



Improving stability through science-led OSD reformulation

Converting a wet-granulated multivitamin tablet to direct compression to resolve an accelerated-stability failure in an already filed and marketed product.

An already filed and marketed multivitamin tablet showed failure within the first month of accelerated stability testing. Recipharm's formulation and analytical experts applied a stability-by-design approach to this complex oral solid dose (OSD) product, simplifying manufacture and delivering a reformulated tablet that remained stable through six months under the same accelerated conditions.

The already commercialised tablet contained eight vitamins across an unusually broad concentration range, from approximately 0.03% to 46% w/w. This breadth of composition created simultaneous challenges in content uniformity, analytical quantitation, physicochemical stability, manufacturability and control of degradation pathways. The highest-concentration active ingredient, present at approximately 46% w/w, constituted the dominant fraction of the tablet matrix and was therefore a major determinant of the product microenvironment, including local acidity, moisture distribution, oxygen susceptibility, particle interactions, porosity and degradation kinetics.

The development objective was to investigate and mitigate the assay decline observed during stability testing, while limiting unnecessary disruption to the registered formulation and manufacturing platform. Recipharm applied a stability-by-design framework integrating root-cause assessment, stability-indicating analytical evaluation, excipient compatibility, moisture and oxygen control, formulation and process optimisation, packaging evaluation, and generation of a scientifically defensible comparability package.

The filed and marketed product was manufactured by wet granulation. The reformulation strategy centred on converting the process to direct compression, while remaining within scientifically justified and regulatory-acceptable boundaries and delivering substantially improved product stability.



THE CHALLENGE: BALANCING STABILITY, UNIFORMITY AND MANUFACTURABILITY

Moving to direct compression offered fewer processing steps and improved manufacturing efficiency, but success depended on the physicochemical, flow, segregation and compression characteristics of the active ingredients and excipients. With eight active ingredients in the formulation, careful selection and control of the particle-size distribution of each was particularly critical to achieving the necessary balance of blend homogeneity, flow, compressibility and content uniformity.

PARTICLE ENGINEERING AND FORMULATION OPTIMISATION

- Particle size and shape were treated as key considerations in selecting the manufacturing pathway, supported by assessment of raw-material attributes, powder behaviour, direct blending and compression performance.
- Particular attention was directed to excipient attributes capable of promoting oxidative instability, including hygroscopicity, residual peroxide content, trace-metal burden and moisture contribution.



CONTROLLING LIGHT EXPOSURE DURING MANUFACTURE

Certain formulation components were light-sensitive, requiring optimisation and control of manufacturing conditions to minimise unnecessary environmental exposure while maintaining blend homogeneity and reproducible compression performance. Formulation composition and compression characteristics were optimised in parallel, while keeping tablet weight, size and shape within regulatory-acceptable and practically manufacturable boundaries.

SIMPLIFYING THE MANUFACTURING PROCESS

The final formulation and process were developed to reduce the number of unit operations. Internal manufacturing assessments demonstrated the operational advantage of direct blending, eliminating the granulation stage compared with the original rapid mixer granulator (RMG)-based process. This simplified manufacture and enhanced productivity.

THE OUTCOME: IMPROVED STABILITY WITH FEWER PROCESS STEPS

The resulting direct-compression product remained stable through six months under accelerated stability conditions, a substantial improvement over the filed and marketed product, which showed failure within the first month under the same conditions. Recipharm connected stability-indicating analytical assessment, excipient compatibility and moisture/oxidation control, meticulous particle-size selection, direct-compression optimisation, controlled manufacturing conditions and packaging-barrier evaluation to deliver a simpler, more efficient and markedly more stable product.

UNDERSTANDING THE DOMINANT DEGRADATION PATHWAY

At approximately 46% w/w, the dominant active ingredient is not simply one of eight actives; it represents a major structural and chemical component of the tablet matrix. Its oxidative degradation proceeds through known intermediate and downstream degradation products, with kinetics influenced by molecular oxygen, moisture, temperature, light, local pH, water activity, trace transition metals and the mobility of reactants within the solid-state microenvironment.

At this high concentration, even modest changes in moisture distribution, particle contact, porosity, oxygen permeability or catalytic impurities can materially alter degradation kinetics, and can also modify the microenvironment experienced by neighbouring vitamins. The reformulation strategy therefore focused on controlling the physicochemical conditions governing oxidative degradation, rather than treating assay loss solely as an analytical endpoint.

CONNECTING FORMULATION SCIENCE AND ANALYTICAL DEPTH

Recipharm's stability-by-design strategy treated formulation, process, analytical and packaging variables as an interconnected control system. The preferred development pathway was the smallest scientifically sufficient intervention capable of producing meaningful stability improvement while preserving critical quality attributes and limiting regulatory impact. Candidate interventions were ranked by anticipated stability benefit, manufacturability, implementation speed, analytical detectability and potential regulatory consequences.

- Stability-indicating analytical evaluation and forced-degradation characterisation.
- Excipient compatibility screening, moisture-management studies, and antioxidant-system evaluation where scientifically justified.
- Particle engineering, process optimisation and packaging-barrier evaluation.

The team used a structured experimental sequence to distinguish mechanisms efficiently: rapid diagnosis of the assay-loss phenomenon, compatibility screening of high-risk ingredient combinations, evaluation of minimal-change formulation prototypes, parallel package-barrier challenges, and confirmatory accelerated and long-term stability studies. A structured factorial, or design-of-experiments (DoE), approach helped distinguish interacting variables and improve confidence in formulation-selection decisions.

OPTIMISING EXCIPIENTS AND PROCESSING FOR PRODUCT PERFORMANCE

Recipharm treated excipient selection as a functional component of the stability-control strategy rather than solely a means of achieving manufacturability. Alternative fillers, binders, disintegrants and excipient grades were evaluated for moisture sorption, peroxide burden, trace-metal content, compatibility, compaction behaviour, disintegration, dissolution and their potential influence on the microenvironment surrounding oxidation-sensitive components.

Karl Fischer titration and loss-on-drying measurements were used to establish the relationship between environmental moisture exposure and product quality attributes, and moisture levels were trended alongside assay and impurity data to strengthen understanding of degradation pathways under different storage conditions.

Manufacturing conditions were optimised to minimise unnecessary environmental exposure, control processing and hold times, maintain blend homogeneity across the extreme concentration range, and establish reproducible compression performance. Particle-size distribution, ordered mixing where applicable, compression behaviour, hardness, friability and disintegration were treated as important variables, since they affect both low-dose uniformity and the diffusion of moisture and oxygen through the dosage form.



PACKAGING: PROTECTING AGAINST MOISTURE AND OXYGEN

Package selection was supported by a mechanistic understanding of moisture-vapour and oxygen-barrier performance, together with comparative product stability. An HDPE bottle with a silica-gel desiccant and an oxygen scavenger was used, reflecting the need for simultaneous moisture- and oxygen-management strategies.

Packaging was treated as complementary to, rather than a substitute for, a sufficiently robust formulation; the preferred configuration was the formulation-process-package combination providing reproducible protection of the critical quality attributes throughout the intended shelf life.

PARALLEL DEVELOPMENT WITHIN A CONSTRAINED WINDOW

With the product already filed, the available development window was substantially constrained. A conventional sequential development model would have increased both timeline and regulatory risk. The programme therefore required parallel execution of analytical verification, root-cause investigation, formulation screening, packaging evaluation, stability studies, regulatory impact assessment and supply-readiness activities, with predefined decision gates allowing low-value options to be eliminated rapidly.

The reformulation followed a deliberate minimal-change principle. Each proposed modification was evaluated for its effect on assay and degradation products, physicochemical characteristics, content uniformity, dissolution, manufacturability, packaging compatibility, process robustness and overall product performance, with the scientific rationale for each change linked explicitly to the hypothesised failure mechanism.

For an already filed product, comparability and regulatory strategy were considered concurrently with formulation development. Depending on the registered dossier, target market and magnitude of change, this included quantitative and qualitative formulation comparison, process comparability, dissolution profiles, assay and degradation-product trends, content uniformity, physical attributes, stability commitments, package justification, elemental-impurity assessment, and evaluation of potential new degradation pathways.

CONCLUSION: SCIENCE-LED REFORMULATION TO MANAGE LIFECYCLE RISK

This programme demonstrates Recipharm's science-led approach to complex oral solid dose reformulation: connecting formulation expertise, analytical depth and manufacturing understanding to address product instability, rather than making isolated changes to processing, analytical methodology or packaging. The approximately 0.03–46% w/w concentration range created a highly heterogeneous system, in which low-dose components demanded stringent uniformity and analytical control while the dominant, high-concentration active ingredient substantially influenced the physicochemical environment governing stability.

Successful reformulation depended on establishing causal relationships among degradation pathways, excipient functionality, ingredient-ingredient and ingredient-excipient interactions, residual and environmental moisture, water activity, oxygen availability, trace metals, particle characteristics, manufacturing conditions and primary-package barrier properties. Relatively small modifications to formulation architecture or processing conditions can change molecular mobility and local microenvironments and thereby alter degradation kinetics.

For late-stage pharmaceutical products, this case illustrates the value of formulation science as a lifecycle risk-management tool. By targeting the dominant instability pathway with a mechanistically justified, minimal-change strategy, Recipharm preserved established product attributes and limited unnecessary disruption to the registered formulation and manufacturing platform.

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