German J Pharm Biomaterials 2023; 2(1): 1-17
https://doi.org/10.5530/gjpb.2023.1.1

GJPB

Review Article

Quality by Design approach for nanosystem based topical drug delivery

Veeranti Vipanchi, Maimuna Fatima, Prasanthi Domaraju*

Department of Pharmaceutics, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana, India.

*Correspondence: prasanthidhanu@gmail.com

Received: 25 August 2022; Revised: 18 November 2022; Accepted: 29 November 2022

Abstract

The skin is increasingly being acknowledged as a chief drug administration route. Its natural barrier stratum corneum (SC) usually obstructs this route's effectiveness; hence, different strategies have been investigated to improve percutaneous drug transport. The design of Nano delivery systems, striving to solve skin delivery issues, is essentially explored, thanks to their prospect of revolutionizing dermal therapies, reducing side effects and enhancing therapeutic effectiveness. Optimization of the nanosystem and the process of manufacturing the nanosystem is complicated, typically involving a vast number of variables. Thus, Quality by design (QbD), the science and risk-oriented approach, provides comprehensive knowledge, rendering drug products of exceptional quality without large-scale regulatory obligation. This review gives an idea of the QbD development strategy, containing preliminary and systematic risk assessments, with CMAs (critical material attributes) and CPPs (critical process parameter) recognition for distinct nanosystems presumably utilized for dermal therapies.

Keywords: Topical formulations; Quality-by-Design; nano-delivery systems; risk assessments

Introduction

Quality by Design (QbD) is a contemporary technique that regularises product design, facilitates troubleshooting and automizes manual testing. To form an infallible quality, it employs a structured strategy by formulating an intensive knowledge of finished product compatibility to any or overall components and procedures concerned with producing that product rather than testing the final product solely. QbD imparts comprehension of upstream throughout the development procedure. The top-quality issue is practically scrutinized, and its principal cause is rapidly recognized. QbD mandates recognition of all process parameters and critical formulation attributes besides specifying the capacity of variations capable of affecting the standards of the final product [1,2]. As per Stéphanie Peika- "*QbD is a systematic strategy for development beginning with predefined objectives emphasizing product as well as process understanding and control, based on rational science and quality risk management*" [3].

Drug items that do not possess the required level of quality should not be recognised as therapeutic products. Neither should they be approved for the use nor should they be recommended. According to the Food and Drug Administration's (FDA) Centre for Drug Evaluation and Research, "A drug product is judged to be of high-quality when it is free of contamination and reproducibly delivering therapeutic advantages to the user as claimed on the label"[4,5].

QbD is a strategy for designing and developing formulations and manufacturing processes that align with predetermined product quality [6]. QbD plays a prominent role in topical dosage forms for maintaining the standards of the product. In Pharmaceutical development, a clear understanding is crucial before utilising the notion of QbD [7]. As per the US FDA, under the guidelines of "International Conference on Harmonisation (ICH) Q8", Pharmaceutical QbD is a methodical procedure elicited on QRM (quality risk management), which commences with a predetermined objective and accentuates understanding of the product and the process [8,9].

The outermost largest organ of humans is the skin, providing an efficient defensive barrier to the body and outer environment by opposing exogenous material penetration; It plays a significant part as a sensory organ. Whilst it is a perfect site for administering therapeutic compounds, the stratum corneum (SC) may hinder the penetration or permeation of most molecules. However, Nanosystems show significant promise as topical delivery carriers for promoting therapeutic and cosmetic substance transportation via the skin, permitting it to transcend the skin barrier reaching particular skin targets in appropriate doses to acquire adequate therapeutic effect.

Skin, the human body's largest organ, comprises the epidermis, dermis and hypodermis. The rate-controlling membrane of the skin, stratum corneum, is a principal barrier to the diffusion of molecules via skin. The SC is a well-identified diverse 2-compartment system comprising keratinized cells enclosed within a multilamellar lipid matrix comprising ceramides and neutral lipids. Crystalline lamellar lipid region surrounds corneocytes, i.e., keratin-filled dead cells. Majorly, medications are introduced via transcellular and intracellular pathways of the skin, whilst skin appendages (i.e., hair follicles and sweat glands) play a secondary part. Drug accumulation within the dermal layer is crucial, and nano-drug delivery is a prospective method for delivering drugs topically. Major dermatological products administered through the skin are meant for local activity. However, a few preparations additionally have a systemic effect and are referred to as transdermal drug delivery systems (TDDS). Preparations that act locally deploy their activity on the skin surface and acclimate functions of the dermis and epidermis. Penetration of drug molecules through the skin generally occurs via a complex and continual intercellular path.

Nanosystems are vehicles having particle sizes between 10 -1000 nm, wherein active substances may be well-dissolved in or encapsulated within or affixed to the surface. Unification of carriers into topical formulations facilitates targeted delivery, improved drug solubility, permeability, bioavailability, stability and prolonged effect, thereby showing enriched drug performance in the dermal region by reducing active toxicity/ skin irritancy and improving therapeutic efficacy.

This review focuses on quality-by-design (QbD) approaches to the development of topical dermatological dosage forms (TDDFs), particularly generic ones. TDDFs are an acronym for topical drug delivery formulations, which are medications that are applied directly to the area of action. The generic version of a TDDF must be identical to the reference-listed drug (RLD) in terms of its pharmacological and therapeutic equivalence. In addition, essential characteristics such as excipients, active pharmaceutical ingredients (API), the physicochemical properties of the drug, the physical and chemical stability of the drug product, the container closure system, the scalability of the preservatives, and the efficacy of the preservatives should be appropriately taken into account during the product development process [8,10]. These characteristics play a significant role in determining the efficacy of the drug product and its level of safety.

Quality by Testing

Product quality is guaranteed by raw substance testing, manufacturing process, in-process testing and testing of the final product done in Quality by Testing (QbT). The standard of materials, including drug substances and excipients, is usually scrutinised by testing. In general, the quality of the finished drug products is assessed based on whether or not they meet the manufacturer's proposal and FDA-approved specifications; if not, the product must be discarded. Core reasons for failure are generally not well comprehended. Usually, manufacturers risk ongoing losses to the final product until the primary cause of failure is comprehended and addressed or the FDA assents supplement to amend the acceptance standards to pass earlier failed batches [8,11].

Quality by Design

"Quality", as per ICH Q8, is described as the appropriateness of the drug product or substance for the intended use. The term Quality comprises such attributes because of strength, identity and purity. QbD in pharmaceuticals is a systematic, risk-based, scientific, proactive and holistic approach concerning pharmaceutical product development that commences with predetermined goals and

accentuates product and process knowledge and process control. It involves designing and developing formulation and manufacturing processes assuring pre-established objectives for product quality. This detail is conditioned- for implementing robust and adaptable manufacturing processes that acclimatize and produce uniform products over time.

Facilitators of Quality by Design are:

a) Quality risk management
b) Knowledge management

They offer a vital role in the development as well as in the implementation of QbD. They are influential in perpetrating the completion of a product, inducting and maintaining a state of control and facilitating improvement constantly [11,12].

a) Quality Risk Management

A fundamental facilitator/enabler for the improvement and vigilance of QbD is QRM (Quality risk management). During improvement, it enables assets to be centred on the perceived vital regions that influence products and techniques. It is a tool that offers a proactive path for recognising, scientifically evaluating and supervising potential risks to efficacy. It additionally allows continuous development of products and techniques' overall performance through the product's life cycle [13].

b) Knowledge Management

Product and technique expertise control is vital to QbD through the layout. Knowledge management is a scientific technique for acquiring, investigating, storing and communicating records associated with products, techniques and components. It additionally accentuates, "If fails", the product is discarded. Material discarded acceptance standards are primarily based on one or more batch data; to establish batch elements, testing must be completed as "Quality by Design: ICH Q8: Pharmaceutical Development", which talks about the diverse factors of quality through the layout. This and the enablers shape an essential foundation for the QbD technique. Knowledge Management (KM) is a crucial enabler for acquiring quality in the lifecycle approach for biopharmaceutical manufacturers. Under the substantial role it plays in the successful execution of QbD, an estimation of Knowledge Management is essential.

Certain Key features of QBD Include

The target product quality profile (TPQP)

TPQP is a device for establishing a strategic basis that is precise to drug improvement applications defined in the context of prescribing record goals. It is a perspective overview of the quality attributes of the drug acquired to assure the expected quality, considering the drug product's safety and efficacy. TPP (target product profile) plays a crucial role in complete drug discovery and improvement of techniques such as robust optimization of the drug, choice-making inside an institution, the layout of scientific studies, strategies and lively conversation with regulatory authorities [14].

Quality attribute (QA)

A physical, chemical or microbiological aspect that correlates to pre-established product quality (such as its purity, identity, strength, safety and marketability) [12,14].

Critical quality attribute (CQA)

In order to guarantee the quality of the product, the physical, chemical, or microbiological characteristics must fall within the allowable range or limit [14].

Process parameter (PP)

The values designated as control levels or operational limitations for the process variables provided (temperature, compression force) [14].

Critical quality parameter (CPP)

Variations in other process parameters can impact critical Quality Attributes (CQA); therefore, these changes must be monitored or regulated to achieve the intended quality product [14].

Design space (ds)

multidimensional blend and reciprocity of process parameters and input variables (such as, material attributes) that exemplifies the provision of quality [14].

Control strategy (CS)

The control strategy is a set of devised controls originating from available product and process knowledge that corroborates both the product's quality and the process's performance. Control strategy may comprise attributes and parameters associated with drug substance/ products, equipment operating conditions, materials and components, in-process controls, facilities, specifications of the finished product, corresponding techniques and frequency of monitoring or control [14].

Quality risk management (QRM)

It is a methodical technique for assessing, controlling, disseminating, and inspecting potential threats to the quality of pharmaceutical goods throughout the product lifetime [14].

Risk assessment

It is a systematized procedure to classify information for supporting risk decisions made within the risk management process involving identifying hazards and analyzing and evaluating risks corresponding to those hazards' exposure [14].

Process analytical technologies (PAT)

PAT is an approach for designing, examining, and controlling production via appropriate measurements concerning the critical quality of raw and in-process materials and procedural performance attributes, guaranteeing a quality product [14].

Process performance and product quality monitoring system

It is an approach for guaranteeing that a controlled state can be maintained while monitoring the quality of both the product and the performance of the process [14].

Corrective action and preventative action system

System for executing remedial measures and preventive efforts as a consequence of examining complaints, product turndowns, recalls, non-conformances, divagations, audits, regulatory inspections, trends from product quality and monitoring process performance [14].

Change management system (CMS)

A standardised process to be used when changes need to be proposed, evaluated, approved, implemented, and reviewed [14].

Design of Experiments (DoE)

DoE is an established approach for deducing the association among elements affecting a design and its output. Examples of DoE include Plackett Burman design, factorial design, and central composite design. Every unit operation has more than one input-output variable comprising process parameters-scrutinizing each is nearly incomprehensible. Additionally, scientists must utilize their expertise and risk control to become aware of crucial process parameters and input-output variables whilst engaging in DoE. The DoE outcomes can assist in locating essential elements related to CQAs. Details concerning interactions and collaborations among the elements can be reviewed too. Depending upon the admissible restraint of CQAs, the layout area for CPPs is specified. When a proper design is applied to the manufacturing technique used for dosage form, it enables enhanced quality of the product and

attributes. DoE decides the method and design areas for CMAs and CPPs. Figure 1 illustrates the QbD approach for the development of pharmaceutical drug products. One can operate DoE to help get an insight regarding the impact on processing parameters that will influence the CQAs of various dosage forms.

Additionally, this can be employed to enforce the Chemistry, Manufacturing and Control approach for comparing product performance, stability and technical manipulation of the dosage form. While executing DoE for topical dermatological product improvement procedures, input elements are process parameters and raw material attributes. At the same time, outputs include CQAs, including pH, viscosity, microscopic structure and uniformity of the dosage form. DoE offers a notion concerning optimized production strategy in a suitable combination to provide high-satisfactory products consistently [12,7].

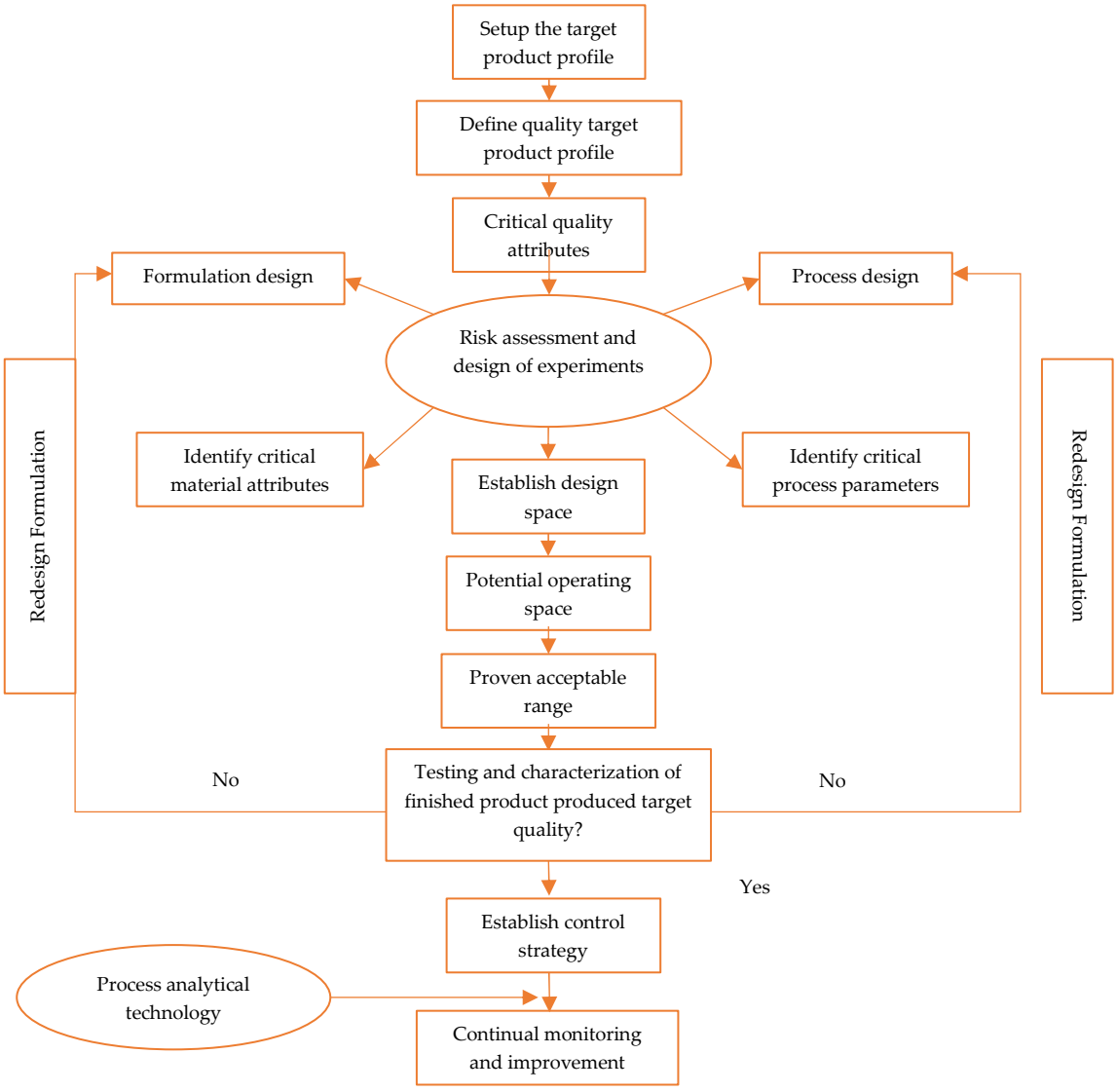

Figure 1. QbD approach for development of pharmaceutical drug product.

Design space

As per ICH Q8, design space is "A multidimensional mixture and interaction of procedure parameters and input variables that have exhibited proof of quality". It offers regulatory pliability for a single unit, multiple units or entire procedures. Functioning within a design space is not regarded as a change, and it affirms detailed process interpretation. However, time and money are two constraints with design space. Additionally, an unfavourable consequence is conceivable if a vital parameter is unnoticed while building design space. Production change in FDA-authorized design space does not

account for change; however, moving out of the space accounts for change. For these changes, a regulatory post-approval change procedure is mandated. Design space differs among sponsors relying on the formulation design and the system utilised for improving drug products [7,12,15].

Response surface designs

Process variables determined via means of screening designs ultimately go through surface optimization. Similar to Box–Behnken (BBD), central composite (CCD), and 3-level factorial design, the Response surface designs can uncover the optimal conditions for processing. Various advantages and disadvantages of this design are illustrated in Figure 2.

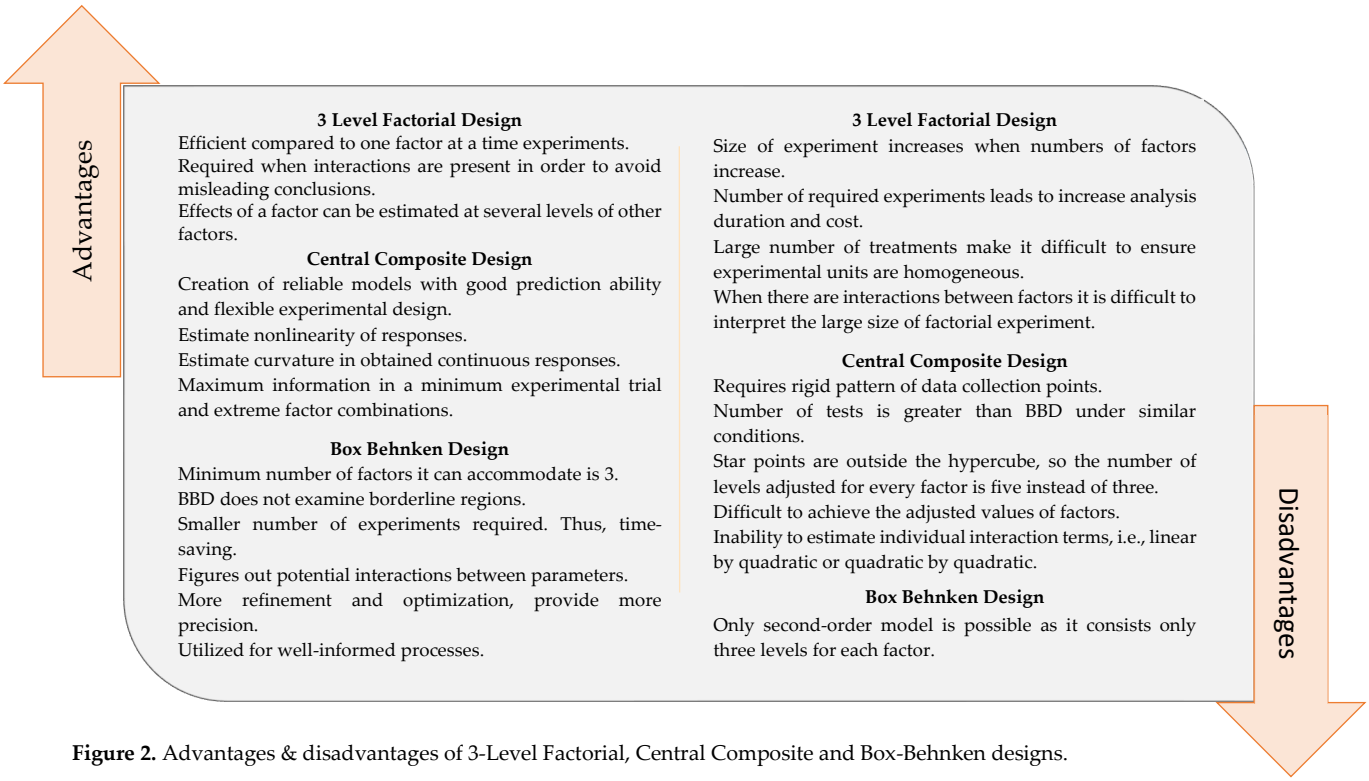

Figure 2. Advantages & disadvantages of 3-Level Factorial, Central Composite and Box-Behnken designs.

The central composite design is favoured because it is robust against mislaid data; centre and corner point trials may be covered from formerly performed factorial experiments. Besides, due to 3 levels for every factor, Box–Behnken design is utilized for facilitating the execution of an experiment. The problem with the design is uniform preciseness; a larger numeral of centre points is needed, and neglecting a single datum point will bring indecisive results. The range that could constantly reproduce a favoured quality product is a robust working area in the design space. Deviations from the standard procedure falling within design space is acceptable. It has pliability in regulatory approval and is most effective during the execution of QbD experimentation at the production scale. Variability through the developmental level at the laboratory scale offers beneficial details for scale-up and industrial batch size. Evaluating deviation assessing laboratory-scale equipment versus industrial-scale system constricts the processing variability. By utilizing CMAs recognized from the components and CPPs recognized from the process layout, the design space for manufacturing formulation can be recognized. With the target product profile, the output variables are represented and approximated. When an output is according to the target, a control approach is devised for the whole procedure. The QTPP ought to be redefined, and formulation and production procedures have to be redesigned with more fabulous product and procedure expertise if the target is to be achieved [12,16,17].

QbD procedures for improvement of conventional topical dermatological products

The QbD concept has acquired growing attention for innovational pharmaceutical development due to its usefulness in high-quality drug product assurances without comprehensive regulatory

surveillance. Implementing QbD requires defining QTPP and CQAs for the drug product, attaining risk assessment [18] to determine CMAs and CPPs, defining design space through DoE, and facilitating a control strategy and continuous advancement and invention through the product lifecycle [19,20]. A more significant interpretation of the product design and manufacturing process is vital for better adaptable regulatory practices [20]. A QbD approach for the development of topical dermatological dosage form is illustrated in Figure 3 [8,12].

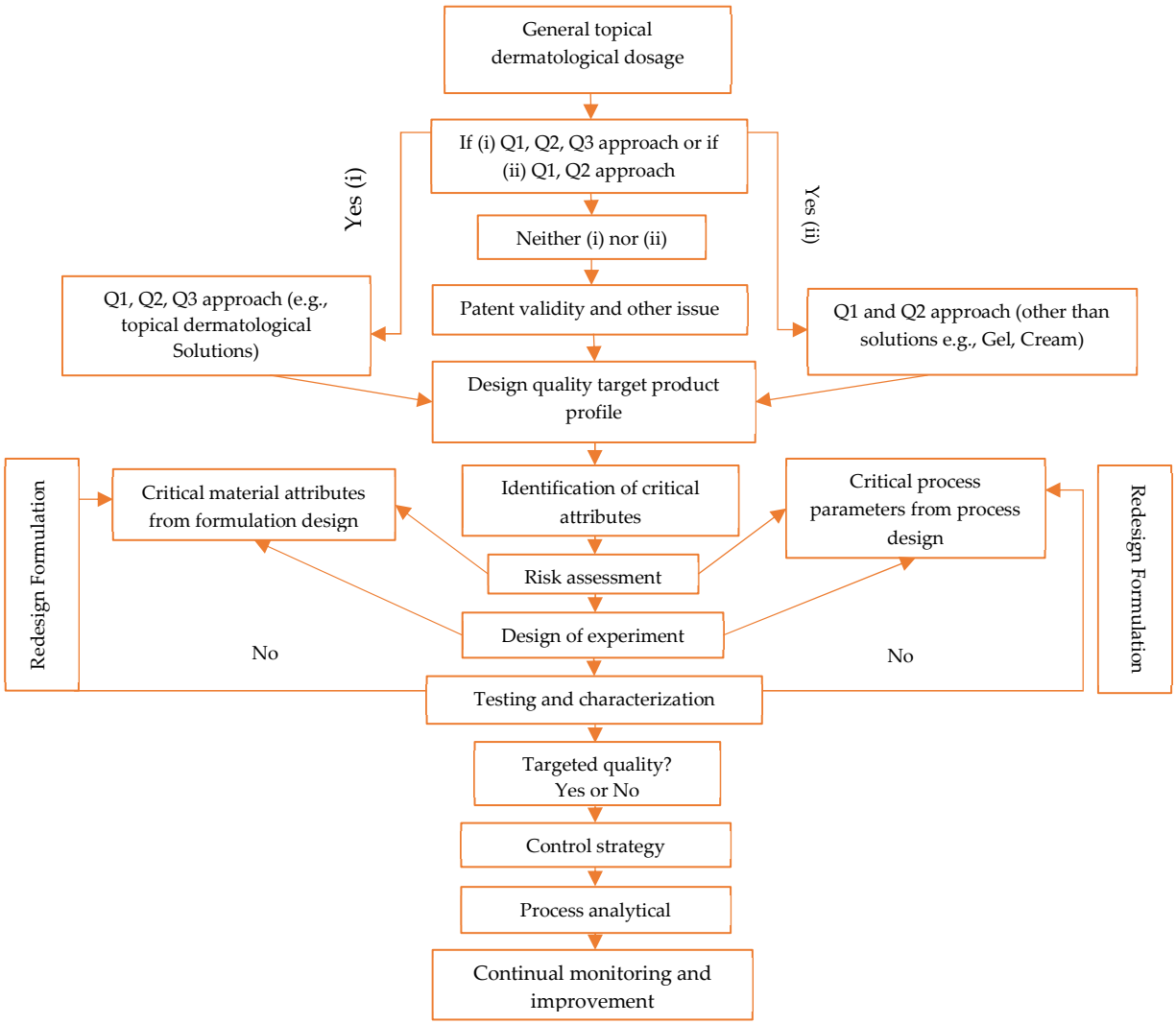

Figure 3. QbD approach for development of topical dermatological dosage form.

The fundamental key is the application of the QbD system in the pharmaceutical industries since it improves the developmental efficiency of pharmaceuticals with triumphant product optimization and a robust process of manufacturing; it enhances the contact between regulators and industry, thereby supplying regulatory solace and flexibility, reduces post-approval modifications and permits quality control in real-time with the successive real-time release [19,20]. Thus, the oblique utilization of the QbD concept for pharmaceutical development comprising nanosystems provides substantial benefits for the pharmaceutical industry and regulatory authorities.

An inadequate familiarity with the production process has provoked researchers to enforce the QbD process to optimise nanosystems, permitting them to invest and accelerate the development of nano-based formulations [21]. Nano-engineered quality assurance is additionally challenging to regulate, but the QbD method can be a beneficial strategy to overcome such hurdles.

Typically, ANDA (Abbreviated new drug application) for topical dermatological use must go through more than one evaluation cycle with FDA before product approval. Then the sponsor needs to wait for a prolonged period for a decision. Developing conventional topical products for dermatological use identical to the RLD (Reference-listed drug) is an actual procedure. These outcomes provide intricate risks concerning pharmaceutical and therapeutic equivalence. In developing topical dermatological methods, diverse standards ought to be considered. In developing conventional TDDF, it is vital to assess the RLD critically and primarily based on its physicochemical characteristics instead of simply relying upon the labelling of dosage form [7].

Topical dermatological drug delivery

Despite the broad usage of conventional creams, the bioavailability of the active ingredient remains contrarily from ideal through topical formulations, usually not surpassing more than 1-2% of the applied dose [22]. In most topical delivery systems, the capability to diffuse or permeate the skin relies on the drug's physicochemical properties, carrier features and skin conditions. Though there has been comprehensive scientific investment in this field, the technical developments in the case of new drug delivery systems (DDS) remain predominantly untrodden concerning skin penetration.

The largest and outermost organ of humans is the skin, which delivers a coherent protective barrier between the external environment and the body opposing exogenous agents' penetration. It also deploys an essential function as a sensory organ. Although it illustrates an exemplary site for therapeutic compound administration, intending to exert local and systemic results, skin is an intricate hindrance to the permeation/penetration of most molecules [23]. It comprises four recognizable parts: the stratum corneum (SC), viable epidermis, dermis and subcutaneous tissues (hypodermis). Appendages, i.e., hair follicles linked with sweat and sebaceous glands, are also available within the skin structure [24].

Stratum Corneum, the outer layer of the epidermis, is a principal barrier to molecular diffusion via the skin. It illustrates a distinctive structure represented as a series of elongated and flat corneocytes, connected or interlinked via desmosomes confined by intercellular lipids. This distinctive constitution of SC comprising intercellular lipids is essential for the skin barrier process. Additionally, appendages and layers possess vital roles and are binding target sites for the delivery of drugs. The preliminary path for transporting substances through SC is via a tortuous pathway specified by lipids surrounding the corneocytes. However, the transcellular path via the corneocytes may be feasible under specific situations. The appendages act as a potential entry path into the skin in certain circumstances. Physiochemical aspects of substances influence these pathways for skin permeation. The process of permeation is complicated, beginning with the release of the drug from the dosage form, followed by diffusion via the SC. This, then, partitions within the aqueous environment of the epidermis and diffuses to deeper tissues or is uptaken by blood vessels. The release of the drug from the vehicle, followed by uptake towards SC, depends on the diffusivity and solubility of the API. The diffusion coefficient of a drug is dependent on the properties of the drug and environmental factors, such as viscosity and tortuosity [22,23,25].

Apart from the skin, physiological aspects such as the drug and vehicle properties also affect drug permeation. The substances suited for diffusion via the SC are typically limited to highly potent molecules because of the low permeating rate of most molecules. Drug substances bearing molecular weight <500 Da are mandated, as size exhibits an inverse relationship with permeation and, after that, with diffusivity within SC.

Balanced lipid and water solubility with log P varying between 1-3 is preferable, as highly hydrophilic drugs cannot partition into SC from the vehicle. In contrast, highly lipophilic drugs exhibit increased affinity to SC, hence challenging to partition into deeper layers of skin. Ionized species exhibit low log P, and drug-ionized species possess a lower permeability coefficient than the respective unionized species. Eventually, a low melting point (< 200°C) too facilitates the solubility of the drug into the SC [22,23]. Therefore, a reasonable knowledge of skin structure is essential to prepare innovative and optimized formulations for topical use.

The vehicle offers a crucial function in the mechanism of delivery. For example, the supersaturation of the cream vehicle enhances the thermodynamic action of the formulation, thus providing an impactful driving force for the transportation of drugs across the skin. Likewise, the barrier role of SC can be narrowed by utilising permeation enhancers (chemical enhancers) or boosting the hydration of SC by occlusive effect [23-26]. In this situation, nanosystems ascertain a promising topical delivery carrier promoting the therapeutic and cosmetic substance transport to and via the skin, permitting the substances to transcend the skin barrier and reach specific skin targets in suitable doses to gain an effective and safe therapeutic outcome.

Nano systems are- "vehicles having particle size range 10 -1000 nm, wherefore active substances can be encapsulated, dissolved or attached to the surface. Integration of these carriers in formulations facilitates enhanced solubility, permeability, targeted delivery, bioavailability, prolonged effect and stability, enriching drugs' dermal performance by increased therapeutic efficacy and reduced skin irritancy or active toxicity. Various features of the nano system affect its characteristics and SC permeability. Likewise, skin ambience cannot be neglected since it influences the extent and depth of nanoparticle penetration [25,27].

Nano delivery systems, including polymer-based and lipid-based nanocarriers, are an appropriate approach to enhance the drug's percutaneous absorption and active substances' transport across the skin [28,29]. **T**hough nano systems are extensively studied as a promising approach for delivering topically, the quality control and safety of pharmaceuticals constituting nanocarriers is a paramount concern. Practically, it is incomprehensible to test all nanostructures. Innovative product development methods must be utilized to assure the quality and safety of the product. Additionally, several obstructions associated with physicochemical attributes, structure destabilization, limited reproducibility, complicated and expensive formulation and production and insufficient familiarity with the manufacturing process impede industrial-scale production and clinical application of nano formulations. Confounding these hindrances is essential nano formulation and process design ought to be optimized by utilizing more suitable scientific and systematic strategies [30].

Excipients

Generally, topical formulations consist of a large number of excipients. Assessing compatibility among the active component, excipients, solvents, and containers is vital. Variations within the different grades of excipients, variations in molecular weight and reactive remnants can cause unpredictable results. The stature of the excipient, i.e., whether it is compendial/ non-compendial, is a vital concern whilst choosing an excipient. Additionally, checks associated with toxicology/pharmacology may be needed if a non-compendial excipient is selected apart from those designated for RLD [10]. In maximum circumstances, various grades of excipients can be well suited to the Active ingredient or APIs; however, a compatibility check with the excipient is usually advised because there might be variation within the chemical and physical properties of excipients procured from distinctive sellers. A combination of emulsifiers with low and high hydrophilic-lipophilic balance (HLB) values is usually suggested. They can produce a film across dispersed droplets or debris to prevent coalescence. Ostwald ripening, i.e., merging or integrating scattered or dispersed small particles to large particles, is a substantial stability concern regarding maximum emulsion-based semi-solid products. Detection of crystallization in arrangements with irregular temperature cycles is referred to as the freeze-thaw cycle.

- Preservatives for TDDF, i.e., water-based preparations: Antimicrobial preservatives are usually significant. A combination of propylparaben and methylparaben, generally between 0.01 - 0.3%, is used.
- Other components, such as antioxidants or chelating agents combined with antioxidants, can be utilised for oxidative problems [12].

Active pharmaceutical ingredient

The source for procuring and the API quality is essential in developing standard topical formulations. It is vital to have a secondary procuring source for the API if the number one supply runs

into crisis. API degradation is important stability consideration, and understanding the deterioration path is a beneficial instrument at some stage for product improvement. As the proportion of solvent within a semi-solid topical product is much more than in different dosage forms, the API is liable to various instability-inflicting determinants apart from solutions. Comprehensive knowledge of the degradation path of API through "forced degradation analysis" for validating and improving the manufacturing approach is crucial to restrict the capability of degradation routes [12,31].

QbD on lipid-based nanosystems

Liposomes

Liposomes have been the first class of nanosystems among nanopharmaceuticals. These drug delivery systems are round amphipathic phospholipids comprising vesicular structures organised within a single/more concentric bilayer surrounding the aqueous core. Hydrophilic drugs can be encapsulated within an aqueous core, while lipophilic drugs can be enclosed within the lipid bilayer. Relying on the composition of lipids, preparation technique, and nature of the drug encapsulated, distinct liposomes can be yielded. Depending on the number of the bilayer, liposomes are categorised as unilamellar vesicles (ULVs) or multilamellar vesicles (MLVs) and based on size, a ULV, which comprises a single phospholipid bilayer, can be subclassified into small unilamellar vesicles (SUVs) and giant unilamellar vesicles (LUVs). Conventional liposomes exhibit outstanding capability as delivery systems of drugs from skin diseases to local remedies. The appeal of these nanocarriers for dermatological medication depends on their biodegradable, amphiphilic nature, biocompatibility, reduced power to offer to sustain drug release and occlusive impact to disrupt cell contents of the SC fusing with SC lipid parts for enhancing penetration properties into SC and the epidermis, enhance the local concentration of drug and therapeutic efficiency. Therefore, traditionally liposomes are considerably explored as a topical delivery system due to their cumulation within the SC, appendages and upper skin layers with minimum systemic delivery [1,32].

Niosomes

These are vesicular self-assembled nanosystems; assembled with amphiphilic molecules and non-ionic surfactants with a closed bilayer structure. Identical to liposomes, niosomes are usually organized as ULV or MLV. Niosomes are appropriate carriers for both lipophilic and hydrophilic drugs. The enhanced impact of permeation is attributed to its flexibility and fusion directly with SC. Additionally, surfactant molecules might alter SC lipid structure, thereby improving the skin permeability of API. The surfactant category impacts the drug release rate from vesicles. Preferentially, niosomes accumulate within the follicles or superficial skin layer, which justifies their improbable utility in dermatological pharmaceuticals.

Different strategies have evolved for manufacturing niosomes and liposomes, like reverse phase evaporation, film hydration technique, emulsification and solvent injection method. Liposomes and niosomes are predominantly developed via the film hydration technique. In this method, the vesicle components (e.g., soy lecithin: cholesterol, phosphatidylcholine: cholesterol) are dissolved with a solvent or aggregate of the natural solvent (including methanol or chloroform) followed by evaporating under reduced pressure or via lyophilization process, to get rid of any of the solvent traces, consequently resulting in lipid film formation. The resulting film is dispersed into the hydration media to provide MLVs aqueous dispersion. SUVs are formulated by lowering the lamellarity of MLVs and length via membrane extrusion or sonication, with specified pore length to achieve liposomes with desired particle size [33]. The niosomes preparation technique accommodates non-ionic surfactant: lipid aggregates hydration, observed through size reduction. The chemical composition, manufacturing strategies and physicochemical properties such as charge, size, vesicle deformation and thermodynamic state influence their effectiveness [1,34].

Ultra-deformable vesicles (UDV)

UDVs are the new era of deformable, elastic, flexible liposomes – Different kinds of UDVs are designed comprising transfersomes, ethosomes and transethosomes. These vesicles present risk-free

features, easy manufacturing and desirable stability. They present an incredible topical delivery capacity, elucidated by their better deformability, which permits the squeezing of elastic vesicles via little spaces in the skin, resulting in improved drug transportation or diffusion throughout the distinctive layer of skin. Phospholipids, surfactants, ethanol and permeation enhancers have substantially been utilised to produce those flexible vesicles [35].

a) *Transfersomes*

The foremost era of the UDV notably comprises amphipathic compounds, which include phospholipids (e.g., phosphatidylcholine) that are self-assembled as vesicles in an aqueous environment. Surfactant functioning as an edge activator is added to perpetrate the permeation behaviour into the lipid bilayer membrane. Tween®80, Span®80, potassium glycyrrhizinate and sodium cholate destabilize the vesicular shape, offering excellent deformability and flexibility. The penetration-enhancing impact of tranfersomes may be broadened to transport hydrophilic drugs, barring the efficient lipophilic drug delivery capabilities. Transfersomes exhibit better entrapment efficiencies (EE) than standard niosomes and liposomes [36]. Different strategies are employed to provide transfersomes, such as thin-film hydration, ultrasonication dispersion and reverse-phase evaporation. The film hydration approach is generally utilized. In this method, phospholipids, surfactants and drugs are initially dissolved in ethanol; then, it is evaporated below reduced pressure, forming a lipid film. The lipid film is hydrated by stirring. Sonication to decrease vesicle size can be used [1,37].

b) *Ethosomes*

These are deformable phospholipid vesicles comprising more percentage of ethanol (i.e., 20-45% of its composition) [38]. These nanostructures are regarded as an appropriate delivery system for the topical use of lipophilic as-well-as hydrophilic drugs. The penetration mechanism of ethosomes into the skin is elucidated to alcohol-penetrating attributes. Ethanol imparts greater vesicular moldability and flexibility, destabilizes the lipid bilayer and disrupts the lipid domain of SC, thereby enriching its fluidity. Additionally, the penetration-improving mechanism and intact ethosomes direct with skin lipids facilitate drug delivery via the skin, resulting in better deposition locally. Different techniques are known for preparing these carriers, like Film hydration, reverse-phase evaporation, or lipids dissolution (e.g., phosphatidic acid, phosphatidylserine or phosphatidylcholine) in ethanol, assembled by hot or cold technique to yield ethosomes [39]. In the classical method, the cold technique, on a magnetic stirrer, phospholipids are dissolved in ethanol and immersed in the water bath. The aqueous phase (buffer solution, water or standard saline solution) is heated, added dropwise to the organic phase, and stirred for 5-30 min. This system is maintained at 30°C. The active substance dissolves based on physicochemical properties in the aqueous/ organic phase. By sonication or extrusion technique, vesicle size reduction can be accomplished [40-42].

c) *Transethosomes*

These are vesicular structures like ethosomes; however, they have an extra compound in their formulation and surfactant (edged activator) or permeation enhancer (oleic acid, propylene glycol). Transethosomes integrate the advantages of deformable transfersomes + classical ethosomes [43]. Transethosomes have proven better skin permeability or penetration, as ethanol and surfactant are present in their composition, making them the most flexible UDV. Transethosomes have a splendid retention time within the sebaceous glands and hair follicles. Different techniques for transethosomes production are available; like liposomal vesicles, the film hydration method may be utilised. Phospholipids, drugs, edge activators and permeation enhancers are initially dissolved in chloroform or a mixture of methanol-chloroform. Then, organic solvent traces are eliminated via a rotary vacuum evaporator. The deposited lipid film is eventually hydrated using ethanol. Unlike ethosomes, the classical cold technique is the broadly used method for preparing transethosomes. The distinction between each vesicle relies upon the organic phase, wherein additional additives (edge activators/permeation enhancers) should be added [44,45].

Nanoemulsions

Nanoemulsions (NEs) are thermodynamic colloidal dispersed systems comprising water-immiscible and oily phases that are stabilized via an interfacial film formed by co-surfactant and emulsifying agents. NEs are biphasic structures of either oil-in-water (o/w) or water-in-oil (w/o) dispersion that permit the supply of lipophilic or hydrophilic drugs. Hydrophilic materials can be loaded into multiple NEs systems [46]. NEs showcase higher balance to flocculation, sedimentation and coalescence than traditional emulsions because of their small particle size, given that narrow size lowers the attractive forces among the droplets [47]. For the development of the product, excipient selection and the respective concentrations, the sequence of addition and preparation technique, including the speed of stirring, are parameters that demand specific alertness. Oily ingredients, including- propylene glycol monoethyl ether, isopropyl myristate, and isocetyl isostearate, were extensively utilized to generate emulsion-based nanosystems. Successfully designed NEs formulations require a judicious selection of emulsifying agents for decreasing interfacial tension between the water and oil phase, achieving kinetic balance in opposition to flocculation, sedimentation and coalescence effect and keeping away from creaming. The primary choice to produce nano-based emulsions is non-ionic surfactants because of their protection and low irritancy. Co-surfactants, like glycerine, propylene glycol and ethylene glycol, are incorporated into the isotropic system to equilibrate the emulsifier's interfacial film and help maintain its fluidity. NEs formation relies upon design components. Individual screening techniques and pseudo-ternary phase studies are usually accomplished to choose the most suitable ratio of the oil phase, surfactant and co-surfactant to acquire strong NEs. Oily phase selection is conducted by determining the relative drug solubility in oils. The surfactant is selected depending on the maximal quantity of the oil solubilized. Co-surfactant selection depends on stabilization efficiency. By fixing the surfactant: co-surfactant ratio and maintaining the surfactant unchanged, the best co-surfactant is decided via the substantial NE region shown in the ternary phase study [48,49].

Lipid nanoparticles

Lipid nanoparticles (LN) are considerably scrutinised for different pharmaceutical applications. However, when it comes to the field of cosmetics and pharmaceutical dermal formulations, there is a growing inquisitiveness in the field containing solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [50]. SLNs arose in the early 1990s as an alternative to conventional emulsions, liposomes, and polymeric nanoparticles [51]. NLC, the second LN generation, was introduced in 2005 [50]. These lipid-based nanosystems comprise a solid lipophilic matrix that contains the API. There are two distinct generations of lipid nanoparticles with lipophilic matrix structures available. These nanosystems are made of o/w nanoemulsions and are solid at body temperature [50]. Because of their drug targeting, biocompatible essence, occlusion effect associated with skin, well-established production techniques, effortless scalability, incorporation of low water-soluble active substances, enhanced skin bioavailability, surface hydration and penetration enhancement, advancement of drug stability, and ability to assure the close connection with the SC lipid domains, SLNs and NLCs are exemplary dermal delivery carriers. Nonetheless, hair follicle penetration is deemed an alternative route. APIs controlled release is modulated by altering lipid composition [51-55].

a) *Solid lipid nanoparticles* (SLNs)

SLNs are regarded to be the first generation of LN technology. The liquid lipid (oil) of an o/w emulsion is substituted with a solid lipid or a combination of solid lipids to form solid lipid nanosystems [51]. During storage, particles derived from distinctly purified solid lipids crystallized in higher energy structures, i.e., metastable β′ and unstable α polymorphic forms, undergo crystal rearrangement, ultimately forming stable β polymorphic form i.e., the most ordered and stable that leads to drug expulsion. The crystal order of the highest order diminishes imperfections of the matrix, confining the space for drug molecules to acclimate and, accordingly, the drug-loading capability of SLN [56].

b) *Nanostructured lipid carriers (NLCs)*

The more innovative second generation of solid lipid-based nanosystems, NLCs, is yielded by combining liquid and solid lipids [55]. Although NLCs are derived from SLNs, they prevail over some constraints accompanying the first generation of LNs, like lower drug loading efficiency and API removal during storage from the lipid matrix. When an oily compound is added, the structural order of the solid matrix is lost, and more imperfections are produced, which prevents the formation of a crystalline structure perfectly. As a result, the liquid lipids with molecules of different-size forms have an amorphous structure that permits enhanced active ingredient loading while avoiding or minimising drug expulsion while storing [50,56]. Emulsification-solvent diffusion, Emulsification-solvent evaporation, double emulsion technique, solvent displacement method, ultrasonication, membrane contact technique, HPH (high pressure homogenisation) and supercritical fluid are all methods for preparing LN [50]. Nevertheless, HPH [51,57] and ultrasonication [58,59] techniques are predominantly used for producing SLNs and NLCs.

Packaging

Packaging materials, i.e., containers and closures, should be amicable with the additives used in the formula. Increased unfamiliar degradable materials occur when there is leaching from the container and closure system. It is practical for the producer to apply identical material as the RLD. While developing topical products, the volatile to non-volatile solvents ratio must be assessed because most semi-solid formulations include a considerably higher quantity of volatile solvents than different additives in the preparation. The evaporation rate of solvent is a prominent issue as this will induce modifications to the performance, dermal absorption and stability of the given product. Drugs with low solubility in the provided solvent necessitate additional cautiousness. Varying rates of solvent evaporation can result in the emergence of issues like crystallisation, precipitation, polymorphism and changes in dissolution (in-vitro and in-vivo) [12,31].

Industrial production of nano-formulations

There are many obstacles to overcome, including nanosystem size, distribution, and functionality, all of which are essential components for successfully implementing effective therapeutics. For this reason, these parameters must be scalable and reproducible. It is necessary to have reproducibility of the drug release profile to attain batch uniformity and quality performance. Because the formulation and production of nanosystems are so complicated, pharmaceutical technology still faces ongoing challenges regarding PDI and size repeatability. Similarly, the instability of nanosystems makes it impossible to preserve them for extended periods, ultimately resulting in insufficient therapeutic efficacy. This is because of the changing conditions. The industry has struggled to decipher nano-based projects into a final drug product in this framework because such plans are established on unproven hypotheses or are challenging to scale up. In the case of nanosystems, when produced on a large scale achieving a binding robustness level is complex, and the reproduction of the results relies on various factors. Material, formulation, and process parameters must all be meticulously chosen. Lipid and polymer nanoparticles are being studied extensively in the nanomedicine era. These nanosystems can be created in the laboratory using a variety of techniques. As a result, understanding and optimising the formulation and production methods and recognising potential scale-up issues are critical because the desired features of nanoparticles usually need to be included when it is up-scaled [60,61]. Many different attempts have been undertaken in order to be successful in overcoming these challenges. Even if the development of QbD-based nanosystems is still up for debate, the prospects for its future applications are encouraging.

Conclusion

QbD has endured much appeal and is accentuated all the more for pharmaceutical producers. However, understanding its standards and nomenclature needs to be improved, resulting in a loss of inquisitiveness while applying its standards for product improvement. The robust production of common TDDFs, with its complex multiple system components and the necessity of stringent similarity

with commercial RLD, calls for an in-depth comprehension of CMAs and CPPs. The knowledge acquired on advancing topical dermatological products and using nanostructures through the years at the laboratory scale operates based on pilot or pivotal scale progression. QbD facilitates not just figuring out and comprehending CMAs and CPPs for pharmaceutical improvement but also helps understand the function and relations among those in accomplishing target quality products. Accordingly, imposing QbD procedures for developing TDDF is intensely recommended. From an industrial viewpoint, the usage of QbD downsizes charges at all levels of improvement and expedites the procedure of commercializing products. The advent of nanotechnology in recent years has unlocked new opportunities within medicine, particularly for developing novel drug delivery systems for dermal application. Nanostructures developed as novel drug carriers attained substantial importance in the twenty-first century because they successfully deliver active hydrophilic and lipophilic substances, enhancing drug solubility, efficacy, permeation, stability, irritancy, and delivery API directly in diseased skin. Nonetheless, the probable risks corresponding with those structures are challenging to assess, if not wholly unknown.

Despite the barrier SC imposes against active substance penetration, topical drug delivery systems have been extensively researched because the skin is deemed an appealing administration route. Generally, nanosystems enable increased skin permeation of the drug by raising the residence time of the drug in the SC, epidermis or by disruption of SC's integrity. As a result, nanosystems emerged as an intriguing technology for improving skin drug delivery, either on the skin's surface or locally in the dermal layer. Liposomes, micelles, niosomes, SLN, NEs, NLCs, and PNPs are nanostructures widely prepared for various topical applications. Numerous process and formulation adjustments are needed during product development, and optimizing these variables is critical to achieving the preferred quality product and desired therapeutic action. Since the early stages of research, the intro of QbD-based nanosystem development has led to systematic research inclusive of a significant number of process and formulation parameters that must be determined, controlled and understood for ensuring predefined product QTPP (Quality-target product profile) and as a result, safety and therapeutic efficacy. Consequently, the QbD-mandated design planning is essential for optimizing formulations and understanding the process of nanosystems' production. For nanosystem development utilizing this structured methodology will significantly improve product design, and there is a greater likelihood of the final product reaching the market.

Authors contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

Financial support

This work has not received any funds from national and international agencies.

References

1. Dey R, Chowdhury DR. Quality by Design- A New Approach to Drug Development. Int J Drug Regul Aff. 2015;3(2):8-16.
2. What is Quality by Design and why should you care? [Internet]. ONdrugDelivery Magazine. 2017;74:6-9. [cited 2023 March 15]. Available from: https://www.ondrugdelivery.com/quality-design-care/
3. Peika S. QbD for Pharmaceuticals: Assessing Quality through Risk. [cited 2023 March 15]. Available from: https://www.theauditoronline.com/qbd-for-pharmaceuticals-assessing-quality-through-risk/
4. Woodcock J. The concept of pharmaceutical quality. Am Pharm Rev. 2004;47(6):1-3.
5. Code of Federal Regulations, Title 21 [Internet] U.S. Food & Drug Administration. [cited 2023 April 04]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=225.1
6. Yu LX. Pharmaceutical quality by design: product and process development, understanding and control. Pharm Res. 2008;25(4):781-91.

7. Lionberger RA, Lee SL, Lee LM, Raw A, Yu LX. Quality by design: concepts for ANDAs. AAPS J. 2008;10(2):268-76.
8. Sivaraman A, Banga A. Quality by design approaches for topical dermatological dosage forms. Research and Reports in Transdermal Drug Delivery. 2015;4:9-21.
9. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771-83.
10. Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products: formulation development, process development, and testing of topical dermatologic products. AAPS J. 2013;15(1):41-52.
11. Patil AS, Pethe AM. Quality by Design (QbD): A new concept for development of quality pharmaceuticals. IJPQA. 2013;4(2);13-9.
12. Simõesa A, Veigaa F, Figueirasa A, Vitorinoa C. A practical framework for implementing Quality by Design to the development of topical drug products: Nanosystem-based dosage forms. Int J Pharm. 2018;548(1):385-99.
13. US Food and Drug Administration. Guidance for industry: Q9 Quality risk management, ICH, June 2006. [cited 2022 January 26]. Available from: http://www.fda. gov/downloads/Drugs/.../Guidances/ucm073511.pdf
14. Quality by design for Biotech, Pharmaceutical and Medical Devices [Internet] QbD Works- Quality by Design [cited 2023 March 25]. Available from: https://qbdworks.com/qbd-definitions/#:~:text=Quality%2Dby%2DDesign%20
15. Herkenne C, Alberti I, Naik A, Kalia YN, Mathy FX, Preat V, et al. In vivo methods for the assessment of topical drug bioavailability. Pharm Res. 2008;25(1):87-103.
16. Rosas JG, Blanco M, González JM, Alcalá M. Quality by design approach of a pharmaceutical gel manufacturing process, part 1: determination of the design space. J Pharm Sci. 2011;100(10):4432-41.
17. Xie L, Wu H, Shen M, Augsburger LL, Lyon RC, Khan MA, et al. Quality-by-design (QbD): effects of testing parameters and formulation variables on the segregation tendency of pharmaceutical powder measured by the ASTM D 6940-04 segregation tester. J Pharm Sci. 2008;97(10):4485-97.
18. ICH Q9. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Q9 Guideline: Quality Risk Management, 2005. [Internet]. [cited 2023 March 25]. Available from: https://www.ema.europa.eu/en/ich-q9-quality-risk-management-scientific-guideline
19. Pramod K, Tahir MA, Charoo NA, Ansari SH, Ali J. Pharmaceutical product development: A quality by design approach. Int J Pharm Investig. 2016;6(3):129-38.
20. ICH Q8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Q8 (R2) Guideline: Pharmaceutical Development, 2009. [Internet]. [cited 2023 March 25]. Available from: https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development-scientific-guideline
21. Marto J, Gouveia L, Jorge IM, Duarte A, Gonçalves LM, Silva SMC, et al. Starch-based Pickering emulsions for topical drug delivery: A QbD approach. Colloids Surf B Biointerfaces. 2015;135:183-92.
22. Hadgraft J, Lane ME. Advanced topical formulations (ATF). Int J Pharm. 2016;514(1):52-7.
23. Benson HAE. Skin Structure, Function and Permeation. In: Benson HAE, Watkinson AC, editors. Topical and Transdermal Drug Delivery: Principles and Practices. New Jersey: John Wiley & Sons, Inc. USA; 2012. p. 1-22.
24. Walters KA, Brain KR. Topical and transdermal delivery. In: Gibson M, editor. Pharmaceutical Preformulation and Formulation: A Practical Guide for Candidate Drug Selection to Commercial Dosage Form. Newyork: USA; 2009. p. 475–525.
25. Roberts MS, Mohammed Y, Pastore MN, Namjoshi S, Yousef S, Alinaghi A, et al. Topical and cutaneous delivery using nanosystems. J Control Release. 2017;247:86-105.
26. Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products, Part II: Quality by design for topical semisolid products. AAPS J. 2013;15(3):674-83.
27. Bastogne T. Quality-by-design of Nanopharmaceuticals- A state of the art. Nanomed.: Nanotechnol Biol Med. 2017;13(7):2151-7.
28. Marto J, Gouveia LF, Gonçalves LM, Gaspar DP, Pinto P, Carvalho FA, et al. A Quality by design (QbD) approach on starch-based nanocapsules: a promising platform for topical drug delivery. Colloids Surf B Biointerfaces. 2016;143:177-85.
29. Neubert RH. Potentials of new nanocarriers for dermal and transdermal delivery. Eur J Pharm Biopharm. 2010;77(1):1-2.

30. Kraft JC, Freeling JP, Wang Z, Ho RJY. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. J Pharm Sci. 2014;103(1):29-52.
31. Lowenborg MA. Troubleshooting guide for topical drug manufacturing. Pharm Technol. 2012;36(11):46-49.
32. Benson HAE. Elastic liposomes for topical and transdermal drug delivery. Methods Mol Biol. 2010;605:77-86.
33. Joseph J, Hari VBN, Devi RD. Experimental optimization of Lornoxicam liposomes for sustained topical delivery. Eur J Pharm Sci. 2018;112:38-51.
34. Fadda AM, Sinico C. Vesicular carriers for dermal drug delivery. Expert Opin Drug Deliv. 2009;6(8):813-25.
35. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. Int J Nanomed. 2015;10:5837-51.
36. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. Adv Drug Deliv Rev. 2004;56(5):675-711.
37. Jain B, Singh B, Katare OP, Vyas SP. Development and characterization of minoxidil-loaded liposomal system for delivery to pilosebaceous units. J Liposome Res. 2010;20(2):105-14.
38. Dayan N, Touitou E. Carriers for skin delivery of trihexyphenidyl HCl: Ethosomes vs. liposomes. Biomaterials. 2000;21(18):1879-85.
39. Chourasia MK, Kang L, Chan SY. Nanosized Ethosomes bearing ketoprofen for improved transdermal delivery. Results Pharma Sci. 2011;1(1):60-7.
40. Abdulbaqi IM, Darwis Y, Khan NAK, Assi RA, Khan AA. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. Int J Nanomed. 2016;11:2279-304.
41. Nandure HP, Puranik P, Giram P, Lone V. Ethosome: a novel drug carrier. Int J Pharm Res Allied Sci. 2013;2(3):18-30.
42. Zhou Y, Wei YH, Zhang GQ, Wu XA. Synergistic penetration of ethosomes and lipophilic prodrug on the transdermal delivery of acyclovir. Arch Pharm Res. 2010;33(4):567-74.
43. Song CK, Balakrishnan P, Shim CK, Chung SJ, Chong S, Kim DD. A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: Characterization and in vitro/in vivo evaluation. Colloids Surf B Biointerfaces. 2012;92:299-304.
44. Garg NK, Sharma G, Singh B, Nirbhavane P, Tyagi RK, Shukla R, et al. Quality by Design (QbD)-enabled development of aceclofenac loaded-nano structured lipid carriers (NLCs): An improved dermatokinetic profile for inflammatory disorder(s). Int J Pharm. 2017;517(1-2):413-31.
45. Ibrahim MA, Darwis Y, Assi RA, Khan NAK. Transethosomal gels as carriers for the transdermal delivery of colchicine: statistical optimization, characterization, and ex vivo evaluation. Drug Des Devel Ther. 2018;12:795-813.
46. Arshady R. Preparation of polymer nano- and microspheres by vinyl polymerization techniques. J. Microencapsul. 1988;5(2):101-14.
47. Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nano emulsions. Adv Colloid Interface Sci. 2004;108-109:303-18.
48. Shafiq S, Shakeel F, Talegaonkar S, Ali A. Design and development of oral oil in water ramipril nano emulsion formulation: in vitro and in vivo assessment. J Biomed Nanotechnol. 2007;3(1):28-44.
49. Aishwarya G, Reza KH, Rajan RK. Development, evaluation and optimization of flurbiprofen nanoemulsions gel using quality by design concept. Asian J Pharm. 2015;9(1):35-43.
50. Müller RH, Petersen RD, Hommoss A, Pardeike J. Nanostructured lipid carriers (NLC) in cosmetic dermal products. Adv Drug Deliv Rev. 2007;59(6):522-30.
51. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009;366(1-2):170-84.
52. Souto EB, Wissing SA, Barbosa CM, Muller RH. Evaluation of the physical stability of SLN and NLC before and after incorporation into hydrogel formulations. Eur J Pharm Biopharm. 2004;58(1):83-90.
53. Souto EMB. SLN and NLC as drug carriers of clotrimazole for hydrogel topical formulations [Dissertation]. Fasculdade de Farmacia: Univesidade do Porto; 2003.
54. Venuganti VV, Perumal OP. Nanosystems for dermal and transdermal drug delivery. In: Pathak Y, Thassu D, editors, Drug Delivery Nanoparticles Formulation and Characterization. New York: Informa Healthcare USA, Inc; 2009. P.126-55.

55. Vitorino C, Almeida A, Sousa J, Lamarche I, Gobin P, Marchand S, et al. Passive and active strategies for transdermal delivery using co-encapsulating nanostructured lipid carriers: in vitro vs. in vivo studies. Eur J Pharm. Biopharm. 2014;86(2):133-44.
56. Mehnert W, Mäder K. Solid lipid nanoparticles. Production, characterization and applications. Adv Drug Deliv. Rev. 2001;47:165-96.
57. Gupta S, Kesarla R, Chotai N, Misra A, Omri A. Systematic approach for the formulation and optimization of solid lipid nanoparticles of Efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. BioMed Res Int. 2017;2017:1-18.
58. Kovács A, Berkó S, Csányi E, Csóka I. Development of nanostructured lipid carriers containing salicyclic acid for dermal use based on the Quality by Design method. Eur J Pharm Sci. 2017;99:246-57.
59. Mennini N, Cirri M, Maestrelli F, Mura P. Comparison of liposomal and NLC (nanostructured lipid carrier) formulations for improving the transdermal delivery of oxaprozin: Effect of cyclodextrin complexation. Int J Pharm. 2016;515(1-2):684-91.
60. Leroux, JC. Drug delivery: too much complexity, not enough reproducibility? Angew Chem Int Ed Engl. 2017;56(48):15170-1.
61. Paliwal R, Babu RJ, Palakurthi S. Nanomedicine scale-up technologies: feasibilities and challenges. AAPS PharmSciTech. 2014;15(6):1527-34.

How to cite this article:
V Veeranti, Fatima M, D Prasanthi. Quality by Design approach for nanosystem based topical drug delivery. German J Pharm Biomaterials. 2023;2(1):1-17.