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Review Paper

Quality Assurance Challenges in Nano pharmaceuticals and Novel Drug Delivery System

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ABSTRACT

Nano pharmaceuticals and Novel Drug Delivery Systems (NDDS) have emerged as advanced pharmaceutical technologies that improve drug targeting, bioavailability, therapeutic efficacy, and patient compliance. These systems utilize nanoscale carriers such as nanoparticles, liposomes, noisome, microspheres, monoclonal antibodies, and resealed erythrocytes to deliver drugs at the desired site and rate. Despite their significant advantages, ensuring the quality, safety, and effectiveness of these complex formulations remains a major challenge. This review highlights the critical quality assurance (QA) challenges associated with nano pharmaceuticals and NDDS, including particle size and size distribution, batch-to-batch variability, scale-up and manufacturing difficulties, characterization and analytical limitations, stability issues, sterility assurance, microbial contamination control, and regulatory compliance. The review also discusses important quality control tests such as particle size analysis, zeta potential measurement, drug loading determination, sterility testing, endotoxin testing, in vitro drug release studies, and stability testing. Furthermore, the application of Quality by Design (QbD) principles, including Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Design of Experiments (DoE), is emphasized as a systematic approach to achieving consistent product quality and regulatory compliance. Overall, effective quality assurance strategies are essential for the successful development, manufacturing, and commercialization of nano pharmaceuticals and novel drug delivery systems

INTRODUCTION

A number of recent reviews have highlighted a crucial part of pharmaceutical delivery,

specifically the precise targeting of the drug to the desired cells or tissue. It should be possible for pharmaceutical targeting systems to regulate how a drug enters the body. The goal of

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nanotechnology is to create nanoparticles for biomedical and biotechnology applications to deliver the medication at the appropriate time and location. The Greek prefix “nano” which meaning “dwarf” or extremely little, is equivalent to one billionth of a meter ($10^{-9} \text{ m} = 0.000000001$). It is important to distinguish between nanoscience and nanotechnology. Nanoscience is the study of molecules and structures with sizes between 1 and 100 nm, in which characteristic phenomenon sanctions novel applications. Nano pharmaceuticals are pharmaceutical drugs accommodating nanomaterials and are employed for diagnosis, therapies, healthcare provisions.

1.1 NANOPHARMACEUTICALS: Nano pharmaceuticals are pharmaceutical products that utilize nanotechnology for the diagnosis, treatment, prevention, and monitoring of diseases. These formulations contain drug particles or carriers in the nanometre size range, generally between 1 and 1000 nanometres (nm). Due to their extremely small size, nano pharmaceuticals exhibit unique physicochemical properties that improve drug delivery, therapeutic efficacy, and patient compliance[1].

1.2 DEVELOPMENT OF NANOPHARMACEUTICALS:

Nowadays, after a medicine is first discovered or developed, it may take up to 20 years for it to get the market.

Among other things, there should be a sufficient number of highly qualified scientists and medical professionals who are willing to devote ten or more years of their lives to a single project; the basic scientific idea should be original and properly protected by intellectual property; and the financial business plan should convince investors of potential profits.

Profit/risk ratios must always be extremely suitable, and market needs must constantly be accurately

evaluated.

Clarification is also required on the distribution and shelf life of medicinal medicines. Intellectual property, technological concerns, overall expenses, and the ethical and regulatory aspects of the situation are all covered in the sections that follow [2].

1.3 NOVEL DRUG DELIVERY SYSTEM: A suitable drug delivery system aims to provide an effective therapeutic dose at the targeted site at the right time and at suitable intervals until the desired cure is achieved [3].

• Carrier Based Drug Delivery System:

1. Nanoparticles
2. Microspheres
3. Liposomes
4. Niosomes
5. Monoclonal Antibodies
6. Resealed Erythrocytes as Drug carriers [4]

1. NANOPARTICLES:

The solid state of nanoparticles, which include nanospheres and nanocapsules with sizes ranging from 10 to 200 nm, can be either amorphous or crystalline.

They can encapsulate or adsorb a medication, shielding it from enzymatic and chemical deterioration.

Biodegradable polymeric nanoparticles have garnered significant interest as possible drug delivery vehicles in recent years due to their potential for controlled drug release, targeting specific organs or tissues, serving as DNA carriers in gene therapy, and delivering proteins, peptides, and genes orally.[5,6]

2. MICROSPHERES:

Microspheres usually have a particle size of 200-500 μm and are made of biodegradable proteins or synthetic polymers. Several techniques for



producing microspheres offer a range of opportunities to regulate drug delivery procedures and enhance a medication's therapeutic efficacy.

3. LIPOSOMES:

Liposomes are a type of vesicle made up of one, several, or many phospholipid bilayers.

Polar medicinal molecules can be encapsulated due to the polar nature of the liposomal core.[7]

Amphiphilic and lipophilic molecules are solubilized within phospholipid bilayer according to their affinity towards phospholipids.[8]

4. NIOSOMES:

Niosomes are multilamellar vesicles made of cholesterol and nonionic surfactants of the alkyl or dialkyl polyglycerol ether family.

Prior research conducted in collaboration with L'Oréal has demonstrated that niosomes generally share characteristics with liposomes as possible medication carriers.

Compared to liposomes, niosomes have some advantages.[9]

5. MONOCLONAL ANTIBODIES:

Usually created by combining a B cell with a single lineage of cells having a specific antibody gene, monoclonal antibodies (MAbs) are collections of homogenous antibody molecules with affinity for a specific antigen.

6. RESEALED ERYTHROCYTES AS DRUG CARRIERS:

Erythrocytes, another name for red blood cells (RBCs), have drawn a lot of interest and have been studied for potential drug delivery and drug-loaded microspheres.

The reason these erythrocytes are called "resealed erythrocytes" is that they are created by drawing blood from the target species, separating the erythrocytes from the plasma, encasing the medication within the erythrocyte, and then sealing the resulting cellular carriers.

2. CONCEPT OF QUALITY ASSURANCE IN NANOPHARMACEUTICALS:

"All those planned and systematic actions needed to provide adequate confidence that a product, service, or result will satisfy given requirements for quality and be fit for use" is the definition of quality assurance (QA), a management technique. "The sum total of the activities aimed at achieving that required standard" is the definition of a quality assurance program.[10]

Since its inception in the 1950s, quality assurance has placed a strong emphasis on ensuring that quality standards are fulfilled. This is crucial for patients, accreditors, and other external parties as well as internal stakeholders like leadership. In order to achieve its objectives, quality assurance uses quality control tools. The data collected is used to confirm that performance stays at the level of specified quality standards.[11]

3. OBJECTIVES

1. Safety
2. Efficacy
3. Purity
4. Identity
5. Consistency

4. MAJOR QUALITY ASSURANCE CHALLENGE

4.1 PARTICLE SIZE AND SIZE DISTRIBUTION: Particle size is one of the maximum essential limits of nanoscale distribution as well as form. The application of electron microscopy is figuring out thickness and appearance. The principal application of Nanomaterials are popular for therapeutic targeting and drug absorption.[12] It has been found that particle size affects the release of medication. Smaller atoms have a expanded coverage area. As a result, the granular surface is exposed to the majority of the medication. leading to quick drug release. On the other hand,



pharmaceuticals progressively enter larger particles. Smaller particles have a tendency to group together during Nanoparticle variation in storage and transit is a benefit. As a result, there is a trade-off between the size of the nanoparticles and the highest level of stability.[13]

4.2 BATCH TO BATCH VARIABILITY:

Industrial-scale processes [e.g., microfluidics] must maintain CQAs. LNPs for mRNA vaccines required CFD modelling to ensure consistency at 1,000-liter scales.[14] Batch-to-batch consistency is key in pharma. Nano pharmaceuticals are tough, though; nanoparticle traits change easily depending on manufacturing. It's hard to get them uniform.

4.3 SCALE UP AND MANUFACTURING CHALLENGES:

Scaling up nano formulations from laboratory to industrial production remains a critical bottleneck in translating nanomedicines to clinical and commercial use. Things are mixed differently in real production. From the lab to the factory, there are significant differences in things like how thoroughly everything is churned or the forces involved.

Particles may clump as a result, affecting the amount of medication loaded and creating an uneven end product.

To be honest, one of the biggest challenges facing the science is creating nanomedicines that can be produced consistently and on a large scale.

4.4 CHARACTERIZATION AND ANALYTICAL CHALLENGES:

Ensuring the quality, safety, and effectiveness of nano pharmaceutical products requires thorough characterization. However, the intricate architectures of nanoparticles necessitate sophisticated analytical methods for accurate assessment. Particle size, morphology, surface charge, drug content, encapsulation efficiency, and

release behaviour are examples of critical factors that need to be precisely assessed.

Commonly employed methods include –

- Zeta Potential Analysis
- Atomic Force Microscopy (AFM)
- Transmission Electron Microscopy (TEM)
- Scanning Electron Microscopy (SEM)
- Dynamic Light Scattering (DLS).

The complexity of quality assurance tasks is increased by the need for advanced equipment, highly skilled workers, and standardized analytical techniques.

4.5 STABILITY ISSUE: For nano pharmaceutical products, stability is a crucial quality concern. During handling, storage, and transportation, nanoparticles may change chemically and physically. Aggregation, sedimentation, crystal growth, and variations in the distribution of particle sizes are examples of physical instability. Oxidation, hydrolysis, drug degradation, and polymer degradation are examples of chemical instability. Product performance and shelf life may suffer as a result of these modifications. To guarantee product integrity during the intended storage period, quality assurance programs must incorporate thorough stability studies under a variety of environmental conditions.[15]

4.6 STERILITY AND MICROBIAL CONTAMINATION CONTROL:

The absence of a live microbe that could be harmful to health is known as sterility. Bacteria and fungi are the main contaminating agents, and operational personnel, used materials, and equipment are the sources of contamination. Many sterilization methods have been developed to eliminate or eliminate microbial contaminations because the sterility of nanoparticles is an essential requirement for their in vivo use in biomedical applications.[16]



Ionizing radiation, nonionizing radiation, autoclaving, and sterile filtration are currently the primary techniques used to sterilize nanoparticles.[17]

4.7 REGULATORY AND COMPLIANCE

CHALLENGES: Regulatory evaluation of nano pharmaceuticals is more complex than that of conventional pharmaceutical products. Existing regulatory frameworks are often insufficient to address the unique properties of nanomaterials.

Challenges: 1. Lack of standardized guidelines:

The approval process is complicated by the current guidelines' frequent inability to address the unique requirements of nanomedicines.

2. Characterization and Quality Control:

Because nanoparticles are dynamic, it is necessary to use sophisticated analytical methods to evaluate their physicochemical characteristics, stability, and biological performance.

3. Safety and toxicity evaluation: Because nanoparticles frequently interact with biological systems in a variety of ways, thorough preclinical research is required to assess potential toxicity, immunogenicity, and biocompatibility.

4. Scalability and manufacturing: Strict quality control procedures are needed to guarantee batch-to-batch consistency when moving from small-scale lab production to commercial manufacturing.[18]

4.8 QUALITY BY DESIGN

IMPLEMENTATION CHALLENGES: QbD is a systematic approach to develop and produce goods based on knowledge and risk management. This approach is widely used in pharmaceutical development to enhance product and process performance, addresses manufacturing challenges, and ensure regulatory compliance. The QbD

principles include identifying Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs), implementing risk management strategies, and utilizing Design of Experiments (DoE) as well as Process Analytical Technology (PAT); it is a powerful tool successfully applied to various nanocarriers, including liposomes, polymeric nanoparticles, and solid lipid nanoparticles.[19]

5. QUALITY CONTROL TESTS:

5.1 PARTICLE SIZE AND DISTRIBUTION:

The way a medicine acts in the body can be affected by slight variations in size. These features are measured using electron microscopy and dynamic light scattering (DLS).[20]

5.2 ZETA POTENTIAL:

This provides information on the electrical charge on the surface of the particle.

This affects the drug's stability in solution and its interactions with cells.

Stability depends on the prevention of particle clumping, which is aided by a high zeta potential.[21]

5.3 DRUG LOADING: These tests verify that the medication is being administered at the proper dosage.

HPLC or UV spectrophotometry are two methods used to quantify encapsulation efficiency and drug loading, or the amount of actual medication contained in the nanoparticle.

5.4 STERILITY AND ENDOTOXIN TESTING:

Sterility and endotoxin testing are essential because many nano pharmaceuticals are injected. Contamination of any kind can be harmful.

The conventional technique for identifying bacterial toxins is the Limulus Amoebocyte Lysate (LAL) test.[22]



5.5 IN VITRO RELEASE TEST: which mimics the drug's release from the body. This aids in determining if the formulation will function as planned.

5.6 STABILITY TESTING: Stability testing in a range of light and temperature settings guarantees that the product maintains its efficacy and safety over time.

6. QUALITY BY DESIGN: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[23]

7. COMPONENTS OF QBD:

7.1 QUALITY TARGET PRODUCT PROFILE (QTPP):

The first step in QbD is to specify the quality target product profile (QTPP), which is a prospective overview of the drug's quality attributes.

This desirable attribute considers the medication product's safety as well as its effectiveness.

Juran states that QTPP should ideally be based on the needs of the patient and incorporates a number of fundamental factors, including the clinical intended use, the dosage form, the administration route, The dosage strength, and the pharmacokinetics.[24]

7.2 CRITICAL QUALITY ATTRIBUTES:

These are the critical quality attributes (CQAs), “physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality” [25]

7.3 CRITICAL PROCESS PARAMETERS: A CPP is “a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to

ensure the process produces the desired quality”.[26]

7.4 DESIGN OF EXPERIMENTS: DoE is a statistical methodology used to study the effect of multiple variables on product quality.

Objectives

- Optimize formulation
- Reduce experimental trials
- Understand interactions

Common Experimental Designs

1. Full Factorial Design
2. Box-Behnken Design
3. Central Composite Design

CONCLUSION

Nano pharmaceuticals and Novel Drug Delivery Systems (NDDS) represent a significant advancement in modern pharmaceutical science by offering improved drug targeting, enhanced bioavailability, controlled drug release, reduced side effects, and better patient compliance. The use of nanosized carriers such as nanoparticles, liposomes, niosomes, microspheres, monoclonal antibodies, and resealed erythrocytes has opened new opportunities for the treatment of complex diseases, including cancer, infectious diseases, and chronic disorders.

Despite these advantages, maintaining the quality, safety, efficacy, and consistency of nano pharmaceutical products remains a major challenge. Factors such as particle size and size distribution, batch-to-batch variability, scale-up difficulties, analytical characterization limitations, stability concerns, sterility assurance, microbial contamination, and complex regulatory requirements significantly affect product performance and market approval. Due to the unique physicochemical properties of nanomaterials, conventional quality assurance



approaches are often insufficient, requiring specialized analytical techniques, advanced manufacturing controls, and comprehensive risk assessment strategies.

Quality assurance plays a crucial role throughout the lifecycle of nano pharmaceutical products, from formulation development to commercial manufacturing. The implementation of Quality by Design (QbD) principles provides a scientific and systematic framework for identifying Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical Material Attributes (CMAs), thereby ensuring consistent product quality and process robustness. In addition, quality control tests such as particle size analysis, zeta potential measurement, drug loading assessment, sterility testing, endotoxin testing, in vitro release studies, and stability studies are essential for ensuring product reliability and regulatory compliance.

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