

Preformulation, Drug–Polymer Compatibility and Analytical Method Validation for an Antidiabetic Dissolving Microneedle Patch

Sakshi Sharma¹, Prof (Dr.) Sushila Kalra²,
Prof (Dr.) Neetesh Kumar Jain³

¹Research Scholar, Department of Pharmacy, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

²Supervisor, Department of Pharmacology, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

³Co-Supervisor Department of Pharmacology and Toxicology Modern Institute of Pharmaceutical Sciences

Abstract:

Dissolving polymeric microneedle patches offer a minimally invasive means of transporting antidiabetic molecules across the stratum corneum, but their development requires more than selecting a soluble polymer and demonstrating needle formation. The active pharmaceutical ingredient must remain stable during solution preparation, mould filling, drying, demoulding and storage; the polymer system must provide adequate rheology, mechanical strength, insertion and rapid hydration; and the analytical procedure must quantify the drug accurately in casting solutions, dry patches, skin extracts and permeation samples. This article presents an integrated framework for preformulation, drug–polymer compatibility assessment and analytical method validation for an antidiabetic dissolving microneedle patch. It describes drug-selection criteria, identity and solid-state characterization, solubility and ionization studies, partition behaviour, hygroscopicity, thermal analysis, spectroscopy, binary-mixture stress studies and compatibility decision-making. It then discusses analytical target profiles, UV–visible and chromatographic method development, matrix-specific sample recovery and validation according to ICH Q2(R2). Particular attention is given to the distinction between absence of a visible incompatibility and evidence of compatibility, and between high nominal drug content and accurate delivered-dose measurement. The paper proposes a risk-linked workflow in which analytical capability is established before formulation optimization and is challenged in all matrices relevant to microneedle manufacture and performance testing. This approach supports scientifically defensible formulation selection, data integrity and later scale-up without claiming unverified experimental results.

Keywords: preformulation; drug–polymer compatibility; dissolving microneedles; antidiabetic drug; analytical target profile; method validation; ICH Q2(R2); transdermal delivery

1. Introduction:

Antidiabetic treatment includes orally administered small molecules, injectable insulin and peptide-

based agents. The effectiveness of these medicines depends not only on pharmacology but also on the ability of the dosage form to place a reproducible amount of drug at the intended biological site. Oral administration can be constrained by gastrointestinal degradation, poor permeability, food effects and first-pass metabolism, whereas repeated injection may impose pain, anxiety, sharps disposal and training burdens. Dissolving microneedles seek to create temporary microchannels through the outer skin and then release drug from a water-soluble matrix, potentially combining the convenience of a patch with the barrier-bypassing function of a needle (Dalvi et al., 2021; Zhao et al., 2022).

The apparent simplicity of the concept can encourage premature formulation. A polymer solution may fill a mould and form visually acceptable needles while the drug is partially degraded, crystallized or unevenly distributed. Conversely, an analytically stable mixture may lack the mechanical properties required for insertion. Preformulation must therefore connect molecular behaviour with the stresses of microneedle manufacture and use. Analytical development must begin early enough to identify those changes and must be specific for the drug in the presence of polymers, plasticisers, stabilisers, skin constituents and receptor media.

Its purpose is to provide a scientifically defensible framework that can be adapted once the actual antidiabetic drug, polymer grades, dose and analytical platform are known. Because no verified experimental dataset was supplied, the manuscript does not present invented numerical results; it defines the experiments, calculations, decision criteria and reporting structure required for an original research study.

2. Development Question and Analytical Target:

The development question is whether a selected antidiabetic drug can be incorporated into a dissolving polymeric microneedle matrix, processed without unacceptable change, quantified reliably throughout manufacture and evaluation, and released in a form suitable for transdermal delivery. This question should be translated into an analytical target profile before selecting an instrument. The target profile defines the analyte, matrices, concentration ranges, required accuracy and precision, specificity, sample volume, run time and intended decisions. A method intended only for drug content in a clean polymer solution may not be suitable for degradation studies or skin permeation samples.

Analytical application	Matrix	Principal requirement
Drug identity/assay	Bulk drug and reference standard	Specific identification and accurate potency
Casting solution	Polymer/plasticiser solution	Tolerance of viscosity and excipient background
Patch drug content	Dissolved microneedle matrix	Complete extraction and content uniformity
Release/permeation	Buffer or receptor medium	Sensitivity at low concentrations and stability during sampling
Skin deposition	Tissue extract	Selectivity, recovery and matrix-effect control
Stability	Aged patch/extract	Separation or detection of relevant degradants

3. Selection of the Antidiabetic Drug:

Drug selection should be based on therapeutic need and developability rather than novelty alone. Relevant factors include required dose, molecular mass, aqueous solubility, potency, ionization, partition coefficient, stability, melting or glass-transition behaviour, protein structure where applicable and availability of a clinically meaningful comparator. The limited volume of a microneedle array favours potent agents. A molecule requiring a very high daily dose may be unsuitable unless the patch area or loading strategy is clinically acceptable.

For insulin or another peptide, the principal risks include aggregation, oxidation, deamidation, adsorption at interfaces and loss of biological activity during drying. For a small molecule, crystallization, polymorphic conversion, pH-dependent solubility and interaction with polymer functional groups may dominate. The intended delivery profile must also be stated. A rapid prandial product, a sustained system and a patch intended only to increase bioavailability require different compositions and tests.

Selection attribute	Question	Development implication
Dose/potency	Can the therapeutic amount fit in the needle volume?	Determines feasibility and tip-loading need
Solubility	Can the drug be incorporated without precipitation?	Controls solvent, pH and solids content
Ionization/pKa	What charge state exists during casting and delivery?	Influences solubility, polymer interaction and permeation
Log P/log D	Is the molecule compatible with skin partitioning?	Guides permeation expectations and enhancement strategy
Thermal/chemical stability	Can the drug tolerate drying and storage?	Defines process temperature and packaging
Analytical detectability	Can relevant concentrations and degradants be measured?	Determines UV or chromatographic approach

4. Preformulation Programme:

4.1 Identity, appearance and reference standard:

Preformulation begins with an authenticated drug substance and a traceable reference standard. Appearance, colour, odour where appropriate, batch number, manufacturer, certificate of analysis, assay, water content and storage condition should be recorded. Identity may be confirmed through infrared spectroscopy, melting behaviour, chromatographic retention and another orthogonal technique appropriate to the molecule. The purpose is not to reproduce every compendial test but to establish that subsequent observations relate to the correct and sufficiently characterized material.

4.2 Solubility and solution stability:

Equilibrium or apparent solubility should be evaluated in water, relevant buffers and candidate casting media over a pH range justified by the drug's pKa and skin compatibility. Temperature, equilibration time, solid excess, agitation, filtration and analytical dilution must be controlled. Visual clarity is not proof of molecular dissolution; supersaturation or colloidal material can give misleading results. The remaining solid should be examined where polymorphic transformation is possible.

Solution stability should be investigated at the temperatures and holding times expected during solution preparation and mould filling. Samples should be protected or exposed to light according to the process risk. Changes in assay, impurity profile, pH, colour, turbidity and protein aggregation should be recorded. These studies define allowable hold time and whether solutions require refrigeration, nitrogen protection, antioxidants or immediate casting.

4.3 Ionization and partition behaviour:

The pH–solubility profile helps distinguish intrinsic solubility from ionization-driven apparent solubility. A formulation pH that maximizes solubility may irritate skin, destabilize a polymer or reduce drug partitioning from the hydrated matrix. Partition coefficient or distribution coefficient data should therefore be interpreted alongside dose, ionization and vehicle composition. For proteins, conventional log P is not a meaningful predictor, and structural integrity, charge and diffusion within hydrated polymer become more relevant.

4.4 Solid-state and thermal characterization:

Differential scanning calorimetry can reveal melting, glass transitions, dehydration and changes associated with mixing, but peak disappearance is not by itself proof of chemical interaction. It may reflect dilution, dissolution of the drug in the polymer, amorphization or overlap. Thermogravimetric analysis identifies water and thermal mass loss and helps define a safe processing range. Powder X-ray diffraction distinguishes crystalline and amorphous contributions, while microscopy can identify drug crystals in dried films or needles. The techniques should be interpreted together rather than as isolated pass/fail tests.

4.5 Hygroscopicity and moisture sensitivity:

Hydrophilic polymers readily exchange water with the environment, and the drug may also be hygroscopic. Moisture can plasticize the matrix, modify viscosity during preparation, promote chemical degradation and alter mechanical strength after drying. Dynamic vapour sorption or controlled-humidity exposure can characterize uptake and reversibility. Residual moisture should be linked to needle strength and dissolution instead of being reported only as a percentage.

Study	Minimum reportable details	Decision supported
Solubility	pH, medium, temperature, time, separation and assay	Casting vehicle and loading feasibility
Solution stability	Concentration, container, light, temperature and duration	Solution hold time
DSC/TGA	Sample mass, pan, purge gas and heating rate	Thermal risk and transitions
PXRD	Range, step size and scan condition	Crystallinity/polymorphic change
FTIR/Raman	Resolution, scans and sample preparation	Functional-group or structural change
Moisture study	Humidity, exposure time and method	Packaging and drying target

5. Drug–Polymer Compatibility Assessment:

5.1 Risk-based selection of mixtures

Compatibility experiments should reflect the actual formulation and likely worst cases. Binary drug–polymer mixtures are useful for isolating interactions, while ternary or complete formulations are needed to capture effects of plasticisers, buffers and stabilizers. Ratios should include the intended composition and a drug-rich condition that increases the probability of detecting change. Physical mixtures, cast films and dried microneedle matrices answer different questions and should not be treated as interchangeable.

5.2 Spectroscopic assessment:

Fourier-transform infrared and Raman spectroscopy can identify shifts, broadening or intensity changes associated with hydrogen bonding, ionic interaction or structural rearrangement. Interpretation should account for dilution and overlapping polymer bands. Small peak shifts are not automatically incompatibilities; they may represent favourable molecular dispersion. For insulin, circular dichroism, fluorescence or other conformational methods may be needed because preservation of secondary or tertiary structure is more important than retention of a single infrared band.

5.3 Thermal and solid-state assessment:

DSC, TGA and PXRD can indicate whether the drug remains crystalline, becomes molecularly dispersed or undergoes a new transition. Loss of a melting endotherm may improve apparent dissolution yet also create a metastable amorphous system. The stability of that state under humidity and temperature should be examined. Thermal data obtained at high heating rates cannot directly predict months of storage; accelerated isothermal stress studies provide a more relevant chemical challenge.

5.4 Isothermal stress and chromatographic evidence:

Mixtures should be stored under selected temperature and humidity conditions in closed or open containers according to the mechanism under investigation. Samples are examined initially and after predefined intervals for appearance, assay and impurities using a stability-indicating method. Chromatographic evidence carries more weight for chemical compatibility than visual or thermal evidence alone. A change should be compared with drug-only and excipient-only controls so that degradation caused by moisture or temperature is not wrongly assigned to interaction.

5.5 Decision rule:

Compatibility is a weight-of-evidence judgement. An excipient should not be rejected solely because a spectral shift appears, nor accepted solely because no new peak is visible. The decision should consider the magnitude and reproducibility of assay loss, impurity growth, physical change, functional performance and likely patient exposure. Where a useful polymer creates a manageable risk, formulation pH, antioxidant, chelator, drying condition or packaging may provide a control strategy.

Observation	Possible interpretation	Required follow-up
FTIR/Raman shift	Hydrogen bonding, ionic interaction or overlap	Repeat, compare ratios and use orthogonal methods
DSC peak loss	Dilution, amorphization or molecular dispersion	PXRD and microscopy; assess storage stability
New impurity peak	Chemical degradation or analytical artefact	Confirm identity, mass balance and controls
Assay decline without impurity growth	Extraction loss, adsorption or undetected degradant	Recovery study and alternative diluent

Visible crystals after drying	Supersaturation or phase separation	Microscopy/PXRD and loading adjustment
Increased moisture uptake	Polymer/drug hygroscopicity	Mechanical testing and packaging study

6. Analytical Method Development:

6.1 Choice of technique:

UV–visible spectrophotometry may be suitable when the drug has adequate absorptivity, excipients do not interfere and degradation products are not the analytical target. It offers speed and low cost for screening. High-performance liquid chromatography is generally preferable for stability, skin-extract and complex formulation work because it can separate the active drug from excipients and degradants. For proteins, size-exclusion, ion-exchange or reversed-phase methods may be combined with bioactivity or structural assays. The technique should follow the analytical target profile, not laboratory familiarity alone.

6.2 Chromatographic development:

Chromatographic development should examine stationary phase, mobile-phase composition, pH, buffer strength, organic modifier, flow rate, column temperature, detection wavelength and injection volume. Resolution of the drug from placebo and degradation products is more important than achieving a short retention time. Peak symmetry, efficiency, carryover and system pressure should be monitored. For ionizable drugs, mobile-phase pH relative to pKa can strongly influence retention and peak shape.

6.3 Sample preparation and extraction:

Microneedle samples create distinctive recovery problems. A patch may contain a drug-rich tip layer, a lower-dose shaft and a backing layer. The extraction solvent must dissolve the relevant polymer and release the drug without causing degradation or excessive viscosity. Mixing time, sonication, temperature, centrifugation, filtration and dilution should be optimized. Filter adsorption and analyte loss to plasticware should be investigated, especially at low concentrations or with proteins.

Skin-deposition and permeation samples require matrix-specific validation or qualification. Tissue homogenates can contain lipids and proteins that alter extraction and detector response. Receptor-media stability should be established over the experiment and autosampler period. Sampling replacement must be considered when calculating cumulative permeation. A method validated only in neat buffer should not be described as validated for skin extracts.

6.4 Forced degradation and specificity:

Forced degradation challenges the method's ability to distinguish the intact drug from likely degradants. Acid, base, oxidation, heat, light and humidity stresses should be selected according to molecular risk and stopped before indiscriminate destruction occurs. The aim is not a predetermined percentage of degradation at any cost, but meaningful pathway coverage. Peak purity tools can support specificity but do not prove mass balance. Orthogonal detection or degradant identification may be required when co-elution remains possible.

Development variable	What is examined	Desired outcome
Diluent/extraction solvent	Solubility, recovery and stability	Complete, reproducible extraction
Wavelength/detector	Sensitivity and selectivity	Adequate response without

		placebo interference
Column/mobile phase	Retention, resolution and symmetry	Separation of analyte and relevant degradants
Filter/container	Adsorption and leachables	No meaningful recovery loss or interference
Run time	Late-eluting peaks and throughput	Sufficient elution window with practical analysis
Autosampler stability	Change during queued analysis	Defined allowable holding period

7. Validation According to ICH Q2(R2):

Validation should demonstrate that the procedure is fit for its stated purpose. The protocol must define the reportable range, matrices, preparation procedure, replication, calculations and acceptance criteria before testing. Validation cannot rescue a poorly understood method; development knowledge should justify the selected conditions and critical parameters. ICH Q2(R2) emphasizes a science- and risk-based approach that is aligned with the analytical procedure's intended use (International Council for Harmonisation, 2023).

7.1 Specificity and selectivity:

Specificity is evaluated with blank, placebo, drug standard, stressed drug and, where relevant, skin or receptor-matrix samples. The drug response should be free from meaningful interference. In chromatographic methods, resolution, retention consistency and peak purity are considered. For a UV method, spectral overlap may make stability indication impossible even when the placebo has low absorbance at the selected wavelength.

7.2 Linearity, range and response model:

Calibration levels should span the concentrations expected after all dilutions, not merely produce a high coefficient of determination. Residuals, back-calculated concentrations and variance across the range should be examined. Weighted regression may be appropriate when variability increases with concentration. The calibration model, number of levels and replicate structure should be justified. A correlation coefficient alone is not adequate evidence of linearity.

7.3 Accuracy and precision:

Accuracy should be tested by recovery from representative placebo or matrix at multiple levels across the reportable range. For patch content, spiking blank polymer matrix before extraction provides stronger evidence than adding standard directly to a final clear solution. Repeatability examines short-term variation, while intermediate precision includes relevant changes in analyst, day, instrument or column. Results should be reported as individual recoveries, mean recovery, standard deviation and relative standard deviation.

7.4 Detection and quantitation limits:

Limits of detection and quantitation are important for impurity, permeation and deposition measurements but may be unnecessary for a high-concentration assay. Signal-to-noise, calibration statistics or another justified approach may be used. The quantitation limit should be confirmed experimentally with acceptable precision and accuracy. Instrumental detection is not equivalent to quantitative capability after extraction from skin or polymer matrix.

7.5 Robustness and system suitability:

Robustness evaluates deliberate small changes in influential conditions such as pH, organic composition, flow rate, temperature or wavelength. Changes should reflect method understanding and realistic operating variation. System-suitability tests—such as resolution, tailing, efficiency, replicate-injection precision and retention—provide an operational check before or during routine analysis. Acceptance criteria should be linked to method performance rather than copied without justification.

Validation characteristic	Suggested design	Typical report
Specificity	Blank, placebo, analyte, stressed and matrix samples	Interference, resolution and peak-purity evidence
Linearity/range	At least five justified levels with residual review	Model, slope, intercept, residuals and back-calculation
Accuracy	Matrix recovery at low, middle and high levels	Individual and mean % recovery
Repeatability	Independent preparations at relevant levels	Mean, SD and %RSD
Intermediate precision	Different analyst/day/instrument as relevant	Pooled variability and comparison
LOQ	Low-level confirmation	Precision and accuracy at LOQ
Robustness	Deliberate small method changes	Effect on assay and system suitability

8. Calculations and Data Integrity:

Drug content is commonly expressed as the measured drug mass per patch or as a percentage of label claim. Content uniformity requires individual patch or array measurements rather than repeated injections from one pooled extract. Extraction recovery should be considered separately from assay precision. For permeation, cumulative amount must correct for sample removal and replacement. Flux is estimated from the justified linear portion of cumulative permeation per unit area versus time, and the permeability coefficient may be calculated as flux divided by donor concentration when assumptions are satisfied.

All calculations should be traceable to raw instrument files, sample weights, dilution factors and patch identifiers. Failed injections, excluded calibration points and reintegration should be documented. The analytical report should distinguish method-development trials from validation runs and should preserve unsuccessful experiments that influenced decisions. Data integrity is not an administrative addition; it is necessary for demonstrating that formulation conclusions are supported by reproducible measurements.

Quantity	Expression	Essential qualification
Drug content	Measured mass $\times$ dilution factor / patch	Validated extraction recovery
% label claim	Measured content / target content $\times$ 100	Verified target and sample identity
% recovery	Recovered amount / added	Representative placebo or

	$\text{amount} \times 100$	matrix
%RSD	$\text{SD} / \text{mean} \times 100$	Independent preparations
Cumulative permeation	Current receptor amount + removed-sample correction	Known receptor volume and sampling schedule
Flux	Slope of linear permeation region / area	Justified steady-state interval

9. Integrated Decision Framework:

The three workstreams converge in a formulation-selection decision. Preformulation identifies whether the molecule can be processed and what stresses must be controlled. Compatibility testing identifies excipients and conditions that preserve chemical and physical quality. Analytical validation establishes whether those differences can be measured with sufficient reliability. Optimization should not begin until the method can distinguish true formulation effects from extraction or measurement error.

Decision gate	Evidence required	Outcome
Drug feasibility	Dose, solubility, stability and analytical response	Proceed, reformulate concept or reject platform
Excipient compatibility	Orthogonal physical and chemical evidence	Select polymer/additive and control risks
Casting readiness	Solution stability, rheology and hold time	Define solution-preparation procedure
Analytical readiness	Specificity, recovery, range and precision	Authorize formulation comparison
Stability readiness	Degradation pathways and stability-indicating method	Define packaging and protocol
Performance readiness	Validated measurement in release/permeation matrices	Support delivered-dose conclusions

10. Conclusion:

Preformulation, drug–polymer compatibility and analytical validation form the scientific foundation of an antidiabetic dissolving microneedle patch. Preformulation determines whether the drug can be loaded, dried and stored without losing relevant quality. Compatibility assessment explains how polymers and additives influence the drug’s chemical and physical state. Analytical validation ensures that formulation, release, permeation and stability conclusions are based on measurements that are specific, accurate and precise.

The most defensible development strategy is integrated and risk-based. Drug selection should reflect dose capacity and therapeutic need; compatibility should be assessed through orthogonal methods and stressed mixtures; analytical target profiles should be matrix-specific; and validation should follow ICH Q2(R2) with transparent calculations and data integrity. Once verified experimental data become available, this framework can support an original research report without exaggerating the meaning of a spectral shift, a high correlation coefficient or nominal patch content.

References:

1. Dalvi, M., Kharat, P., Thakor, P., Bhavana, V., Singh, S. B., & Mehra, N. K. (2021). Panorama of dissolving microneedles for transdermal drug delivery. *Life sciences*, 284, 119877. <https://doi.org/10.1016/j.lfs.2021.119877>
2. Donnelly, R. F. (2017). How can microneedles overcome challenges facing transdermal drug delivery?. *Therapeutic delivery*, 8(9), 725-728. <https://doi.org/10.4155/tde-2017-0028>
3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (2003). Q1A(R2): Stability testing of new drug substances and products.
4. International Diabetes Federation. (2021). *IDF diabetes atlas* (10th ed.).
5. Shriky, B., Babenko, M., & Whiteside, B. R. (2023). Dissolving and Swelling Hydrogel-Based Microneedles: An Overview of Their Materials, Fabrication, Characterization Methods, and Challenges. *Gels* (Basel, Switzerland), 9(10), 806. <https://doi.org/10.3390/gels9100806>
6. Tuan-Mahmood, T. M., McCrudden, M. T., Torrisi, B. M., McAlister, E., Garland, M. J., Singh, T. R., & Donnelly, R. F. (2013). Microneedles for intradermal and transdermal drug delivery. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 50(5), 623-37. <https://doi.org/10.1016/j.ejps.2013.05.005>
7. Zhao, J., Xu, G., Yao, X., Zhou, H., Lyu, B., Pei, S., & Wen, P. (2022). Microneedle-based insulin transdermal delivery system: current status and translation challenges. *Drug delivery and translational research*, 12(10), 2403-2427. <https://doi.org/10.1007/s13346-021-01077-3>
8. Yu, X., Zhao, J., & Fan, D. (2023). The Progress in the Application of Dissolving Microneedles in Biomedicine. *Polymers*, 15(20), 4059. <https://doi.org/10.3390/polym15204059>
9. Li, M., Vora, L. K., Peng, K., & Donnelly, R. F. (2022). Trilayer microneedle array assisted transdermal and intradermal delivery of dexamethasone. *International journal of pharmaceutics*, 612, 121295. <https://doi.org/10.1016/j.ijpharm.2021.121295>
10. Nasiri, M. I., Vora, L. K., Ershaid, J. A., Peng, K., Tekko, I. A., & Donnelly, R. F. (2022). Nanoemulsion-based dissolving microneedle arrays for enhanced intradermal and transdermal delivery. *Drug delivery and translational research*, 12(4), 881-896. <https://doi.org/10.1007/s13346-021-01107-0>
11. Kim, M. J., Seong, K. Y., Kim, D. S., Jeong, J. S., Kim, S. Y., Lee, S., Yang, S. Y., & An, B. S. (2022). Minoxidil-loaded hyaluronic acid dissolving microneedles to alleviate hair loss in an alopecia animal model. *Acta biomaterialia*, 143, 189-202. <https://doi.org/10.1016/j.actbio.2022.02.011>
12. Yang, G., Yang, J., Diao, Z., Long, J., Shu, Z., Liu, C., & Wan, W. (2025). Cascade-targeting pH/ROS microneedles promote scarless diabetic wound healing by macrophage metaboimmune reprogramming. *Science advances*, 11(44), eadw3834. <https://doi.org/10.1126/sciadv.adw3834>
13. Chen, Q., Cheng, Y., Huang, Z., Du, S., Lyu, Q., Chen, S., Tao, J., Zhang, L., & Zhu, J. (2026). All Drug Glassy Microneedle Patches for Instantaneous Transdermal Delivery. *Advanced materials* (Deerfield Beach, Fla.), 38(2), e12849. <https://doi.org/10.1002/adma.202512849>
14. World Health Organization. (2024). *Guidance on global monitoring for diabetes prevention and control: Framework, indicators and application*.