical narrative review was conducted rather than a systematic review or meta-analysis because the evidence base is heterogeneous and includes regulatory quality assessments, product labelling, clinical pharmacokinetic studies, solid-state research, international quality guidance, pharmacopeial materials, and patent disclosures. Searches were completed on 31 July 2026 using the websites and databases of the U.S. Food and Drug Administration, European Medicines Agency, International Council for Harmonisation, PubMed, the United States Pharmacopeia, Espacenet, and the World Intellectual Property Organization. Search concepts included eltrombopag, eltrombopag olamine, eltrombopag choline, solubility, salt and solid form, polymorphism, particle-size distribution, morphology, dosage-form exposure, polyvalent-cation interaction, reference composition, manufacturing approach, excipient compatibility, dissolution, stability, impurities, bioequivalence, and additional-strength biowaiver. Sources were included when they directly addressed at least one of these domains and provided an identifiable regulatory basis, experimental method, or primary technical disclosure. Statements that could not be verified from a primary or authoritative source were excluded or explicitly reframed as hypotheses.

Evidence Appraisal and Synthesis

Evidence was appraised according to source type, methodological transparency, product specificity, and directness. Regulatory assessments were assigned the greatest interpretive weight for approved product attributes and accepted control logic; peer-reviewed experimental studies were used for mechanistic or clinical interpretation; international guidelines provided the general development and analytical framework; and patents were used only to identify claimed forms, compositions, or technical strategies. Conflicting findings were retained and interpreted within their product and method context rather than collapsed into a single universal conclusion. This review is qualitative and hypothesis-generating; no original experimental data were generated or analysed (Table 1).

Table 1: Evidence hierarchy used to separate verified findings from hypotheses.

Evidence source	Interpretive weight	Permitted use in this review
Regulatory assessments	Highest	Approved product attributes, assessed quality risks and accepted control logic
Peer-reviewed experimental studies	High	Mechanistic or clinical evidence with identifiable methods and results
International guidelines	Framework	Risk, pharmaceutical development, analytical lifecycle and bioequivalence principles
Patents	Hypothesis-generating	Alternative technical claims; not evidence of product superiority

Evidence Synthesis

Physicochemical and Solid-State Constraints

The current United States prescribing information describes eltrombopag olamine as practically insoluble in aqueous buffer from pH 1 to 7.4 and sparingly soluble in water [1]. Commercial strengths are labelled as eltrombopag free-acid equivalents although the drug substance is the bis-olamine salt. This requires explicit salt-factor and potency correction in material balance, assay and batch documentation. The free acid also has a complex crystal landscape, with more than twenty reported forms, hydrates or solvates in the solid-state literature [2]. Public regulatory assessments therefore place justified emphasis on solid-form identity and particle-size control [3-5]. These findings do not prove that every small change in particle size or solid form will alter clinical performance. They establish instead that the attributes are plausible risk drivers whose criticality must be demonstrated within the specific formulation and process. This is a stronger and more defensible conclusion than treating a single particle-size limit as universally optimal.

Chelation and Dosage-Form Dependence

Clinical pharmacokinetic evidence provides the clearest mechanistic signal in the dataset. The current label reports that a standard high-calcium meal reduced tablet exposure by approximately 59% for area under the concentration-time curve and 65% for peak concentration [1]. The powder for oral suspension generated approximately 22% higher fasting exposure than the tablet, while its exposure was also substantially reduced by a high-calcium meal [1,6,7]. These observations confirm chelation as a major external determinant and are consistent with dosage-form-dependent availability; however, the available clinical evidence does not isolate product microstructure as the sole cause of the exposure difference. The clinical food interaction does not establish that normal lot-to-lot differences in trace elements within compliant excipients will produce a measurable in vivo effect. It does, however, provide a scientific basis for investigating whether excipient selection, pigment systems, supplier variability, or process-created microenvironments alter local coordination, wetting, or apparent dissolution. More recent formulation-specific studies reported bioequivalence between test and reference eltrombopag olamine tablets under fasting conditions and, in one study, under both fasting and fed conditions; these findings demonstrate that bioequivalence can be achieved but do not establish a universal formulation or manufacturing strategy [8,9].

Reference Formulation Logic

The reference tablet core contains mannitol, microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate [1]. Functionally, this is a coherent system: mannitol is a non-reducing soluble diluent, microcrystalline cellulose supports compactability, povidone provides binding, sodium starch glycolate promotes disintegration and magnesium stearate provides lubrication. The coating varies by strength and contains selected pigments and polymers [1]. This composition should be interpreted as a benchmark rather than a ready-made development answer. Pharmacopeial name does not capture grade, particle size, surface area, water content, peroxide level or elemental profile. Qualitative similarity may reduce uncertainty, but product understanding requires evidence that selected grades and suppliers produce robust blend, granule, tablet and dissolution behaviour.

Particle-Size Criticality is Context Dependent

Public regulatory assessments evaluate active-substance particle size because eltrombopag is poorly soluble and because particle attributes can influence both release and processing [3-5]. Product-spe-

cific evidence nevertheless indicates that the effect may be absent or mitigated within an evaluated formulation and process. These findings are not contradictory when interpreted correctly: they demonstrate that particle-size criticality is conditional rather than universal. These findings support a "particle-size paradox": an attribute may be sufficiently important to characterise and monitor while remaining insufficient, on its own, to predict dissolution or in vivo performance. The available public record does not isolate particle-size effects from morphology, specific surface area, agglomeration, wetting, excipient distribution, or process-created microstructure.

Manufacturing Process and Microstructure

Public assessment reports indicate that more than one manufacturing approach has been used for approved eltrombopag products, but most quantitative process details are redacted [4,5]. The public record therefore supports only a limited conclusion: process history may influence particle presentation, porosity and wetting, while no route can be identified as universally preferred from public evidence alone. Any stronger claim would require product-specific data that are not publicly available.

Dissolution as a Development Model

Dissolution findings for eltrombopag are strongly method dependent because of its very low aqueous solubility. Surfactant level, buffer composition, ionic strength, agitation, filtration and sample stability can change apparent release, but public sources do not establish a universal condition applicable to all products [3,10,11-16]. Published profiles should therefore be interpreted within the exact method used rather than compared across studies without qualification. Regulatory documents discuss robustness and discrimination as product-specific concepts; they do not provide a transferable recipe. A rapid or complete profile may reflect the test environment as much as the dosage form, so method sensitivity must be supported for the product under evaluation.

Stability and Analytical Control

Public quality reviews identify solid-form stability, particle-size change, impurities, tablet appearance and dissolution as interconnected lifecycle concerns. In the alternative-salt product, accelerated-condition discoloration was identified and resolved during review [3]. This example shows why colour cannot be treated as a cosmetic observation alone. It should be interpreted together with water content, related substances, coating composition and solid-state data. A stability-indicating analytical package should connect chemical degradation with physical performance. International guidelines support a lifecycle approach to analytical procedure development, validation, elemental impurities, and quality risk management [17-22]. Specific degradation pathways cannot be assigned without supporting mass balance, peak-purity assessment, and appropriate structural evidence (Table 2).

Table 2: Key findings and their formulation-science interpretation.

Evidence domain	Verified finding	Formulation interpretation
Aqueous solubility	Practically insoluble over physiological pH; sparingly soluble in water [1]	High formulation and dissolution risk; conventional buffers may not provide sink conditions
Cation interaction	High-calcium meal markedly reduces exposure [1,7]	Chelation is clinically established; formulation-level elemental effects remain a hypothesis
Dosage-form effect	Oral suspension provides higher fasting exposure than tablet [1,7]	Differences in dispersion state and product architecture may contribute to exposure differences
Solid state and particle attributes	Repeatedly assessed; effect differs among products [3-5,2]	Criticality is conditional rather than universal
Reference excipient system	Non-reducing diluent/cellulose/binder/disintegrant/lubricant core [1]	Q1 similarity is informative but not sufficient without grade and supplier understanding
Dissolution method	Low solubility produces high method-development risk [3]	Discrimination must be demonstrated with meaningful product changes

Integrated Evidence Framework

The proposed framework is intentionally non-prescriptive. It organises public evidence around dosage form, solid state, particles, excipients, dissolution, stability and strength bridging without presenting a commercial formula or fixed process parameters.

Evidence Domains and Product-Quality Questions

Table 3.

Table 3: Product-quality domains considered in the public evidence base.

Evidence domain	Publicly relevant question	Why it matters
Dosage form	How is immediate-release performance characterised?	Dosage-form differences can alter exposure.
Assay and uniformity	Are labelled strength and unit-to-unit consistency supported?	Low strengths and cohesive material may increase uncertainty.
Dissolution	How method-dependent are comparative profiles?	Low solubility can confound cross-study interpretation.
Solid state	Is the reported form maintained and adequately characterised?	Alternative forms may change surface behaviour.
Impurities and appearance	Are chemical and physical trends interpreted together?	Colour or release changes may occur without major assay loss.
Bioequivalence and strengths	What public evidence supports strength bridging?	Final, draft, and product-specific guidance must be distinguished.

Evidence Certainty and Interpretive limits

Table 4.

Table 4: Evidence-confidence map and interpretive limits.

Evidence topic	Public evidence level	What the evidence supports	Interpretive limit
Solid-form change	Conditional	A plausible influence on surface properties, stability and release.	No universal product specification can be inferred.
Particle/morphology variation	Conditional	Regulatory attention is justified for a poorly soluble compound.	Magnitude and relevance are product specific.
Excipient grade or supplier variation	Adjacent evidence/hypothesis	Compendial names can conceal physical and chemical variability.	No public clinical proof for eltrombopag excipient-lot effects.
Process-created microstructure	Mechanistic plausibility	Porosity and distribution can influence apparent release.	Proprietary product data are largely unavailable.
Method-dependent dissolution	Established methodological concern	Test conditions can mask or amplify product differences.	No universal method is established.
Chelation extrapolation	Clinical interaction established; formulation extrapolation unproven	Food and antacid effects confirm cation sensitivity.	Trace excipient-element effects are not established.

Evidence Gaps in the Public Record

Public sources do not resolve whether morphology, excipient grade, product ageing or process history independently explain observed release differences. These uncertainties are recorded here as evidence gaps rather than as an experimental plan.

Discussion

The synthesis leads to three broad insights. First, eltrombopag is not merely a poorly soluble compound; it is a system in which solubility, chelation and dosage-form microstructure interact. Second, particle-size distribution is neither universally dominant nor irrelevant. Its effect emerges from the formulation and process context. Third, dissolution is an experimental model that can either reveal or conceal product differences depending on how it is designed. Together, these observations provide an integrated interpretation that extends beyond an excipient-by-excipient review. The principal contribution is the reconciliation of regulatory and experimental observations that may initially appear inconsistent when considered outside their product and method context. Public sources remain insufficient to rank specific active-substance lots, excipient grades, or manufacturing approaches.

Molecular Ionisation, Apparent Solubility and Precipitation Risk

Eltrombopag cannot be understood by a single equilibrium-solubility number. The molecule contains multiple ionisable and coordination-capable groups, and the marketed olamine salt changes handling and salt-factor calculations without eliminating the low-solubility behaviour of the pharmacologically active moiety. The United States label describes the olamine salt as practically insoluble in aqueous buffers across pH 1-7.4 and only sparingly soluble in water [1]. Consequently, conventional compendial buffers may operate under non-sink or borderline-sink conditions, making the observed release profile a composite of disintegration, wetting, surface conversion, complexation, dissolution and possible precipitation rather than a simple measure of tablet rupture. A useful formulation interpreta-

tion distinguishes intrinsic solubility, total apparent solubility, transient supersaturation and the amount remaining molecularly available after contact with ions or colloidal components. A formulation can produce an early concentration maximum without maintaining that concentration throughout gastrointestinal transit.

Conversely, a slower but more sustained release may generate similar systemic exposure if the dissolved fraction remains available for absorption. This is one reason why a faster in vitro profile should not automatically be labelled superior. The scientifically meaningful question is whether the formulation and method reproduce the rate-limiting events that matter *in vivo*. The alternative choline salt illustrates the importance of separating salt identity from dose equivalence. FDA reviews for ALVAIZ describe development of a lower nominal choline-salt strength to match exposure from the established olamine product, demonstrating that equal labelled mass across salts cannot be assumed to produce equal exposure [3,23]. Evidence from the choline product is valuable for illustrating salt-dependent developability and bridging, but it must not be transferred directly to an olamine formulation as if the salts were interchangeable. Salt selection, solid form, free-acid equivalence and product microstructure must be evaluated as a connected system (Table 5).

Table 5: Molecular and biopharmaceutical questions highlighted by public evidence.

Question	Why it matters	Current public evidence status
What quantity is being compared?	Salt mass, free-acid equivalent and potency-corrected content can differ.	Regulatory documents require explicit equivalence accounting, but proprietary calculations are not public.
Is observed release method limited?	Product rankings can depend on medium capacity and analytical design.	Public sources show strong method dependence; no universal dissolution medium is established.
Does an early concentration peak persist?	Transient supersaturation may not represent sustained availability.	Published eltrombopag data are insufficient to establish a general relationship.
Can polyvalent ions change availability?	Clinical food and antacid interactions establish chelation as an exposure determinant.	Clinical interaction is established; excipient-level effects remain unconfirmed.
Is salt evidence product specific?	Different salts and strengths may have different performance relationships.	FDA evidence for the choline-salt product is product-specific and cannot be transferred directly.

Solid-State Landscape: Identity Is Necessary but Not Sufficient

The solid-state literature reports an extensive crystal landscape for eltrombopag free acid, including numerous forms, solvates and hydrates [2]. The marketed drug substance is the bis-olamine salt, so free-acid polymorph literature does not by itself define the commercial solid-state specification. It does, however, demonstrate a strong tendency of the molecular scaffold to form alternative lattices and solvent-associated phases. Regulatory assessments accordingly evaluate drug-substance identity, crystallinity and particle attributes [3-5]. A robust review should therefore avoid two opposite errors: assuming that every reported free-acid form is relevant to the finished product, or assuming that a single initial powder-diffraction match eliminates lifecycle solid-state risk. Orthogonal characterisation is important because each technique answers a different question. Powder X-ray diffraction is sensitive to long-range order but may miss low-level amorphous material; differential scanning calorimetry and thermogravimetry detect thermal events and solvent loss but are not uniquely specific; Raman or infrared mapping can reveal spatial heterogeneity; dynamic vapour sorption probes moisture-driven behaviour; microscopy and surface-area measurements address morphology and exposed surface. No single test should be promoted as a universal release specification.

The control strategy should be proportional to demonstrated risk and should link the analytical signal to a relevant product attribute. Process history can alter the effective solid-state presentation even when the named crystalline form remains unchanged. Milling can increase defect density and electrostatic charging; wet processing can create transient dissolution-reprecipitation; drying can change residual solvent or water distribution; compression can modify porosity and contact area. These effects may alter wetting and release without producing a new bulk polymorph detectable by routine diffraction. For eltrombopag, the most informative solid-state programme is therefore not merely an identity check but a before-and-after comparison across representative material and product states (Table 6 & Figure 2).

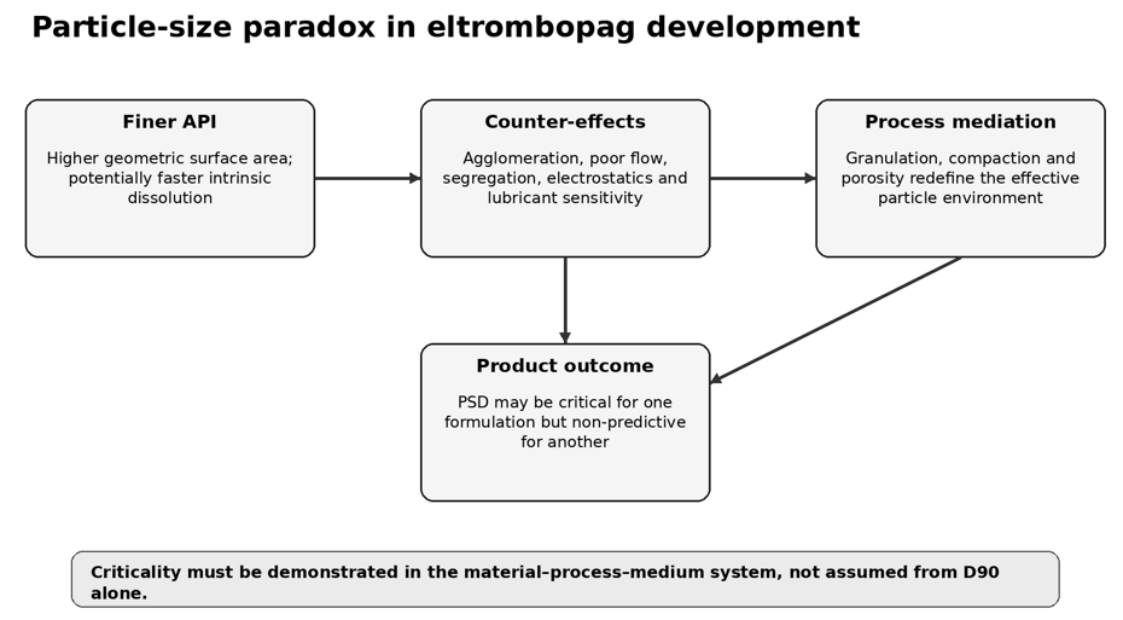

Figure 2: The particle-size paradox: a material attribute may remain scientifically important while its independent effect on bioperformance is moderated by morphology, agglomeration, excipients, process-created microstructure and the dissolution environment.

Table 6: Orthogonal solid-state and particle-characterisation toolkit.

Technique	Primary question	Interpretive caution
Powder X-ray diffraction	Is the expected crystalline phase present and is a new bulk phase detectable?	Detection limits and preferred orientation can obscure minor or poorly crystalline fractions.
Thermal analysis	Are there melting, desolvation, glass-transition or decomposition events?	Thermal events may overlap and heating itself can induce transformation.
Raman/infrared spectroscopy	Are molecular environments or spatially localised changes present?	Spectral differences require reference libraries and chemometric validation.
Dynamic vapour sorption	Does moisture uptake trigger reversible or irreversible change?	Powder behaviour may not reproduce the microenvironment inside a coated tablet.
Laser diffraction and imaging	What are the size distribution and morphology?	Percentile values alone do not capture shape, agglomeration or surface roughness.
Specific surface area	How much surface is accessible to gas adsorption?	Accessible gas surface is not identical to liquid-wetted surface during dissolution.

The Particle-Size Paradox and the Need for Multivariate Specifications

Poor solubility makes particle-size distribution an intuitive risk, but a simple D90 limit can create false confidence. Two lots with similar D10, D50 and D90 values may differ in shape, fines content, agglomerate strength, surface area, electrostatic behaviour and crystal defects. Those differences can influence flow and segregation before they influence dissolution. Conversely, a formulation with rapid disintegration, favourable wetting and a porous microstructure may buffer moderate API particle-size differences. This explains why regulatory assessments can justifiably request particle-size evaluation while a product-specific study concludes that the tested range did not affect dissolution or bioavailability [3-5].

Criticality should therefore be framed as a conditional relationship rather than a permanent label. The relevant model is not 'PSD causes dissolution', but 'PSD interacts with morphology, excipient distribution, granulation history, compression and medium properties to influence the effective surface presented to the liquid'. This multivariate view changes specification strategy. Development data should first establish which representation of the particle population is predictive: percentiles, surface area, image-derived shape descriptors, fines fraction or a combination. A tight numerical limit without predictive value can increase supply risk without improving product understanding. Public evidence does not establish which particle representation-percentiles, morphology, surface area or agglomeration-best predicts performance across products. The absence of comparative multi-product data is itself a central limitation and prevents a universal particle specification from being inferred.

Excipient Chemistry: Functionality, Reactive Impurities and Local Coordination

The reference excipient list is deceptively simple. Mannitol, microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate form a conventional immediate-release core [1], but each material carries physical and chemical attributes that are invisible in a qualitative composition list. Mannitol grade affects particle habit, soluble-pore formation and residual reducing-sugar content. Microcrystalline cellulose varies in moisture, density, particle morphology and compactability. Povidone may vary in molecular-weight distribution and hydroperoxide burden. Sodium starch glycolate can differ in substitution, swelling kinetics and electrolyte response. Magnesium stearate introduces both a hydrophobic surface effect and a divalent metal-containing material, although this fact alone does not establish clinically relevant chelation. Reactive impurities deserve explicit consideration because compendial compliance does not ensure identical stability behaviour among suppliers or lots.

Hydroperoxides have been measured in commonly used polymeric excipients, and published studies show that peroxide impurities in povidone or crospovidone can promote oxidation of susceptible drug substances [24-27]. Reducing sugars, aldehydes, organic acids, and trace metals are additional classes of reactive impurities described in the excipient literature [24,25]. No public evidence demonstrates that these mechanisms necessarily control eltrombopag degradation; accordingly, they should be treated as plausible, testable risks whose priority is determined by forced-degradation knowledge and observed impurity trends. Chelation creates a separate but related question. The clinical effect of calcium-rich food and polyvalent-cation antacids is established [1,7,28]. It would be an overstatement to infer that normal trace elements in a compliant excipient automatically reduce bioavailability. Public evidence does not establish a product-level effect of excipient-grade elemental variability; any such relationship remains unconfirmed (Table 7).

Table 7: Excipient chemistry risk matrix for eltrombopag olamine tablets.

Material/function	Potential hidden variable	Formulation-science interpretation
Mannitol / diluent	Particle habit, soluble fraction, moisture and reducing-sugar traces	Supports a non-reducing formulation concept, but grade and impurity profile remain relevant.
Microcrystalline cellulose / filler-binder	Moisture, density, morphology, surface area and lot-dependent compactability	Can alter blend flow, tensile strength, pore network and release without changing Q1 composition.
Povidone / binder	Molecular-weight distribution, water and hydroperoxides	May influence granule architecture and oxidative-risk screening; eltrombopag-specific relevance requires evidence.
Sodium starch glycolate / disintegrant	Substitution, particle size, swelling kinetics and ionic environment	Nominal concentration does not fully describe disintegration performance.
Magnesium stearate / lubricant	Specific surface, fatty-acid composition, mixing sensitivity and magnesium content	Hydrophobic film formation is an established process risk; chelation relevance should not be assumed.
Film-coating pigments	Elemental composition, opacity and colour stability	May affect appearance and elemental-risk assessment; direct impact on release must be demonstrated.

Manufacturing-Route Evidence and Its Limitations

Public sources describe direct-compression and granulation-based approaches across eltrombopag-related filings and patents, but the disclosed details are incomplete and frequently framed for regulatory or legal purposes. The routes may differ in how they affect distribution and porosity, yet the public evidence does not establish a generally superior process. Because process parameters, material grades and manufacturing scale are largely confidential, cross-product comparisons remain limited. Apparent differences in release cannot be attributed to route alone without matched material and product data. General quality guidance discusses process monitoring, but no public eltrombopag dataset demonstrates a validated relationship between a specific process signal and clinical performance. Such relationships should therefore be described as unconfirmed (Table 8).

Table 8: Manufacturing-route evidence and limitations in the public record.

Route described in public sources	Possible material-level influence	Public-evidence limitation	Review conclusion
Direct compression	Closer retention of incoming powder attributes.	Public grade, scale and process details are limited.	No universal superiority can be inferred.
Dry granulation	Densification and redistribution may occur.	Eltrombopag-specific public comparisons are sparse.	Cross-product attribution is uncertain.
Wet granulation	Granule structure and local distribution may change.	Quantitative conditions are generally confidential.	Interpret only within the assessed product.
Downstream compression/coating	Porosity, surface and appearance may change.	Matched comparative datasets are not public.	Mechanistic claims remain product specific.

Dissolution Evidence is Method Dependent

Published dissolution findings are method-specific observations. For a very poorly soluble compound, incomplete release may reflect medium capacity, while complete release may reflect strong solubilisation. Neither pattern alone proves inferior or superior product performance. Public regulatory sources identify method discrimination as important but do not define one transferable set of conditions. Differences in buffer species, surfactant, apparatus hydrodynamics, filtration and solution stability can change apparent profiles and limit cross-study comparison. Profile statistics such as f2 summarise similarity under the tested conditions; they do not identify mechanism and can be misleading when their assumptions are not met [12,13]. Biorelevant media may support mechanistic interpretation, but without matched in vivo data they should not be described as predictive of bioequivalence [14,15], (Table 9).

Table 9: Method-dependent dissolution issues and interpretive cautions.

Issue	What public evidence shows	Interpretive caution
Medium capacity	Low solubility may produce incomplete release.	Incomplete release may reflect the method rather than the dosage form.
Strong solubilisation	Surfactants can increase apparent release.	Complete release may conceal product differences.
Hydrodynamics and sample handling	Apparatus, filtration and solution stability affect results.	Cross-study comparison requires identical methods.
Profile statistics	f2 summarises similarity under stated assumptions.	It does not identify the underlying mechanism.
Biorelevant media	May add mechanistic context.	Not automatically predictive of bioequivalence.

Stability and the Analytical Lifecycle

Stability should be interpreted as a network of physical and chemical changes. Assay and related substances remain essential, but a tablet can retain chemical compliance while its pore structure, disintegration, colour or dissolution changes. Moisture redistribution can plasticise binders, alter disintegrant performance or promote local mobility; coating pigments and polymers can change appearance; continued solid-state relaxation can modify wetting. The stability programme should therefore trend chemical impurities alongside water, appearance, mechanical attributes, disintegration, dissolution and, where risk indicates, solid-state markers.

Stress studies are most informative when they establish degradation mechanisms and analytical selectivity rather than merely generate a percentage loss.

Oxidative, hydrolytic, thermal, photolytic and humidity stresses should be interpreted against plausible excipient impurities and packaging exposures. If oxidation is observed, peroxide-containing excipients become a more credible risk; if moisture changes dissolution without chemical degradation, microstructural and disintegrant mechanisms deserve priority. This cause-and-effect reasoning is consistent with the analytical lifecycle principles in ICH Q14 and Q2(R2) [19,20]. Packaging is part of the formulation system. Moisture-vapour transmission, oxygen ingress, light protection, headspace, and desiccant use may alter the relative importance of risks identified during development. Accelerated conditions are useful for ranking and mechanism exploration, but extrapolation must recognise that transformation pathways can differ from long-term storage. A lifecycle control strategy should define which incoming-material and process changes trigger comparability work, which analytical trends act as early-warning signals, and how the dissolution method remains capable of detecting meaningful drift. This interpretation is consistent with the pharmaceutical quality-system, knowledge-management, and lifecycle principles described in ICH Q10 and ICH Q12 [29,30], (Table 10).

Table 10: Stability mechanism-to-signal map.

Potential mechanism	Early signal	Confirmatory evidence	Control implication
Moisture redistribution	Water trend, hardness/disintegration shift	Sorption behaviour, microscopy or porosity, dissolution change	Packaging and moisture-control strategy tied to performance.
Oxidation from reactive impurities	Specific related-substance growth	Forced-degradation match and excipient-impurity correlation	Risk-based supplier/lot controls rather than generic exclusion.
Solid-state relaxation or conversion	Thermal/spectroscopic or diffraction change	Orthogonal solid-state confirmation and performance linkage	Lifecycle monitoring only when clinically or pharmaceutically relevant.
Hydrophobic ageing	Slower wetting or disintegration with little chemical change	Surface/porosity and lubrication-history analysis	Process and storage understanding; discriminatory dissolution.
Coating or pigment change	Colour or surface change	Spectral colour measurement and layer-specific investigation	Appearance specification supported by mechanism and packaging.

Evidence-Confidence Architecture

An evidence-confidence framework is more appropriate than a prescriptive control strategy in a public review. Poor aqueous solubility and cation-sensitive exposure are established findings; particle-size effects, excipient impurities and process-created microstructure are conditional; several other proposed mechanisms remain hypotheses. Negative product-specific evidence can reduce the apparent importance of a variable within a studied range, but it should not be generalised to every product. Likewise, a single successful batch cannot establish a universal relationship. The review therefore ranks evidence rather than recommending specifications (Table 11 & Figure 3).

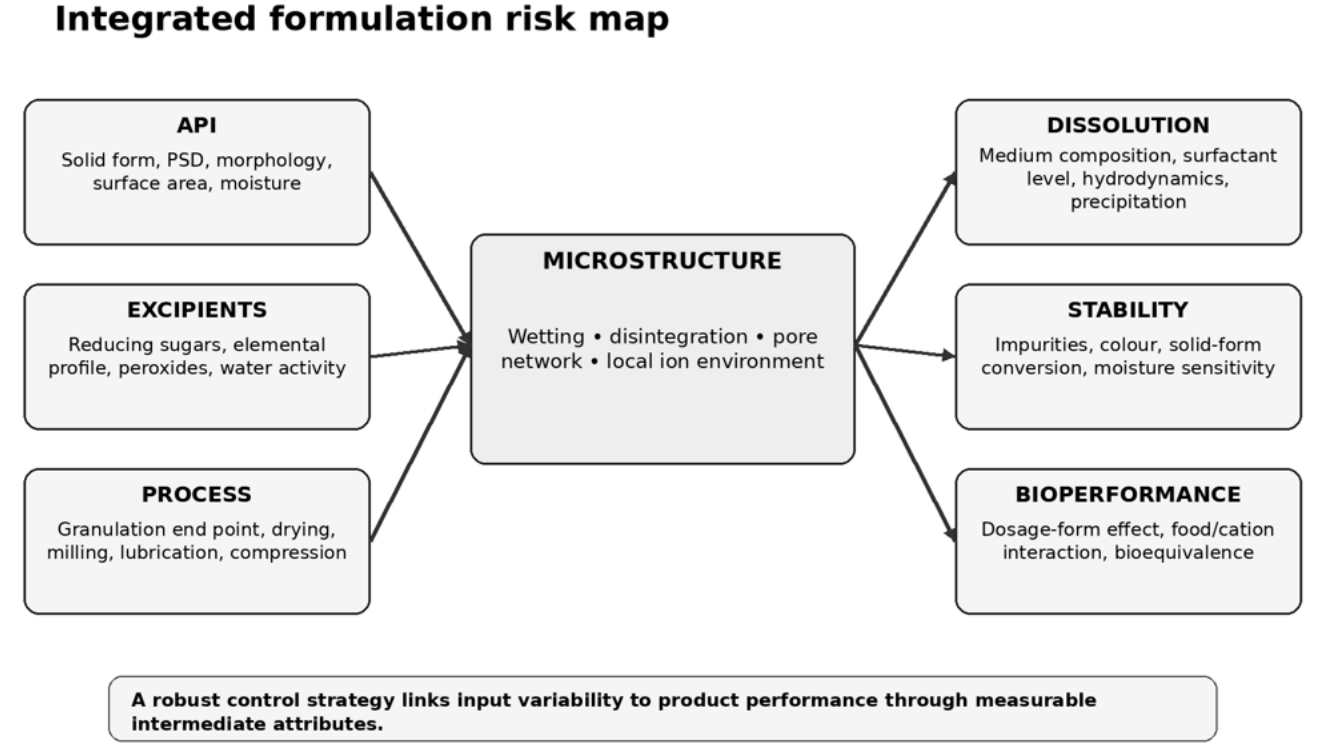

Figure 3: Integrated risk architecture separating established evidence, conditional product-specific risks and hypotheses requiring experimental confirmation.

Table 11: Evidence domains, relevance and interpretive limits.

Evidence domain	Potential relevance	Evidence status	Interpretive limit
Salt factor and solid-form identity	Assay accounting and material identity.	Established accounting need; performance effect product specific.	No universal solid-state limit from public evidence.
Particle size and morphology	Processing and apparent release.	Conditional.	Percentiles alone may be insufficient.
Excipient impurities and elemental profile	Stability and local interactions.	Hypothesis supported by adjacent literature.	Eltrombopag-specific clinical significance unproven.
Process-created microstructure	Porosity, wetting and disintegration.	Mechanistically plausible.	Public matched datasets are limited.
Dissolution conditions	Measured release profile.	Established method dependence.	No transferable recipe.
Packaging and storage	Appearance, impurities and release over time.	Product specific.	Long-term public data are incomplete.
Strength bridging	Regulatory justification.	M13A final; M13B released as a Step 2b draft; EMA eltrombopag guidance adopted at the review cut-off.	EMA guidance becomes legally effective on 1 October 2026; M13B had not reached Step 4 at the review cut-off.

Regulatory And Patent Evidence: How to Use Apparently Conflicting Sources

Regulatory assessments and patents answer different questions. An assessment report records the evidence considered for a specific approved product, often with confidential details redacted. A patent seeks legal scope and may describe broad option sets, predicted advantages or examples that are not equivalent to an approved control strategy. Patents are therefore useful for mapping formulation concepts, claimed solid forms and possible manufacturing routes, but they cannot establish that a composition is clinically superior or commercially implemented [31-37]. The regulatory record supports a product-specific interpretation. EMA assessments examine solid form and particle size because of the compound's poor solubility, while product-level evidence may reduce the apparent criticality of particle size within the studied range [4,5]. FDA evaluation of the choline salt demonstrates that salt conversion, nominal strength, and exposure bridging require integrated evidence [3,23]. The EMA adopted product-specific bioequivalence guidance for eltrombopag in March 2026, with a legal effective date of 1 October 2026 [38]. General bioequivalence principles remain governed by the EMA bioequivalence guideline and ICH M13A [39,40]. The product-specific document should be distinguished from broader harmonised guidance. ICH M13B had been released as a Step 2b draft for regional consultation and had not reached Step 4 at the review cut-off [41]. M13B should therefore not be cited as final adopted guidance when discussing additional-strength biowaivers (Table 12).

Table 12: Regulatory and patent evidence map.

Source type/example	What it can establish	What it cannot establish
Current product label [1]	Approved composition categories, administration constraints and clinical interaction statements	Proprietary grade details or a generic-product design space.
EMA public assessment reports [4,5]	Product-specific quality questions, accepted evidence and public control logic	Universal PSD or process limits applicable to every product.
FDA ALVAIZ reviews [3,23]	Salt-specific development, strength selection and exposure-bridging rationale	Direct interchangeability of choline and olamine formulation strategies.
Eltrombopag patents [31-37]	Claimed forms, compositions and technical hypotheses	Regulatory acceptance, commercial use or clinical superiority.
ICH/EMA/FDA guidance [10-22,39,41]	General principles for development, risk, analytics, dissolution and bioequivalence	A product-specific formulation or specification without supporting data.
EMA eltrombopag product-specific bioequivalence guidance [38]	Product-specific study and strength-bridging expectations for eltrombopag	A commercial formulation, process design space, or universal dissolution specification

Unresolved Knowledge Gaps

The public literature leaves several unresolved questions. It does not establish whether morphology or microstructure consistently predicts dissolution better than conventional particle-size percentiles, whether excipient-grade variability materially changes product performance, or whether physical ageing can precede chemical instability. Guidance relevant to lower-strength bridging continues to evolve. ICH M13A is final; ICH M13B had been released as a Step 2b draft and had not reached Step 4 at the review cut-off; and EMA product-specific guidance for eltrombopag had been adopted but was scheduled to become legally effective on 1 October 2026 [38,40,41]. These gaps identify priorities for future peer-reviewed work. The present article does not present an operational formulation, a manufacturing programme, or original experimental results. Future original research should use predefined methods, actual product-specific data, appropriate statistical analysis, and relevant ethical and regulatory oversight (Table 13).

Table 13: Unresolved knowledge gaps in the public evidence base.

Knowledge gap	What is missing in public evidence	Why it matters
Particle descriptors	Direct comparison of morphology, surface area and conventional percentiles across products.	Limits general conclusions about particle-size criticality.
Excipient-grade variability	Public product-level links between grade variability and performance.	Q1 similarity alone may not explain behaviour.
Dissolution interpretation	Matched in vitro and in vivo evidence for deliberately different products.	Prevents unsupported claims of biopredictivity.
Physical ageing	Parallel public trends in microstructure, dissolution and chemical stability.	Could explain changes not captured by assay alone.
Lower-strength bridging	Final harmonised M13B criteria and product-specific evidence supporting proportional strengths.	Affects the scientific and regulatory justification of additional strengths.

Limitations

This review is limited by redaction of proprietary manufacturing details and quantitative specifications in public assessment reports. Patent disclosures are selective and legally framed, and evidence from an alternative salt cannot be transferred directly to the olamine salt. The structured narrative approach did not include a formal risk-of-bias tool or quantitative meta-analysis and may therefore be affected by source-selection and publication biases. No original experimental data were generated, so the proposed relationships cannot establish causality or validate a commercial control strategy. In vitro chelation experiments, if performed in future work, would not by themselves establish clinical relevance. The framework should therefore be interpreted as a product-development evidence map and a basis for hypothesis-driven studies.

Conclusion

Eltrombopag olamine tablet development is best interpreted as an integrated problem of solid state, particle attributes, excipient chemistry, product microstructure, dissolution, stability, and packaging. The strongest public evidence supports very low aqueous solubility, clinically relevant sensitivity to polyvalent cations, dosage-form-dependent exposure, regulatory attention to solid form and particle attributes, and the need for a product-relevant dissolution strategy. The evidence does not support a universal particle-size target, a single preferred manufacturing route, or direct transfer of conclusions between the olamine and choline salts. Overall, the available evidence supports a product-specific, multivariate development strategy in which material attributes, excipient functionality, process-created microstructure, analytical conditions, packaging, and strength bridging are evaluated as an interacting system rather than as isolated variables.

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3. **Author Contributions:** C.Y.: Conceptualization, methodology, investigation, data curation, visualization, writing - original draft, writing - review and editing, and project administration. C.T., G.G., and E.B.: Validation, scientific interpretation, writing - review and editing, and supervision. All authors reviewed and approved the final manuscript.

4. **Data Availability:** No original data sets were generated. All regulatory documents, publications, guidelines, pharmacopeial materials, and patent sources evaluated in this review are publicly available and cited in the reference list.

5. **Ethics Approval and Consent to Participate:** Not applicable. This review did not involve human participants, human biological samples, or animals.

6. **Use of Generative AI and AI-Assisted Technologies:** An AI-assisted language tool was used during drafting, restructuring, and language refinement. The authors reviewed and verified the scientific content, source attribution, interpretation, and final wording and take full responsibility for the manuscript.

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