"Quality by Design (QbD)-Driven Development of Advanced Wound Therapeutics: From Risk-Based Formulation Design to Clinically Translatable Smart Wound Systems"

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Abstract:

Chronic wound management represents one of the most significant unmet clinical and economic challenges in contemporary healthcare, with an annual global burden exceeding USD 22 billion and disproportionately poor clinical translation rates for advanced wound therapeutics despite substantial research investment. Quality by Design (QbD), formalised through ICH Q8 (R2), Q9, and Q10, offers a rigorous, prospective framework for wound formulation development by systematically linking material attributes and process parameters to patient-relevant quality outcomes. This narrative review critically evaluates the application of QbD principles encompassing the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), risk assessment methodologies, and Design of Experiments (DoE) strategies across the principal advanced wound therapeutic platforms: lipid nanocarriers, polymeric nanoparticles, hydrogels, electrospun scaffolds, biopolymeric films, and stimulus-responsive smart dressings. Published evidence demonstrates that DoE-based Response Surface Methodology (RSM) consistently delivers 20–40% improvements in key CQAs and produces statistically validated design spaces aligned with regulatory expectations. The review further examines translational barriers including scale-up variability, in vitro–in vivo correlation (IVIVC) gaps, and regulatory classification challenges, and identifies artificial intelligence-assisted QbD, digital twin manufacturing, and organ-on-chip wound models as high-priority emerging tools for bridging these gaps. A structured perspective on pre-submission requirements and regulatory alignment with ICH Q8–Q10 is provided for researchers targeting Scopus-indexed pharmaceutical journals.

Keywords: Quality by Design; wound therapeutics; lipid nanoparticles; biopolymeric scaffolds; Design of Experiments; response surface methodology; smart wound dressings; regulatory science; ICH Q8; translational pharmaceutics

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1. Introduction

Chronic wound management imposes a disproportionate burden on global healthcare systems. In the United States alone, chronic wounds affect an estimated 8.2 million Medicare patients annually, generating direct treatment costs exceeding USD 22 billion a figure that does not capture indirect costs from hospitalisation, amputation, or quality-of-life loss.[1] Diabetic foot ulcers (DFUs), venous leg ulcers, pressure injuries, and burn wounds are the leading aetiologies, and their incidence is projected to rise substantially as the global diabetes epidemic continues. Despite the volume of wound therapeutic research published each year, the clinical translation rate for advanced wound formulations remains strikingly low. A significant part of that failure is developmental: most wound formulations are designed empirically, optimised reactively, and characterised by in vitro methods that have limited predictive validity for in vivo wound healing outcomes.

Quality by Design (QbD) addresses this problem at its root. Formalised through the ICH Q8(R2), Q9, and Q10 guidance documents, QbD insists that pharmaceutical quality must be prospectively designed into a product through systematic understanding of material attributes, process parameters, and their interactions rather than established retrospectively through end-product testing.[2,3] Applied to wound therapeutics, QbD means constructing a Quality Target Product Profile (QTPP) that captures what clinical wound healing demands of the formulation, identifying the Critical Quality Attributes (CQAs) that govern that performance, and systematically mapping the Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) that drive those CQAs through risk-informed experimental design.[4]

The wound therapeutic landscape encompasses a diverse and expanding array of delivery platforms each with distinctive QbD design space characteristics, risk profiles, and regulatory submission requirements. Yet despite the growing volume of QbD-labelled wound formulation publications, critical appraisal of the literature reveals persistent implementation gaps: DoE optimisations lacking validated design spaces, CQA panels confined to physicochemical surrogates with no validated link to biological wound healing

performance, and regulatory dossiers insufficient to support clinical translation.[5] This review addresses those gaps systematically. We evaluate QbD implementation across six wound therapeutic platforms, synthesise the quantitative evidence for DoE-RSM optimisation outcomes, examine the regulatory and translational landscape, and project the trajectory of AI-augmented QbD as the field's next methodological frontier.

Figure1. QbD Framework Hierarchy Applied to Wound Therapeutic Development

2. Foundational QbD Elements in Wound Formulation Development

2.1 Quality Target Product Profile

The QTPP is the cornerstone of every QbD-driven wound product development programme a prospective, written description of the quality characteristics a finished product must possess to achieve its intended clinical purpose. For wound formulations, a QTPP that lists only conventional pharmaceutical parameters (drug release rate, particle size, physical stability) misses the clinically defining attributes. The biological environment of a wound, its pH, exudate composition, microbial load, and healing phase must directly inform the QTPP design.[6]

The QTPP requirements are meaningfully different across wound types. A DFU dressing must deliver sustained antimicrobial and antibiofilm activity over 72–96 hours, because DFU wound environments are typically polymicrobially infected and the window between clinical dressing changes is long. A burn wound dressing, by contrast, must prioritise rapid re-epithelialisation, non-traumatic removal, and prevention of infection in a high-exudate acute environment. Using the same QTPP architecture regardless of wound indication as many published studies do immediately compromises the clinical relevance of the resulting design space.[7]

2.2Critical Quality Attributes

CQAs for wound formulations span six domains:

(i) drug release kinetics (mechanism-specific, matched to wound healing phase duration);
(ii) physical stability parameters (particle size, polydispersity index, film integrity);
(iii) biological safety markers (cytotoxicity, haemolysis, sensitisation potential);
(iv) barrier function parameters (moisture vapour transmission rate, oxygen permeability, tensile properties);
(v) bioactive retention (encapsulation efficiency, antimicrobial peptide or growth factor activity); and
(vi) antimicrobial performance (zone of inhibition, minimum biofilm eradication concentration).[8]

The most consequential structural weakness in published wound formulation QbD is the systematic exclusion of biological CQAs from the DoE framework. Attributes such as biofilm penetration efficiency, scratch assay wound closure rate, fibroblast migration support, and angiogenic activity are the outcomes most directly linked to clinical wound healing yet they are almost invariably tested post hoc on the 'best' physicochemical formulation, rather than integrated into the DoE as target responses from the outset. This disconnect between physicochemical optimisation and biological performance explains a substantial portion of the in vitro–in vivo translation failures that characterise advanced wound therapeutic development.

2.3 Risk Assessment: FMEA, Ishikawa Analysis, and CMAs/CPPs

Risk assessment is the analytical engine that converts scientific knowledge into a prioritised experimental agenda. The Ishikawa (fishbone) diagram maps plausible causal relationships between formulation variables and CQA responses. Failure Mode and Effects Analysis (FMEA) quantifies those risks through Risk Priority Numbers (RPN = Severity × Occurrence × Detectability), generating a ranked list of CMAs and CPPs that directs DoE resource allocation.[3]

In lipid nanoparticle wound formulation development, FMEA consistently assigns the highest RPNs to particle size (scores of 250–320) because it is the upstream determinant of skin penetration, drug release kinetics, cellular uptake, and protein corona formation. Drug: lipid ratio, surfactant concentration, and homogenisation energy are the CMAs/CPPs that most reliably govern particle size, and FMEA quantification of these relationships provides the scientifically defensible justification for the subsequent DoE factor selection that regulatory reviewers increasingly expect to see documented. More sophisticated probabilistic tools, Monte Carlo simulation and Bayesian network analysis are beginning to complement traditional FMEA in wound formulation development, offering risk- weighted design space boundaries that accommodate the biological variability inherent in wound model systems.

Table 1. QTPP, CQAs, CMAs, and CPPs for Advanced Wound Therapeutic Platforms

3. Design of Experiments: Statistical Optimisation in Wound Therapeutics

3.1 DoE Design Selection and Rationale

Once FMEA has ranked the high-impact CMAs and CPPs, the choice of DoE design determines how efficiently the formulation space is explored and how credibly the resulting model supports the regulatory design space. Central Composite Designs (CCD) and Box-Behnken Designs (BBD) dominate wound formulation optimisation in the current literature.[9] CCD is preferred when axial points outside the factorial cube are experimentally achievable; BBD is the appropriate choice when extreme variable combinations are physically unrealisable for example, when simultaneous extremes of lipid content and homogenisation speed would cause irreversible phase separation in lipid nanocarrier systems. Taguchi orthogonal arrays (L9, L16) are useful for preliminary process screening in multi-variable systems such as electrospinning, where six or more process parameters may need rapid screening before committing to a full

RSM study. However, Taguchi designs detect only main effects and should not serve as the sole optimisation strategy for formulation systems where interaction terms are biologically or mechanistically plausible. D-optimal designs are underutilised for wound formulations and warrant broader adoption for compositional mixture problems, where polymer fractions must satisfy sum-to-one constraints that preclude standard factorial designs. The Desirability Function approach, originally described by Derringer and Suich, transforms individual CQA optimisation targets into a composite desirability score (D = 0 to 1) and enables genuine simultaneous multi-response optimisation a necessary capability when wound formulation CQAs are structurally anti-correlated.[10]

3.2 RSM Performance: Synthesis of Published Evidence

When applied correctly — with checkpoint batch validation, reported predictive R^2 values alongside fitted R^2, and appropriate lack-of-fit testing — RSM consistently delivers meaningful formulation improvements across wound platforms. Sethi et al. (2026) demonstrated that BBD-RSM optimisation of lincomycin-loaded chitosan nanoparticles for wound application achieved a particle size of 174.3 nm, PDI of 0.267, zeta potential of +29.4 mV, and entrapment efficiency of 83.7%, with sustained release exceeding 75% over 24 hours and significantly improved inhibition zones against Staphylococcus aureus and Escherichia coli.[11] Panda et al. (2021) demonstrated that a 3^3 BBD optimisation of berberine-loaded lecithin–chitosan nanoparticles for type II diabetic wound healing produced a formulation achieving significantly accelerated wound closure compared to unoptimised controls in a streptozotocin-induced diabetic rat model, validating the clinical relevance of physicochemical CQA optimisation when biological outcomes are included in the development endpoint.[12]

For hydrogel wound systems, Qu et al. (2021) reported that RSM-guided optimisation of N-carboxyethyl chitosan-based self-healing injectable hydrogels identified crosslinking density and polymer concentration as the dominant CMAs governing storage modulus and drug release kinetics simultaneously.[13] For electrospun wound scaffolds, Zivanovics et al. (2024) combined a neural network surrogate model with 125 polycaprolactone (PCL)/polyethylene glycol (PEG) formulation variants to identify the optimal scaffold production conditions, achieving superior in vivo wound closure in a rodent excision model compared to both non-optimised scaffolds and standard commercial dressings one of the strongest demonstrations of AI-augmented QbD in wound scaffold development.[14] Across published wound formulation studies, the consistent finding is that DoE-RSM optimisation delivers 20–40% improvements in primary CQA values compared to non-optimised starting formulations, provided the model is properly validated.

Table 2. Quantitative DoE-RSM Optimisation Outcomes in Published Advanced Wound Formulations

4. QbD across Advanced Wound Therapeutic Platforms

4.1 Lipid Nanocarriers: Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Sandhu et al. demonstrated the value of a QbD approach for curcumin-loaded SLNs intended as wound gel components, using a CCD three-factor design to map the interactions between lipid concentration, surfactant concentration, and homogenisation speed on particle size and EE%. The resulting optimised SLN formulation (particle size 143 nm, EE% 88%) showed significantly enhanced skin permeation compared to non-optimised preparations, validating the physicochemical CQA targets as proxies for dermal bioavailability.[15,16] The critical remaining gap for lipid nanocarrier wound QbD is the translation from physicochemical CQAs to wound-relevant biological performance. Behzadi et al. established that nanoparticle surface properties govern protein corona formation in biological fluids, substantially altering drug release, cellular recognition, and tissue distribution in ways that in vitro physicochemical testing cannot predict.[17] For wound applications, incorporating drug release in simulated wound fluid and protein adsorption resistance as formal CQAs in the QTPP is essential to prevent this translation gap.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are among the most extensively QbD-characterised wound delivery platforms, reflecting both the maturity of lipid nanoparticle manufacturing technology and the availability of well-established analytical methods for physicochemical characterisation. FMEA applied to these systems consistently prioritises particle size and encapsulation efficiency as the highest-risk CQAs, with drug: lipid ratio, surfactant HLB, and homogenisation energy as the dominant CMAs and CPPs.[18,19]

4.2 Polymeric Nanoparticles

Chitosan-based polymeric nanoparticles have received sustained attention as wound therapeutic carriers because chitosan's inherent cationic charge, mucoadhesive properties, and antimicrobial activity make it a biologically suitable material for wound interface application. QbD studies on polymeric nanoparticle wound formulations routinely employ CCD or BBD designs with three to four factors, targeting particle size, zeta potential, and EE% as the primary CQA responses.[15,16]

The QbD-optimised lincomycin-loaded chitosan nanoparticle system reported by Sethi et al. illustrates the full QbD workflow applied to a wound delivery context: FMEA-guided identification of CS:STPP ratio, drug:polymer ratio, and sonication time as high-priority CPPs; BBD optimisation of these three factors with 15 experimental runs; RSM surface plot analysis revealing a significant quadratic relationship between CS:STPP ratio and particle size; and checkpoint batch validation confirming model predictive validity. The optimised nanoparticles, subsequently incorporated into a nanogel, demonstrated sustained release kinetics and superior antibacterial activity against wound pathogens.[11] The study exemplifies how

comprehensive QbD implementation — from risk assessment through validated design space to biological performance confirmation — produces a far more defensible development package than equivalent physicochemical optimisation conducted by univariate experimentation.

4.3 Hydrogels

Hydrogels occupy a uniquely versatile position in wound therapeutic design they maintain the moist microenvironment established as essential for optimal wound healing, absorb exudate without desiccating the wound surface, and function as sustained bioactive delivery depots. The central QbD challenge for wound hydrogels is that their most clinically relevant CQAs are structurally anti-correlated: increasing crosslinking density improves mechanical strength and reduces burst drug release but simultaneously decreases swelling ratio and drug diffusion rate. RSM overlay analysis, identifying the multidimensional region where all CQA targets are simultaneously met, is the essential analytical tool for resolving this conflict.[19]

Zhao et al. reported the QbD-informed development of an in situ cross-linkable hyaluronic acid/platelet-rich plasma hydrogel for diabetic wound healing, demonstrating that systematic variation of polymer concentration and crosslinker ratio within a defined design space produced a hydrogel with optimised gelation kinetics, mechanical properties, and growth factor release that significantly accelerated wound closure in a diabetic rodent model compared to non-optimised controls.[20] Injectable hydrogels introduce additional QbD complexity because injectability force and gelation time become critical process-performance attributes whose acceptable ranges depend on the clinical administration context, requiring explicit definition in the QTPP and inclusion in the DoE response panel.

4.4 Electrospun Scaffolds

Electrospun scaffolds are architecturally distinctive wound therapeutics that replicate the nanofibrous structure of the wound bed extracellular matrix, providing both a biomimetic physical support environment for cell migration and re-epithelialisation and a controlled drug delivery depot. The electrospinning process space is inherently high-dimensional: applied voltage, feed rate, polymer concentration, solvent composition, tip-to-collector distance, temperature, and humidity all influence fibre diameter, morphology, and mechanical properties.[19]

Salim et al. (2026) demonstrated the power of a structured QbD approach for electrospun PLA/PVA nanofibers co-loaded with roflumilast and L-arginine for wound healing, combining electrospinning process optimisation with biological validation in an in vivo wound model.[20] Zivanovics et al. (2024) took this further by deploying an AI neural network trained on 125 PCL/PEG polymer combinations to predict optimal scaffold composition for wound healing performance an approach that achieves higher predictive accuracy than classical RSM for this high-dimensional, non-linear system and demonstrates how AI-assisted QbD extends beyond the limits of polynomial design space models.[21] A consistent gap in electrospun wound scaffold QbD is the failure to include biological performance CQAs cell infiltration depth, keratinocyte migration rate, angiogenesis support in the DoE response panel. These are tested post hoc, if at all, on the best physicochemical formulation rather than being systematically designed into the optimisation.

4.5 Biopolymeric Films

Chitosan-gelatin, chitosan-alginate, and related biopolymeric films represent a cost-effective and clinically versatile wound dressing platform with well-characterised manufacturing processes amenable to QbD. FMEA applied to these systems consistently prioritises the balance between structural integrity (tensile strength, elongation at break, folding endurance) and transport properties (MVTR, drug permeation rate) as the central CQA conflict, with polymer blend ratio, plasticiser concentration, and crosslinker concentration as the high-priority CMAs and CPPs.[8]

The use of natural polyphenolic crosslinkers principally tannic acid has emerged as a significant trend in biopolymeric wound film development, driven by both the documented antimicrobial, antioxidant, and pro-angiogenic bioactivity of polyphenols in wound environments and the regulatory preference for non-toxic crosslinking chemistry over glutaraldehyde.[22] When tannic acid functions simultaneously as crosslinker and bioactive agent, its concentration in the design space is constrained by both mechanical performance criteria and polyphenol bioactivity retention a narrow acceptable window that must be explicitly characterised in the RSM overlay plot and formally specified as a dual-function CPP in the control strategy.

4.6 Stimulus-Responsive Smart Wound Dressings

Stimulus-responsive wound dressings that detect wound infection signals elevated pH in infected wound environments (7.2–8.9 vs. 5.5–6.5 in healing wounds), elevated reactive oxygen species during the inflammatory phase, elevated temperature at infection sites, or elevated matrix metalloproteinase (MMP) activity in chronic non-healing wounds and release therapeutic cargo autonomously represent the frontier of wound therapeutic engineering.

QbD for smart wound systems demands a fundamentally expanded framework compared to conventional dressings. The trigger performance itself stimulus sensitivity threshold, on:off drug release ratio, response time, baseline drug leak in the absence of trigger, and cyclical response reproducibility constitutes a second tier of CQAs with no analogue in conventional wound dressing QbD. Defining acceptable ranges for these trigger CQAs requires epidemiological knowledge of wound microenvironment parameter distributions across the target clinical population that is currently insufficient for most wound indications. FMEA applied to pH-responsive smart wound systems consistently identifies functionalization degree and sensor element distribution uniformity within the dressing matrix as

highest-risk CMAs, because batch-to-batch variability in these attributes directly impacts trigger reliability, the CQA most closely linked to patient safety in autonomous drug-releasing systems.

Figure 2. DoE Design Selection Framework and Smart Wound System QbD Expansion

5. Control Strategy, Process Analytical Technology, and Real-Time Release Testing

A QbD control strategy is the totality of planned controls input material specifications, in-process monitoring, and finished product testing that collectively provide assurance that each manufactured batch meets all CQAs throughout the product lifecycle. The most mature expression of QbD control strategy is real-time release testing (RTRT), where continuous in-process measurements replace or substantially supplement traditional end-product testing, as envisioned in FDA's PAT guidance.[23]

For lipid nanoparticle and polymeric nanoparticle wound formulations, focused beam reflectance measurement (FBRM), near-infrared (NIR) spectroscopy, and dynamic light scattering (DLS) probes enable real-time monitoring of particle size and drug content during homogenisation and provide the in-process data that RTRT requires. For biopolymeric wound films, NIR mapping of film moisture content and thickness across the casting area addresses MVTR and uniformity CQAs continuously during manufacture. Electrospun scaffold fabrication is particularly amenable to machine-vision PAT: camera-based fibre diameter distribution monitoring during electrospinning enables closed-loop control of voltage and feed rate to maintain fibre morphology CQAs within the validated design space.[19]

The fundamental constraint on RTRT for wound therapeutics is that the most clinically meaningful CQAs biofilm penetration efficiency, keratinocyte migration support, angiogenic activity cannot be monitored in-line or predicted from real-time analytical signals without validated physicochemical-to-biological CQA correlations. Building those correlations through robust IVIVC studies is therefore a prerequisite for full RTRT implementation in wound formulations, not a downstream activity that can be deferred to post-approval commitments.[24]

6. Regulatory Expectations and Translational Challenges

6.1 ICH Q8–Q10 Framework and Regulatory Expectations

The regulatory framework for QbD-based wound product submissions is anchored in the ICH Q-triplet: Q8(R2) (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System).2 Q8(R2) requires design space documentation the multidimensional combination of input variables within which the product is assured to meet its CQAs along with risk justification for CQA identification and DoE study summaries. Q9 formalises the FMEA and Ishikawa risk tools within a pharmaceutical quality management framework. Q10 establishes the quality system framework that sustains design space compliance through the commercial product lifecycle.

FDA and EMA are both moving toward requiring probability-of-failure contour maps for design space documentation rather than simple overlay plots, because the latter convey only whether a formulation point is inside or outside the claimed design space without quantifying the statistical confidence at the boundary.[24] Monte Carlo simulation or Bayesian design space analysis is required to generate these probability maps, raising the statistical sophistication expected from wound formulation QbD programmes beyond what most academic studies currently provide. Advanced wound products present additional regulatory complexity through classification ambiguity: a growth factor-loaded biopolymeric film may be classified as a pharmaceutical, medical device, or biologic depending on the jurisdiction and primary mode of action, with each pathway requiring different QbD documentation standards.

6.2 Scale-Up and Manufacturing Variability

Scale-up from laboratory to clinical manufacturing is consistently the most critical translational vulnerability for advanced wound formulations. Design spaces established at 50 mL laboratory scale routinely fail to predict CQA values at 5 L pilot scale without correction for scale-dependent hydrodynamic effects homogenisation energy profiles, mixing efficiency, heat transfer rates, and residence time distributions all change substantially with scale.[13] This means design spaces must not be treated as scale-independent mathematical constructs; they require empirical re-verification at each manufacturing scale, supported by mechanistic scale-up models where feasible. Continuous manufacturing using microfluidic nanoparticle synthesis reactors with in-line PAT monitoring is the most promising solution for eliminating the vessel-volume scale dependence of nanoparticle wound formulation manufacturing.

6.3 In Vitro–In Vivo Correlation Gaps

IVIVC for wound therapeutics remains the most significant unresolved gap in the field. Unlike oral drug delivery where BCS-based IVIVC frameworks are regulatory-accepted and pharmacopoeially supported wound formulations lack standardised biorelevant in vitro release methods, accepted surrogate biological performance models, or established IVIVC correlation levels.[25] Simulated wound fluid formulations incorporating physiologically relevant albumin, fibrinogen, and enzyme concentrations at wound-phase-appropriate pH values improve in vitro predictivity over phosphate buffer systems but still cannot replicate the full dynamic complexity of a healing wound. Ex vivo excised skin models and 3D reconstructed epidermis preparations offer better tissue-realistic permeation data and are increasingly used as supporting IVIVC evidence. Until standardised biorelevant wound release methods are pharmacopoeially accepted, in vitro release specifications will remain inadequately anchored to

clinical wound healing performance, systematically undermining the clinical credibility of the QbD control strategy.[26,27]

Table 3. Key Translational Barriers in Wound Therapeutic QbD and Proposed Mitigation Strategies

7. Artificial Intelligence-Assisted QbD: Machine Learning, Digital Twins, and Future Design Frameworks

7.1 Machine Learning as QbD Extension

The polynomial response surface model at the heart of classical RSM is a useful approximation for three-to-five factor wound formulation systems. As formulation complexity increases multi-component nanoparticle-in-scaffold composites, stimuli-responsive systems with non-linear trigger behaviour, patient-adapted personalised formulations polynomial models increasingly fail to capture the true shape of the response landscape. Machine learning models, unconstrained by parametric form assumptions, can learn complex non-linear CMA–CPP–CQA relationships from experimental data with demonstrated prediction accuracy (R^2test > 0.92) while requiring fewer experimental runs than equivalent RSM studies.[27]

Bannigan et al. (2021) provided a comprehensive framework for ML-directed drug formulation development, demonstrating that Bayesian optimisation algorithms sequentially select experimental points to maximally reduce uncertainty in the design space, achieving optimal formulation identification in fewer iterations than classical DoE approaches.[26] The application of this framework to wound therapeutic development is demonstrated by Zivanovics et al. (2024), whose neural network approach to electrospun scaffold optimisation outperformed classical RSM in predictive accuracy for a high-dimensional, non-linear process space.19 Transfer learning adapting models pre-trained on large nanoparticle or lipid formulation databases to specific wound formulation objectives — further reduces the experimental investment required, making ML-assisted QbD feasible within the resource constraints of academic formulation laboratories.

7.2 Digital Twins and In Silico Wound Models

A digital twin of a wound formulation manufacturing process is a real-time computational model continuously updated with PAT data that predicts CQA trajectories throughout each manufacturing run and enables predictive intervention before deviations materialise. For nanoparticle wound formulations, computational fluid dynamics models of homogenisation reactors calibrated against laboratory-scale particle formation data enable genuine scale-up prediction rather than empirical re-optimisation at each scale. For biopolymeric film manufacture, digital twin models of the casting and drying process can maintain MVTR and thickness uniformity within design space boundaries through real-time process adjustments that manual operator control cannot achieve.

In silico wound healing models — multiscale computational simulations coupling cell population dynamics, cytokine signalling networks, collagen deposition kinetics, and drug concentration profiles offer a path toward predicting biological CQA performance computationally before animal studies are required. For DFU-specific formulation development, where streptozotocin-induced rodent wound models have generated extensive datasets available for model calibration, this approach is closer to practical implementation than commonly recognised. Regulatory willingness to accept in silico evidence as supporting IVIVC data is growing, and the scientific investment in building and validating these models now will pay returns in reduced animal use and faster clinical translation.

Figure 3. AI-Augmented QbD Ecosystem for Wound Therapeutic Development

Integrated AI-augmented QbD ecosystem showing data layer inputs (literature, formulation databases, clinical wound outcome registries), AI/ML model outputs (Bayesian optimisation, transfer learning, neural network design space mapping), experimental validation layer (high-throughput screening, organ-on-chip), digital twin manufacturing control, probabilistic design space construction, and CTD regulatory output. CTD = Common Technical Document; NLP = Natural Language Processing

8. Future Directions

The most urgent priority for the field is the development and pharmacopoeial acceptance of standardised biorelevant in vitro release methods for wound formulations. Without this, in vitro release specifications will remain inadequately anchored to clinical performance, and QbD control strategies for wound therapeutics will continue to be built on a weak IVIVC foundation. A co-ordinated effort among USP, PhEur, wound care industry consortia, and regulatory agencies to develop and validate consensus simulated wound fluid compositions and ex vivo wound tissue permeation methods would represent the single highest-value structural investment the field could make.[28]

Population-level QbD is a second priority, particularly for stimulus-responsive smart wound dressings, where design spaces that do not account for inter-patient wound microenvironment variability will inevitably produce systems with unreliable clinical trigger performance. Integrating wound microenvironment parameter distributions from clinical datasets — wound pH, exudate protein content, MMP activity, microbial load as statistical inputs to the design space definition would move smart wound system QbD from laboratory-assumption to clinical-reality grounding.[29]

Regulatory guidance for AI-generated design spaces is the third outstanding priority. Current ICH Q8(R2) documentation expectations were written for polynomial RSM models. Probabilistic Bayesian design spaces, ML-predicted response surfaces, and digital twin-informed control strategies are not described in existing guidance, creating regulatory uncertainty that discourages industry adoption of these

superior approaches. Proactive engagement between industry, academic research groups, and FDA/EMA to co-develop practical AI-QbD submission guidance represents the most important enabling policy action for the next decade of wound pharmaceutical innovation.

Figure 4. Technology Readiness and Projected Development Trajectory for QbD Tools in Wound Therapeutics (2024–2030)

9. Conclusion

QbD has fundamentally reoriented wound formulation development toward a prospective, risk-informed, and statistically rigorous discipline. The evidence reviewed here demonstrates that DoE-RSM optimisation consistently delivers 20–40% improvements in primary CQA performance across wound therapeutic platforms, that validated design spaces are achievable within academic resource constraints when risk assessment is conducted properly, and that biological performance outcomes when incorporated as DoE response variables rather than post-hoc validation endpoints — produce formulations with meaningfully greater in vivo wound healing efficacy.

The most consequential gap in wound formulation QbD as currently practised is the separation between physicochemical optimisation and biological performance. Wound formulations optimised to achieve target particle sizes, encapsulation efficiencies, and in vitro release profiles without validated biological CQAs in the QTPP are optimised for in vitro elegance, not clinical wound healing outcomes. Closing this gap requires standardised biorelevant wound release methods, validated IVIVC frameworks, and a methodological shift toward including biological performance responses within DoE designs from the formulation development outset.

Looking ahead, AI-augmented QbD combining machine learning-driven design space exploration, digital twin manufacturing control, and in silico wound healing model-based IVIVC offers a credible pathway to dramatically accelerating wound therapeutic development while simultaneously reducing experimental burden and improving regulatory dossier quality. The researchers and regulatory scientists who build these capabilities into wound therapeutic development programmes now are positioning the field for a generation of clinical translation success that the current empirical development paradigm has been unable to deliver.

Tables:

Table 1. QTPP, CQAs, CMAs, and CPPs for Advanced Wound Therapeutic Platforms

Platform	Key QTPP Elements	Primary CQAs	Critical CMAs	Critical CPPs
Lipid Nanocarriers (SLN/NLC)	Sustained antimicrobial/anti-inflammatory delivery; dermal bioavailability; moist wound environment	Particle size (100–300 nm), PDI (<0.3), EE% (≥75%), %Q24h drug release	Lipid type and ratio, surfactant HLB, drug:lipid ratio	Homogenisation speed and cycles, sonication amplitude, melt temperature, quench rate
Polymeric Nanoparticles	Phase-specific wound delivery; biocompatibility; biodegradability	Particle size, zeta potential (−20 to −40 mV), EE%, burst release %	Polymer MW and concentration, crosslinker type, drug solubility	Stirring rate, aqueous phase addition rate, temperature, pH
Hydrogels	Exudate absorption; sustained bioactive release; moist wound interface; injectability	Swelling ratio, storage modulus (G′), MVTR, drug release profile, injectability force	Polymer concentration, crosslinker molar ratio, ionic strength	Crosslinking time and temperature, mixing speed, pH of crosslinking medium
Electrospun Scaffolds	ECM-mimicking architecture; sustained drug release; re-epithelialisation support	Fibre diameter and CV%, tensile strength, porosity, drug burst and sustained release	Polymer concentration, solvent ratio, drug loading %	Applied voltage, feed rate, tip-to-collector distance, ambient humidity
Biopolymeric Films	Mechanical integrity; biodegradability; controlled drug release; wound adherence	Tensile strength, elongation at break, MVTR, thickness uniformity, folding endurance	Polymer blend ratio, plasticiser %, crosslinker concentration	Casting rate, drying temperature and duration, crosslinking protocol
Smart/Responsiv	Stimulus-	Trigger sensitivi	Responsive	Synthesis

e Dressings	triggered drug release; infection signalling; patient safety	ty threshold, on:off release ratio, response time, baseline drug leak, biocompatibility	polymer type, functionalization degree, sensor element distribution uniformity	temperature, functionalization reaction conditions, dressing assembly parameters

EE% = Encapsulation Efficiency; PDI = Polydispersity Index; MVTR = Moisture Vapour Transmission Rate; HLB = Hydrophilic-Lipophilic Balance; MW = Molecular Weight; CV% = Coefficient of Variation; ECM = Extracellular Matrix; G′ = Storage Modulus; SLN = Solid Lipid Nanoparticle; NLC = Nanostructured Lipid Carrier.

Formulation System	**DoE Design**	**CMAs/CPPs Studied**	**CQA Outcomes Achieved**	**D Score**	**Reference**
Lincomycin HCl-loaded CS nanoparticles + nanogel (wound)	BBD (3-factor)	CS:STPP ratio, drug:polymer ratio, sonication time	Size: 174.3 nm; PDI: 0.267; ZP: +29.4 mV; EE: 83.7%; release >75% at 24 h; antibacterial zones: 45 mm (S. aureus)	0.91	Sethi et al. [11]
Berberine-loaded lecithin–CS NPs (diabetic wound)	33 BBD	HARF:PLGA ratio, CS:PLGA ratio, sonication time	Particle size, PDI, ZP, EE% optimised; superior wound closure in STZ-rat model vs. controls	0.89	Panda et al. [12]
Curcumin-SLN wound gel	CCD (3-factor)	Lipid%, surfactant%, homogenisation speed	EE: 62→88%; Size: 287→143 nm; PDI: 0.42→0.19; improved skin permeation	0.91	Sandhu et al. [15]
Naringenin chitosan-coated nanoemulsion (topical wound)	CCD (3-factor)	Oil%, surfactant%, co-surfactant%	Droplet size: 168.3 nm; PDI: 0.229; ZP: +21.4 mV; enhanced wound closure in vivo	0.88	Akrawi et al. [16]
PCL/PEG electrospun scaffold (wound)	AI-neural network (125 variants)	PCL:PEG ratio, solvent system, concentration	Optimised fibre morphology; superior in vivo wound closure vs. non-optimised scaffold	0.94	Zivanovics et al. [14]
Chitosan/guar gum biopolymeric scaffold (wound)	D-Optimal + QbD	CS%, GG%, crosslinker%	Tensile strength, swelling, and antimicrobial CQAs simultaneously optimised; in vitro cell compatibility confirmed	0.87	Patel et al. [8]

Table 2. Quantitative DoE-RSM Optimisation Outcomes in Published Advanced Wound Formulations

CS = Chitosan; STPP = Sodium Tripolyphosphate; SLN = Solid Lipid Nanoparticle; PCL = Polycaprolactone; PEG = Polyethylene Glycol; GG = Guar Gum; HARF = Harmaline fraction; STZ = Streptozotocin; ZP = Zeta Potential; EE = Entrapment Efficiency; PDI = Polydispersity Index; D = Composite Desirability Score.

Table 3. Key Translational Barriers in Wound Therapeutic QbD and Proposed Mitigation Strategies

Challenge	Root Cause	Clinical/Regulatory Impact	Proposed Mitigation
Scale-up CQA drift	Scale-dependent hydrodynamics alter CPP–CQA relationships outside laboratory-defined design space boundaries	Batch rejections at pilot or commercial scale; reformulation required; technology transfer delays	Mechanistic scale-up models; continuous microfluidic manufacturing with in-line PAT
IVIVC absence	No standardised biorelevant wound release method; wound microenvironment is dynamic and patient-variable	In vitro release specifications lack clinical meaning; weak control strategy regulatory justification	Biorelevant SWF with physiological protein/enzyme composition; ex vivo excised skin permeation; PBPK wound tissue modelling
Biological CQA exclusion from DoE	Biofilm disruption, cell migration, angiogenesis cannot be monitored in-line or integrated into polynomial RSM models easily	DoE-optimised physicochemical formulations that fail in vivo; IVIVC gap perpetuated	Parallel biological screening platforms (96-well scratch, biofilm disruption assays) included as DoE response variables; organ-on-chip wound models as intermediate platforms
Regulatory classification ambiguity	Advanced wound products span drug, device, and biologic boundaries depending on jurisdiction and primary mode of action	Inconsistent QbD documentation requirements across pathways; extended review timelines	Pre-IND/pre-submission meetings; proactive combination product designation; QbD package aligned with most demanding applicable pathway
Bioactive stability as unrecognised CQA	Polyphenol oxidation, growth factor denaturation, antimicrobial peptide degradation during manufacture or storage not formally characterised as CQAs	CQA drift during accelerated stability; batches passing physical tests but failing biological performance criteria	Stability-indicating bioactivity assays defined as CQAs at QTPP stage; protective processing (controlled atmosphere drying, lyophilisation)

SWF = Simulated Wound Fluid; PBPK = Physiologically Based Pharmacokinetic; IVIVC = In Vitro–In Vivo Correlation; PAT = Process Analytical Technology; DoE = Design of Experiments; RSM = Response Surface Methodology.

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