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OPTIMISING NANOPARTICLES: HARNESSING QUALITY BY DESIGN THROUGH 3-LEVEL FACTORIAL DESIGN AND BOX-BEHNKEN METHODOLOGY

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Abstract

Nanoparticles (NPs) have become essential elements in a number of scientific and industrial domains, such as materials research, drug delivery, and diagnostics, because of their special qualities and potential for focused uses. An ideal formulation procedure is essential to maximising the effectiveness and efficiency of nanoparticles. In order to optimise the formulation and production processes for nanoparticles, this research investigates the application of Quality by Design (QbD) principles in conjunction with sophisticated statistical approaches, namely the 3-level factorial design and the Box-Behnken methodology. The Quality by Design methodology is a methodical approach that prioritises predetermined goals, in-depth process comprehension, and careful control grounded in reliable science and quality risk management. When QbD is incorporated into nanoparticle optimisation, reliable and repeatable formulations that adhere to specifications with little variation are guaranteed. To look into how different factors interact and affect the properties of nanoparticles, the 3-level factorial design is used. With this design approach, a thorough understanding of the process variables can be obtained by exploring a broad variety of component values. Critical quality attributes (CQAs) include important parameters such drug encapsulation efficiency, zeta potential, polydispersity index (PDI), and particle size. These parameters are methodically examined to determine the ideal amounts of each. To further refine the 3-level factorial design, the Box-Behnken methodology is applied. Without the requirement for extensive combination testing, this response surface methodology (RSM) is especially useful for building second-order polynomial models and investigating quadratic response surfaces. By enabling a more accurate comprehension of the interactions between inputs and responses, the Box-Behnken design improves the optimisation process and makes it easier to identify the ideal circumstances for nanoparticle synthesis. By utilising both approaches in tandem, this work methodically determines ideal formulation parameters that minimise nanoparticle size and polydispersity while optimising stability and drug loading efficiency. The outcomes highlight how important a QbD framework is for directing the creation of reliable nanoparticle systems that function consistently and predictably.

Keywords: Nanoparticles, Quality by Design (QbD),

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Introduction

Nanoparticles are materials with sizes between 1 and 100 nanometres. Because of their distinct qualities, which set them apart from their bulk counterparts, they have become essential in a number of scientific and industrial fields. Because of their small size, high surface area-to-volume ratio, and unique optical properties, nanoparticles are extremely useful in a variety of applications. They also have improved reactivity and strength. Nanoparticles are transforming drug delivery systems in medicine by enabling tailored therapy that maximises treatment efficacy while minimising negative effects [1]. To reduce injury to healthy organs, liposomes and polymeric nanoparticles, for instance, are designed to carry chemotherapy medications directly to cancer cells. Additionally, nanoparticles like gold and quantum dots are utilised as contrast agents and in diagnostic imaging to

accurately and early detect disorders. Nanoparticles improve device performance and miniaturisation in electronics [2]. One of the most well-known areas of nanotechnology study is nanomedicine. It develops highly targeted medical interventions for illness detection, prevention, and therapy using nanotechnology. The field of nanomedicine has experienced significant growth in the past few decades, and this growth is now being translated into global commercialisation efforts that will ultimately lead to the launch of many products. Nowadays, drug delivery systems account for more than 75% of overall sales in nanomedicine. The active medicinal component is encapsulated, dissolved, or attached to the nanoparticle matrix (API). It is possible to create nanoparticles by modifying the creation process [3]. Because they increase the efficiency of energy conversion and storage, nanoparticles are essential to the development of fuel cells, batteries, and solar cells. Lithium-ion batteries use carbon and silicon nanotubes to boost their charge-discharge rates and energy density, which increases the batteries' longevity and efficiency. Nanoparticles are used in pollution management and water purification, among other environmental applications. Iron oxide nanoparticles help remove heavy metals from contaminated soil and water, whereas titanium dioxide nanoparticles are utilised in photocatalytic processes to break down organic contaminants in water [4]. Nanoparticles are used in the personal care and cosmetics industries to improve product compositions. Sunscreens often contain zinc oxide and titanium dioxide nanoparticles, which offer excellent UV protection and skin transparency. Furthermore, nanoparticles improve the effectiveness of anti-aging creams and moisturisers by enhancing the delivery of their active ingredients. Through the creation of nano-insecticides and nano-fertilisers, which provide controlled release of nutrients and pesticides, lowering environmental impact and increasing crop yields, nanoparticles in agriculture support sustainable farming methods. The uses also include food packaging, where nanoparticles are added to increase the shelf life and antibacterial qualities of food items [5]. Research on optimising nanoparticles is essential because of their wide range of applications and revolutionary potential. An organised and strong strategy is needed to guarantee that nanoparticles fulfil exact quality requirements and function as planned. One such process that is being used more and more to design and create nanoparticles with predetermined goals and ensure consistent quality and performance is called Quality by Design, or QbD. Understanding the link between the features of the end product and the production process is a prerequisite for Quality-by-Design (QbD), which enables the control and identification of variables that impact the properties of nanoparticles.Within the QbD framework, experimental design techniques like the Box-Behnken Methodology and 3-Level Factorial Design are crucial instruments. Researchers can optimise the synthesis process, forecast results, and systematically examine the influence of many factors on nanoparticle properties thanks to these statistical methodologies [6]. An effective substitute for examining quadratic response surfaces without necessitating a complete three-level factorial experiment is the Box-Behnken Methodology, which looks at three levels of each component and provides thorough insights into linear and interaction effects. By using these techniques, scientists may create durable, superior nanoparticles that are suited for particular uses, spurring creativity and guaranteeing efficacy and safety in use. Transitioning from laboratory research to commercial production is made easier by the incorporation of QbD and advanced experimental design methodologies, which not only improves the optimisation process but also helps with regulatory compliance and industrial scalability [7-9]. It is crucial to optimise the synthesis and application of nanoparticles using rigorous and systematic methods as the field of nanotechnology develops. This fusion of cutting-edge scientific techniques with real-world applications highlights how nanotechnology is revolutionising a number of industries and has the potential to solve some of the most important problems in the fields of energy, environment, health, and other fields [10].

Qualitative Design (QbD) Principles in Nanotechnology

The methodical approach to pharmaceutical development known as Quality by Design (QbD) places a strong emphasis on comprehending processes and managing them to guarantee the quality of the finished product. FDA defines QbD as a “systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management”. The idea, which originated from manufacturing principles, has been used more and more in the field of nanotechnology, where it is essential to precisely regulate material properties at the nanoscale. QbD seeks to guarantee the safety, effectiveness, and reproducibility of nanomaterials and nanomedicines in the context of nanotechnology. Tailoring these broad concepts to the particular opportunities and problems posed by nanoscale materials is the process of applying QbD principles to nanotechnology [11].

Fig 1: Quality by Design

Core Principles

1. Establishing the Quality Target Product Profile (QTPP): The QTPP establishes the desired attributes of the finished product and is the first stage in the Quality by Design process. Particle size, surface charge, drug loading efficiency, and release patterns are a few examples of this in nanotechnology. The QTPP for nanoparticles may have characteristics like:

a) The size and distribution of particles play a crucial role in guaranteeing consistency, bioavailability, and the capacity to target.
b) Surface characteristics that impact stability, biodistribution, and cellular uptake include surface charge and functionalization.The profiles of drug loading and release are crucial for managing release kinetics and achieving therapeutic efficacy.
c) The ability to maintain both chemical and physical integrity in biological settings and throughout storage [12].

2. Finding the Critical Quality Attributes (CQAs): To guarantee product quality, qualities that are chemical, biological, physical, or microbiological must be regulated. Particle size distribution, zeta potential, stability, and encapsulation efficiency are examples of CQAs for nanoparticles.Typical CQAs for nanoparticles consist of

a) Particle Size Distribution: Biodistribution and medication release rates may be impacted by size variation.
b) Zeta Potential: Surface charge is a signal that affects stability and how biological systems interact with it.
c) Encapsulation Efficiency: The quantity of medication that is effectively incorporated into nanoparticles, impacting dosage and treatment results.The speed at which the medication leaves the nanoparticles is known as release kinetics [14].

3. Comprehending the Process and Formulation Variables: This entails determining the material attributes (CMAs) and critical process parameters (CPPs) that influence the CQAs. For example, during the synthesis of nanoparticles, variables like temperature, speed of mixing, and type of solvent can greatly affect the quality of the finished product.CPPs and CMAs in the production of nanoparticles could be

a) Particle formation and solubility are affected by the type and concentration of the solvent.
b) Particle size and distribution are influenced by mixing time and speed.
c) Temperature: Affects the stability and kinetics of reactions.Particle formation and stability are impacted by pH and ionic strength [15].

4. Risk Management and Assessment: To identify and rank any threats to product quality, QbD necessitates a comprehensive risk assessment. To assess the impact and possibility of different hazards, tools like Ishikawa diagram, cause and effect chart, risk matrices and Failure Mode and Effects Analysis (FMEA) are frequently employed. When developing nanoparticles, risk assessment entails:

a) Finding Possible Failure Points: Drug release that is inconsistent, aggregative, or degradative.
b) Assessing Effect and Probability: Setting risk priorities with tools like FMEA.
c) Implementing controls to reduce recognised risks, including modifying process parameters or including stabilisers, is known as a mitigation strategy[16].

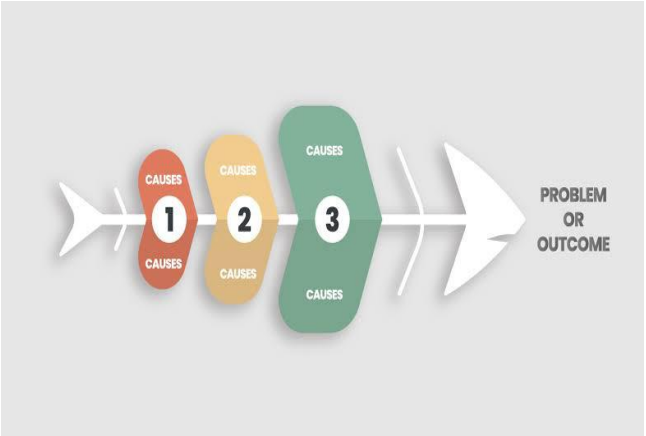

Fig 2: Ishikawa or Fishbone diagram

5. Utilising Design of Experiments (DoE): A statistical approach called DoE is used to methodically look into how different variables affect CQAs. Through the analysis of variable interactions and the identification of ideal conditions, researchers can optimise processes through the use of techniques such as 3-level factorial design and Box-Behnken approach methods such as Box-Behnken methodology and 3-level factorial design are very useful for

a) Formulation and Process Parameter Optimisation: By methodically examining the impacts of various variables.
b) Comprehending Interactions: Among variables and pinpointing circumstances that optimise coefficients of variation.
c) Minimising Test Runs: While acquiring thorough information on variable impacts [17].

6. Control plan: To guarantee constant quality, a strong control plan is necessary. This covers specifications, acceptance criteria, and in-process controls for CQAs. This could entail real-time zeta potential and particle size monitoring during manufacturing in nanotechnology.

7. Continuous Improvement: Quality by Design (QbD) encourages ongoing observation and enhancement of the production process. In order to increase quality and efficiency, this entails gathering data throughout the product lifecycle and using it to inform improvements [18].

Three-Level Factorial Design Overview

A helpful method for examining the primary and secondary impacts of the variables selected in any experiment design is the factorial design. This method is useful for examining how different independent factors interact with dependent variables or process outcomes. Three variables' effects on the reaction to fracture toughness serve as an example relevant to the current study. A potent statistical technique used in experimental research to examine the impacts of several factors on a response variable is the three-level factorial design. By adding a level for every factor, it expands on the conventional two-level factorial design and offers a more thorough comprehension of the interactions and nonlinear effects within the system under study. This method is especially helpful in areas like materials science, engineering, and pharmaceuticals where complicated processes frequently display complex behaviours that are difficult to capture with more basic experimental methods [18-19]. Each factor is examined at three distinct levels in a three-level factorial design; these levels are commonly indicated by the notations -1, 0 and +1. The factor's low, middle, and high values are represented by these levels. The levels may be 50°C (low), 75°C (middle), and 100°C (high), for instance, if temperature is an issue. For the factors being studied, the design calls for conducting tests at every possible combination of these levels.One way to visualise the three-level factorial design is as a matrix, where each row denotes a different combination of factor levels. If (k) factors are present, with each factor having three levels, then (3^k) experimental runs are needed in total. For example, the design would include 27 runs (i.e., (3^3)) given three components. With this configuration, scientists may investigate not just the primary impacts of every component but also their interrelationships [20]. Finding and measuring each factor's and its interactions' principal impacts is the major objective of the three-level factorial design. While interactions evaluate how the amount of one element affects the effect of another, main effects discuss the influence of each factor separately. For example, interactions may show that the impact of temperature on yield varies with pressure in a study looking at the impacts of temperature, pressure, and time on yield [21-22]. The factorial design with three levels has various benefits. Researchers are able to identify nonlinear correlations and more subtle effects that two-level systems might overlook by adding a third level. Although three-level factorial designs need more runs than two-level designs, they may nevertheless be more resource-efficient than doing independent tests for every component or interaction. A deeper comprehension of the process is possible through the analysis of interactions and nonlinear effects, which enables more intelligent decision-making and optimization [23]. In three-level factorial designs, data analysis entails fitting a statistical model to the outcomes of the experiments. In order to account for curvature in response surfaces, this model contains equations for main effects, interactions, and occasionally quadratic effects. Regression analysis and analysis of variance (ANOVA) are two popular methods for interpreting data and determining the importance of the variables and their interactions [24].

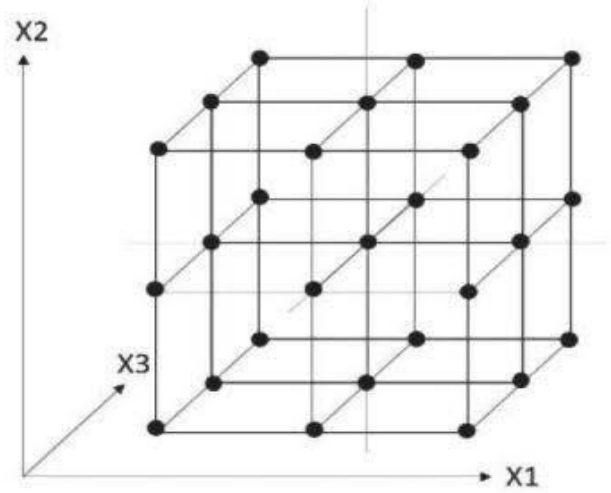

Fig 3: Three Level Factorial Design

The Box-Behnken Technique: A Sturdy Method

A variation on the three-level factorial design is the Box-Behnken design, which has a particular layout. It combines factorial points on the edges of the design space, but not at the corners, with trials conducted at the midpoints of each factor level, or the high, low, and middle levels. As a result, an efficient design matrix is produced in terms of the quantity of experimental runs required. One kind of response surface design used to simulate second-order (quadratic) effects is the Box-Behnken design. Three levels of evaluation are applied to each factor: low, middle, and high. Usually, these levels are indicated by the numbers -1, 0 and +1. The Box-Behnken design does not contain combinations where all factors are at their extreme levels, such as -1 and +1, in contrast to full factorial designs. Rather than using corner points, it makes use of a combination of factorial points at the edges and midpoints of the design space. The Box-Behnken design requires fewer experimental runs than full three-level factorial designs. The Box-Behnken design calls for (k(k-1) + 2) runs for (k) factors. This is more realistic and economical for complicated optimization problems because it requires fewer runs than the (3^k) runs required for a complete three-level design [25-27]. The Box-Behnken design's main benefit is that it concentrates on capturing factor interactions and quadratic effects. This is especially helpful for maximising the attributes of nanoparticles when non-linear connections and interactions between variables, such concentration, pH, and temperature, are crucial.Through resource optimisation, the Box-Behnken design captures important interactions and non-linear effects while minimising the number of experimental runs. This is particularly helpful in the field of nanoparticle research, as each experiment might cost a lot of money

and take a long time[28]. Regression models can be used to assess data from Box-Behnken designs in order to determine the correlation between responses and factors. Through the analysis of major effects, interactions, and quadratic effects, this modelling enables the selection of ideal conditions for the synthesis and characterisation of nanoparticles[29]. The Box-Behnken design is used to optimise a number of nanoparticle characteristics, including release profiles, drug loading, surface charge, and particle size. Researchers can determine the ideal circumstances for desired nanoparticle properties by methodically changing the synthesis conditions and characterising the results.Even in the presence of small disruptions, the design is resistant to experimental noise and fluctuations, yielding trustworthy findings. For nanoparticle optimisation, where process conditions might be delicate and prone to perturbations, this robustness is essential [29-30].

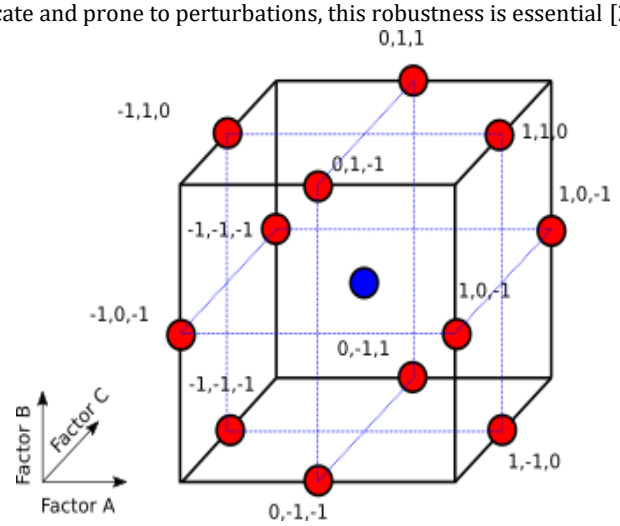

Fig 4: Box Behnken Design

Compared to complete three-level factorial designs, the Box-Behnken design uses resources more effectively. The design takes (k(k-1) + 2) runs for (k) factors, which is less than the (3^k) runs required for a complete three-level design. The estimation of quadratic effects and interactions is maintained despite this reduction. Because it requires a high number of experimental runs, it is especially helpful for modelling nonlinear connections and optimising processes where a full factorial design would be prohibitive to conduct. In many different industries, the Box-Behnken design is commonly employed to improve stability studies, nanoparticle synthesis conditions, and medication compositions and maximise process parameters, material qualities, and reaction conditions to optimise design parameters, improve production processes, and increase product quality[31-33]. If those severe situations are of interest, the design may be limited if it lacks extreme points where all factors are at their highest or lowest levels and for really high-dimensional situations, this might be difficult because the number of runs grows quadratically as the number of factors increases [34].

Comparative Analysis of 3-Level Factorial Design and Box-Behnken Methodology

Table 1. Comparison between 3-level factorial design and box behnken design [18-34].

S.No	3-LEVEL FACTORIAL	BOX-BEHNKEN DESIGN
1	A 3-Level Factorial Design (also known as a Full Factorial Design) involves studying the effects of factors (variables) on an outcome at three different levels.	The Box-Behnken Design is a type of response surface methodology (RSM) used for building a second-order (quadratic) model for the response variable without requiring a full factorial design.
2	Full factorial design with all possible combinations of factors at three levels (-1, 0, +1).	Rotational or spherical design with factorial points at midpoints and edges but not at extreme corners.
3	Number of Runs: (3^k), where (k) is the number of factors. For example, for 3 factors, 27 runs are needed.	Number of Runs: (k(k-1) + 2), where (k) is the number of factors. For 4 factors, 14 runs are required
4	All combinations of factors at low, middle, and high levels.	Factorial points at edges and centre points but not extreme corner points.

5	Captures main effects of factors directly.	Captures main effects with reduced experimental runs.
6	Includes interaction effects between factors at all levels.	Includes interaction effects and can also model interactions effectively with fewer runs.
7	Quadratic effects require additional experimental runs or extensions to capture.	Directly captures quadratic effects due to the design's focus on second-order terms.
8	Less efficient in terms of the number of runs needed, especially with a large number of factors.	More efficient due to fewer runs required while still capturing critical interactions and quadratic effects.
9	Higher complexity due to a larger number of experimental runs, which can complicate setup and analysis.	Lower complexity due to fewer runs and reduced experimental points, simplifying setup and analysis.
10	Robust but with potential variability due to the larger number of runs	More robust with fewer runs and reduced experimental points, less sensitive to noise.
11	Suitable for understanding linear and interaction effects, but may require extended designs to capture non-linearities	Well-suited for optimising non-linear relationships and identifying optimal conditions with fewer experimental runs.
12	Highly flexible, can be adjusted to different numbers of levels and factors, but at the cost of increased experimental runs.	Designed to be efficient with three levels, making it ideal for practical applications where fewer runs are desired.
13	More complex due to the larger number of runs; analysis can be computationally intensive.	Easier to implement with fewer experimental runs and simpler analysis.
14	Determining the effects of factors like temperature, pressure, and concentration on nanoparticle size, yield, or other properties using a full factorial setup	Optimising conditions for nanoparticle synthesis such as polymer concentration, drug-to-polymer ratio, and solvent type, focusing on achieving desired particle size and drug release profile efficiently.
15	Design efficiency can be low due to the extensive number of experimental runs required.	High design efficiency with fewer runs and the ability to capture a wide range of effects.
16	Requires extensive data to create a predictive model, which may lead to overfitting in complex scenarios.	Provides strong predictive capability with fewer data points by focusing on essential effects and interactions.
17	Provides strong predictive capability with fewer data points by focusing on essential effects and interactions.	Ideal for scenarios requiring optimization with fewer experiments, particularly when dealing with non-linear effects.

Applications of Quality by Design (QbD) In Nanoparticle Formulation

QbD principles can be applied using various experimental designs, including 3-Level Factorial Design and Box-Behnken Design.

1. Utilising Several Solvent Types and Polymer Concentrations to Optimise Particle Size: By systematically varying solvent types and polymer concentrations, researchers can fine-tune the nanoparticle size to meet specific requirements. Different solvents can affect the solubility and dispersion of the polymer, influencing nanoparticle formation. Adjusting polymer concentration alters the viscosity and interactions, impacting particle size. Combining these variables allows for precise control over nanoparticle dimensions, optimising them for applications such as drug delivery or imaging.
2. Enhancing Drug Loading Effectiveness by Modifying Processing Parameters and Drug-to-Polymer Ratios: Effective drug loading is crucial for therapeutic efficacy. By varying processing parameters such as stirring speed, temperature, and reaction time, and

adjusting the drug-to-polymer ratio, researchers can maximise the amount of drug encapsulated within nanoparticles. Optimising these factors ensures that the nanoparticles carry the desired drug payload, improving treatment outcomes and minimising required dose [35].

3. Enhancing Nanoparticle Stability in a Range of pH Values and Storage Conditions: Stability of nanoparticles is necessary to sustain their effectiveness over time. Comprehending the behaviour of nanoparticles at varying pH values and storage circumstances aids in determining their stability profile. Researchers can determine the ideal pH ranges and storage conditions for nanoparticles that maintain their integrity and functionality by putting them to the test in a variety of settings.
4. Changing the Polymer Types and Cross-Linking Densities to Regulate the Release Rate Drug release from nanoparticles can be regulated by altering the types of polymers and cross-linking densities. Drug release is normally slowed down by higher cross-linking densities, yet the chemical makeup of various polymers might influence the rate of release. By adjusting these variables, medication release can be regulated and sustained to meet therapeutic goals [36-37].
5. Changing the pH and Surfactant Concentrations to Examine Surface Charges: The pH and surfactant concentration have an impact on the surface charge, or zeta potential, of nanoparticles. Researchers can attain the desired surface charge, which influences the stability of nanoparticles and their interactions with biological systems, by methodically altering these parameters. By examining these impacts, one can create nanoparticles with the ideal charge characteristics for particular uses.
6. Maximising Encapsulation Efficiency by Trial and Error with Different Drug Solubility and Mixture Methods: The drug's solubility and the technique of preparation both affect encapsulation efficiency. Researchers can enhance the efficacy of drug encapsulation within nanoparticles by experimenting with different drug solubilities and formulation procedures. Better therapeutic efficacy and increased medication loading are guaranteed by this optimization [38].
7. Decreasing Size Distribution in Response to Variations in Polymer Concentrations and Agitation Speed: Uniform size distribution is critical for consistent performance. By adjusting polymer concentrations and agitation speeds during synthesis, researchers can control the size distribution of nanoparticles. Fine-tuning these variables reduces size variation and enhances the uniformity of the nanoparticle population.
8. Analyzing How the Properties of Nanoparticles Change as a Process is Scaled Up to Determine Its Scalability: Scaling up the nanoparticle production process often introduces new challenges. By studying how nanoparticle properties such as size, morphology, and drug content change during scale-up, researchers can assess the scalability of the process. This ensures that the nanoparticles produced on a larger scale maintain the same quality and characteristics as those produced in small batches.
9. Changing the Synthesis Process's Temperature and Reaction Duration to Get the Needed Nanoparticle Properties: Two important factors in the creation of nanoparticles are temperature and reaction time. Researchers can regulate the size, shape, and quality of nanoparticles by refining these parameters. By modifying these parameters, one can make sure that the nanoparticles fulfil the necessary requirements for the medication administration, imaging, or other uses for which they are designed.
10. Ensuring Process Variability to Examine Formulation Uniformity Across Batches: For consistent performance, batch consistency is essential. Through the examination of process variability and its influence on nanoparticle characteristics, scientists can devise methods to guarantee consistency among various manufacturing batches. Maintaining the quality of the product and commercial production depend on this uniformity [39-40].

Future Directions and Challenges in Nanoparticle Optimization Using QbD

Using sophisticated analytical techniques like spectroscopy, high-resolution microscopy, and complex characterisation tools can improve our knowledge of the characteristics and behaviour of nanoparticles. These methods can offer more in-depth understanding of the structure and functionality of nanoparticles, resulting in more accurate optimisation By forecasting how different parameters would affect the properties of nanoparticles, applying AI and machine learning algorithms helps quicken the optimisation process. These technologies enable more effective and economical QbD implementations by analysing massive datasets and identifying patterns that are not immediately obvious. A primary goal will be to advance QbD techniques to facilitate the creation of customised nanomedicines based on the unique characteristics of each patient [41]. This entails fine-tuning nanoparticles to target particular genetic, biochemical, or physiological requirements in order to maximise effectiveness and minimise adverse consequences. It is imperative to create and improve regulatory rules that take into account the intricate compositions of nanoparticles. In order to expedite approval procedures and guarantee safety and efficacy, future work will probably concentrate on developing more precise standards and protocols for QbD in nanoparticle development. The effectiveness and scalability of nanoparticle production can be increased by integrating

QbD with continuous manufacturing procedures. Real-time control and monitoring are provided by continuous production, which is in line with the QbD tenets. interdisciplinary methods Nanoparticle optimisation will be stimulated by interdisciplinary collaboration across chemistry, engineering, biology, and material science. Multidisciplinary groups are capable of taking on difficult problems and creating cohesive solutions. Applying QbD principles is significantly hampered by the intrinsic complexity of nanoparticle systems, which includes their size, shape, surface characteristics, and interactions. Comprehensive experimentation and sophisticated methods are needed to comprehend and regulate these variables [42-43]. It might be difficult to transfer optimised nanoparticle formulations from small-scale experimental settings to large-scale manufacturing. Thorough process development and validation are necessary to guarantee that the same characteristics and performance are preserved at scale. The constantly changing field of nanoparticle technology and its uses may result in unclear regulations. It can be difficult to follow these rules and maintain compliance while putting QbD into practise. It might be difficult to handle the massive amounts of data produced by QbD studies and sophisticated analytical methods [44]. To get valuable insights and make wise judgements, efficient data management, storage, and analysis are essential. Extended Stability and Safety: It is imperative to guarantee the extended stability and safety of nanoparticles in diverse applications. Addressing possible toxicity and environmental damage is part of this, and it calls for constant study and observation.Personalisation and Variability: Creating nanoparticles that can be tailored to each patient has issues with variability. Maintaining QbD principles while guaranteeing consistency and reliability in customised formulations is a major problem [45].

Conclusion

To sum up, the utilisation of Quality by Design (QbD) concepts in the optimisation of nanoparticles is a noteworthy progress towards guaranteeing the dependability and efficiency of nanoparticle compositions. The advantages and disadvantages of both 3-Level Factorial Design and Box-Behnken Design are emphasised by their comparative study. 3-Level Factorial Design is perfect for in-depth research of interactions and effects because it covers every potential factor combination in detail. But it can require a lot of resources, especially when there are a lot of variables involved. Box-Behnken Design, on the other hand, provides a more effective method by concentrating on important variables with fewer experimental runs, capturing crucial quadratic and interaction effects, and using the fewest resources possible. Future directions for QbD-based nanoparticle optimisation include applying machine learning and artificial intelligence, integrating sophisticated analytical tools, and enhancing personalised nanomedicine. It will also be essential to build improved regulatory frameworks and sustainable practices. To fully realise the potential of QbD in this industry, obstacles like data administration, scaling challenges, regulatory uncertainties, and the complexity of nanoparticle systems must be overcome. All things considered, the successful use of QbD principles in the creation of nanoparticles holds promise for developing nanotechnology, augmenting therapeutic efficacy, and improving drug delivery systems. Through the use of both conventional and innovative experimental designs, together with the resolution of emergent issues, scientists and engineers can tailor the properties of nanoparticles to fulfil certain requirements and accomplish intended results. To develop the discipline and achieve breakthroughs in nanoparticle applications, QbD approaches must continue to evolve and be integrated with cutting-edge technologies.

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Inform Consent

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Ethical Statement

This review is following all the relevant ethical aspects

Author Contribution

All the authors have the equal contribution.

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