



Received on 09 April 2025; received in revised form, 19 May 2018; accepted, 14 June 2025; published 01 November 2025

REVIEW ARTICLE ON QBD APPROACHES TO IMPROVE NANOTECHNOLOGY BASED DRUG PRODUCT

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Keywords:

Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), Design of Experiments (DoE), Process Analytical Technology (PAT)

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ABSTRACT: Quality by Design (QbD) is a systematic approach in pharmaceutical development that focuses on predefined objectives, scientific understanding and quality risk management. It involves defining a Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). It is implemented for control strategies to ensure product quality, safety and efficacy by using tools such as risk assessment, Design of Experiments (DoE), Process Analytical Technology (PAT) and Ishikawa diagrams support QbD throughout the product lifecycle. Simultaneously, Nanotechnology has revolutionized drug delivery by improving solubility, bioavailability and targeted delivery. Nano-pharmaceuticals like liposomes, polymeric nanoparticles and nanosuspensions benefit greatly from QbD principles. Integrating QbD into nano-drug development enables better control of particle size, zeta potential, drug loading, and release kinetics, which are critical for performance and safety. Computational tools and design optimization techniques further streamline this development. The integration of QbD and nanotechnology enhances the reliability, effectiveness, and regulatory compliance of advanced drug products. This synergy not only accelerates innovation and improves therapeutic outcomes but also ensures consistent quality and supports efficient approval and lifecycle management in line with global regulatory standards.

INTRODUCTION: Dr. Joseph M. Juran, a pioneer of quality, first developed the concept of Quality by Design (QbD). Dr. Juran strongly believed that quality should be designed into a product¹.

According to Woodcock (Director for the Center for Drug Evaluation and Research), a high-quality drug product is contamination-free and consistently delivers the therapeutic benefits promised on the label to consumers.

So, to get this high-quality product, we have to do an initial plan or design, where QbD comes into action². Quality by Design (QbD) emphasizes the importance of enhancing both process and product understanding through precise scientific principles and deliberate design efforts aimed at achieving predefined objectives.

QUICK RESPONSE CODE 	DOI: 10.13040/IJPSR.0975-8232.16(11).2890-03
	This article can be accessed online on www.ijpsr.com
DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(11).2890-03	

QbD is a regulatory-driven approach that promotes systematic product development, beginning with clearly defined goals. It focuses on controlling both the product and the process, as well as understanding the processes involved, all based on sound scientific principles and effective quality risk management¹. In Quality by Design (QbD), the assurance of product quality relies on a comprehensive understanding and rigorous control of formulation and manufacturing variables. This structured approach ensures that consistent product quality is achieved through the careful design and management of both the formulation and manufacturing processes. By implementing the QbD methodology, organizations can develop robust formulations that markedly enhance the likelihood of successful regulatory approvals. Utilizing advanced multivariate statistics and design of experiments techniques, QbD enables developers to optimize every aspect of the development process, ultimately improving product reliability and market readiness³.

Over the past two decades, nanotechnology has grown rapidly, especially in the biotechnology and medicine divisions. It's also getting huge recognition in the treatment of cancer by the National Cancer Institute (NCI). To promote nanotechnology and make it more successful, the National Nanotechnology Initiative (NNI) was founded in 2000. Every year, NNI invests roughly 150 us dollars in training and development nanotechnology⁴. Nanotechnology-based drug development is an advanced field that utilizes nanomaterials to enhance drug delivery, effectiveness, and safety.

This involves the design of nanomedicines such as liposomes, polymeric nanoparticles, dendrimers, and metal nanoparticles into a suitable formulation to develop targeted therapy, reduce the side effects, and improve bioavailability. Nanoparticles utilized as a drug delivery vehicle consist of different natural or synthetic polymers, lipids or metals. Our body cells take these nanoparticles more effectively than other micro-molecules. Therefore, it's the most efficient drug delivery system⁵. Nanotechnology is a promising approach to overcome the drawbacks of conventional therapy systems and major restrictions on drug development like poor solubility, low

bioavailability, drug toxicity, etc. Nano-scale drug-delivery platforms may be designed to modulate and regulate the pharmacokinetics and pharmacodynamics, solubility, immune compatibility, cellular uptake, biodistribution and eventually reduce the toxic side effects. These modulations result in improving the therapeutic index of classical pharmaceuticals. They can deliver small-molecule drugs and a variety of classes of biomacromolecules, including peptides, proteins, plasmid DNA, and synthetic oligodeoxynucleotides. Nano-formulation, therefore has tremendous potential in contributing to drug development, which is reliant on conventional formulation strategies. Found between *in-vitro* potency characteristics of a drug candidate, physicochemical properties, absorption, distribution, metabolism, excretion, and toxicity usually cited as the primary responsible for drug development failure.

Other than the sustained release of drugs supported through nanocarriers that provide clear therapeutic benefits, the targeted delivery of drugs in the body is required to prevent the release of therapeutics in non-targeted locations that would cause adverse effects. By incorporating targeting moieties to the surface of the drug-loaded nanoparticles, receptor-mediated and targeted delivery can be achieved. Such targeted nanoparticles should possess properties as a perfect drug delivery system, which will act to optimize the therapeutic activity while minimizing the unwanted side effects of drugs⁶.

In recent years, the application of QbD principles to nanotechnology-based drug development has gained significant attention due to the unique challenges and opportunities presented by nanomedicines. Nanotechnology-based drug delivery systems are transforming the pharmaceutical industry by significantly improving therapeutic efficacy, enabling precise targeted delivery, and effectively overcoming various biological barriers. However, the complexity of these systems poses significant challenges in terms of ensuring manufacturing consistency, maintaining stability, and achieving regulatory compliance. By integrating Quality by Design (QbD) principles into the development of nanotechnology-driven therapeutics, we create a robust framework for systematic design, thorough

risk assessment, and stringent quality control. This approach facilitates the identification and management of critical quality attributes (CQAs), which are essential for ensuring the safety and efficacy of nanomedicines. Adopting QbD not only enhances our ability to meet regulatory standards but also paves the way for innovative therapies that can markedly improve patient outcomes⁷.

This review article aims to explore how Quality by Design (QbD) principles can enhance drug development based on nanotechnology. We will discuss the key elements of QbD, focusing on identifying critical material attributes (CMAs) and critical process parameters (CPPs) specific to nanomedicines. Additionally, we will examine how various QbD tools, such as risk assessment, design of experiments (DoE), and process analytical technology (PAT), can be utilized to optimize the development and manufacturing processes of nano-formulations. For instance, the use of DoE allows for an efficient exploration of complex interactions between formulation and process variables, which is crucial for optimizing nanomedicine formulations^{7,9}.

The QbD approach is a transformative strategy for improving nanotechnology-based drug development by ensuring product quality, safety, and efficacy. By systematically identifying and controlling CQAs, optimizing formulation parameters, and leveraging advanced PAT tools, QbD enables the consistent production of high-quality nanomedicines. Future advancements in AI-driven quality control and regulatory harmonization will further strengthen QbD implementation, paving the way for the next generation of nano pharmaceuticals⁷. By adopting Quality by Design (QbD) approaches, researchers and pharmaceutical companies can improve the efficiency of nanomedicine development, reduce variability in product quality, and simplify the regulatory approval process. This is especially important for nanomedicines, where even small changes in formulation or manufacturing conditions can significantly affect the final product⁸. Moreover, Quality by Design (QbD) can enhance the development of more robust and scalable manufacturing processes, which are essential for transitioning nanomedicines from the laboratory to clinical practice¹⁰.

This review will provide insights into the current state of QbD implementation in nanotechnology-based drug development and highlight future perspectives for advancing this field.

Quality by Design (QbD):

Quality: In the context of Quality by Design (QbD), quality is a crucial term. It refers to the “standard or suitability for intended use,” encompassing attributes such as identity, potency, and purity.

Quality by Design: The U.S. FDA and the International Council for Harmonisation (ICH) have advocated various approaches for the development and manufacturing of pharmaceutical products. This approach is known as Quality by Design (QbD) and is defined as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding as well as process control, based on sound science and quality risk management.” Pharmaceutical industries recognize the importance of product quality, safety, and efficacy.

By implementing scientific tools associated with QbD, product quality has improved significantly. These scientific approaches provide clear and comprehensive knowledge from product development to manufacturing, helping to minimize risks while enhancing output and quality. Today, the QbD approach is successfully applied in common formulation development. The FDA has released specific QbD guidance for both immediate and extended-release drug products, as well as for biotechnological products. Regulatory authorities continually encourage the adoption of ICH quality guidelines, including Q8, Q9, Q10, and Q11¹⁻⁵.

Objective of QbD: In pharmaceutical industry, QbD is a structured development approach that starts with clearly defined objectives, focusing on a deep understanding of both the product and process. It relies on sound scientific principles and quality risk management to ensure control and consistency. The objectives of pharmaceutical QbD may include the following:⁷

- a. Establishing meaningful product quality specifications based on clinical performance.

- b. Enhancing process capability while minimizing product variability and defects through improved product and process design, understanding, and control.
- c. Improving efficiency in product development and manufacturing.
- d. Strengthening root cause analysis and facilitating post-approval change management.

Elements of QbD:

Quality Target Product Profile QTPP: The QTPP serves as the foundation for product development. It outlines the information about the drug during a specific stage of its development and encapsulates the overarching goals of the drug development program. Typically, the QTPP is structured in alignment with the main sections of drug labelling, connecting the drug development activities to particular concepts that are planned for incorporation into the labelling¹⁴. Therefore, the QTPP can be described as a forward-looking summary of the quality characteristics that a drug product aims to attain in order to guarantee the desired quality, while also considering the safety and efficacy of the product^{5,8}.

Considerations for inclusion in the QTPP could include the following:

- Dosage strength(s)
- Drug product quality criteria (e.g., purity, stability, sterility, and drug release) appropriate for the intended marketed product
- Intended use in a clinical setting, route of administration, delivery system(s), and dosage form
- Therapeutic delivery or moiety release and attributes affecting characteristics (e.g., the pharmacokinetic aerodynamic and dissolution performance) appropriate to the drug product dosage form being developed
- Container closure system

Consequently, the absence of a clearly defined QTPP can lead to the inefficient use of resources and time. The International Society of Pharmaceutical Engineers (ISPE) refers to this as

the Pharmaceutical Target Product Profile (TPP). It's important to note that the QTPP is not a specification; it encompasses tests, such as stability or bioequivalence, that are not performed with each batch release. Instead, the QTPP should focus solely on patient-relevant product performance. For instance, if particle size significantly affects the dissolution of a solid oral product, the QTPP should include dissolution as a quality characteristic, but not particle size itself. Particle size would be classified as a critical material attribute, therefore included in the process description and control strategy. The QTPP should emphasize performance rather than mechanism. It serves as a definition of the product's intended use and pre-defines quality targets concerning safety, efficacy, and clinical relevance. This summary highlights the essential quality attributes required to ensure patient safety and efficacy^{4,7}.

Critical Quality Attributes CQA: The next step in drug product development is the identification of the Critical Quality Attributes (CQAs). These attributes are derived from the QTPP and play a crucial role in guiding both product and process development. A CQA refers to a physical, chemical, biological, or microbiological property or characteristic of an output material, including the finished drug product. It must be maintained within a specific limit, range, or distribution to ensure the desired quality of the product. Additionally, the CQAs establish the acceptable limits or ranges necessary for a quality product, ensuring that the final output meets the expected quality standards⁶.

CQAs can be employed to articulate the elements of the QTPP, such as dissolution, as well as to identify mechanistic factors, like hardness and particle size, that influence product performance. Therefore, CQAs serve to express both the aspects of product performance and the determinants that affect it. This comprehensive understanding helps in optimizing the formulation and ensuring that the product meets its intended quality standards⁴.

The quality attributes of a drug product encompass various factors, including identity, assay, content uniformity, drug release or dissolution, degradation products, moisture content, residual solvents, microbial limits, and physical characteristics such as shape, size, colour, odor, score configuration,

and friability. These attributes can be categorized as critical or non-critical, with the criticality determined by the potential severity of harm to the patient if the product deviates from the acceptable range for that particular attribute. It's important to note that the probability of detectability, occurrence, or controllability does not influence the criticality of an attribute. While Critical Quality Attributes (CQAs) are primarily associated with the final product, they can also be relevant for intermediates or raw materials, highlighting their importance throughout the drug development process⁵.

Critical Material Attributes CMA: Critical Material Attributes (CMAs) refer to the physical, chemical, biological, or microbiological properties and characteristics of an input material. They represent one of the primary categories of factors that can lead to variability in Critical Quality Attributes (CQAs), and they are closely related to the composition of the formulation preparation. To ensure the desired quality of a drug substance, excipient, or in-process material, CMAs must be maintained within an appropriate range, limit, or distribution. These attributes are directly linked to the raw materials used and the parameters of the manufacturing process.

Independent CMAs provide the clearest mechanistic relationship between product quality and critical process parameters in manufacturing. Additionally, distinguishing between CMAs (properties) and multi-faceted performance tests marks a shift from a quality-by-testing (QbT) approach to a quality-by-design (QbD) philosophy. This distinction is also reflected in the evolution of ICH Q8 guidelines, which emphasize the importance of differentiating CMAs from performance tests⁸.

Tools of QbD: For the successful implementation of QbD, some tools are needed. Those tools are as follows:

Risk Assessment: The tools minimize risks associated with the product; it also helps to take risk-based decision. According to ICH Q9, there are nine Risk assessment tools, which includes^{19, 20, 21}.

i. An evaluation of the basic risks

- ii. Evaluation of the tree diagram (Ishikawa fishbone template, scatter diagrams, assess sheets)
- iii. Facilitation strategies
- iv. Initial risk analysis
- v. Vulnerability scans with control laws
- vi. An evaluation of malfunction and consequences
- vii. Review of failure, effects, and dissipation
- viii. Assessment of serviceability hazards
- ix. Statistical methods to assist.

Pharmaceutical development through QbD may be broken down into six main elements^{16, 17, 18}:

Profiling the Drug: this task results in creation of a quality target product profile (QTPP)

Identifying Quality Attributes: quality attributes are developed from a deep understanding of the product, the process as well as the QTPP. A criticality analysis of the attributes results in the determination of critical quality attributes (CQA)⁴⁷.

Identifying Risk Factors: ICH Q9 describes the quality risk management process that utilizes risk assessment tools to determine which input variables impact the CQAs. These input variables are critical material attributes (CMA) and critical process parameters (CPP).

Determination of a Regime of Safety and Quality: the development of a design space (DS) is the final output of this task. It determines an acceptable range for the CMA and CPP and correlates them with the CQAs.

Establishment of a Control Strategy: a control strategy based on extensive knowledge of the process and the product includes control over the CMA of the input materials and intermediates, control of the process parameters, final drug product quality and final packaging. All these components of control strategy are covered under process analytical technology (PAT).

Manufacturing and Management of Product Lifecycle: one of the most important aspects of

QbD is that once a drug product has cleared FDA approval and entered manufacturing, the CQAs are continuously monitored. This is done to ensure that both the process and the materials fall within the

acceptance criteria defined in the design space and the QTPP is maintained. ICH Q10 provides details on the continual improvement and monitoring of the drug product¹⁸.

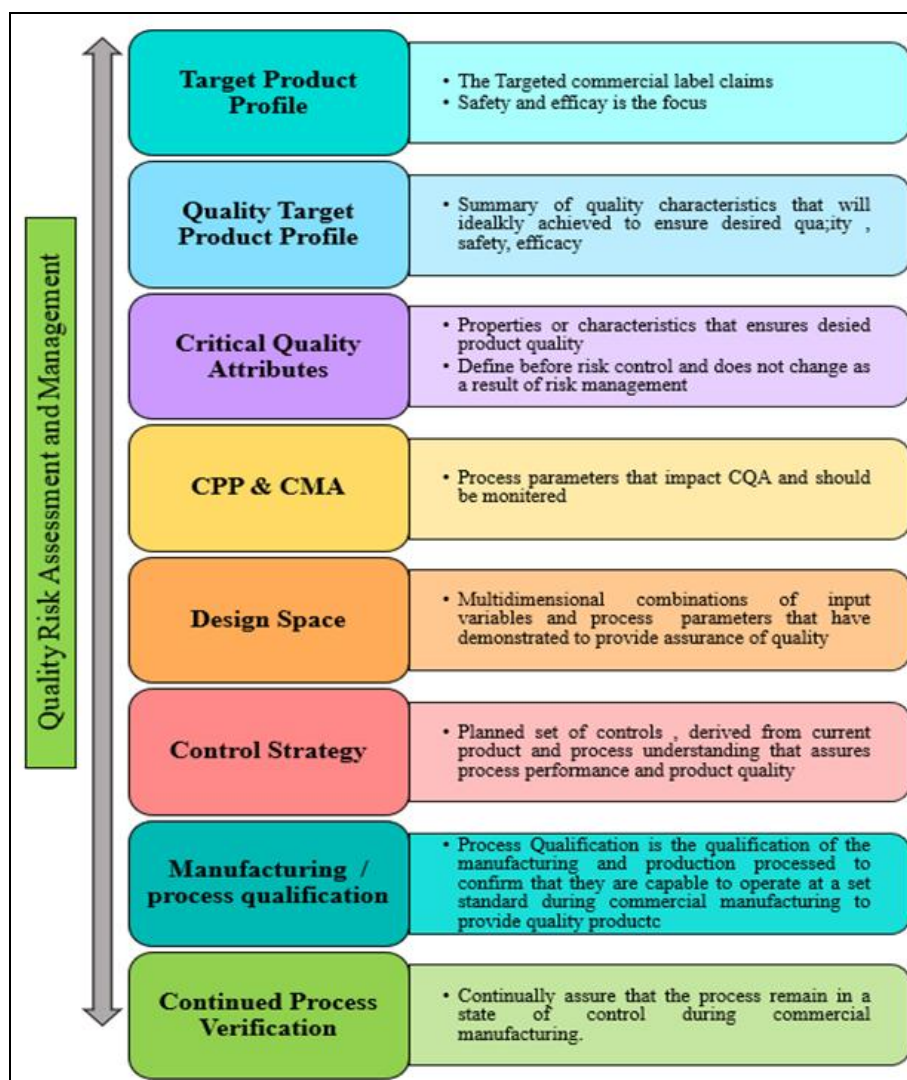


FIG. 1: THE USFDA RECOMMEND RISK BASED QBD APPROACH TO ENSURE THAT QUALITY INHERENT TO THE PROCESS AND PRODUCT

Design of Experimentation (DoE): DOE is a computational approach that is used to plan and carry out studies as well as analyse the data produced by the experimental effort. This kind of computer modelling is used to statistically analyse a model, approach, and resource that controls input parameters in order to examine how those factors affect the response variable that is calculated. Researchers can examine variables using this fantastic tool in accordance with a preset design. DoE is a useful method for determining connections between process inputs and outputs in order to have a better understanding of processes and products. It is particularly useful for identifying

optimal settings, critical process parameters (CPPs), critical material attributes (CMAs), and defining the design space^{9, 10, 11}.

Plackett- Burman (PB) Design: In present system, product quality is ensured by fixing the process to produce the active ingredient, raw material testing, performing the drug product manufacturing process as described in a fixed batch record, in-process material testing, and end product testing. Thus, in present study Process risk analysis was performed to identify CPP effecting CQA's and develop a design space using placket Burman

design and propose a controlled strategy for manufacturing process^{56, 57}.

Process Analytical Technology (PAT): PAT is defined as a method that constantly produces a finished product that satisfies predetermined quality and performance standards by using real variables throughout the manufacturing process to offer information to assist optimized computing. The application of PAT to guarantee cycle consistency in a pre-existing design space is recognized by ICHQ8. When all significant causes of variability are identified and explained, the system manages variation, and the performance of product equity can be precisely and successfully quantified, the system is said to have been created from a PAT perspective²². Process analysis can be divided into three categories, according to FDA's PAT policy statement: online, in-line, and at-line. The sample is collected, extracted, and examined close to the processing stream during at-line

estimation. The specimens could be returned into the flowing fluid after being taken out of the apparatus by online prediction. The sample stays inside the processing stream during in-line estimation, which may cause disruptions or intrusions^{14, 15, 16}.

Ishikawa Fishbone Diagram: This cause-effect analysis was originally developed by Ishikawa (1990) as a quality control tool of products to identify potential factors causing an overall effect and to prevent the quality defects of products. Each cause is a source of variation of the phenomena under study. Causes are usually grouped into major categories to identify the overall sources of variation that leads to a main effect. In general, Fishbone diagram can be used as an appropriate visual representation of phenomena that involve the investigation of multiple cause-and-effect factors of specific events^{23, 24, 25}.

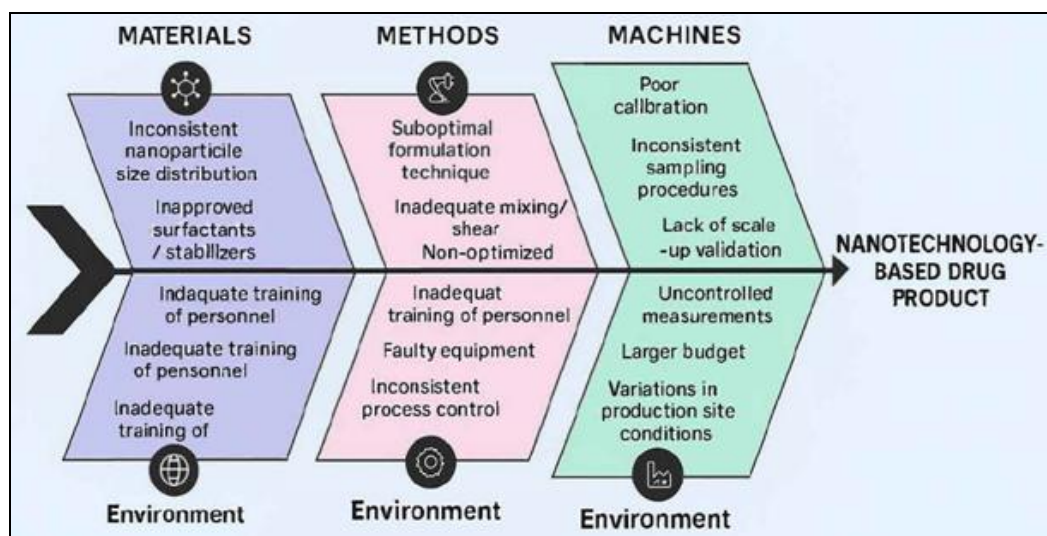


FIG. 2: ISHIKAWA FISHBONE DIAGRAM

Nanotechnology Based Drug Product: Since, ancient times, humans have relied on plant-based natural products as medicines to combat various diseases. Modern medications are primarily derived from herbs, based on traditional knowledge and practices. Approximately 25% of the major pharmaceutical compounds and their derivatives available today come from natural resources. Natural compounds, which possess diverse molecular structures, provide a foundation for the discovery of novel drugs. A recent trend in drug discovery based on natural products is the focus on designing synthetic lead molecules that imitate the

chemistry of their natural counterparts. Natural products possess remarkable characteristics, including extraordinary chemical diversity, unique chemical and biological properties with specific interactions at the macromolecular level, and reduced toxicity²⁶⁻²⁹. Pharmaceutical companies are often hesitant to invest in natural product-based drug discovery, opting instead for existing chemical libraries. However, there is renewed interest in screening natural compounds for major diseases such as cancer, diabetes, cardiovascular conditions, inflammatory disorders, and microbial infections due to their lower toxicity, fewer side

effects, and cost-effectiveness. Despite these advantages, concerns about biocompatibility and toxicity present challenges, leading many natural compounds to fail in clinical trials³⁰⁻³².

Nanotechnology serves as a bridge between biological and physical sciences, particularly in nanomedicine and nano-based drug delivery systems, where nanostructures are crucial. Nanomaterials, sized between 1 and 100 nm, impact areas like biosensors, microfluidics, and tissue engineering. Nanomedicines use nanoscale curative agents for targeted drug delivery, enabling precise administration of drugs to specific tissues with controlled release. This emerging field employs nano-dimensional materials, including nanorobots and nano sensors, for diagnosis and treatment. For example, a novel nanoparticle method combines cancer treatment with imaging capabilities. The first generation of nanoparticle therapies includes FDA-approved lipid systems like liposomes and micelles, which can incorporate inorganic nanoparticles. These advancements improve drug delivery and therapeutic functions while protecting drugs from degradation.

Nanodrugs also show higher oral bioavailability and prolonged circulation time, allowing for controlled release and reduced side effects³³⁻³⁸.

Impact of Nanotechnology on Modern Medicine: Nanotechnology-based drug products have a significant impact on modern medicine by improving drug delivery, enhancing therapeutic efficacy and reducing side effects. Nowadays, there has been substantial progress in traditional treatments, with advancements in nanoparticles and nanotechnology leading to improved quality and promising results^{39, 40}. Nanoparticles and Nanotechnology can be specifically designed to interact with cells and tissues at the molecular (sub-cellular) level with exceptional precision. This allows for an unprecedented integration of technology with biological systems. It is essential to understand that nanotechnology is not a single emerging discipline but rather a fusion of traditional sciences such as chemistry, physics, materials science and biology⁴¹. So, it has emerged as a revolutionary field with vast applications in medical field. The applications are enlisted below:

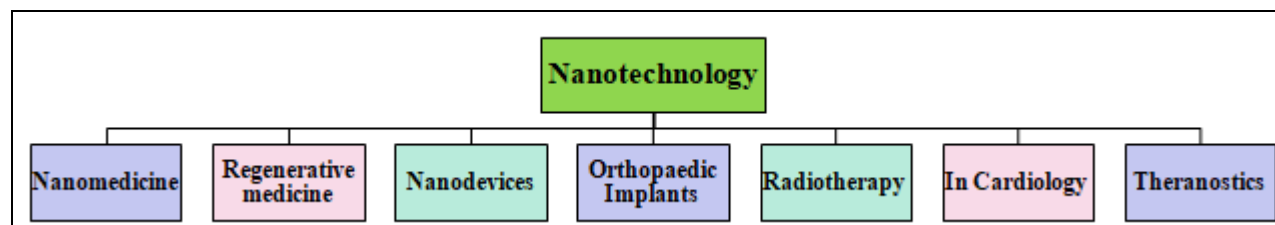


FIG. 3: IMPACT OF NANOTECHNOLOGY ON MODERN MEDICINE

Nanomedicine: Nanomedicine is a branch of medicine that applies the principles and tools of nanotechnology for the diagnosis, treatment, and prevention of diseases. It involves manipulating materials at the nanoscale (typically 1-100 nm) to improve medical outcomes. It enhances cellular function more efficiently, mimicking the effects of natural tissues and organs. It focuses on cancer treatment, gene therapy, neurological disorders etc⁴².

Regenerative Medicine: Regenerative Medicine is a branch of medical science that focuses on repairing, regenerating, or replacing damaged tissues and organs. The primary goal is to create scaffolds that trigger molecular processes essential for tissue regeneration. These synthetic constructs must be biodegradable and biocompatible to avoid

long-term adverse effects. Additionally, they should be designed to support cell migration, attachment, and growth for effective tissue formation^{43, 44}.

Nanodevices: In the Medical Field, it is revolutionizing healthcare by enhancing diagnosis, treatment, and monitoring of various conditions. These devices operate at the nanoscale, enabling precise interactions with biological systems.

For example, the Respirocyte, a 1-micron spherical artificial red blood cell, can deliver more oxygen to tissues and regulate carbonic acidity better than natural red blood cells. Similarly, the Microbivore, an artificial white blood cell (3.4 μm x 2.0 μm), is designed for microscopic immune functions⁴⁵.

Orthopaedic Implants: Nanotechnology plays a crucial role in developing biomaterials for medical applications, such as orthopaedic implants and tissue-engineered scaffolds. Designing a hip implant at the nanoscale can help mimic the mechanical properties of human bone, reducing stress shielding and minimizing bone loss. The extracellular matrix (ECM) offers a complex web of nanofibers that supports cells and guides their behaviours. Its structure varies across tissues and developmental stages, shaped by molecular interactions and arrangements of collagens, elastins, proteoglycans, and adhesion proteins like fibronectins and laminins⁴⁶.

In Radiotherapy: Ongoing research is focused on developing innovative nanodevices to detect cancer early, locate it within the body, and deliver targeted chemotherapy. Nanowires, known for their selectivity and specificity, can identify molecular markers of cancer cells. Positioned across a microfluidic channel, they allow cells or particles to pass through. These nanowires can be coated with probes like antibodies or oligonucleotides, short DNA sequences that recognize specific RNA markers⁴⁷.

In Cardiology: Nanotechnology has diverse applications in cardiology, both for diagnostics and therapy. In cardiovascular gene therapy, the process involves identifying a protein that promotes blood vessel formation, producing and packaging DNA strands with the gene for that protein, and delivering the DNA to heart muscle with delivery being the most challenging step. Nanotechnology also enhances treatments for atherosclerosis and coronary artery disease (CAD) by improving biocompatibility and addressing key molecular limitations in percutaneous transluminal coronary angioplasty (PTCA) through nanoparticles^{47, 48}.

Theranostics: *In-vitro* diagnostic devices, such as gene chips, protein chips, and lab-on-a-chip systems, avoid the safety concerns linked to nanoparticles in the body. Advances in DNA sequencing technologies, including nanopores for

ultra-rapid, real-time sequencing, are promising for cancer detection. While developing protein chips and lab-on-a-chip devices is more complex than gene chips, these innovations are expected to drive personalized medicine by merging diagnostics and therapeutics in the emerging field of "theranostics"⁴⁶.

QbD Approaches to Nano-technology Based Drug Development: Quality by Design (QbD) has been widely adopted throughout the drug product development pipeline in the pharmaceutical industry. However, there remains significant potential to extend QbD applications to complex products, such as nano pharmaceuticals (nanomedicines). The current era of disease treatment has led to the utilization of therapeutically effective and efficient nanomedicines. Applying QbD to nano-pharmaceutical products offers several advantages for optimizing product performance. This includes managing complex designs, dynamic material properties, and meeting stringent regulatory requirements for critical attributes (CAs), such as particle size, zeta potential, drug loading, in vitro drug release profiles, surface morphology, pharmacokinetic performance, drug stability, and impurity profiling^{52, 53}.

Table 1 outlines commonly used critical material attributes (CMAs), critical process parameters (CPPs), and critical quality attributes (CQAs) in nano pharmaceutical products. The ongoing stream of research publications regarding the regulatory approval of nano-pharmaceutical products by the FDA and EMA highlights the successful application of QbD. A variety of nanotechnology products, including liposomes, niosomes, nanoparticulate systems (polymeric, lipidic, metallic, and hybrid), micro/nanoemulsions, nanosuspensions, and nanogels, have been explored in the literature. These products demonstrate the systematic development of QbD tools, resulting in substantial benefits along with impressive quality and performance^{47, 48, 49}.

TABLE 1: EXAMPLES OF QBD APPROACHES TO NANOTECHNOLOGY BASED DRUG PRODUCT

Types of delivery system	CMAs	CPPs	CQAs
Nanostructured lipidic carriers	Lipid concentration, drug:lipid ratio, surfactant concentration, volume of	Stirring speed, time, rate, temperature of water bath, homogenization speed,	Particle size, zeta potential, surface charge, encapsulation efficiency, drug release

Nano-emulsions	aqueous to oily phase Amount of oils, surfactants, cosurfactants, cosolvents	number of cycles Type of mixing, mixing speed, temperature. Homogenization, speed, number of cycles	profile Drug permeation flux, refractive index, viscosity, globule size, zeta potential
Self-nanoemulsifying systems	Amount of lipids, surfactants, cosurfactants, cosolvents, polymeric precipitation inhibitors	Types of mixing, mixing speed, temperature	Emulsification time, globule size, zeta potential, drug release profile
Nano-vesicular system	Molar concentration of phospholipids, cholesterol, surfactants, stabilizers	Temperature, stirring time, shaking time, hydration stime, sonication time	Percent encapsulation, entrapment efficiency, vesicle size, drug leakage, percent drug content
Nanosuspensions	Drug: surfactant ratio, concentration of surfactant, stabilizer	Mill speed, milling time, type of beads	Particle size, entrapment efficiency, drug release
Polymeric nanoparticles	Monomer concentration, concentration of polymer, surfactant, molecular weight of polymer	Manufacturing method, stirrer type, stirring speed and time	Percent yield, entrapment efficiency, drug loading,

Screening Study Design for Nanotechnology-Based Drug Development: Nanotechnology has revolutionized drug development by improving drug solubility, stability, and targeted delivery. The screening study aims to identify potential nanocarriers for drug encapsulation, assess their physicochemical properties, and evaluate their biocompatibility for therapeutic applications⁵⁰⁻⁵².

Study Objectives: To screen and characterize various nanocarriers (liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles) for drug loading efficiency. To assess the stability and release profile of drugs encapsulated in nanocarriers. To evaluate in vitro cytotoxicity and biocompatibility of selected nanocarriers.

Materials and Methods

Selection of Nanocarriers: Four different nanocarriers will be synthesized and screened:

Liposomes: Composed of phospholipids and cholesterol to enhance drug bioavailability^{53, 54, 55}.

Polymeric Nanoparticles: Made from biodegradable polymers such as PLGA for controlled release^{56, 57}.

Dendrimers: Highly branched nanostructures for efficient drug loading^{58, 59, 60}.

Metallic Nanoparticles: Gold or silver nanoparticles for targeted drug delivery⁶⁰.

Drug Encapsulation and Loading Efficiency: The encapsulation efficiency (EE) and drug loading capacity (DLC) will be determined using UV-Vis spectrophotometry and HPLC analysis.

Stability and Drug Release Kinetics: Nanocarrier stability will be assessed by:

Dynamic Light Scattering (DLS) for particle size and zeta potential.

Drug release studies in simulated physiological conditions (pH 7.4 and pH 5.5) using dialysis.

Cytotoxicity and Biocompatibility:
MTT Assay: Evaluates cell viability after nanoparticle exposure.

Haemolysis Assay: Assesses nanoparticle-induced red blood cell damage.

Expected Outcomes: Identification of nanocarriers with optimal drug-loading efficiency and stability. Selection of biocompatible nanocarriers with minimal cytotoxicity. Insights into drug release kinetics for potential therapeutic applications.

Design Optimization Study: A Design Optimization Study in nanotechnology-based drug products is a systematic approach to refining nanoparticle formulations and manufacturing processes to achieve the best possible drug performance while meeting quality, stability, and regulatory requirements.

This study focuses on optimizing key parameters such as particle size, drug loading efficiency, surface charge, and release kinetics to enhance therapeutic efficacy and safety. There are various methods for design optimization of the drug product: Evolutionary Operations, The Simplex Method, the Lagrangian Method, Search Methods and Canonical Analysis. Among these methods, Evolutionary Operations (EVOP) is widely used because it helps optimize critical parameters like particle size, drug loading efficiency and release profile which are particularly beneficial when dealing with nonlinear and multi-objective optimization problems, which are common in nanoparticle formulations⁶²⁻⁶⁵.

Steps of Evolutionary Operations (EVOP):

Define the Objective Function: Identify the key response variables to optimize (e.g., nanoparticle size, drug loading, encapsulation efficiency, release rate) and then, define a performance criterion (e.g., minimizing particle size while maximizing drug release).

Select Key Process Variables: Identify critical formulation parameters (e.g., polymer concentration, surfactant ratio, sonication time, stirring speed) and select two or more process variables that influence the response⁶³.

Initial Process Conditions: Choose an initial operating condition based on prior knowledge or experimental data. Define a small range of variation for each selected variable (e.g., $\pm 5\%$ of current values).

Implement a Cyclic Experimental Design: Conduct small systematic changes in variables while keeping other factors constant. Common designs include factorial or fractional factorial designs (e.g., two-level or three-level experiments)⁶⁵.

Measure and Analyze Results: Record responses for each experimental condition (e.g., measure nanoparticle size, zeta potential, and drug release). Analyze whether the changes lead to an improvement in performance.

Decide the Next Iteration: If there is an improvement, shift the operating conditions toward the improved values. If there is no improvement,

adjust the experimental step size or explore a different variable range.

Continue Iterative Optimization: Repeat the process until no further significant improvement is observed. The optimal conditions are achieved when responses reach a desirable level.

Validate the Optimized Conditions: Conduct confirmation experiments to ensure reproducibility.

CONCLUSION: The integration of Quality by Design (QbD) into nanotechnology-based drug development marks a significant advancement in pharmaceutical research. By systematically applying QbD principles, developers can better control critical material attributes (CMAs), process parameters (CPPs), and quality attributes (CQAs), leading to improved reproducibility, safety, and regulatory compliance. This approach is particularly valuable for complex nanocarriers like liposomes, polymeric nanoparticles, dendrimers, and nanosuspensions, where small changes can significantly affect product performance.

Using design optimization methods such as Evolutionary Operations (EVOP), researchers can refine key formulation parameters such as particle size, drug loading efficiency, and release kinetics enhancing drug stability and therapeutic efficacy. Screening studies that evaluate encapsulation efficiency, biocompatibility, and cytotoxicity further ensure the selection of suitable nanocarriers for targeted delivery.

Ultimately, QbD provides a structured framework for optimizing nano pharmaceuticals, facilitating the development of safe, effective, and high-quality drug products. This integrated approach accelerates innovation while meeting stringent regulatory standards, supporting the advancement of precision medicine and addressing complex healthcare challenges.

ACKNOWLEDGEMENT: We, Annaysha Kundu, Pabitra Bhaumik, Shreyan Chatterjee and Tanmoy Dey, students of Guru Nanak Institute of Pharmaceutical Science and Technology, M. Pharm (Pharmaceutical Quality Assurance), would like to express sincere gratitude to Guru Nanak Institute of Pharmaceutical Science and Technology for providing the necessary resources and support

during the preparation of this review article. Special thanks to Jaydip Ray (Corresponding Author), Associate Professor of Guru Nanak Institute of Pharmaceutical Science and Technology whose insightful feedback and guidance significantly enriched the quality of this work. We also acknowledge the contributions of fellow researchers and peers for their valuable discussions and suggestions. We are also grateful to the journal named "International Journal of Pharmaceutical Sciences and Research" for accepting our Review and giving us the opportunity.

CONFLICT OF INTEREST: We, Annaysha Kundu, Pabitra Bhaumik, Shreyan Chatterjee and Tanmoy Dey, students of Guru Nanak Institute of Pharmaceutical Science and Technology, M. Pharm (Pharmaceutical Quality Assurance) declared on behalf of our corresponding author Jaydip Ray (Associate Professor of Guru Nanak Institute of Pharmaceutical Science and Technology) that there is no conflict of interest for this Review.

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How to cite this article:

Bhaumik P, Kundu A, Chatterjee S, Dey T and Ray J: Review article on QbD approaches to improve nanotechnology based drug product. *Int J Pharm Sci & Res* 2025; 16(11): 2890-03. doi: 10.13040/IJPSR.0975-8232.16(11).2890-03.

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