Recipharm

Analytical method development, validation, and technology transfer for multivitamin tablets

A Demonstration of advanced analytical capability for Complex Multi-Active pharmaceutical products.

Analytical method development for multi-component pharmaceutical products has become increasingly demanding as modern formulations incorporate chemically diverse actives with wide potency variations and complex degradation behaviour. Multivitamin tablets, in particular, present significant scientific challenges due to overlapping spectral properties, highly variable solubility, and susceptibility to oxidative and thermal degradation. These factors heighten the risk of coelution, poor sensitivity at trace levels, and inconsistent impurity detection, making it essential to design highly selective, stability-indicating methods that can remain reliable across the product lifecycle. The need for such robust analytical solutions is reinforced by evolving regulatory expectations that emphasise data integrity, specificity, and reproducibility across laboratories.

In response to these challenges, this project focused on developing a comprehensive analytical framework for a multi-active vitamin tablet containing eight chemically distinct components spanning a broad dosage range. Through systematic chromatographic optimisation, detailed impurity mapping, forced degradation studies, and rigorous validation, a suite of high-performance methods was established to support assay, dissolution, impurity profiling, and cleaning verification. These methods demonstrated strong ruggedness and transferability during implementation at QC laboratories, ensuring dependable performance across instruments and analysts. The work highlights the organisation's capability to solve high-complexity analytical problems and deliver scientifically robust, regulatory-aligned solutions for demanding pharmaceutical products.

INTRODUCTION

The analytical characterisation of multi-component pharmaceutical products requires a heightened level of scientific rigour due to the coexistence of structurally diverse compounds that differ widely in potency, stability, and physicochemical behaviour. Multivitamin formulations exemplify this complexity, as they often include components with overlapping chromatographic profiles, distinct degradation pathways, and challenging solubility characteristics. These attributes demand analytical methods that are highly selective, stability-indicating, and capable of reliably quantifying both major and trace-level components within a single dosage form.

Developing such methods necessitates a strategic, multi-faceted approach that integrates chromatographic refinement, impurity profiling, stress testing, and robustness evaluation. Achieving consistency across laboratories further requires methods that are rugged, transferable, and resilient to operational variability. Multivitamin products intensify these demands because of their wide potency range, multiple impurities and degradants, excipient interactions, and the need for diverse analytical techniques across assay, dissolution, impurity profiling, and cleaning analysis. These complexities increase the risk of co-elution, insufficient sensitivity, inadequate specificity, and inconsistent reproducibility.

This project was initiated to establish a complete analytical solution for multivitamin tablets by developing high-selectivity chromatographic methods, performing full ICH-aligned validation, and ensuring reliable technology transfer to two laboratories with demonstrated ruggedness and reproducibility.

PROJECT BACKGROUND

The Multivitamin tablets analytical program was initiated to address the unique challenges posed by a formulation containing eight vitamins present across an exceptionally wide dosage range. Early feasibility assessments indicated that the product's components differed significantly in solubility across physiologically relevant pH conditions, requiring targeted studies to identify suitable dissolution media and ensure complete extraction of both high-dose and trace-level vitamins. In parallel, preliminary stress-testing revealed multiple degradation pathways, underscoring the need for stability-indicating analytical methods capable of resolving actives from their degradants with reliable peak purity.

Given these complexities, the project scope was defined to establish a comprehensive suite of analytical methods covering assay, dissolution, impurity profiling, and cleaning verification. This required a coordinated development strategy that aligned chromatographic conditions with solubility behaviour, ensured adequate sensitivity for low-potency actives, and incorporated stability outcomes into method design. The background phase also included evaluating method compatibility with routine QC environments and determining transfer readiness for external laboratories. Collectively, these elements formed the scientific and operational foundation for the detailed method development, validation, and technology-transfer work that followed.

THE CHALLENGE

The analytical development for multivitamin tablets presented several inherent challenges due to the co-existence of eight chemically diverse vitamins with markedly different potency levels, stability characteristics, and solubility profiles. Components present at trace levels required highly sensitive and noise-free detection, while high-dose vitamins demanded methods capable of maintaining linearity and accuracy across a very broad calibration range. These extremes complicated chromatographic optimisation and imposed stringent requirements on detector settings and sample preparation.

Marked differences in solubility across various pH conditions further complicated dissolution testing. While some vitamins dissolved readily in acidic or neutral media, others exhibited poor solubility, making it difficult to identify a single discriminatory medium suitable for all components. Extensive solubility screening was required to prevent partial release, precipitation, or artificially elevated recoveries.

Stability concerns added additional complexity, as several vitamins underwent rapid oxidative, hydrolytic, or photolytic degradation, generating degradants that overlapped with active peaks or interacted with excipients. Achieving stability-indicating resolution demanded repeated refinement of mobile phase composition, buffer pH, gradient slope, and detector wavelength selection. Co-elution between vitamins, their degradants, and placebo-derived peaks was frequently observed during early method trials.

Ensuring ruggedness and inter-laboratory reproducibility presented further operational challenges. Small shifts in chromatographic conditions, such as variation in column lots, system dwell volume, or environmental factors—led to retention time drifts and peak distortion, especially for sensitive vitamins. Robustness studies and iterative fine-tuning were essential to ensure consistent performance across different QC laboratories.

- **Wide potency range** requiring analytical methods with a high dynamic detection range for both major and trace-level vitamins.
- **pH-dependent solubility** differences making dissolution media selection and extraction efficiency difficult to standardize.
- **High degradability of several vitamins** resulting in complex impurity profiles and demanding stability-indicating chromatographic separation.
- **Co-elution risks:** Overlapping peaks among vitamins, degradants, and excipients demanded fine-tuning of gradients, pH, and wavelengths.
- **Multiple analytical methods required:** Dissolution, assay, impurities, and cleaning methods all required independent development and optimisation.
- **Chromatographic selectivity limitations:** Required evaluation of different column chemistries and mobile phase compositions.
- **Inter-lab variability risks,** where minor operational differences affected retention, resolution, and reproducibility during method transfer.

RECIPHARM'S TECHNICAL APPROACH AND SOLUTIONS

Foundational studies: Solubility & dissolution medium selection
We began with saturation solubility studies across relevant pH conditions to quantify media-dependent behaviour for each vitamin. These data guided selection of a discriminatory dissolution medium (and conditions) capable of ensuring adequate release for poorly soluble components without masking rapid releasers. The solubility outputs also informed sample preparation (diluent choice, pH adjustment, and wetting needs) and the guardrails for method robustness under routine QC use.

Method architecture: Dual paths for assay & dissolution
Given the wide label-claim spread, we implemented a two-method architecture for both assay and dissolution:

Method I (Medium- to high-label-claim vitamins): Optimised for high sensitivity, minimized background noise, and controlled carryover to quantify trace-level actives with reliable accuracy.

Method II (Low-label-claim vitamins): Tuned for linearity and accuracy over an extended range, with injection load and detector settings adjusted to prevent saturation and maintain peak shape. Degradation profiling was handled via separate, dedicated methods to ensure stability-indicating performance with sufficient resolution from impurities and excipient-related peaks. Forced-degradation learnings (oxidative, hydrolytic, photolytic, and thermal) were used to finalize gradient programs, buffer pH, and organic strength for unambiguous separation.

Streamlined detection strategy: Single wavelength per method
To increase operational efficiency and reduce data processing complexity, we adopted a single-wavelength detection strategy for each method (rather than multiple component-specific wavelengths). This choice:

- Eliminated multi-channel result stitching, reducing analyst workload and error risk,
- Improved throughput, and
- Preserved adequate sensitivity/selectivity via careful wavelength selection aligned to the dominant chromophores of the vitamin set in each method.

Robustness & reproducibility: Columns, systems, and parameters
Each method underwent robustness challenges (± pH, buffer strength, organic ratio, gradient slope, flow rate, and column temperature). To demonstrate reproducibility, we evaluated multiple column lots of the selected stationary phase(s) and ran the methods on different HPLC makes/models. Particular attention was paid to dwell-volume differences and extra-column effects; system-suitable gradient adjustments and clear setup instructions were embedded in the final SOPs to ensure consistent retention and resolution.

Excipients & compatibility
We executed a targeted excipient compatibility study to verify that the chosen formulation excipients did not induce or accelerate degradation of any vitamins under expected storage and processing conditions. Where minor interactions were observed, sample preparation and chromatographic conditions were refined to suppress interference (e.g., pH adjustment, chelating agents when justified, light protection, and minimized residence times in autosampler).

Stability study integration
Stability samples from predefined stations (e.g., accelerated and long-term conditions) were analyzed to confirm on-study performance of the methods and to track any time-dependent degradation of APIs. These data validated the stability-indicating capability and informed long-term system suitability criteria.

Validation & technology transfer
All methods were validated per ICH Q2 attributes—specificity, linearity, range, accuracy, precision (repeatability and intermediate precision), detection/quantitation limits (where applicable), robustness, and system suitability. Following validation, we executed a structured transfer to the QC laboratory, including method familiarisation, side-by-side comparative runs against transfer acceptance criteria, and a short troubleshooting window to lock in instrument-specific settings and column care practices.

THE FINAL OUTCOME

The analytical development program resulted in a set of robust, selective, and stability-indicating methods capable of accurately assessing all key quality attributes of the multivitamin tablet. The solubility-driven selection of dissolution medium ensured consistent release profiles across vitamins with widely differing physicochemical properties, eliminating issues of partial extraction and enhancing discriminatory power. The dual-method design, separate pathways for low-dose and medium-to-high-dose vitamins proved highly effective in balancing sensitivity with extended linearity, enabling precise quantification across an exceptionally wide potency range.

Chromatographic refinement and wavelength consolidation into a single-wavelength strategy per method significantly improved operational efficiency. Analysts were able to process data faster, with fewer integration complexities and reduced risk of channel-wise discrepancies. Forced-degradation and stability-station samples confirmed that each method reliably resolved actives from degradants, validating true stability-indicating capability. Compatibility studies also verified that none of the formulation excipients induced or accelerated degradation, strengthening confidence in method specificity.

Robustness assessments demonstrated strong method resilience under deliberate variations in flow rate, pH, gradient composition, and column temperature. Multi-lot column evaluation and cross-platform HPLC testing further confirmed reproducibility, ensuring that the methods were dependable for routine deployment. Following successful validation aligned with ICH Q2 criteria, all methods were smoothly transferred to the QC laboratory, where they consistently met system suitability requirements without the need for further adjustment. Together, these outcomes highlight a comprehensive analytical solution that is technically sound, operationally efficient, and fit for long-term quality control of complex multivitamin formulations.

IMPACT AND VALUE DELIVERED

The analytical development program for the multivitamin tablets demonstrated our organisation's capability to execute complex, multi-layered scientific work with precision, speed, and technical depth. By integrating foundational solubility insights, stability behaviour, and chromatographic selectivity into method design, we delivered a solution that not only met regulatory expectations but also strengthened the scientific robustness of the entire analytical package. This comprehensive approach showcased our ability to translate complex product characteristics into reliable, routine-ready methods.

CONCLUSION

This complex project demonstrates the organisation's capability to deliver regulatory-ready, stability-indicating methods for a chemically diverse, multi-active product with a potency span of three orders of magnitude. By integrating mechanistic chromatographic design (column chemistry, pH, and gradient control), rigorous forced-degradation studies, and ICH-compliant validation, the team established methods that are specific, sensitive, robust, and reproducible.

A structured technology transfer, grounded in readiness checks, comparative testing, and collaborative troubleshooting, confirmed inter-laboratory equivalence and reduced method-related risk at the receiving QC sites. The resulting analytical package consistently achieved baseline separation of actives and degradants, met tight system-suitability criteria, and maintained precision and accuracy across instruments, analysts, and column lots.

Beyond immediate execution, this work creates durable value:

Quality & compliance: True stability-indicating capability, comprehensive impurity understanding, and lifecycle documentation strengthen regulatory confidence and support reliable shelf-life assignment.

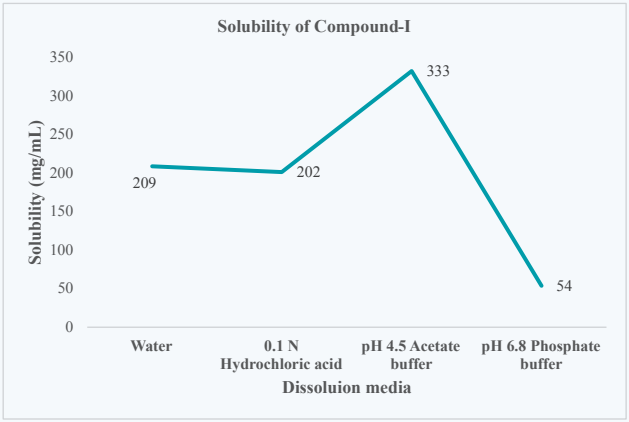
Operational reliability: Harmonised methods and clear SST guardrails reduce OOS/OOT rates, shorten investigations, and enable dependable batch release.

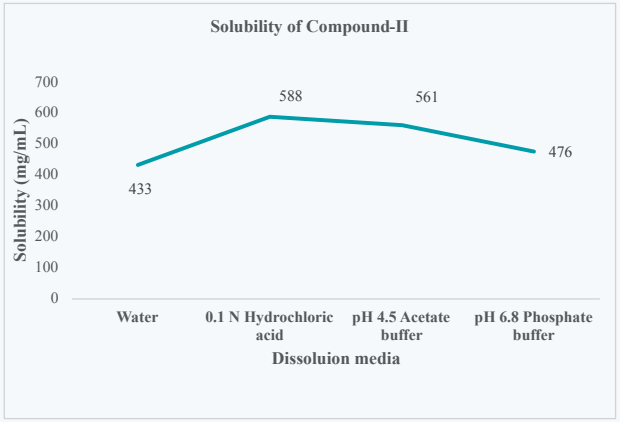
Scalability and transferability: Proven ruggedness across sites provides a template for rapid onboarding of partner laboratories and future products with similar complexity.

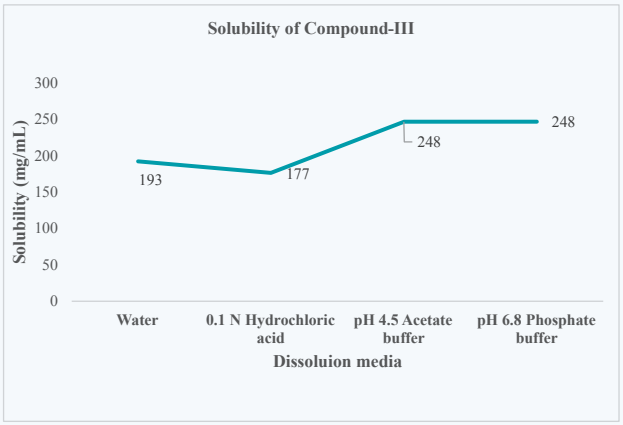
Knowledge capital: A reusable playbook, covering stress design, specificity enhancement, and transfer governance, now exists for subsequent multi-active programs.

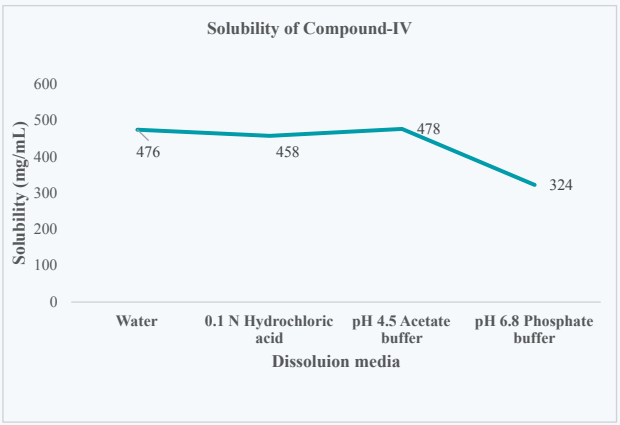
With these outcomes, the organisation is well positioned to support commercial supply of this and for other high-complexity formulations. The program exemplifies how sound analytical science, disciplined validation, and thoughtful technology transfer combine to deliver methods that are not only fit for purpose today but are resilient to tomorrow's variability, across people, platforms, and places.

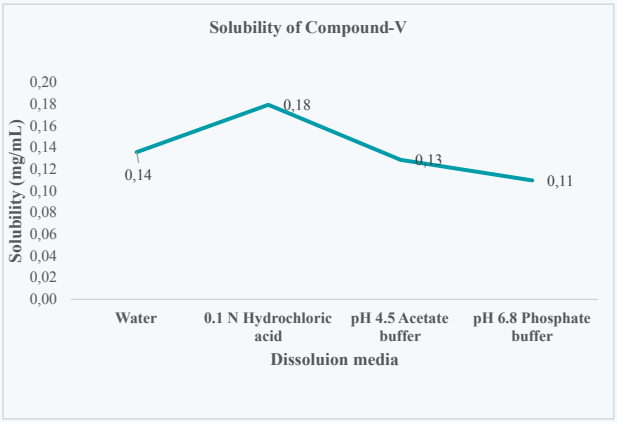
FIGURE 1: SOLUBILITY STUDY DATA

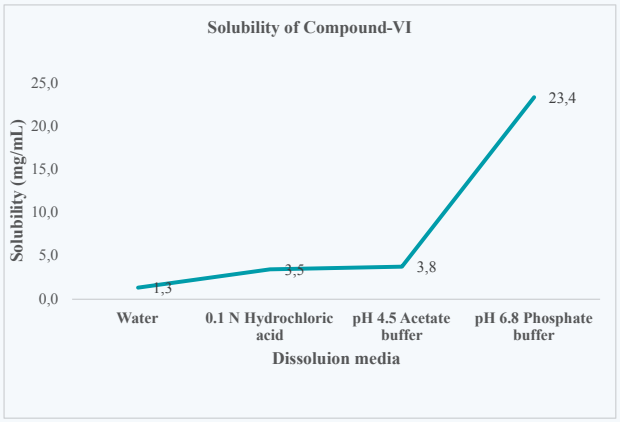


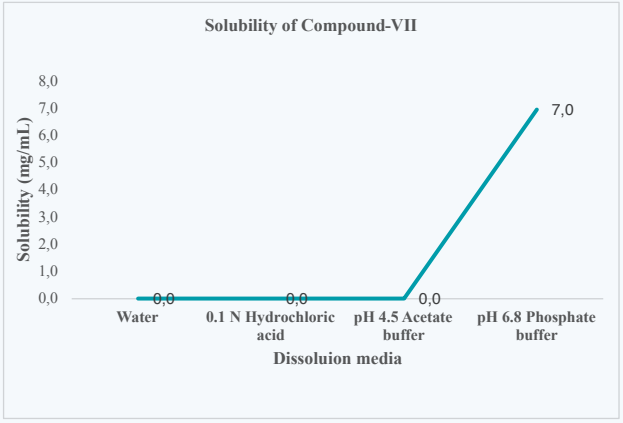












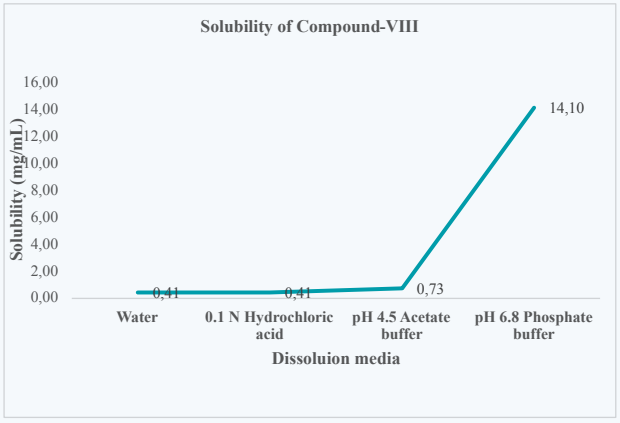
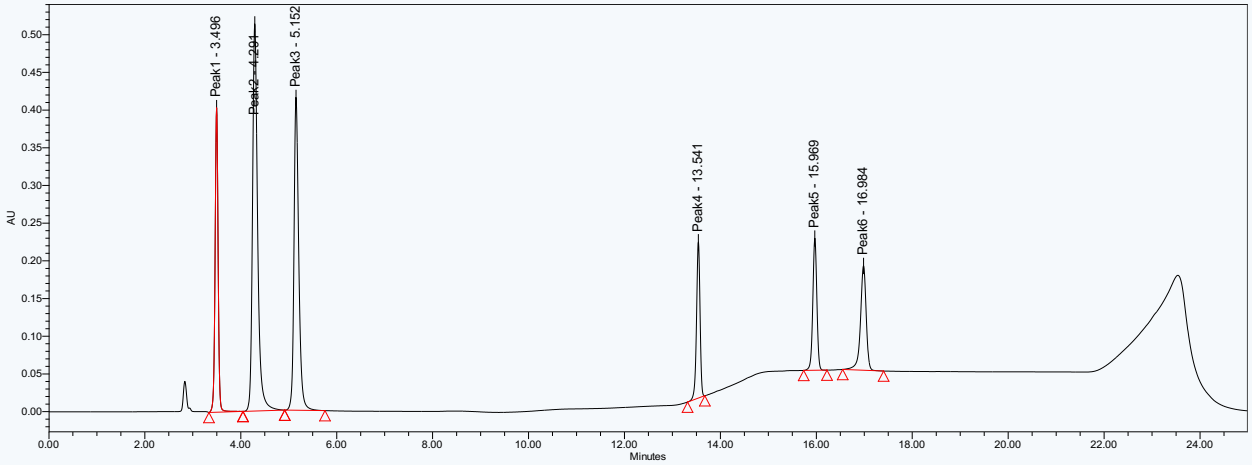


FIGURE 2: CHROMATOGRAMS OF ASSAY METHOD

(a) Chromatogram of sample solution for Assay Method-I



(b) Chromatogram of sample solution for Assay Method-II

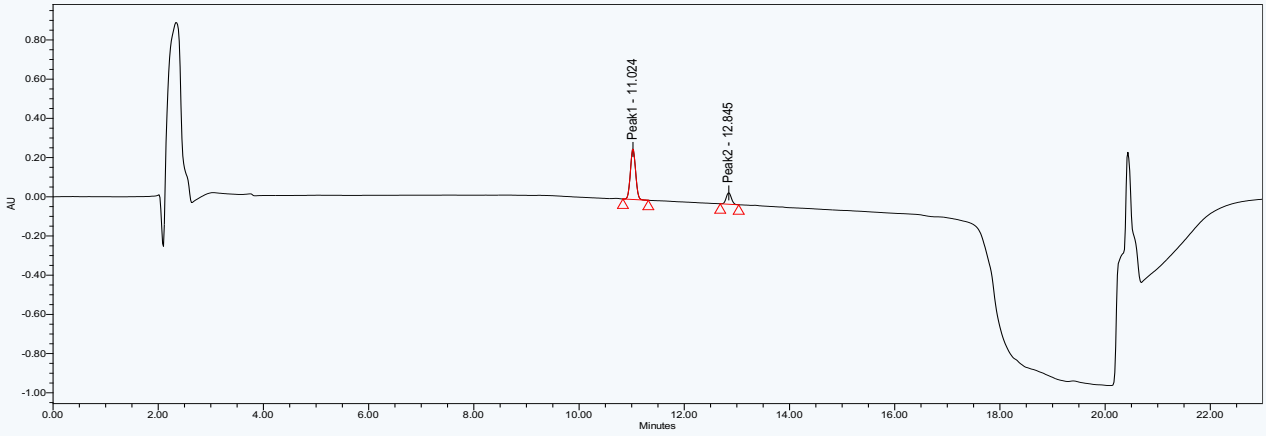
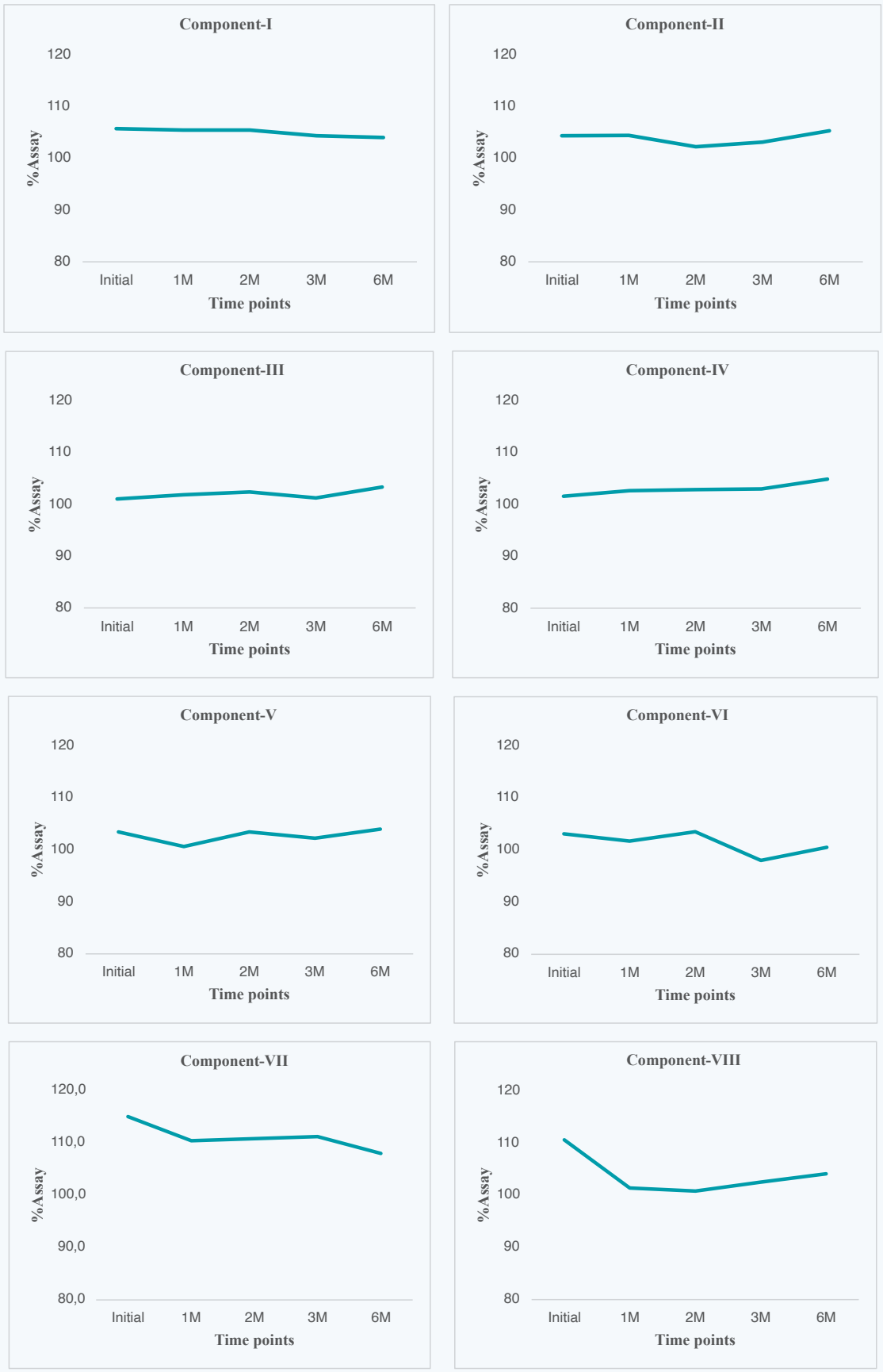
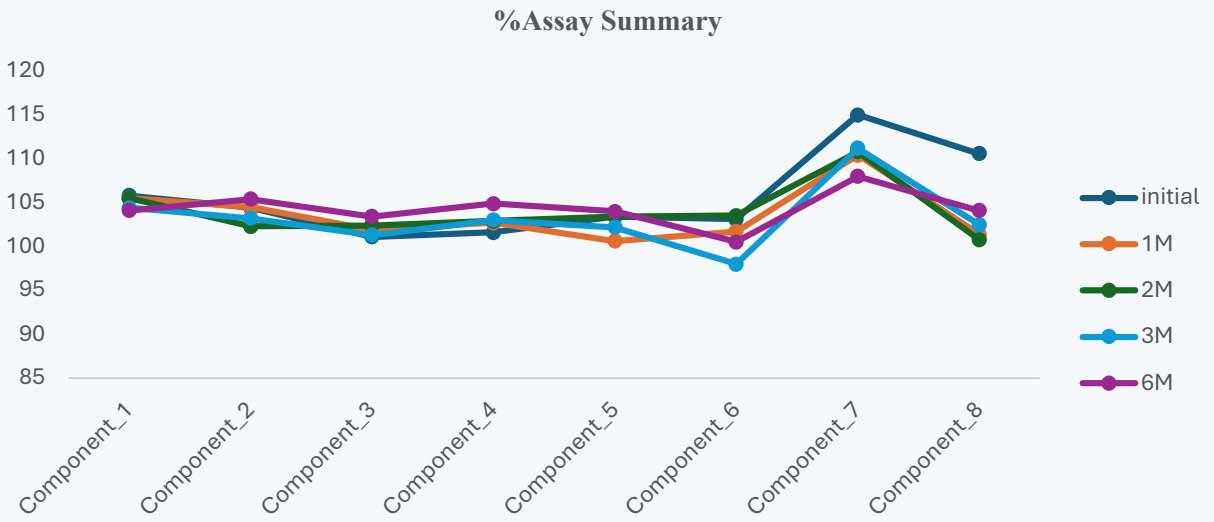


FIGURE 3: % ASSAY RESULTS DURING ACCELERATED STABILITY STUDIES (40°C/75%RH)




%Assay Summary
120
115
110
105
100
95
90
85
Component_1
Component_2
Component_3
Component_4
Component_5
Component_6
Component_7
Component_8
initial
1M
2M
3M
6M

About Recipharm

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Italy, Portugal, Spain, Sweden and the US and are continuing to grow and expand our offering for our customers. We are supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 30 years, we have partnered with our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. We conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do.