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Review Article

Nanoemulsion - Based Cosmeceuticals: Formulation Strategies and Quality by Design Approach- A Comprehensive Review

Chinnaguravagari Saranya, Vothani Sarath Babu, Velpuri Nikitha Lakshmi

Department of pharmaceutics, S.V.U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati, India

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ABSTRACT

Nanotechnology has a modernized cosmetic formulation by improving the delivery, stability, and efficacy of active ingredients. Cosmetic systems, particularly nano emulsions, are widely used to enhance skin penetration, protect sensitive bioactive, and enable controlled release in products such as anti-aging creams, sunscreens, and moisturizers. However, these systems pose challenges related to formulation variability, stability, safety, and solubility. The Quality by Design (Qb-D) approach provides a systematic and science-based framework for addressing these challenges by ensuring a thorough understanding of formulation and process variables. This review emphasizes the role of QbD in nano emulsion-based cosmeceuticals, focusing on key elements such as Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs). The application of risk assessment tools and design of experiments (DoE) for optimization also discussed. In addition, the review summarizes current methods for preparation of nanoemulsion, safety assessment. Overall, QbD-guided development offers effective strategy for producing safe, effective, and high-quality nano-cosmetic formulations.

INTRODUCTION

The cosmetic industry has swiftly progressed from traditional beauty products to advanced cosmeceuticals with both aesthetic and medicinal properties. Modern cosmetic formulations increasingly formulated not just to improve appearance but also to deliver biologically active chemicals that promote skin health, hydration, anti-aging properties, and photo protection. However, many conventional cosmetic formulations have disadvantages such as low solubility of active ingredients, insufficient stability, and restricted penetration across the skin barriers.

***Corresponding Author:** Chinnaguravagari Saranya
Address: *Department of pharmaceutics, S.V.U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati, India*
Email : saranyareddy187@gmail.com
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Nanotechnology has emerged as a useful technique for addressing these difficulties. Nanoemulsions have gained popularity in cosmetic and pharmaceutical formulations because to their small droplet size, huge surface area, and improved physicochemical stability. These systems typically comprise oil, water, surfactants, and co-surfactants that create nanosized droplets capable of enhancing active chemical solubilization and cutaneous administration. Because of these benefits, nanoemulsions are commonly used in products such as moisturizers, sunscreens, anti-aging creams, and therapeutic skincare formulas.(15,17) Despite their benefits, developing stable nanoemulsion systems is challenging since formulation composition and processing factors have a significant impact on droplet size, stability, and performance. In recent years, the Quality by Design (QbD) method has gained prominence as a systematic framework for formulation development. QbD focuses on a detailed understanding of formulation variables and process parameters to assure consistent product quality, safety, and efficacy. The QbD technique involves determining critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs). The QbD technique allows for optimal and reproducible nanoemulsion formulations. (10,11)

These review paper also discusses nanoemulsion preparation methods, uses in cosmetic items and the significance of statistical tools such as Design of Experiments (DoE) in attaining robust formulation development.

NANOEMULSIONS:

Nanoemulsions are nano scale dispersions composed of two immiscible liquids stabilized by surfactants. Although they are thermodynamically unstable systems, they exhibit significant kinetic stability due to their extremely small droplet size. , Flow chart of Mechanism of nanoemulsion based cosmeceuticals with QbD approach followed in Fig.1

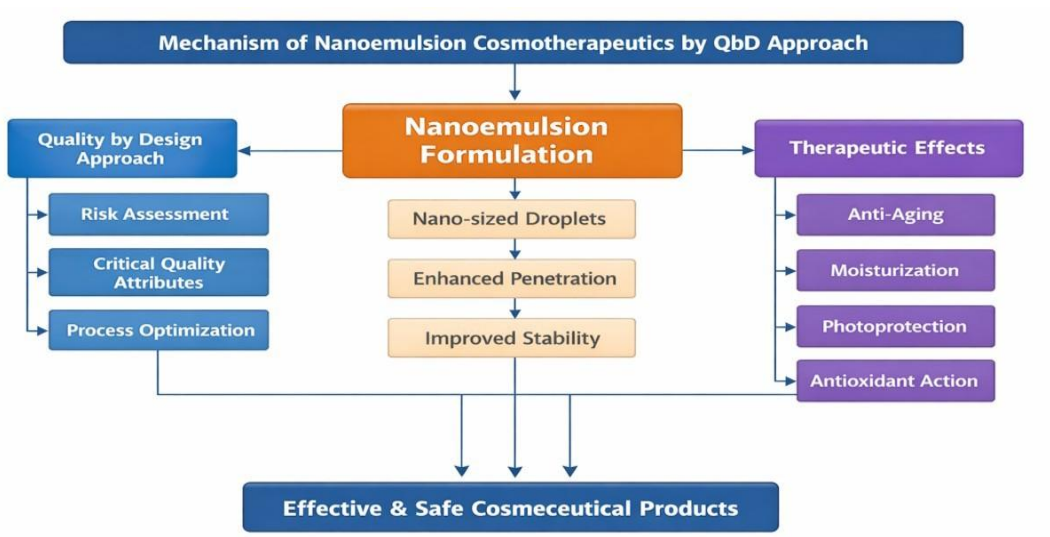


Fig .1 Mechanism of nanoemulsion of cosmeceuticals by QbD Approach

1.2 Mechanism of Nanoemulsion-Based Cosmeceuticals with QbD:

Nanoemulsions enhance drug delivery by improving solubilization, penetration, and controlled release of active ingredients (17, 18). Their nanoscale droplet size increases surface contact with the skin, while surfactants disrupt the lipid structure of the stratum corneum, facilitating permeation through intercellular, transcellular, and follicular pathways (21, 22). They also protect active compounds from degradation and enable sustained release, resulting in prolonged therapeutic effects such as hydration, anti-aging, antioxidant, and photo protective benefits (25). Mechanism of Skin Cosmo therapeutics by Nanoemulsion followed in Fig.2

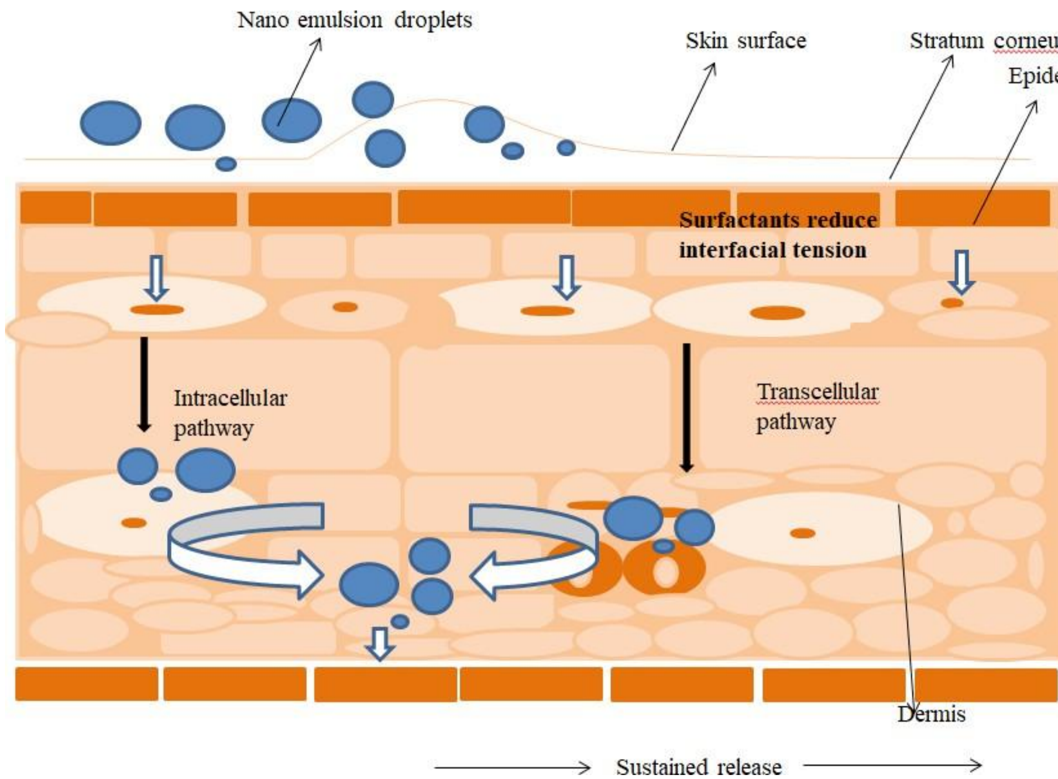


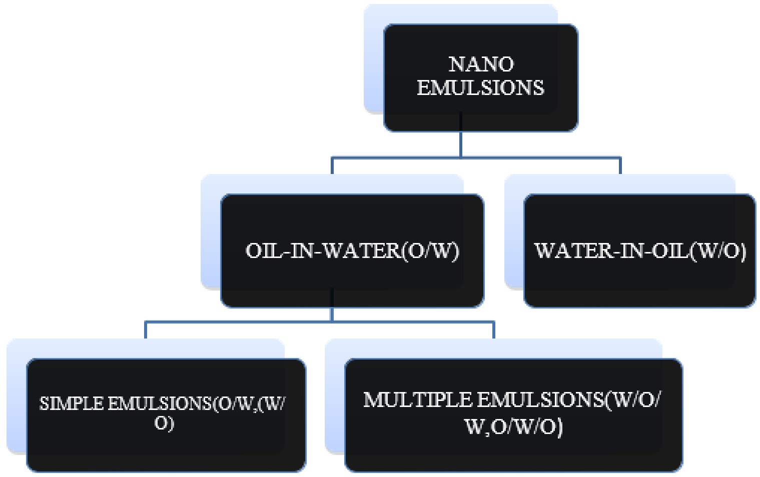
Fig.2. Mechanism of Skin Cosmotherapeutics by Nano emulsion

Under the QbD framework, critical material attributes (CMAs) and process parameters (CPPs) optimized to achieve desired critical quality attributes (CQAs) like droplet size, stability, and drug release. Tools such as Design of Experiments (DoE) help establish optimal conditions, ensuring reproducibility and enhanced product performance (9, 10).Overall, integrating Nano emulsion technology with QbD provides a robust and scientific approach for developing safe and effective cosmeceutical formulations (14, 32).

1.3. NANO EMULSION FUNDAMENTALS:

Nanoemulsion is a mixture of active ingredients and other functional excipients, namely oils, surfactants, co-surfactants and aqueous phase. The composition of nanoemulsion is vital in defining its characteristics like stability, droplet size, viscosity, drug release, etc (19)

1.4. TYPES OF NANO EMULSIONS:



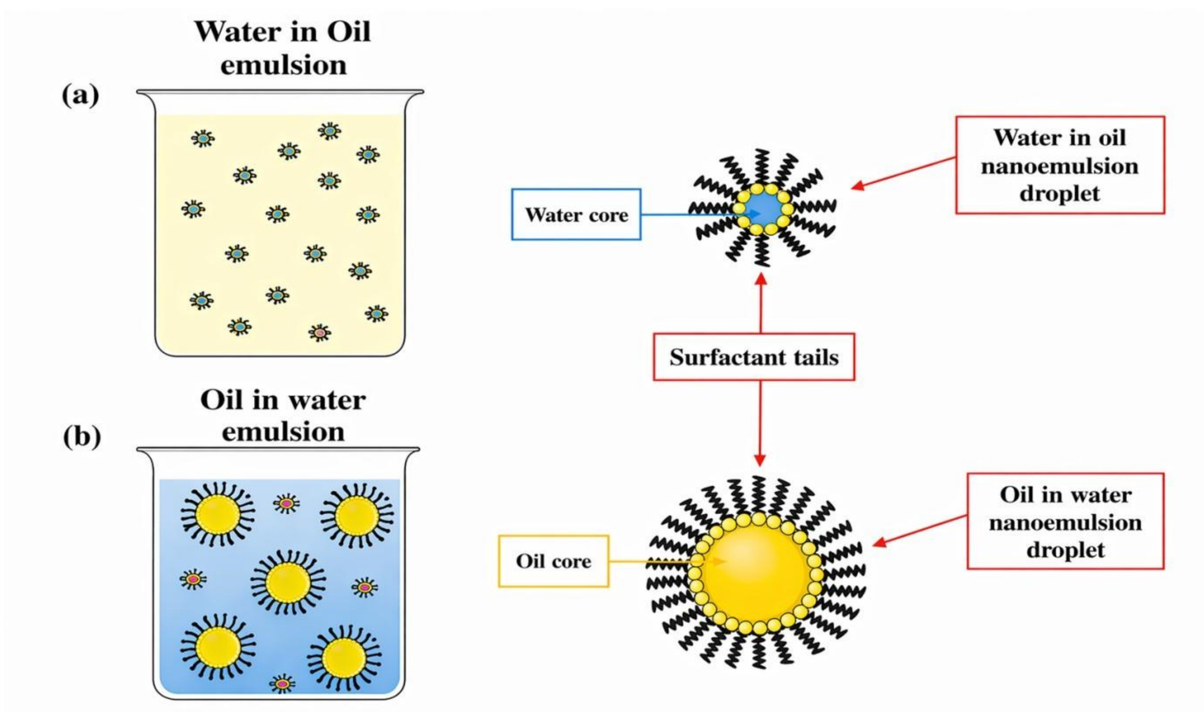


Fig.3. Basic Structure of Water-in-Oil and Oil-in-Water Emulsions

1.5. COMPONENTS OF NANO EMULSION

1. Oil Phase (influences droplet size):

The oil phase serves as the dispersed phase in oil-in-water nanoemulsions. The type of oil (natural oils like coconut or olive oil, lipids like oleic acid, or essential oils) directly affects droplet size, solubility of active ingredients, and overall stability. Oils with lower viscosity and appropriate polarity typically produce smaller droplets.

2. Aqueous Phase (controls viscosity):

This is the continuous phase, usually consisting of purified water or buffer solutions. It determines the viscosity, pH, and ionic strength of the system, which in turn influence droplet distribution and stability.

3. Surfactants (stabilize nano droplets):

Surfactants such as Tween 80, Span 60, and lecithin reduce interfacial tension between oil and water, enabling the formation of nanosized droplets and preventing coalescence. Their hydrophilic-lipophilic balance (HLB) is crucial for efficient emulsification.

4. Co-surfactants (improve stability):

Co-surfactants like PEG 400, glycerol, and propylene glycol enhance the flexibility of the interfacial film, further reducing interfacial tension and improving long-term stability and droplet uniformity.

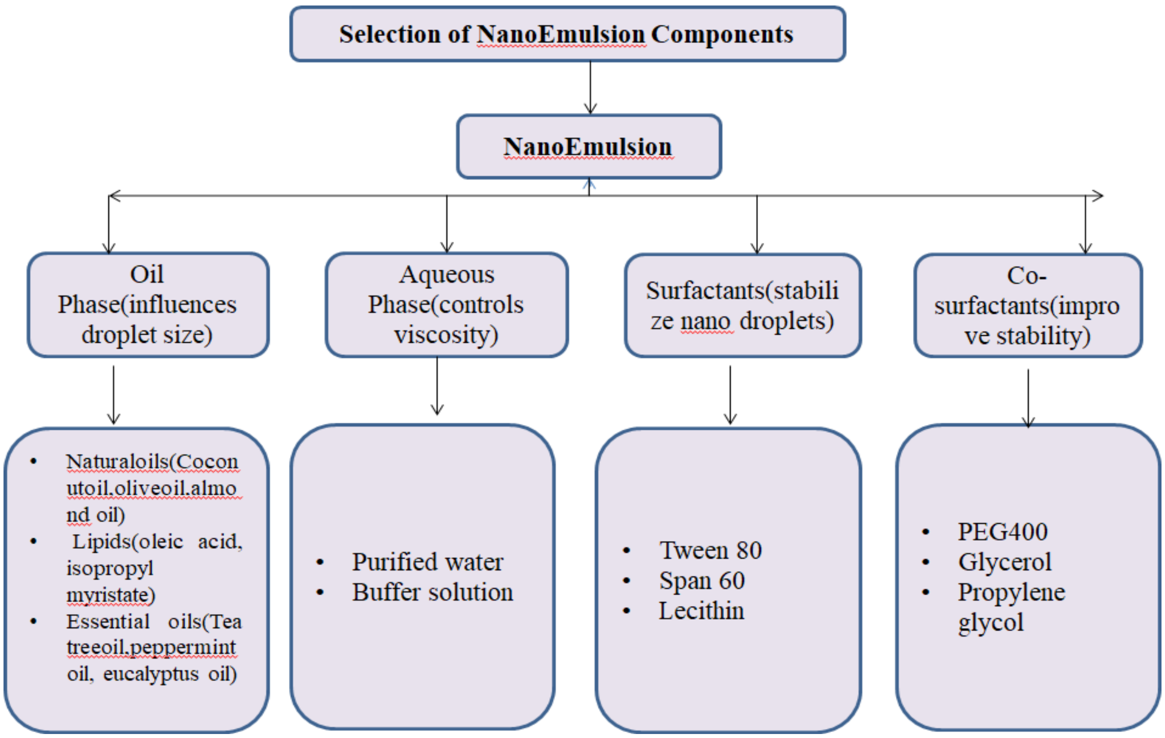


Fig.4. Selection of nano emulsion components

Fig.4 emphasizes that nanoemulsion formulation is highly dependent on the careful selection and balance of these components, as each one plays a distinct role in determining droplet size, stability, viscosity, and overall performance of the system.

2. METHODS OF PREPARATION

Nanoemulsions are nanosized colloidal systems whose characteristics depend on the method of preparation, classified as high-energy or low-energy techniques. Incorporation of QbD ensures controlled development by optimizing formulation parameters through DoE, resulting in reproducible, stable, and efficient nanoemulsion systems. Methods of preparation of nanoemulsion flowchart is followed in Fig.5

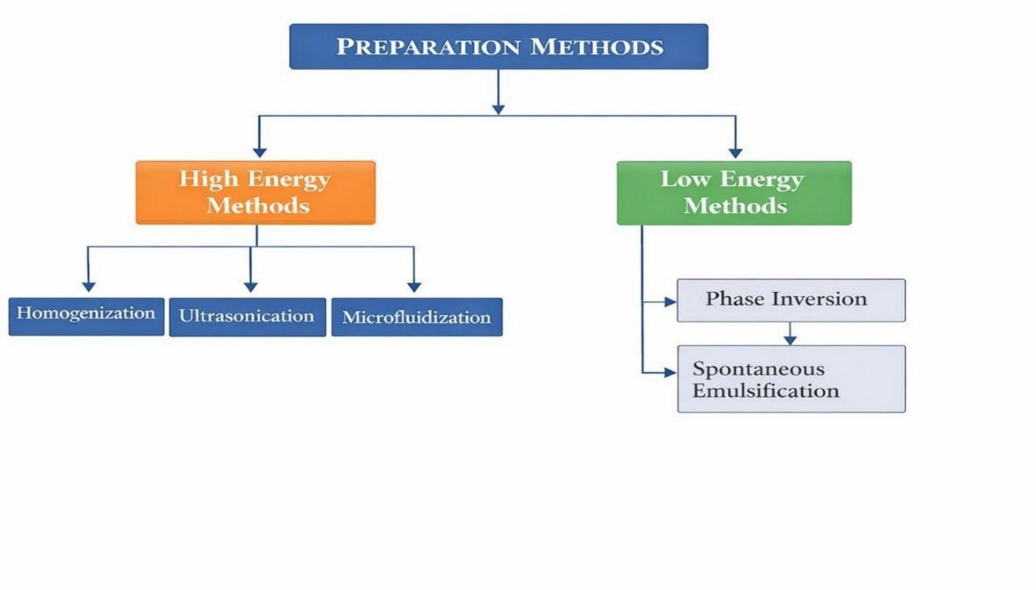


Fig. 5 Methods of preparation of nanoemulsion formulation

1. **High-Energy Methods:** High-energy techniques utilize mechanical devices to generate intense disruptive forces that break coarse emulsions into nanosized droplets. The application of **Quality by Design (QbD)** in these methods ensures systematic optimization of process parameters, leading to reproducible and stable Nano emulsions. (18, 19)

a) **High-Pressure Homogenization (HPH):**

This is one of the most widely used industrial techniques. A coarse emulsion forced through a narrow gap under high pressures (500–5000 psi), generating intense shear forces, cavitation, and turbulence that reduce droplet size.

Applications: Frequently used in cosmetic creams, lotions, and pharmaceutical formulations.

Role of QbD:

- Identification of **Critical Process Parameters (CPPs)** such as pressure, number of homogenization cycles, and temperature.
- Optimization of **Critical Material Attributes (CMAs)** like oil phase and surfactant concentration.
- Control of **Critical Quality Attributes (CQAs)** such as droplet size, polydispersity index (PDI), and stability.
- Use of **Design of Experiments (DoE)** to determine optimal pressure and cycles for uniform nano-droplet formation.
- Ensures scalability and batch-to-batch consistency.

b) **Ultrasonication** Ultrasonication uses high-frequency sound waves (20–200 kHz) to produce cavitation bubbles. Their collapse generates shock waves that break droplets into nanoscale sizes.**Applications:** Ideal for laboratory-scale formulations and research development.

Role of QbD:

- Optimization of sonication time, amplitude, and energy input as **CPPs.**
- Control of temperature rise to prevent degradation of active ingredients.

- Adjustment of surfactant concentration (**CMAs**) to improve emulsification efficiency.
- Application of DoE to achieve desired droplet size and stability.
- Ensures reproducibility in small-scale formulations.

c) Microfluidization

This technique involves passing emulsions through microchannels where streams collide at high velocities, producing strong shear forces and uniform droplet size.

Applications: Widely used in pharmaceutical, cosmetic, and food industries for stable and uniform nanoemulsions.

Role of QbD:

- Optimization of pressure, flow rate, and number of passes (**CPPs**).
- Control of formulation composition (**CMAs**) for improved performance.
- Monitoring of CQAs such as droplet size distribution and zeta potential.
- DoE helps define **design space** for consistent nanoemulsion production.
- Enhances scalability and industrial applicability.

6 **Low-energy methods:** Low-energy methods rely on the physicochemical properties of surfactants and spontaneous interfacial changes, requiring minimal mechanical energy. QbD plays a vital role in optimizing formulation composition and ensuring stability. (16)

a) Phase-InversionTemperature(PIT)Method

This method utilizes temperature-dependent changes in the solubility of nonionic surfactants. At the phase inversion temperature, the surfactant shifts from hydrophilic to lipophilic, resulting in the formation of very small droplets.

Applications: Commonly used in cosmetic and pharmaceutical formulations for stable nanoemulsions with enhanced drug delivery.

Role of QbD:

- Identification of optimal **phase inversion temperature** as a critical parameter.
- Optimization of surfactant type and concentration (**CMAs**)
- Control of heating and cooling rates (**CPPs**)
- Monitoring CQAs such as droplet size and stability.
- DoE ensures reproducibility and robust formulation design.

b) Spontaneous Emulsification

This process occurs when an organic phase containing oil, surfactant, co-surfactant, and solvent mixed with water, leading to rapid diffusion and formation of nanosized droplets.

Applications: Widely used for improving bioavailability of poorly soluble actives in pharmaceutical, nutraceutical, and cosmetic formulations.

Role of QbD:

- Optimization of oil-to-surfactant ratio and composition (**CMAs**)
- Control of mixing conditions and addition rate (**CPPs**)
- Evaluation of CQAs such as droplet size, PDI, and thermodynamic stability.
- Use of DoE to identify optimal formulation region (design space).
- Ensures consistent performance and improved formulation robustness.

6 NANO-EMULSIONS IN COSMECEUTICALS

Nano-emulsions extensively used in various cosmetic applications due to their enhanced delivery and Pleasing properties. (4, 25)

.1 SKIN CARE PRODUCTS

Nanoemulsions are widely used in anti-aging creams, moisturizers, sunscreens, and serums to increase the penetration of antioxidants, vitamins, and herbal extracts. Overview of Nanoemulsion Applications in Skin care Cosmetics with QbD Considerations followed in Table.1

TABLE.1. Nanoemulsion-Based Skin Care Products in cosmetics (21, 22, 23)

Skin Care Product	Active Ingredients	Role of Nanoemulsion	Role of QbD	Applications
Moisturizers	Jojoba oil, ceramides, hyaluronic acid	Enhances hydration and improves spreadability	Optimization of oil–surfactant ratio and droplet size to ensure stability and skin hydration efficiency	Daily hydration creams and lotions
Anti-aging creams	Vitamin C, Vitamin E, Coenzyme Q10, retinol	Promotes deeper penetration and controlled release	Control of CQAs like droplet size, PDI, and release profile for enhanced collagen stimulation and reduced irritation	Anti-aging and firming products
Sunscreens	Zinc oxide, titanium dioxide, octocrylene	Improves dispersion of UV filters and photostability	Optimization of particle size and dispersion uniformity to ensure consistent SPF and photostability	Broad-spectrum sun protection
Acne treatment products	Tea tree oil, salicylic acid, neem extract	Enhances delivery of antimicrobial agents	Controlled formulation variables to improve stability and targeted delivery while minimizing irritation	Acne gels and medicated creams
Skin	Niacinamide,	Protects active	Optimization of	Pigmentation

brightening creams	alpha-arbutin, licorice extract	from degradation and increases bioavailability	formulation parameters to enhance stability of sensitive actives and improve delivery efficiency	and brightening treatments
Sensitive skin formulations	Aloe vera, chamomile, calendula	Provides gentle and uniform release	Selection of mild surfactants and controlled processing conditions to ensure safety and minimize irritation	Products for reactive or delicate skin
Cleansers	Essential oils, mild surfactants	Improves solubilization of oily impurities	Optimization of surfactant concentration and formulation pH to maintain cleansing efficiency and skin compatibility	Facial cleansers and makeup removers
Under-eye creams	Peptides, caffeine	Facilitates targeted delivery	Control of droplet size and release kinetics for precise delivery to delicate skin areas	Under-eye treatments

3.2 HAIR CARE PRODUCTS

They boost the delivery of conditioning chemicals, eliminate frizz, and increase hair shine while leaving no greasy residue. Overview of Nanoemulsion Applications in Hair care Cosmetics with QbD Considerations followed in Table.2

TABLE 2.Nanoemulsion-Based Hair Care Products in cosmetics (3, 25, 26, 27, 32)

Hair Care	Active Product Ingredients	Role of Nanoemulsion	Role of QbD	Applications
Shampoos	Tea tree oil, peppermint oil, zinc pyrithione	Enhancessolubilization of essential oils an	Optimization of surfactant concentration, pH, and droplet size to ensure stability and effective cleansing performance	Anti-dandruff and clarifying shampoos

		d antimicrobial agents		
Conditioners	Argan oil, coconut oil, silk proteins	Enables uniform distribution on hair fibers	Control of formulation parameters to achieve optimal viscosity and uniform deposition on hair strands	Daily conditioners and smoothing products
Hair growth tonics	Minoxidil, caffeine, biotin, herbal extracts	Promotes deeper penetration into hair follicles	Optimization of droplet size and release kinetics to enhance follicular delivery and efficacy	Hair regr owth treatments
Hair serums	Vitam in jojoba kerati n E oil,	Provides lightweight formulation with rapid absorption	Adjustment of oil phase and surfactant ratio to ensure non-greasy texture and stability	Leave-in serums and gloss enhancers
Anti-hair fall formulations	Ginseng extract, cast or oil, bhringraj	Improves bioavailability of nutrients to follicles	Optimization of CMAs and CPPs to enhance delivery efficiency and formulation stability	Therapeutic scalp treatments
Scalp treatments	Aloe vera, neem extract, salicylic acid	Facilitates controlled release of soothing agents	Selection of mild excipients and controlled processing to ensure safety and sustained release	Products for sensitive or irritated scalp
Hair repair masks	Shea butt er, hydrolyzed proteins, ceramides	Enhances penetration damaged structure into hair	Optimization of formulation viscosity and droplet size to improve adherence and penetration into hair fibers	Intensive repair masks
Color protection products	Green extrac t, filters tea UV	Protects act ives from degradation	Control of formulation stability and photostability through optimized composition and processing parameters	Products for chemically treated hair

3.3 HERBAL AND NATURAL COSMETICS

Nano-emulsions are excellent transporters of plant-based actives, increasing their stability and bioavailability. Overview of Nanoemulsion Applications in Herbal Cosmetics with QbD Considerations followed in Table.3

TABLE.3.Herbal/Natural Nanoemulsion products in cosmetics (11, 32)

Herb/Extract Loaded	Nanoemulsion Carrier	Stability Results	Role of QbD
Curcuma aromatica extract (antioxidant)	O/W nanoemulsion stabilized with Tween 80/Span 80	Stable (PZ 12–547 nm, PDI 0.29–0.84) with maintained physical parameters over storage	Optimization of surfactant ratio (Smix), droplet size, and PDI to ensure physical stability and consistent antioxidant delivery
Hydroxy-safflor yellow A (Carthamus tinctorius)	Nanoemulsion	Enhanced physicochemical stability vs free compound	Control of formulation variables and process parameters to improve stability and reproducibility
Elemene oil (Curcuma sp.)	Nanoemulsion	Improved stability relative to conventional emulsion	Optimization of oil phase composition and processing conditions to enhance formulation stability
Quercetin (plant flavonoid)	Nanoemulsion	More stable colloidal system	Optimization of droplet size and surfactant concentration to maintain stability and uniform dispersion
Essential oils (multiple EOs)	Nanoemulsion (O/W with Tween/Span stabilizers)	Nano droplets <200 nm show dynamic and thermodynamic stability	Selection of appropriate surfactant system and process optimization to ensure stability and minimize variability

4. Quality by Design (QbD) Approach in Nanoemulsions based Cosmeceuticals

Quality by Design (QbD) is the most recent appeal added by the International Council for Harmonization (ICH) to the annexure to the ICH Q8 guidelines. It is a scientific and systematic idea that results in the manufacture of high-quality products by planning and developing pharmaceutical formulations and preparation methods [18]. It is founded on the notion that "quality cannot be proven into things; rather, quality should be incorporated in by design" [19]. QbD is rapidly replacing the conventional technique (one variable at a time) and solidifying its position in the industry. Prior to formulation development, a quality target product profile (QTPP) established. It is necessary to define and establish the relationship between various aspects of QbD, such as QTPP, CQAs, CPPs, and CMAs. Common tools of QbD include risk assessment and design of experiment (DOE). (9, 10, 11)

It analyzes how the material and process parameters affect the CQAs of the final product. It determines the source of variability and helps to control it. It ultimately designs the product with optimized parameters. Most importantly, the process of statistical optimization and analysis guarantees the product quality to the regulatory bodies.

4.3 QUALITY TARGET PRODUCT PROFILE (QTPP)

QbD ensures that each QTPP parameter is systematically defined and achieved through optimization of formulation and process variables, resulting in a stable, effective, and consumer-acceptable nanoemulsion product. Determines desired product qualities such as appearance, droplet size, viscosity, stability, and safety. Quality by Design (QbD) Elements

and Target Product Profile (QTPP) for Nanoemulsion-Based Cosmetic Formulations followed in Table.4

Table 4: Quality by Design (QbD) Framework for Nano-Emulsion–Based Cosmetics (9, 10, 11)

QbD Element	Parameter	Description	Role of QbD
QTPP	Dosage form	Cream, gel, lotion, or serum intended for topical cosmetic use	QbD helps in selecting an appropriate dosage form based on target performance, stability, and consumer acceptability
	Route of application	Topical (skin application)	Ensures formulation is designed for effective dermal delivery and safety
	Droplet size range	< 200 nm to qualify as nanoemulsion and enhance skin interaction	Optimization of formulation and process parameters to achieve desired nanoscale size for better penetration
	Product appearance	Transparent or translucent for consumer acceptability	QbD ensures control of formulation variables to maintain clarity and aesthetic appeal
	pH	Skin-compatible pH (≈ 5–6) to avoid irritation	Helps in selecting suitable excipients and maintaining pH within safe limits for skin compatibility
	Stability	No phase separation, creaming, or coalescence during shelf life	Identification and control of factors affecting physical stability to ensure product robustness
	Intended cosmetic function	Anti-aging, moisturizing, antioxidant, sunscreen, etc.	Guides formulation design to meet desired cosmetic outcomes effectively

4.2 CRITICAL QUALITY ATTRIBUTES (CQAs)

Critical Quality Attributes (CQAs) such as droplet size, PDI, and zeta potential directly influence skin penetration, stability, and uniformity of the formulation. Maintaining these within acceptable limits ensures effective delivery and product consistency. Key CQAs and their role in QbD Optimization of Nanoemulsions is followed in Table.5

Table.5 Key Critical Quality Attributes (CQAs) and their role in optimization of nano emulsion formulation

QbD Element	Parameter	Description	Role of QbD
CQAs	Mean droplet size	Governs skin penetration, optical clarity, and physical stability	QbD optimizes formulation and process variables to achieve desired nanoscale size
	Polydispersity Index (PDI)	Indicates droplet size uniformity and formulation robustness	Ensures uniform distribution by controlling formulation conditions
	Zeta potential	Reflects electrostatic stabilization of nano-droplets	Helps maintain stability by optimizing charge-related parameters
	pH	Ensures skin compatibility and active stability	Maintains safe and effective pH through excipient selection
	Viscosity / Rheology	Influences spreadability, sensory feel, and application	Optimizes formulation composition for desired texture and performance
	Physical stability	Resistance to creaming, flocculation, Ostwald ripening	Identifies and controls instability factors for long-term stability
	Active content uniformity	Ensures consistent cosmetic performance	Ensures uniform distribution of actives across batches

4.3 CRITICAL MATERIAL ATTRIBUTES (CMAs)

Critical Material Attributes (CMAs) such as oil type, surfactant concentration, and co-surfactant ratio determine interfacial properties, solubilization capacity, and overall stability of nanoemulsions. Key CMAs and their role in QbD Optimization of Nanoemulsions is followed in Table.6

Table.6 Key Critical Material Attributes (CMAs) and their role in optimization of nano emulsion formulation

QbD Element	Parameter	Description	Role of QbD

CMAs	Oil phase type	Natural oils/esters affect droplet formation, penetration, and skin feel	Selection based on solubility, compatibility, and performance
	Oil concentration	Influences droplet size and emulsion viscosity	Optimization ensures balance between stability and performance
	Surfactant type & HLB	Determines interfacial tension reduction and emulsion stability	Selection ensures proper emulsification and stability
	Co-surfactant ratio	Enhances flexibility of interfacial film	Optimized to improve droplet stability and uniformity
	Cosmetic active	Lipophilicity and stability	Ensures compatibility and
	nature	affect loading and release	efficient delivery of actives
	Stabilizer	Controls viscosity, stability, and release behaviour	Selection improves formulation stability and controlled release

4.4 CRITICAL PROCESS PARAMETERS (CPPs)

Critical Process Parameters (CPPs) including homogenization speed, time, ultrasonication amplitude, and temperature significantly affect droplet formation and size reduction. Proper control of these parameters prevents instability and ensures reproducibility. Key CPPs and their role in QbD Optimization of Nanoemulsions is followed in Table.7

Table.7.Key Critical Process Parameters (CPPs) and their role in optimization of nano emulsion formulation

QbD Element	Parameter	Description		Role of QbD
CPPs	Homogenization speed	Controls droplet breakup and size reduction		Optimization ensures efficient droplet size reduction
	Homogenization time	Excess time may over-processing instability	cause and	Identifies optimal time to avoid degradation or instability
	Ultrasonication amplitude	Generates cavitation forces for nano-droplet formation		Controls energy input for consistent droplet formation
	Processing temperature	Affects viscosity, surfactant behavior, and active stability		Maintains temperature within limits to prevent instability

	Order addition	phase	Impacts initial formation and distribution	droplet size	Standardizes process sequence for reproducibility

4.5. RISK ASSESMENT TOOLS

Risk assessment tools in QbD provide a structured approach to identify, evaluate, and control variables affecting nanoemulsion quality, ensuring efficient and reliable formulation development. Risk assessment tools and their role in optimization of nano emulsion formulation is followed in Table.8

Table.8 Risk assessment tools and their role in optimization of nano emulsion formulation

QbD Element	Tool	Description	Role of QbD
Risk Assessment	Ishikawa diagram	Identifies potential causes affecting CQAs (e.g., material, method, equipment, environment)	Helps in systematic identification of factors influencing product quality and guides risk-based formulation development
	FMEA (Failure Mode and Effects Analysis)	Prioritizes high-risk CMAs and CPPs based on severity, occurrence, and detectability	Enables ranking of risks and focuses optimization on critical variables to ensure robust and stable nanoemulsion formulation

4.5 DESIGN OF EXPERIMENTS (DOE)

Design of Experiments (DoE) is a systematic statistical approach used in the Quality by Design (QbD) framework better understand the link between formulation variables and product quality. In nanoemulsion-based nanocosmetics, DoE aids in determining the best mix of ingredients and processing conditions required to achieve desired quality features such as small droplet size, high stability, and uniform dispersion.

Factorial designs and response surface methodology used to optimize formulation variables and establish design space. (8, 9, 12) Key QbD elements and Statistical tools used in Design of Experiments for optimization of Nanoemulsion formulations is followed in Table.9

Table.9 Key QbD elements and Statistical tools used in Design of Experiments for optimization of Nanoemulsion formulations.

QbD Element	Parameter	Description	Role of QbD

DoE	Box–Behnken / Central Composite Design (CCD)	Statistical experimental designs used to evaluate interaction effects between variables and optimize formulation	Enables systematic optimization of formulation and process variables with minimal experimental runs
	Independent variables	Oil %, surfactant %, homogenization speed (rpm)	Identified as CMAs and CPPs that significantly influence nanoemulsion characteristics
	Dependent responses	Droplet size, PDI, zeta potential	Represent CQAs used to evaluate formulation performance and quality
	ANOVA analysis	Statistical tool to determine significance of variables and model fitness	Helps identify critical factors and validate the experimental model
	Response surface plots	Graphical representation of variable interactions	Assists in understanding combined effects of variables on responses
	Optimization	Selection of best formulation conditions	Ensures achievement of desired CQAs such as stability and uniformity
Design space		Range of variables where product quality remains acceptable	Provides flexibility in manufacturing without affecting product performance
Software used	Design-Expert®, JMP®, MODDE®	Minitab®,	Facilitates experimental design, statistical analysis, modeling, and optimization of nanoemulsion formulations

Software's Used in QbD for Nanoemulsions:

Various statistical and modelling software tools used to design experiments, analyse data, and optimize formulations:

- **Design-Expert® (Stat-Ease)** – Most widely used for DoE, response surface methodology (RSM), and optimization
- **Minitab®** – Used for statistical analysis and experimental design
- **JMP® (SAS)** – Advanced data visualization and predictive modeling
- **MODDE®** – Used for QbD-based formulation optimization and design space establishment
- **GraphPad Prism** – For data analysis and graphical representation
- **MATLAB®** (optional) – For advanced modeling and simulation

These tools help in establishing relationships between variables and responses, enabling precise optimization.(8,9,12)

6 CONTROL STRATEGY

Effective control strategy under QbD ensures consistent product quality by controlling raw materials, monitoring processes, and verifying final product performance (8, 9, 10, and 11). Control Strategy elements in Quality by Design (QbD) to ensure process control and quality of nano emulsion formulation is followed in Table.10

Table.10. Control Strategy elements in Quality by Design (QbD) to ensure process control and quality of nano emulsion formulation.

QbD Element	Parameter	Description	Role of QbD
Control Strategy	Raw material specifications	Ensures consistency of oils, surfactants, and active ingredients used in formulation	QbD ensures selection and control of high-quality materials to maintain batch-to- batch consistency
In-process controls		Monitoring of CPPs during manufacturing (e.g., temperature, speed, time)	Enables real-time control of process variables to ensure desired CQAs are achieved
Finished product testing		Confirms CQAs meet predefined acceptance criteria	Ensures final product quality, safety, and performance before release

6 Procedure for QbD Application in Nanoemulsion Development (9, 10, 11, 14)

The implementation of QbD in nanoemulsion formulation involves the following steps:

Step 1: Define QTPP (Quality Target Product Profile)

- Desired properties: droplet size, stability, skin compatibility, release profile.

Step 2: Identify CQAs

- Droplet size, PDI, zeta potential, viscosity, drug release.

Step 3: Identify CMAs and CPPs

- CMAs: oil type, surfactant concentration, Smix ratio.
- CPPs: homogenization speed, sonication time, temperature.

Step 4: Risk Assessment

- Use Ishikawa diagram and FMEA to identify high-risk variables.

Step 5: Experimental Design (DoE)

- Select design (Box–Behnken, Central Composite Design).
- Define independent variables (e.g., oil percentage, surfactant %, speed).
- Define responses (e.g., droplet size, PDI, zeta potential).

Step 6: Data Analysis & Optimization

- Use software (Design-Expert, Minitab).
- Generate response surface plots.
- Identify optimal formulation.

Step 7: Design Space Establishment

- Define range where CQAs remain acceptable.

Step 8: Validation

- Prepare optimized batch.
- Compare predicted vs experimental results.

Step 9: Control Strategy

- Maintain consistency during scale-up and production.

5. CHALLENGES AND LIMITATIONS

- **Sensitivity to formulation and processing conditions:**

Nanoemulsions are highly dependent on formulation composition (oil, surfactant ratio) and processing parameters (temperature, homogenization). Small variations can lead to significant changes in droplet size, polydispersity, and stability, affecting product performance and reproducibility.(16,17,19)

- **High surfactant concentration:**

To achieve stability, nanoemulsions often require higher amounts of surfactants, which may cause skin irritation, toxicity, or allergic reactions upon prolonged use, especially in sensitive skin formulations.(22,24,25)

6 SUMMARY

The adoption of the Quality by Design (QbD) approach in nanoemulsion-based cosmeceutical development marks a shift away from traditional formulation approaches and toward a more structured and science-driven process. Unlike traditional trial-and-error procedures, which frequently lack consistency and process awareness, QbD emphasizes the proactive integration of quality into both formulation and manufacturing processes from the start. Nanoemulsions have significant interfacial surface area and nanoscale droplet size, making them complex and sensitive systems (17). These properties render them susceptible to physical instability mechanisms such as creaming, flocculation, and coalescence. The QbD framework allows for a comprehensive understanding of the factors that influence formulation performance and stability by linking the Quality Target Product Profile (QTPP) with Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs). This integrated method assures that the final product constantly fulfills predetermined quality, safety, and efficacy standards.

Among the identified CQAs, droplet size and polydispersity index (PDI) are critical in determining nanoemulsion behavior. These factors have a direct impact on not just physical stability, but also skin penetration, visual appearance, and sensory properties, all of which are crucial for consumer approval of cosmetic products. The use of systematic risk assessment methods like Ishikawa diagrams and Failure Mode and Effects Analysis (FMEA) enables the identification of high-impact variables in CMAs and CPPs. As a result, formulation efforts can be strategically oriented toward regulating these essential parameters, increasing efficiency and minimizing development time.

The increased demand for herbal and organically derived cosmetic actives continues emphasizes the importance of QbD in nanoemulsion systems. Such bioactives frequently present problems like poor water solubility, sensitivity to degradation, and unpredictability in function. QbD facilitates the stabilization and effective delivery of these sensitive compounds by selecting and optimizing formulation components such as oil phase, surfactant systems, and stabilizers, as well as precisely controlling processing conditions. This improves both product performance and shelf life.

Furthermore, including Design of Experiments (DoE) into the QbD framework provides a useful tool for assessing the combined impacts of various factors. Unlike traditional one-factor-at-a-time approaches, DoE allows for the detection of interaction effects and aids in the construction of prediction models. The creation of a well-defined design space guarantees that acceptable product quality is maintained even with modest alterations in formulation or processing conditions, increasing robustness and allowing scale-up for industrial production. Although originally created for pharmaceutical development, the use of QbD concepts in cosmetics is becoming increasingly significant as regulatory standards rise and consumers seek safe, effective, and scientifically validated goods. Overall, applying QbD to nanoemulsion-based cosmeceuticals provides a dependable and forward-thinking technique for achieving consistent product quality, increased performance and successful commercialization.

CONCLUSION

The advancement of nanoemulsion-based nano cosmetics highlights the need for a more rational and controlled formulation strategy, which is effectively addressed by the Quality by Design (QbD) approach. By integrating scientific understanding with statistical optimization tools, QbD enables precise control over formulation variables and processing conditions, resulting in improved product reliability and reproducibility.

This approach is particularly valuable in managing the complexities associated with nanoscale systems, including stability challenges and variability in performance. It also supports the efficient incorporation of bioactive compounds by enhancing their protection and delivery within the formulation matrix.

In the context of evolving regulatory expectations and increasing demand for high-performance cosmetic products, QbD-driven nanoemulsion development offers a robust pathway for innovation, scalability, and commercialization.

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