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Quality-by-Design Approaches in Nano-Enabled Topical and Transdermal Drug Delivery Systems: A Regulatory and Industrial Perspective

[1] Abubakar Mohamedali Omer Idress, [2] Nawaz Mahammed, [3] Dr Nawaz Mahammed

[1, 2] Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli Cross, Anantapur, Chiyyedu, Andhra Pradesh, India

[3] Associate Professor, Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli Cross, Anantapur, Chiyyedu, Andhra Pradesh, India

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Corresponding Author: **Dr Nawaz Mahammed**

Abstract

Topical and transdermal delivery systems utilizing nanotechnology have a major advantage in enhancing the solubility of drugs, skin penetration and their therapeutic activities but they are complex to develop, changeable in materials and sensitive to scale. Quality-by-Design (QbD) is a scientifically-based approach to these issues, which establishes a clear connection between the Quality Target Product Profile (QTPP), nano-specific Critical Quality Attributes (CQAs), and product performance. Based on the published literature, regulatory guidelines, and topical and transdermal formulations in nano format, this review critically reviews the application of QbD principles, especially with respect to risk assessment tools, Design of Experiments, and control strategies. Regulatively, world bodies are progressively prioritizing on submissions based on QbD with the aim of supporting sound risk management, design space justification, and sound lifecycle control, although some issues of characterization complexity, bioequivalence testing, and *in vitro- in vivo* correlation continue to persist. Industrial-wise, QbD increases the strength of manufacturing, uniformity in batches, scalability and cost efficiency, reducing development risk, and commercializing. Moving ahead, it is predicted that the combination of artificial intelligence-aided QbD, digital twins, and continuous manufacturing will further enhance predictive development, process perception, and regulatory congruence of nano-enabled topical and transdermal systems of drug delivery.

Keywords: Quality-by-Design (QbD), Nano-Enabled Drug Delivery, Topical Drug Delivery, Transdermal Drug Delivery Systems, Regulatory Science, Pharmaceutical Manufacturing

1. Introduction

Topical and transdermal drug delivery systems (T/T DDS) are nanoparticle-enabled pharmaceutical delivery systems that have become the next-generation pharmaceutical delivery systems able to solve the inherent flaws of traditional dermal delivery systems [1]. Poor drug penetration and low bioavailability, dose variability and limited control over drug release are common characteristics of traditional topical dosage forms whereas transdermal systems are limited by high barrier properties of the stratum corneum [2]. Carriers based on nanotechnology, such as liposomes, niosomes, nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers, polymeric nano carriers, and nano gels, provide better solubilization of drugs that are poorly soluble in water, skin permeation, and residence time and delivery to either a specific layer of the skin or the bloodstream [3]. The properties have increased the therapeutic potential of nano-enabled T/T DDS in dermatology, pain treatment, hormone treatment, wound healing, and vaccine delivery.

With these technological improvements, the development of pharmaceuticals has ceased to be conducted empirically and through trial and error mechanisms and begun to be carried out in a systematic, science-focused, methodology represented in the Quality-by-Design (QbD) paradigm [4]. According to the guidelines of the International Council for Harmonisation (ICH) (Q8-Q11), QbD focuses on the overall knowledge of formulation and process variables and their effects on the quality of products [5]. The main QbD components are defining Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), evaluating risks to identify Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs),

and defining a design space with the help of statistical Design of Experiments (DoE). The regulatory bodies like the US Food and Drug Administration and European Medicines Agency are highly recommending the use of QbD to increase the robustness of manufacture, the regularity of product activity, and the regulatory adaptability [6].

There has been an upward trend in the use of QbD principles in nano-enabled topical and transdermal preparations in recent years. There is a large number of studies to DoE-guided optimization of particle size, polydispersivity index, zeta potential, entrapment efficiency, rheology, and *in vitro* release characteristics of nanocarriers embedded into semisolid or patch-based platforms. More sophisticated analytical techniques are finding their way into QbD processes (such as dynamic light scattering, electron microscopy, rheological studies, *in vitro* skin permeation studies in Franz diffusion cells, etc.) to determine correlations among CQAs and formulation performance. Regulatively, nanomedicines tend to be reviewed under the current pharmaceutical regulations under a risk-based approach, as long as there are sufficient characterization and safety data supplied. Even though the industrial case studies point at the fact that early QbD implementation can lead to reduced formulation failures, scale-up, and post-approval change management, the majority of the marketed nano-topical products are still based on a partially empirical approach to development [7].

Although this has attracted increased interest, there are various knowledge gaps that prevent systematic use of QbD in nano-enabled T/T DDS. The linkage of nano-specific CQAs, including particle size, surface charge, lipid composition, and release kinetics, and clinically significant endpoints has not been adequately developed. Technically, because nanocarriers are complex to analytically characterize in complex topical matrices, there is no harmonized set of tests which are universally agreed upon. In addition, there are no strong *in vitro-in vivo* correlations (IVIVC) of dermal and transdermal delivery that can make it difficult to justify regulatory design spaces. Reproducibility in scale-up and manufacturing also are a major issue since the properties of nanoscales are extremely sensitive to processing factors including homogenization pressure, temperature and rate of solvent removal. New regulatory requirements of nanomaterials also differ between jurisdictions, especially concerning safety evaluation and post approval modifications, which pose confusion to international development agendas [8].

Such scientific, industrial and regulatory blind spots make effective laboratory-to-market translation of nano-enabled topical and transdermal formulations difficult. Despite the strong approach provided by QbD to variability and risk management, there is no harmonized standard concerning the nano-specific CQAs, analytical approach, IVIVC development, and alignment with regulatory standards when applying the QbD to dermal nanomedicines. As a result, the developers have a problem defining defensible design spaces, scaled manufacturing and regulatory submissions that provide a clear product knowledge and control [8].

This review aims to critically analyze how the concepts of QbD have been applied in the design of nano-enabled topical and transdermal delivery systems of drugs. In particular, the goal of this study is to review the existing literature on QbD-oriented solutions in dermal and transdermal nanocarriers, define and assess the relevant CQAs, CMAs, and CPPs to control the quality of products and their functionality, and comment on the current regulatory requirements and industrial trends. The review also suggests a realistic regulatory-congruent QbD model to facilitate robust development, scalable manufacturing, and efficient lifecycle management and brings forth areas of future research, which are necessary to overcome current gaps. The hypothesis directing this review is that a QbD approach specific to nano-enabled T/T DDS can contribute to the robustness of the formulations, enhance predictability of *in vivo* behavior, enhance IVIVC with the help of standardized analytical methods, and mitigate the development and regulatory risk.

2. Nano-Enabled Carriers For Topical And Transdermal Drug Delivery: A Critical Review

The application of nano-enabled carriers has revolutionized topical and transdermal drug delivery by providing a means of overcoming the stratum corneum barrier, increasing drug solubility, and increasing therapy. Nevertheless, few nano-based dermal systems have been successful to attain clinical and commercial success despite positive preclinical results. The important platforms of nano-enabled platforms are thus to be critically appraised to see through their actual translational potential [9].

2.1 Liposomes

One of the earliest and best studied nanocarriers available to topical and transdermal delivery are liposomes. Their encapsulation capability of hydrophilic and lipophilic drugs is permitted by their phospholipid bi-layer structure and their biocompatibility is excellent because they are similar to biological membranes. Liposomes (used topically) can be utilized to improve the deposition of drugs in the stratum corneum and viable epidermis as opposed to delivering drugs deep into the system. Lipid exchange and localized drug release is mostly dictated by their interaction with the skin, characterized by lipid exchange and lipid fusion with stratum corneum lipids [10].

These benefits notwithstanding, traditional liposomes have a low physical stability, are prone to oxidation and hydrolysis, can only carry limited drug load and are expensive to make. Furthermore, intact liposomes may hardly penetrate the stratum corneum, but they are considered to serve as drug reservoirs and this limits their use in actual transdermal delivery. Liposomal formulations have only applied clinically in dermatological indications like antifungal, anti-inflammatory and cosmetic applications as opposed to systemic therapy [11].

2.2 Niosomes

Niosomes are vesicles made of non-ionic surfactants and cholesterol which are cost effective and offer better chemical stability compared to liposomes but still have the benefits of vesicles [12]. They improve the penetration of the skin by fluidizing stratum corneum lipids and augmenting the drug partitioning into the skin. Niosomes have also shown better retention of drugs in the skin layers and hence are a good choice in targeted dermal therapy [13].

Niosomes, however, have batch-to-batch variability, have the potential of being surfactant induced skin irritation, and

have limited long-term stability. Similar to liposomes, their ability to transport drugs systemically through the transdermal route is also limited. Niosomal systems remain clinical and have limited commercial products, and many remain limited to early and experimental translational studies [14].

2.3 Solid Lipid Nanoparticles (SLNs)

SLNs are an important improvement because the nanoscale size is combined with a solid lipid matrix to allow the drug to be released in a controlled manner with increased stability. Their blocking nature augments the skin skin hydration, which indirectly enhances the penetration of drugs. The SLNs have been shown to be particularly effective with lipophilic drugs and have been demonstrated to be effective in dermatological conditions that demand long-term local effect [15].

However, SLNs have weaknesses in low drug load and expulsion of drugs in storage because of crystallization of lipids and polymorphic changes. These formulation problems limit their use with drugs that need more payloads. Topical anti-inflammatory and cosmetic SLNs have been studied clinically, although their widespread usage has not been embraced [16].

2.4 Nanostructured Lipid Carriers (NLCs)

NLCs represent another type of lipid nanoparticles with the aim of eliminating the limitations of SLNs, which entails including a blend of solid and liquid lipids, which leads to a less ordered lipid matrix. This defect in the structure provides greater drug loading capacity, lesser drugs expulsion, and better stability in the long run. The NLCs have an improved skin adhesion and longer residence time, which renders it to be suitable in both dermal and transdermal applications [16].

In spite of these benefits, NLCs have complexity in formulation, sensitivity to processing conditions, and difficulty in specifying strong quality characteristics. Clinically, there is high potential in NLCs especially in the treatment of chronic skin conditions, yet regulatory experience in such systems is currently developing [17].

2.5 Nanoemulsions

Nanoemulsions are thermodynamically unstable and kinetically stable systems that are typified by a small droplet size and a high surface area. As penetration enhancers, they can increase drug solubilization and drug permeation through the skin by rupturing stratum corneum lipid packing. Nanoemulsions are more or less simple to create and expand, and consequently are desirable in industry [18].

But their large content of surfactants concerns the skin irritation and long term safety, especially when used repeatedly. Also, nanoemulsions do not have controlled release characteristics and can cause a rapid diffusion of drugs and systemic exposure. They are clinically appropriate when used topically to deliver antifungal, anti-inflammatory as well as cosmetic actives, but not when used as a long term transdermal modality [19].

2.6 Polymeric Nanoparticles

Polymeric nanoparticles provide superior design freedom, which allows them to be released under control, be functionally modified on their surface, and targeted. Biodegradable polymers PLGA and chitosan have been extensively studied in dermal delivery, specifically as a vaccine, anticancer and anti-inflammatory drug delivery. The fact that they only interact with the skin through follicular targeting and increased retention in deeper layers of the skin is a primary characteristic [20].

Although polymeric nanoparticles are versatile, there are issues associated with complicated manufacture procedures, toxicity of residual solvents, large-scale manufacturing problems, and regulatory concerns. Furthermore, intact polymeric nanoparticles do not easily permeate the stratum corneum, which can be used to deliver drugs to the systemic circulation via transdermal delivery. There has been limited clinical translation and most of the uses have been restricted to localized or intradermal administration [21].

2.7 Microneedle-Assisted Systems

Microneedle-assisted delivery is a paradigm shift as it bypasses the stratum corneum barrier physically. Micro needles when used together with nano enabled formulations allow direct delivery of drugs and nanoparticles to viable epidermal or dermal layers, with a significant increase of bioavailability and systemic absorption. This modality is especially appealing with respect to vaccines, peptides, proteins and poorly permeable drugs [22].

Micro needle systems, however, bring into play a range of complexities associated with the device, issues with patient compliance, regulatory issues and increased costs of manufacturing. Careful consideration is also required on long-term safety particularly when it has to be used repeatedly. Micro needle based products are considered to be one of the most sophisticated transdermal technologies clinically with a number of systems in late clinical phase or early commercial development [23].

3. Comparative Perspective and Clinical Relevance

Nano-enabled carriers maximize dermal targeting and local drug retention as opposed to actual passive transdermal delivery. The majority of nanocarriers have an indirect mechanism of action through the alteration of skin barrier properties or act as drug reservoirs, with microneedle-assisted systems being the best choice of systemic transdermal delivery method. These technologies are also based on clinical success with not only increased permeation but also increased formulation robustness, safety, manufacturability, and acceptance by the regulators [9].

Translational nano- enabled topical systems have the highest clinical applicability in dermatology, cosmetics and local therapies whereas systemic delivery necessitates either physical enhancement strategies or a hybrid approach. The next generation is based on the combination of mechanistic skin penetration knowledge with Quality-by-Design concepts in order to provide predictable performance and scalable production along with regulatory assurance [21].

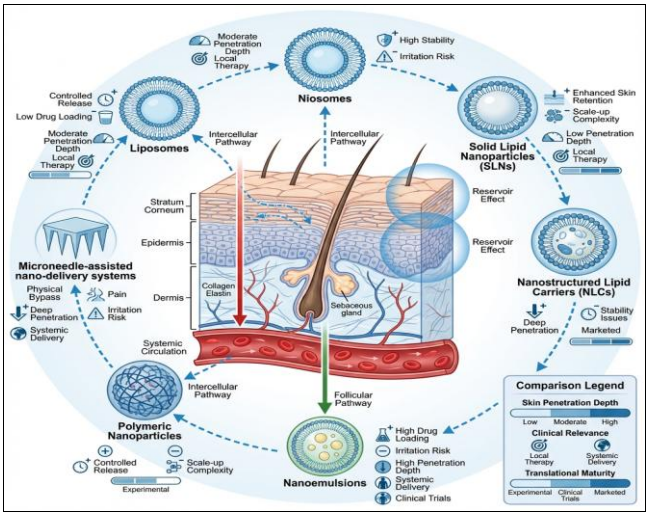

Fig 1: Critical Comparison of Nano-Enabled Drug Delivery Systems for Topical and Transdermal Applications

4. Core Principles of Quality-by-Design (Qbd) in Pharmaceutical Development

Quality-by-Design (QbD) is a scientific, risk-assessed method of pharmaceutical development, which starts with set goals and focuses on understanding the product and the process in full lifecycle. QbD, which is championed by regulatory organisations like the International Council for Harmonisation and the US Food and Drug Administration, is especially applicable in nano-formulations because of their complexity in structure, increased sensitivity to material and process variability, and scaling up.

4.1 Quality Target Product Profile (QTPP)

The Quality Target Product Profile (QTPP) is a future report of the desirable quality features that are in place to guarantee quality products in the form of safety, effect and performance. QTPP in nano-enabled topical and transdermal drug delivery system goes beyond the traditional requirements of dose strength, route and release profile to incorporate nano-specific performance requirements. These are the targeted site of action in layers in skin, retention / transdermal flux balance between skin, targeted or controlled release behavior, stability of nanoscale architecture in storage and application, and patient acceptability. Therefore, the QTPP in small-scale nano-formulations is mechanistically associated with skin contact and clinical efficacy as opposed to when it is strictly compositional.

4.2 Critical Quality Attributes (CQAs)

Critical Quality Attributes (CQAs) refer to the physical, chemical, biological, or microbiological characteristics, which should be managed to guarantee the quality of the products. In the case of nano-formulations, the CQAs of relevance usually include particle (or droplet) size and distribution, polydispersity index, surface charge, drug loading and encapsulation efficiency, release and skin permeation characteristics, and physical and chemical stability. Semisolid systems are also of importance in rheological properties. Their identification and regulation is especially important since minor differences in these CQAs may result in disproportional alterations in the areas of the skin penetration, safety, and therapeutic effectiveness.

4.3 Critical Material Attributes (CMAs)

Critical Material Attributes (CMAs) are those attributes of raw materials and excipients which affect CQAs. CMAs in nano-formulations encompass lipid type, lipid grade, lipid crystallinity and lobular lipid polymorphism; polymer molecular mass and polymer degradation characteristics, surfactant hydrophilic-lipophilic balance, and physicochemical properties of the drug, solubility, and lipophilicity. Compared to the traditional dosage forms, nanocarriers are much more susceptible to the variation of the excipients; hence, regardless of the variation in CMAs, the stringent control is required to provide reproducibility and scalability.

4.4 Critical Process Parameters (CPPs)

Process variables that have a direct impact on CQAs are called Critical Process Parameters (CPPs). Homogenization pressure and cycles, sonication time and amplitude, mixing speed and shear rate, emulsification or melting temperature, conditions of solvent removal, and cooling rate are typically CPPs in the manufacturing of nano-formulations. Relationships between CPP-CQA in nano-systems are commonly nonlinear and even minor changes may lead to aggregation, instability or changes in drug release behavior.

4.5 Design Space

Design space is described as a multidimensional set of CMAs and CPPs illustrated in order to provide product quality. In the case of nano-formulations, a design space is difficult but critical to set up, with nanoscale properties being strongly correlated with process behavior. High quality design space helps in scale-up, lowers batch-to-batch, eliminates a risk of nanostructure instability, and enables flexibility in manufacturing without regulatory re-approval.

4.6 Control Strategy

Strong control strategy comes out of product and process knowledge in order to maintain uniform quality. In nano-formulations, this involves raw material qualification, in-process testing of essential parameters (particle size, temperature) and end-product testing of nanoscale properties, stability indicating tests peculiar to nanocarriers, and discriminating utilization of Process Analytical Technology. The reason why analytical control is especially relevant is that nano-formulations do not usually have apparent signs of quality failure.

4.7 Lifecycle Management

QbD lifecycle management is a method that allows continuous improvement and the accumulation of knowledge over the commercial lifespan of a product. Lifecycle management in nano-enabled systems aids post times approval modifications, communication of regulatory information, prior knowledge and incorporation of real-world stability and performance data. On the whole, QbD is not only a regulatory requirement of nano-formulations but it is a science requirement. QbD offers an organized process by which nano-enabled drug delivery systems can be successfully translated in moving through the laboratory to the clinic and marketplace through systematic connection of QTPP, CQAs, CMAs, and CPPs in a specific design space and a powerful approach to control [24, 25].

Table 1: Mapping of CQAs–CMAs–CPPs for Nano-Enabled Topical and Transdermal Drug Delivery Systems

Nanocarrier System	Key CQAs (What must be controlled?)	Critical Material Attributes (CMAs)	Critical Process Parameters (CPPs)
Liposomes	• Vesicle size & size distribution • Lamellarity • Drug encapsulation efficiency • Zeta potential • Leakage rate • Physical & chemical stability	• Phospholipid type & purity • Cholesterol ratio • Drug lipophilicity • Buffer pH & ionic strength	• Hydration temperature • Sonication time/amplitude • Homogenization pressure • Film hydration time • Cooling rate
Niosomes	• Vesicle size & PDI • Entrapment efficiency • Surface charge • Drug release profile • Physical stability	• Surfactant type (HLB value) • Cholesterol content • Drug–surfactant compatibility	• Mixing speed • Hydration time & temperature • Sonication conditions • Organic solvent removal rate
Solid Lipid Nanoparticles (SLNs)	• Particle size & PDI • Drug loading • Crystallinity & polymorphism • Drug expulsion tendency • Occlusivity	• Lipid type & melting point • Lipid polymorphic form • Surfactant concentration • Drug solubility in lipid	• Homogenization pressure & cycles • Emulsification temperature • Cooling rate • Stirring speed
Nanostructured Lipid Carriers (NLCs)	• Particle size & distribution • Drug loading & retention • Physical stability • Skin adhesion • Release kinetics	• Solid-to-liquid lipid ratio • Type of liquid lipid (oil) • Surfactant system • Drug partition coefficient	• Homogenization parameters • Lipid melting temperature • Cooling profile • Mixing/shear rate
Nanoemulsions	• Droplet size & PDI • Physical stability (coalescence, creaming) • Drug solubilization capacity • Skin permeation rate	• Oil phase composition • Surfactant/co-surfactant ratio • HLB value • Drug solubility	• Energy input (high-shear/ultrasonication) • Emulsification time • Temperature • Order of addition
Polymeric Nanoparticles	• Particle size & PDI • Drug loading • Release profile • Polymer degradation rate • Residual solvent levels	• Polymer type & molecular weight • Polymer–drug compatibility • Solvent type • Stabilizer concentration	• Emulsification speed • Solvent evaporation rate • Phase volume ratio • Stirring time
Microneedle-Assisted Nano-Systems	• Needle geometry & strength • Drug content uniformity • Insertion efficiency • Dose delivery accuracy	• Polymer/mechanical material type • Nanocarrier stability in matrix • Drug loading per needle	• Micromolding pressure • Drying temperature • Casting time • Demolding conditions

5. Application of Quality-by-Design (Qbd) to Nano-Enabled Topical and Transdermal Drug Delivery Systems

Quality-by-Design (QbD) offers a science- and risk-based approach to the development of pharmaceutical products whose quality and performance can be predicted. The International Council of Harmonisation and the US Food and Drug Administration regulatory bodies highlight QbD to shift the development not to empirical screening of the trial and error but to the mechanistic interpretation and control of lifecycle. In the case of nano-enabled topical and transdermal drug delivery system (T/T DDS), QbD is especially paramount as the nanoscale characteristics of the material and the process are quite sensitive to variation, and even minor changes may impact the skin interactions, safety and efficacy in disproportionate measure [7, 26].

5.1 QbD Workflow in Nano-Enabled T/T DDS

The QbD process involves the definition of Quality Target Product Profile (QTPP), the identification of Critical Quality Attributes (CQAs), assessment of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), identifying a design space and applying a strong control strategy. In nano-formulations these processes are closely connected to each other since the process of particle formation, stabilization, and skin performance occur all at the same time during the manufacturing process [27].

In nano-enabled topical and transdermal systems, the QTPP is concerned with site-specific performance of the skin, as well as nanoscale stability, in addition to dose and dosage form. The conceptual correlation between the QTPP elements and key CQAs **as shown in Table 2**.

Table 2: QTPP → CQA Relationship (Nano-Enabled T/T DDS)

QTPP Element	Linked CQAs	Rationale for Nano-Systems
Route of administration (topical vs transdermal)	Particle size, PDI, skin permeation	Determines whether formulation favors skin retention or systemic absorption
Site of action (SC, epidermis, dermis, systemic)	Particle size, zeta potential, drug release	Nanoscale dimensions govern penetration pathway and depth
Therapeutic performance	Drug loading, release rate, permeation flux	Controls local concentration and duration of action
Safety and tolerability	Zeta potential, excipient composition, stability	Surface charge and degradation influence irritation and toxicity
Product stability & shelf life	Particle size growth, PDI, chemical stability	Nano-systems are prone to aggregation and drug expulsion
Patient acceptability	Rheology, spreadability, appearance	Semisolid properties affect compliance and dose uniformity

5.2 Critical Quality Attributes (CQAs) in Nano-Enabled T/T DDS

5.2.1 Particle Size and Polydispersity Index (PDI)

Particle size is one of the main CQAs as it has a direct effect on the penetration paths of particles (intercellular, follicular, or reservoir behavior). Small size distribution (low PDI) will guarantee reproducibility in skin interaction as well as batch-to-batch consistency. Changes in size by small amounts can significantly modify permeation and stability in nano-system.

5.2.2 Zeta Potential

Surface charge and colloidal stability is indicated by zeta potential. It influences aggregation of nanoparticles, contact with skin lipids as well as in certain instances, uptake in cells. Excessive charges and nearly neutral charges are both damaging to safety or stability and zeta potential is a critical CQA in dermal tolerance.

5.2.3 Drug Loading and Encapsulation Efficiency

Drug loading controls the dose delivery per unit application and influences the release kinetics. Under-dosing or burst drug release Under-dosing or burst drug release in nano-carriers can be caused by poor or uncontrolled loading of drugs, compromising the reliability of the therapeutic effect.

5.2.4 Skin Permeation and Retention

Topical and transdermal systems CQAs that define the performance of their systems are skin permeation parameters (flux, lag time, retention in skin layers). These CQAs provide a linkage between the formulation qualities and the clinical outcomes and are the key to regulatory justification of product efficacy.

5.2.5 Rheology and Spreadability

In the case of semisolid nano-formulations, rheological behavior triggers dose uniformity, application thickness, and residence time on skin. Rheology has an indirect effect on permeation, where it determines contact time and occlusivity.

5.2.6Physical and Chemical Stability

Nano-systems are thermodynamically unstable thus, particle size, PDI, drug content, and chemical integrity throughout shelf life is an essential quality parameter.

5.3 Material Variability (CMAs) and Impact on Product Performance

Formulations that are nano-enabled are highly sensitive to material properties. CQAs can considerably be modified by variability in lipid grade, surfactant purity, polymer molecular weight or drug polymorphic form. For example:

The alteration of lipid crystallinity may cause the expulsion of drugs in lipid nanoparticles.

The variability of surfactant HLB can change the particle size and skin permeation.

Changes in polymer molecular weight are able to alter the degradation rate and drug release.

These sensitivities require strict control of the raw-materials, the qualification of suppliers and CMA risk evaluation by QbD.

5.4 Process Variability (CPPs) and Impact on Product Performance

High-pressure homogenization, ultrasonic, solvent evaporation, or micromolding are manufacturing processes that add variability as a result of the processing. CPPs such as homogenization pressure, shear rate, temperature and cooling profile have direct influence on the formation and stabilization of nanoparticles [28-30].

In nano-formulations, irreversible aggregation or polymorphic transitions may occur when small deviations of CPP occur, scale-up may magnify the effects of CPP resulting in variation of particle size and release and CPP-CQA relationships are usually nonlinear and multivariate Design of Experiments (DoE) is necessary to characterize a credible design space.

6. Role of Risk Assessment and Design of Experiments in Optimizing Nano-Enabled Topical and Transdermal Systems

Based on intricate interactions among formulation contents, processing environment, nanoscale properties, and skin functionality, the development of nano-enabled topical and transdermal drug delivery systems (T/T DDS) can be achieved. In the Quality-by-Design (QbD) model, risk assessment tools and Design of Experiments (DoE) complement each other in determining key variables, the relationships between variables, and strong optimization [31].

Risk Assessment Tools, the principles of risk management that are described in the ICH Q9 offer an organized mechanism of recognizing and prioritizing risks that impact the key quality attributes (CQAs) which include: particle size, polydispersibility index, drug loading, stability, and skin permeation. Early risk assessment is imperative in the nano-formulations where a small deviation can have a lasting effect on the performance [32].

During the early development, ishikawa (fishbone) diagrams are typically applied to qualitatively determine possible sources of variability in the materials (lipids, surfactants, polymers) and methods (homogenization, sonication), equipment, and environmental conditions. As it may be illustrated, in nanostructured lipid carrier (NLC)-based dermal systems, the lipid composition, the homogenization pressure, and the rate at which the samples cool have been recognized to be high-risk factors that determine the particle size and the drug retention [33].

The process is further narrowed to Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) which are semi-quantitatively ranked according to severity, occurrence and detectability by the Failure Mode and Effects Analysis (FMEA). FMEA has been applied in QbD-based development of niosomal and SLN-based topical formulations to prioritize the type of surfactant, lipid ratio, and sonication parameters, as applied in further optimization of experiments [33].

Design of Experiments (DoE), Risk prioritization is followed by DoE, used to measure the impact of CMAs and CPPs selected on CQAs quantitatively and a design space. Factorial designs are often applied as preliminary screening instruments to determine important main effects and interactions. As an example, factorial studies in SLN model have shown that there are significant interactions among lipid concentration, homogenization pressure and particle size and entrapment efficiency.

Box-Behnken Design (BBD) and Central Composite Design (CCD) are popular response surface techniques that are used to optimize. BBD is especially applicable to the nano-enabled topical system because it involves fewer experimental runs and obviates extreme factor combinations which can destabilize nanocarriers. It has been effectively

employed to optimize gels based on NLC to predict the impact of lipid ratio, surfactant concentration, and processing conditions on particle size, stability and skin permeation. CCD is more expensive but provides a better representation of curvature and has been used in optimization of nanoemulsions and polymeric nanoparticles and nanosystems in transdermal delivery [34].

7. Global Regulatory Expectations for QbD-Based Nano-Enabled Topical and Transdermal Drug Products

A regulatory assessment of nano-enabled topical and transdermal drug delivery systems is becoming more consistent with the Quality-by-Design (QbD) concept, which is a global trend in science- and risk-based pharmaceutical development. Nanotechnology has been recognised by agencies such as the International Council for Harmonisation, US Food and Drug Administration, European Medicines Agency and the World Health Organization as having potential therapeutic use in both dermal and transdermal applications but with understanding of the products, variability control and lifecycle management; the complexity of nanoscale is considered rather an issue [35].

QbD regulatory submissions are based on the ICH Q8-Q12 guideline construct. ICH Q8 (Pharmaceutical Development) obliges to define a strong Quality Target Product Profile (QTPP) and clearly connects with Critical Quality Attributes (CQAs). In the case of nano-enabled topical products, the regulators are looking increasingly to justify nano-specific CQAs including particle size, polydispersivity index, surface charge, drug loading, stability and skin penetration characteristics. Quality Risk Management (ICH Q9) is especially applicable to nano-formulations where the change in the material or process conditions can produce a large impact on the performance of the product. ICH Q10 and Q11 focus on the quality systems of pharmaceutical and lifecycle management, whilst ICH Q12 facilitates regulatory flexibility of post-approval modifications in an approved design space- a key motivator towards the adoption of QbD in nano-enabled products [36].

According to the United States, the FDA does not consider nano-enabled topical and transdermal products as a separate category but evaluates them in the existing regulatory pathways. The agency heavily focuses on total physicochemical characterization, lot-to-lot uniformity and risk-based control measures. One of the obstacles to generic nano-topical products is the bioequivalence assessment: it is a fact that due to the effects of formulations on skin interactions, the traditional bioequivalence methods are less applicable. Therefore, justification of design space and control strategies through QbD is perceived positively to facilitate the manufacturing robustness and flexibility after approval [37].

The EMA takes a risk-based case-by-case approach on nano-enabled dermal products. Guidance by EMA focuses on the early detection of nano-specific CQAs, application of orthogonal analytical methods and clinical use of *in vitro* data on skin permeation. QbD may be promoted, but it cannot eliminate the need of sponsors to show product specific safety and efficacy especially in the extrapolation of *in vitro* findings to the *in vivo* exposure [26].

The WHO lens is concerned with quality, safety, and accessibility, especially with the topical products that are applicable in global health environments. WHO does not reject the idea of adopting QbD but points to the problem of low standardization of nano-specific characterization techniques, as well as the regionally-specific variability in regulatory capacity.

All in all, the global regulators are increasingly considering QbD as a requirement to the nano-enabled topical and transdermal products. Nevertheless, there are still issues in the analytical characterization, bioequivalence determination and reliable *in vitro-in vivo* correlations. These issues can be tackled by developing QbD based development mechanisms, gaining mechanistic insight and lifetime management that is essential in attaining regulatory approval, as well as international harmonization [8].

8. Industrial Challenges in Scaling Up QbD-Based Nano-Enabled Topical and Transdermal Formulations

The industrial issues involved in scaling up nano-enabled topical and transdermal drug delivery systems on a Quality-by-Design (QbD) platform are special because of the sensitivity of nanoscale systems to material and process differences. Although QbD provides an organized route towards a thriving development, there is intricacy in the transformation of the laboratory level nano-formulations into commercial production [38].

Raw material variability is a primary challenge, Nano-formulations are very delicate in regards to the variations in grade of lipids, purity of surfactant, molecular weight of polymers, and variation in the excipient polymorphism. Even small variations in terms of suppliers to suppliers or lots to lots may have a big change on particle size, drug loading, and stability that will directly affect Critical Quality Attributes (CQAs). This requires higher qualification of suppliers, greater material specifications and increased testing of incoming materials than traditional topical products [39].

Process robustness and scale-up represented another major hurdle. Some of the manufacturing methods including high-pressure homogenization techniques, ultrasonication, solvent evaporation, and micromolding usually do not perform in the same manner at the commercial level. Non-linear CPP- CQA relationships imply that parameters to be optimized in a laboratory scale may not be directly transferable and as a result, aggregation, change in release profile or loss of nanoscale integrity, will occur. It is thus more difficult to have a defensible design space with nano-enabled systems under QbD [40].

It is especially challenging to ensure batch-to-batch consistency. Nano-formulation contains no visible signs of failure and little variations in particle size distribution or surface characteristics may influence skin permeation and safety. This means that manufacturers are forced to place a lot of trust on high quality analytical controls and statistically warranted acceptance-criteria.

The use of Process Analytical Technology (PAT) is promoted but not much practiced. It is complicated and expensive to monitor the manufacture in real time on particle size, temperature, or viscosity. Availability of validated and in-line PAT tools that can be applied to nano-formulations is limited, limiting real time process control [41].

Commercialization is also further complicated by stability and packaging. Nano-systems are susceptible to aggregation, release of drugs as well as chemical degradation during storage. The packaging materials should

be resistant to moisture, oxygen and light, at the same time be compatible with nanoscale carriers, which further complicated development [42].

The issue to consider in industries is cost-effectiveness. The manufacturing costs are raised by high-energy processes, special tests of analysis, long development cycles and strict quality control. This means that a tradeoff between QbD-driven strength and commercial feasibility is necessary to adopt it in industries.

In general, even though QbD is a highly effective model to cope with risk and variability, to be able to enable successful industrial scale-up of nano-enabled topical and transdermal formulations, improved process knowledge, increased analytical proficiency, and prudent cost-benefit optimization are necessary to achieve regulatory compliance and market success [43].

9. Case Studies

9.1 Liposomes - Tenofovir

Xu *et al*. used the entire QbD workflow to Tenofovir-loaded liposomes: QTPP/CQA definition, risk assessment, screening experiments, DoE optimization, and development of a laboratory scale design space. The experiment indicated better vesicle size control, encapsulation and short-term stability and achieved a clear design space cutting on preparation variation. Nevertheless, the article was at lab scale and demonstrated how challenging it is to scale design-space constraints to industrialized equipment without additional scale-specific research. The case demonstrates the strength of QbD to map CPP CQA relationships, although it is also indicative of the scale-up gap [44].

9.2 Solid Lipid Nanoparticles (SLNs) - Triamcinolone example

The Circumscribed Central Composite Design applied by Talarico *et al*. was optimized to triamcinolone (particle size, zeta, drug load). The DoE methodology came up with sensitive formulation and sonication factors, and generated verified predictive models of CQAs, allowing lot-to-lot consistency at bench sizes. Another emphasis in QbD in the study was on the development of analytical methods (stability-indicating assays). However, issues like lipid polymorphism and long-term drug expulsion were observed to pose a hindrance to simple scale-up and shelf-life assertions [45].

9.3 Nanoemulsion/Nanoemulgel - Clobetasol nanoemulgel

Risk assessment and response-surface DoE were used to optimise a nanoemulgel of clobetasol guided by QbD to control droplet size, viscosity and permeation. The article has claimed an increase in dermal delivery and given a clear roadmap on translation (design space, control strategy). It also talked about regulatory-relevant endpoints (*in vitro* permeation and stability testing), which focuses on how QbD outputs could be formatted to be presented in regulatory discussions. The restriction was only that *in vivo* IVIVC and human data were not presented meaning they could not be regulatory without clinical bridging [46].

9.4 NLC / Lipid Nanocarriers - From lab to industrial

The lab-to-industrial review by Buya is a synthesis of various lipid-nanocarrier QbD projects and presents some practical scale-up case studies: focus on raw material control (CMA tight specifications), developing robust CPP regimes (homogenization energy, cooling behaviour), and early integration of PAT. The review emphasizes iterative scale-up experiments and how successful tech transfers were in which QbD documentation (design space + control strategy) significantly decreased regulatory CMC queries. It comments though that the adoption of PAT is still restrained by the cost and maturity of the tool [47].

9.5 Microemulsion / Topical microemulsion

Srishti *et al*. described a tacrolimus microemulsion using QbD-based microemulation accompanied by the DoE optimization and risk evaluation. The paper has indicated that the use of QbD has helped to identify the CQAs (droplet size, release), which are clinically meaningful and consequently targeted the analytical development. Similar to others, it highlighted the chronic IVIVC/regulatory knowledge gap of topical nanosystems [48].

QbD can be considered as a reliable way to enhance the understanding of formulations and minimise risk during development of nano-enabled topical/ transdermal system. The other regulatory acceptance and commercialization obstacles being encountered are proving IVIVC/clinical relevance, proving long-term stability at scale and investing on PAT and material control. These need to be tackled in a systematic way in QbD, through the incorporation of IVIVC studies into the design space, stabilization-reduction strategies (e.g., excipient choice to avoid lipid recrystallization) and piloting PAT in scale-up: the practical way to transform QbD promise into marketed and approved nano-dermal products.

10. Challenges, Gaps, and Future Directions

Even with the increased use of Quality-by-Design (QbD) principles, a number of scientific, industrial and regulatory issues keep hindering their use in nano-enabled topical and transdermal drug delivery systems (T/T DDS) in full.

10.1 Current Challenges and Gaps

Regulatory vagueness is one of the main constraints. Although the global authorities like the International Council for Harmonisation, the US Food and Drug Administration and the European Medicines Agency highly promote the use of QbD, nano-specific regulatory requirements of topical or transdermal products are absent. Consequently, the nano-related Critical Quality Attributes (CQAs), equivalence evaluation and changes after approval are still uneven and mostly product-oriented.

Another significant obstacle is to characterization complexity. Nano-enabled topical products need to be characterized in multidimensional ways in terms of physicochemical and performance (size distribution, surface properties, release, skin permeation, and stability of the products in semisolid matrices). There is however no single commonly accepted analytical battery or standardized test hierarchy making it incredibly hard to risk-assess, justify design space, and regulators.

These challenges are further aggravated by lack of harmonized standards. Variations of the methods of analysis, *in vitro* skin models, and bioequivalence methods across the regions are barriers to global development, as well as further complicate multinational submissions by raising costs and time.

On the industrial end, scale-up and manufacturing resiliency is still a major gap. The difficulty with reproducible large-scale manufacturing is brought about by non-linear relationships between Critical Process Parameters (CPPs) and CQAs, inappropriateness of appropriate Process Analytical Technology (PAT) tools, and sensitivity to changes in raw materials. A large number of published QbD case studies are limited in scope to laboratory or pilot scale, and have little evidence of commercial translation [49, 50].

10.2 Future Directions

The future developments of QbD implementation of nano-enabled T/T DDS are likely to be influenced by data-oriented and digitalization. Machine learning-supported QbD with artificial intelligence (AI) can expedite risk evaluation, make predictions between CPP-CQA and decrease experimental load as it becomes familiarized with previous formulation and process information. Simulation Digital twins- virtual models of manufacturing processes- promise to simulate scale-up situations, stress-test design-space, and assist in managing changes in regulations.

Continuous manufacturing is also a revolutionary opportunity. Continuous processes can be used together with QbD and real-time PAT to enhance control of processes, decrease the variability of batches, and scale nano-formulations. Nonetheless, alignment in the regulation, validated digital tools, and well-established lifecycle management plans will be needed to achieve success in adoption.

To bridge the existing gaps in the areas of harmonized standards, advanced analytics, and digital frameworks of quality by design, it will be necessary to translate the nano-enabled topical and transdermal systems that have been currently studied in an experimental context into high-quality, commercially feasible pharmaceutical products [51-53].

11. Conclusion

The incorporation of Quality-by-Design (QbD) in nano-enabled topical and transdermal drug delivery systems development is a critical transition in nano-pharmaceutical development between the empirical formulation and science- and risk-based development of pharmaceuticals. Regulatory QbD offers a regulated structure to meet the international expectations and allows categorically connecting the Quality Target Product Profile with the nano-specific Critical Quality Attributes and effective control measures. Such product and process knowledge is critical to help in dealing with the inherent complexity, variability and scale-up sensitivity of nanosystems, to enhance regulation confidence and enable lifecycle management and post-approval flexibility.

Industrially, QbD raises the level of formulation robustness, increases the consistency of batches and improves failures in late-stage development which are especially expensive with nano-enabled products. QbD facilitates scalable production, transfer of technology in an efficient manner and controls costs rationally by systematically managing variation of materials and processes. Notably, the subsequent increases in the quality and performance of the products directly lead to increased patient safety, predictive therapeutic performance and general user acceptability of topical and transdermal interventions. In general, QbD is not only a regulatory compliance strategy, but a strategic facilitator to a successful commercialization of nano-enabled drug delivery systems, in between scientific innovation and industrial feasibility, and the effect on the population health.

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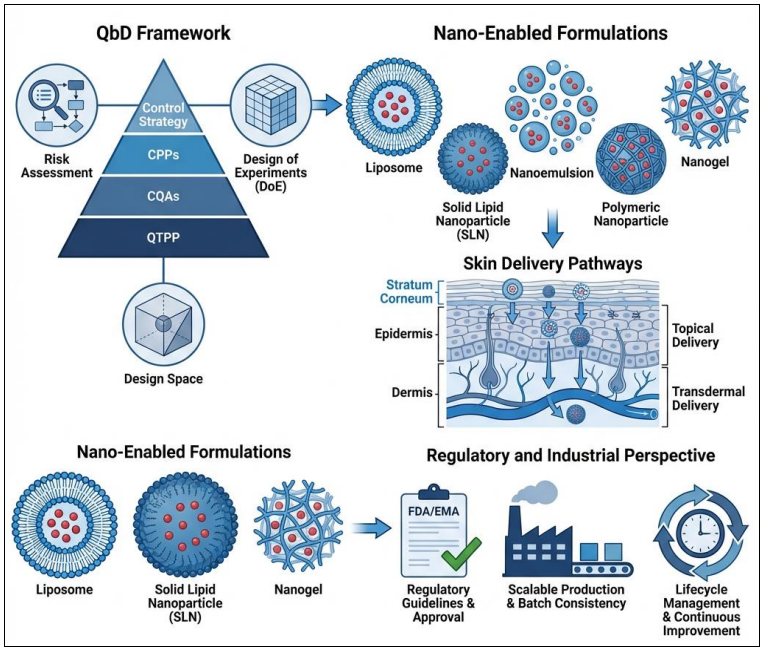
13. Conflicts of Interest

The authors declare no conflicts of interest related to the content of this manuscript. All opinions and conclusions expressed are solely those of the authors and do not reflect the views of their affiliated institutions.

Graphical Abstract



14. References

1. Otake H, Yamaguchi M, Ogata F, Deguchi S, Yamamoto N, Sasaki H, *et al*. Energy-dependent endocytosis is responsible for skin penetration of formulations based on a combination of indomethacin nanoparticles and l-menthol in rat and Göttingen minipig. International Journal of Molecular Sciences. 2021; 22(10):5137.
2. Alkilani AZ, Nasereddin J, Hamed R, Nimrawi S, Hussein G, Abo-Zour H, *et al*. Beneath the skin: A review of current trends and future prospects of transdermal drug delivery systems. Pharmaceutics. 2022; 14(6):1152.
3. Souto EB, Cano A, Martins-Gomes C, Coutinho TE, Zielińska A, Silva AM. Microemulsions and nanoemulsions in skin drug delivery. Bioengineering. 2022; 9(4):158.
4. Pannu MS. Recent Advances In Pharmaceutical & Medical, 2025.
5. Mohite P, Gholap A, Pardeshi S, Puri A, Rajput T. Quality by design in pharmaceutical development: current advances and future prospects. Software and Programming Tools in Pharmaceutical Research, 2024, 68-107.
6. Lee S-H, Kim J-K, Jee J-P, Jang D-J, Park Y-J, Kim J-E. Quality by Design (QbD) application for the pharmaceutical development process. Journal of Pharmaceutical Investigation. 2022; 52(6):649-682.
7. Mohseni-Motlagh SF, Dolatabadi R, Baniassadi M, Baghani M. Application of the quality by design concept (QbD) in the development of hydrogel-based drug delivery systems. Polymers. 2023; 15(22):4407.
8. Lousa IR. Pharmaceutical regulation of nanomedicines: Principles and challenges: Universidade de Lisboa (Portugal), 2024.
9. Zhao Y, Xiu R, Wang C, Wang J, Guo D, Luo W, *et al*. Nanoformulation-Based Transdermal Drug Delivery: A Paradigm Shift in Antiparasitic Therapy for Zoonotic Diseases. Pharmaceutics. 2025; 17(9):1216.
10. Akombaetwa N, Ilangala AB, Thom L, Memvanga PB, Witika BA, Buya AB. Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics. 2023; 15(2):656.
11. Raszewska-Famielec M, Flieger J. Nanoparticles for topical application in the treatment of skin dysfunctions-an overview of dermo-cosmetic and dermatological products. International Journal of Molecular Sciences. 2022; 23(24):15980.
12. Patel P, Parashar AK, Kaurav M, Yadav K, Singh D, Gupta G, *et al*. Niosome: A vesicular drug delivery tool. Nanoparticles and Nanocarriers Based Pharmaceutical Preparations: Bentham Science Publishers, 2022, 333-364.
13. Souto EB, Fangueiro JF, Fernandes AR, Cano A, Sanchez-Lopez E, Garcia ML, *et al*. Physicochemical and biopharmaceutical aspects influencing skin permeation and role of SLN and NLC for skin drug delivery. Heliyon. 2022; 8(2).
14. Xing H, Zhao Z, Zhu X, Zhang Z, Li G, Ma D. Transdermal liposomal delivery systems: Advantages, Applications, Challenges, and prospects. MedComm-Biomaterials and Applications. 2025; 4(3):e70023.
15. Jacob S, Rao R, Gorain B, Boddu SH, Nair AB. Solid lipid nanoparticles and nanostructured lipid carriers for anticancer phytochemical delivery: Advances, challenges, and future prospects. Pharmaceutics. 2025; 17(8):1079.
16. Queiroz MDCV, Muehlmann LA. Characteristics and preparation of solid lipid nanoparticles and nanostructured lipid carriers. Journal of Nanotheranostics. 2024; 5(4):188-211.
17. Patil TS, Gujarathi NA, Aher AA, Pachpande HE, Sharma C, Ojha S, *et al*. Recent advancements in topical anti-psoriatic nanostructured lipid carrier-based drug delivery. International Journal of Molecular Sciences. 2023; 24(3):2978.
18. Ajayi O. Thermodynamic and Kinetic Stability of Cosmetic Nanoemulsions. Design and Applications of Self-Assembly Aggregates-From Micelles to Nanoemulsions: From Micelles to Nanoemulsions, 2024, 163.
19. Godge G, Bharat S, Shaikh A, Randhawan B, Raskar M, Hiremath S. Formulation Perspectives in Topical Antifungal Drug Therapy: A Review. Journal of Drug Delivery & Therapeutics. 2023; 13(5).
20. Beach MA, Nayanathara U, Gao Y, Zhang C, Xiong Y, Wang Y, *et al*. Polymeric nanoparticles for drug delivery. Chemical Reviews. 2024; 124(9):5505-5616.
21. Liu L, Zhao W, Ma Q, Gao Y, Wang W, Zhang X, *et al*. Functional nano-systems for transdermal drug delivery and skin therapy. Nanoscale Advances. 2023; 5(6):1527-1558.
22. Zhou L, Xu S, Li S. Microneedle-Mediated Transdermal Drug Delivery for the Treatment of Multiple Skin Diseases. Pharmaceutics. 2025; 17(10):1281.
23. Gattu K, Godugu D, Jain H, Jadhav K, Cho H, Rojekar S. Microneedle Technologies for Drug Delivery: Innovations, Applications, and Commercial Challenges. Micromachines. 2026; 17(1):102.
24. Vasave BL, Bhamare SM, Bachhav LR, Jadhav PS, Mahajan KS. Quality by Design (QbD) in Pharmaceutical Development: A Review of Principles and Case Studies. Research Journal of Pharmaceutical Dosage forms and Technology. 2025; 17(3):203-211.
25. Sreelekha S, Kumar KV, Mahammed N, Reshma T, Sree GU, Basha SS, *et al*. Quality by Design Approaches in Pharmaceutical Development and Solid Dosage Forms Production: A Narrative Overview. Jordan Journal of Pharmaceutical Sciences. 2023; 16(4).
26. Bastogne T, Caputo F, Prina-Mello A, Borgos S, Barberi-Heyob M. A state of the art in analytical quality-by-design and perspectives in characterization of nano-enabled medicinal products. Journal of Pharmaceutical and Biomedical Analysis. 2022; 219:114911.
27. Benetti C, Benetti AA. Quality by Design in Formulation Development. Introduction to Quality by Design (QbD) From Theory to Practice: Springer, 2024, 139-159.
28. Kumari A, Aggarwal G, Kaur A. Applications of quality by design in pharmaceutical product development lifecycle. Introduction to Quality by Design (QbD) From Theory to Practice: Springer, 2024, 419-453.
29. Sharma MM, Brahmbhatt H, Shah P, Vaghela UP. Quality by Design: A Strategic Approach to Pharmaceutical Development. International Journal of

Pharmaceutical Investigation. 2025; 15(4).
30. Krishna AV, Mounika P, Sai GV, Venkatesh K. A Review on Quality by Design Approach (QbD) and it's Benefits.
31. Shadab A, Ansari AF. Adaptive Nanocarriers: A New Era in Transdermal Delivery with Transferosomes. Journal of Drug Delivery & Therapeutics. 2025; 15(11).
32. Pazhayattil AB, Sharma S, Philip JP, Gischewski-Silva M, Ingram M. Quality risk management (QRM). Technology Transfer: Drug Product Manufacturing Process: Springer, 2023, 29-42.
33. Glevitzky M, Glevitzky I, Mucea-Ștef P, Popa M, Dumitrel G-A, Vică ML. Integrated Risk Framework (IRF)-interconnection of the Ishikawa diagram with the enhanced HACCP system in risk assessment for the sustainable food industry. Sustainability. 2025; 17(2):536.
34. Szpisják-Gulyás N, Al-Tayawi AN, Horváth ZH, László Z, Kertész S, Hodúr C. Methods for experimental design, central composite design and the Box-Behnken design, to optimise operational parameters: A review. Acta Alimentaria. 2023; 52(4):521-537.
35. Herdiana Y. Bridging the gap: The role of advanced formulation strategies in the clinical translation of nanoparticle-based drug delivery systems. International Journal of Nanomedicine, 2025, 13039-13053.
36. Uriti MSV. Quality-by-Design in Pharmaceutical Development. Computer Aided Drug Development, 2024, 80.
37. Rodríguez-Gómez FD, Monferrer D, Penon O, Rivera-Gil P. Regulatory pathways and guidelines for nanotechnology-enabled health products: A comparative review of EU and US frameworks. Frontiers in Medicine. 2025; 12:1544393.
38. Naseri M, Ghobakhlou S, Heidarizade N, Akbari ME, Lotfabadi A, Malvajerd SS, *et al*. Advances in Drug Delivery Science for Diacerein: Strategies to Enhance Solubility, Bioavailability, and Pharmacokinetic Performance. Pharmaceutics. 2025; 17(12):1539.
39. Ashwini M. Design and evaluation of Nano-Lipid Carrier (NLC) loaded transdermal patches of selected oral antidiabetic drug for the treatment of gestational diabetes: Rajiv Gandhi University of Health Sciences (India), 2022.
40. Jacob S, Kather FS, Boddu SH, Attimarad M, Nair AB. Nanosuspension innovations: Expanding horizons in drug delivery techniques. Pharmaceutics. 2025; 17(1):136.
41. Lunter D, Klang V, Eichner A, Savic SM, Savic S, Lian G, *et al*. Progress in topical and transdermal drug delivery research-focus on nanoformulations. Pharmaceutics. 2024; 16(6):817.
42. Ashraf M, Zulfiqar F, Rauf U, Riaz M, Arshad S, Khan MJ, *et al*. Nanotechnology, nano-systems and applications of nanoparticles in novel drug delivery-a comprehensive review. Pakistan Journal of Pharmaceutical Sciences. 2025; 38(2).
43. Chadha M, Malik DS. Vesicular Nanocarriers: A Potential Platform for Topical/Transdermal Delivery of Antibiotics. Recent Patents on Nanotechnology. 2025; 19(3):336-355.
44. Xu X, Khan MA, Burgess DJ. A quality by design (QbD) case study on liposomes containing hydrophilic API: I. Formulation, processing design and risk assessment. International Journal of Pharmaceutics. 2011; 419(1-2):52-59.
45. Talarico L, Pepi S, Susino S, Leone G, Bonechi C, Consumi M, *et al*. Design and optimization of solid lipid nanoparticles loaded with triamcinolone acetonide. Molecules. 2023; 28(15):5747.
46. Devadiga S, Sermasekaran A, Singh AD, Agrawal S, Sharma S, Choudhary D. Quality by design driven systematic development of nanoemulgel of clobetasol-17-propionate for effective treatment of psoriasis. Journal of Drug Delivery Science and Technology. 2024; 93:105422.
47. Buya AB, Mahlangu P, Witika BA. From lab to industrial development of lipid nanocarriers using quality by design approach. International Journal of Pharmaceutics: X. 2024; 8:100266.
48. Srishti SA, Pinky PP, Taylor R, Guess J, Karlik N, Janjic JM. Quality by Design (QbD)-Driven Development and Optimization of Tacrolimus-Loaded Microemulsion for the Treatment of Skin Inflammation. Pharmaceutics. 2024; 16(12):1487.
49. Hu X, He T, Zhang D, Zhou C, Liang P. Nano-enabled delivery of anesthetics: mechanistic insights, technological advances and translational challenges. Journal of Materials Chemistry B. 2025; 13(43):13844-13866.
50. Peddinti V, Gomte SS, Yallappa D, Patil S, Jain A. Regulatory Considerations of Nanocrystal in Pharmaceutical Sciences. Nanocrystal Technologies in Biomedical Sciences: Advances in crystal development, characterization and targeted drug delivery: Springer, 2026, 287-309.
51. Kumar S, Alsaidan OA, Alzarea SI, Kumar A, Kondaveeti SB, Sharma D, *et al*. Integrating Quality by Design (QbD) in Phytosomal Drug Delivery: A New Era in Precision Phytotherapy. AAPS PharmSciTech. 2025; 26(7):198.
52. Krishnaswami V, Muruganantham S, Raja J, Arthanari S, Selvaraj BR, Dharmian JP. Artificial Intelligence in Pharmaceutical Drug Development-challenges and the Way Forward. Current Artificial Intelligence. 2025; 3(1):E29503752359512.
53. Heindl N. Development of a PAT-controlled process for the production of pharmaceutical polymers with low drug concentration, 2020.