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QBD APPROACHES WITH ARTIFICIAL INTELLIGENCE IN TOPICAL NANOPARTICLE DRUG DELIVERY SYSTEMS

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ABSTRACT

The introduction of new software applications for pharmaceutical research and design has radically changed the way people assess quality standards. In this sense, Artificial Intelligence (AI) and Quality by Design (QbD) are related concepts that work together to make products more efficient by making them more robust and easier to follow. Topical drug delivery methods the utilization nanoparticular systems, like nano emulsions, liposomes, solid lipid nanoparticles, and polymeric nanoparticles, are becoming more popular because they can get deep into the body and release drugs in a controlled way. However, the complex and changing properties of nano systems make it hard to make high-quality products.

This review determines the role of AI in facilitating QbD implementation throughout the creation of topical nanoparticle formulation pharmaceutical products. Digital twin technology, autonomous manufacturing systems, Industry 4.0 integration, and personalized medicine are just a few of the new technologies that will change the way drugs are made and tested in the future. In general, the combination of AI and QbD creates a strong and smart framework for making topical nanoparticle drug delivery systems are safe, effective, and high quality.

Keywords: Artificial Intelligence; Quality by Design; Nanoparticles; Topical Drug Delivery; Process Analytical Technology; Machine Learning; Pharmaceutical Quality Assurance

1. INTRODUCTION

The main aim of the Drug delivery system is to deliver a proven active agent to the specific site at an appropriate concentration to reduce side effects and improve disease treatment. Furthermore, the conventional drug delivery method is facing challenges such as poor availability, non-specific drug distribution, and some inadequate pharmacokinetic behaviours **[1]**. Nanotechnology based carriers has proven to deliver the active constituent significantly through the development of nanoparticle-based systems, liposomes, polymeric nanoparticles, and nanoemulsions **[2]**. This system has used for drug solubility, stability, and targeted drug delivery. Now, some transformations are observed in the pharmaceutical sectors, like regulatory progress and innovation in material science, as well as advances in technology **[3]**. The incorporation of nanotechnology in drug delivery systems, which is liposomes, nanoemulsions, solid lipid nanoparticles, and polymeric nanoparticles, designed for skin application, has produced numerous beneficial outcomes. However, the development of such vehicles is quite complex because of the influence of several formulation variables such as size, charge, encapsulation efficiency and stability of the nanoparticles on the result **[4]**. The integration of AI techniques with QbD principal approaches is transforming drug delivery formulation from a conventional trial-and-error approach to a more predictive, efficient, and data-driven process **[5] [6]**. With computers we will predict the best conditions for making drugs and make design spaces that work well for those conditions **[7]**.

2. QUALITY BY DESIGN (QBD) IN PHARMACEUTICAL DEVELOPMENT

Quality by Design represents scientifically proven approach to ensure sure quality through understanding what determines the product and method during the manufacturing phase, predicting and controlling product quality **[6]**. The QbD strategy encompasses quality control at all stages of development, e.g. formulation and manufacture. Traditional QA systems, by contrast, are mainly concerned with testing the end product **[8]**. QbD says that you cannot inspect quality into a product. Instead, it needs to be baked into the product itself. Major advantages of implementing Quality by Design (QbD) in the modern pharmaceutical industry is the establishment of a design space. The use of QbD in nanoparticle-based drug delivery systems is of great importance due to the complex interactions between the formulation variables and process parameters that often complicate the prediction of the outcomes. To overcome this challenge, QbD uses

systematically created experiments and risk evaluation techniques to develop a complete understanding of critical process variables and their effect on product quality **[9]**.

2.1 QbD: Key Elements

Several key characteristics must work together in a coordinated way to successfully implement Quality by Design (QbD).

2.1.1 Quality Target Product Profile (QTPP)

QTPP mainly defines desired quality characteristics of the final product **[10]**.

2.1.2 Critical Quality Attributes (CQAs)

CQAs are measurable product specifications that influences safety, efficacy, and overall quality **[11]**.

2.1.3 Critical Material Attributes (CMAs)

CMAs referred as material properties that may affects the performance and quality of the formulations **[12]**.

2.1.4 Critical process parameters (CPP)

CPPs mainly includes the manufacturing factors related to the process, such as temperature, stirring speed and homogenization conditions, that may act on the CMAs of the end formulation **[13]**.

2.1.5 Design Space

It establishes safe operating limits for formulation process variables to ensure consistent product manufacturing and process control **[14]**.

2.1.6 Control Strategy

Control strategy is established to warrant consistent manufacturing and preservation of established product quality through constant surveillance of formulation and process variables.

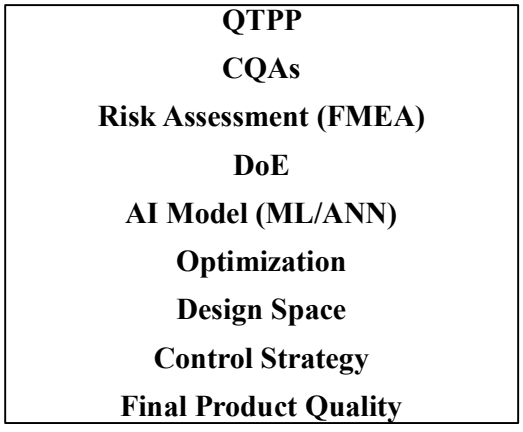


Figure 1: QbD Workflow Figure

2.2 Importance of QbD

QbD offers a science-based approach for process knowledge, development, increasing efficiency, decision making, boosting regulatory confidence by improving transparency and better

understanding of manufacturing process **[15]**. This is particularly true for nanoparticle-based delivery systems, where small variations in formulation or processing parameters can greatly affect product functionality and treatment outcomes **[16]**.

2.3 Seven Steps to Quality by Design Startup Plan

1. Define the QTPP
2. Determine CQAs
3. Conducting risk assessment
4. Identify CMAs and CPPs
5. Generate design space using DoE
6. Develop control strategy
7. Implement life cycle management **[17] [18]**.

2.4 ICH Guidelines and Their Role in QbD

The ICH guidelines form the regulatory backbone of QbD:

- **ICH Q8(R2):** Focuses on pharmaceutical development and design space
- **ICH Q9:** Emphasizes quality risk management
- **ICH Q10:** Defines pharmaceutical quality systems

These guidelines ensure a standardized approach to quality across the industry **[19]**

2.5 Tools of Quality by Design

2.5.1 Design of Experiments (DoE)

Design of experiments (DoE) is a scientific technique used to study the effect of variables on results produced by variables. Design of Experiments methods can help to conduct an experiment efficiently and determine a reduced number of trials by adjusting the variables **[20]**.

2.5.2 Process Analytical Technology (PAT)

The main goal of PAT is to handle the raw materials as well as processing substances and operational parameters used in manufacturing to conform to the desired quality of the formulated product. Process analytical technology determines that quality must be developed into the product rather than at the final stage **[21]**.

2.5.3 Risk Assessment

Evaluating risks is crucial for identifying the characteristics of materials and process parameters that influence the CQAs of the medication. This task is performed across the entire lifecycle of the product **[22]**. By conducting risk assessments, it is feasible to rank the experiments according to their associated risks and areas of knowledge that are lacking **[23]**.

2.6 QbD and Quality Assurance

Quality assurance (QA) is an essential approach that promotes the final products possess the necessitate qualities. Conventional QA methods focused on testing the end product, yet this technique has shown to be inadequate in identifying variations linked to manufacturing processes. Quality assurance cantered on QbD highlights the comprehension of the

production process and regulation. Conventional QA systems evaluated the end product. The QA method is ineffective as it fails to identify all defects. Contemporary QA systems emphasize quality control based on processes **[24]**.

3. TOPICAL NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

Topical nanoparticles are being investigated as a new technology for dermatological and transdermal application, as they can bypass the barrier of protection of the stratum corneum. Nanoparticles based drug delivery systems enhance drug distribution, release, and bioavailability **[25]**. Nanoparticles are nanosized carriers as particles with diameters from 1 to 1000 nm. The quality by design technique emphasizes the nanoparticle systems being a multifaceted system which means that many variables must be taken into consideration during the development of nanoparticle-based drug delivery systems **[26]**. Artificial intelligence-based techniques are highly useful in this domain as they help in modelling complex and nonlinear connections between formulation parameters and performance outcomes and thus improve the accuracy of the prediction of optimal conditions and reduce the need for experimentation **[27]**.

3.1 Types of Nanoparticles

Base on the nanoparticle drug delivery systems can be majorly classified as several categories, each of them has distinct advantages and limitations **[28]**.

3.1.1 Liposomes

These is the type of vesicles mainly contains of phospholipid bilayers they possesses both lipophilic and hydrophilic medications. Liposomes are perfect for topical delivery systems but are liable to uncertainty and degradation due to leakage and oxidation **[29]**.

3.1.2 Solid Lipid Nanoparticles (SLNs)

SLNs mainly gives strengthen stability and manageable drug release. SLNs could encounter expulsion issues when kept for long durations as a result of lipid crystallization **[30]**.

3.1.3 Nanostructured Lipid Carriers (NLCs)

The difference among NLCs and SLNs lies in the presence of liquid lipids, leading to lower crystallinity and higher drug loading **[31]**.

3.1.4 Polymeric Nanoparticles

Polymeric nanoparticles offer opportunity for precise drug delivery, but the safety and biocompatibility of the carriers depend on the particulars polymer used **[32]**.

3.1.5 Nanoemulsions

Nanoemulsions can increase the drug solubility and the drug penetration into the skin **[33]**.

Table 1: Types of Nanoparticles and their specification [34]

Type	Composition	Advantages	Limitation
Liposomes	Phospholipids	Biocompatible good penetration	Stability issues
SLN	Solid lipids	Control release	No drug loading
NLC	Solid + liquid lipids	Improve stability	Complex formation
Nanoemulsion	Oil-water system	High absorption	Surfactant toxicity

4. ROLE OF ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL DEVELOPMENT

It is very useful to complex systems such as nanoparticles because of its potential to analyse massive data sets and to identify the essential patterns. The growth in the field of Artificial Intelligence has had a great impact on the formulation development procedure across many industries includes formulation development, analysis of pharmaceutical compounds, process-control, Ensures quality. Traditional statistics does not account for non-linear relationships between variables, whereas AI helps in understanding the patterns intrinsic **[35]**.

4.1. Types of Artificial Intelligence Used in Pharma

4.1.1 Machine Learning (ML)

Regression, decision tree, and support vector machine models fall under machine learning category.

4.1.2 Artificial Neural Networks (ANNs)

An artificial neural network is a form of intelligence that replicates the workings of the human brain and is particularly effective at modelling non-linear relationships in formulations.

4.1.3 Deep Learning

It encompasses methods such as convolutional neural networks (CNNs) to perform image-related tasks like defect identification.

4.1.4 Learning by Reinforcement

It is a way of systems adaptation to improve processes based on feedback **[36]**

Table 2: AI technique pharmaceutical application [36] [37]

AI Technique	Application	Benefit
Machine learning	Prediction of CQAs	High accuracy
ANN	Formulation optimization	Handle complexity
Deep learning	Big data analysis	Advanced prediction

4.2 AI-Enabled QbD Optimization

The use of artificial intelligence in QbD approaches improves the efficiency and accuracy of pharmaceutical development. AI models can analyse large data sets obtained via DoE and find the optimal parameters for formulation and process optimization**.** AI-driven QbD enables Faster design space exploration, improved prediction accuracy, reduced experimental workload, enhanced process understanding **[7] [38]**.

4.3 Design Space Prediction Using AI

One of the major advantages of integrating AI in the QbD process is the prediction capability of design spaces especially with the use of neural networks with deep layers. Statistical frameworks have been traditionally used in the design of processes, which can be challenged to model non-linear interactions. However, AI algorithms can precisely represent very complex design spaces **[36] [39]**.

4.4 Optimization of Formulation

AI can be used to optimize the formulation elements, leading to better results in drug manufacturing. The effect of distinct independent variables on parameters like the size of the particles and drug distribution could be predicted using machine learning algorithms. These distinct variables may include, for example, the lipid level, the surfactant level and the processing parameters. In that some methods been used to optimizes the formulation i.e. Levenberg-Marquardt algorithm, Models with cross validation, Methods for early stopping **[40]**.

5. AI FOR QUALITY ASSURANCE

AI can be utilized for continuous monitoring of the process using machine learning algorithms in the QbD process. AI models can analyse current trends and predict possible quality issues before they happen **[41]**.

6. REAL-TIME RELEASE TESTING (RTRT)

RTRT is a highly advanced method of ensuring quality by releasing products in real-time based on data instead of waiting until the end of production and testing the product. Artificial intelligence becomes very important in RTTT by analysing PAT data and predicting the quality of the products **[42]**.

7. DEFECT DETECTION USING AI

There is a substantial growth in the application of Artificial Intelligence (AI) based image analysis systems, particularly deep learning model, for fault detection in pharmaceutical production. Such systems are efficient in spotting flaws such as particle aggregation, contamination, and packing **[43]**.

8. CASE STUDIES AND RECENT ADVANCES

Multiple case studies carried out in recent times have thoroughly proven the application of Artificial Intelligence (AI) and QbD. For example, a recent study by Vamathevan *et al*. applied the machine learning algorithms to make predictions based on a physiochemical property and process parameters, and the prediction accuracy is much higher than the traditional regression method. Similarly, machine learning was used to predict the formulation and reduce the development time by up to 30% **[44]**. The use of artificial neural network (ANN) models in the nanoparticle

formulation models has been found to be effective to predict particle size, drug encapsulation and delivery rate correctly **[45]**. An additional significant achievement is the application of AI technology within the PAT. The combined use of artificial intelligence technologies alongside real-time monitoring allowed for real-time verification along with real-time release testing (RTRT), which contributed to significant improvements in efficiency in production **[46] [47]**. It is significant to note that many AI models used in present-day research have been trained on insufficiently large datasets, which affects the applicability of models. At the same time, standard model verification methods have not been developed **[48]**.

9. REGULATORY PERSPECTIVE

Regulatory agencies recognize, the context of AI technologies in drug development, regulatory agencies (e.g., FDA, EMA) recognize the significant benefits of applying AI and QbD principles, resulting in increased product quality and production efficiency. Nevertheless, challenges concerning transparency and validation of AI models emerge in the deployment of AI technologies **[49] [50]**. Another issue that triggers regulatory questions is the so-called “black box” effect caused by the lack of transparency of AI algorithms **[51]**. Regulatory organizations mandate transparency in the procedures of decision making, especially when decisions are related to product quality and patient safety. In the short term, strong cooperation between the industry and the regulatory authorities should become an integral part of the regulatory framework for AI deployment **[52] [53]**.

10. FUTURE PERSPECTIVES

The future pharmaceutical setup will be to smart, automated systems using AI, machine learning, deep learning, QbD, and real-time process monitoring. AI-driven pharmaceutical manufacturing may bring personalized medicine, autonomous formulation optimization, digital twins and smart quality assurance systems in topical nanoparticle-based drug delivery. It looks very optimistic and thrilling for the area of AI-based QbD in drug development and covers the subsequent trends as discuss in type of AI **[49] [54] [52]**.

11. CRITICAL DISCUSSION

Although the combination of AI and QbD appears valuable and positive, it is necessary to think carefully about its prospective limitations and effects. One of the big challenges of heavy reliance on data models is the lack of understanding of the underlying mechanism of the phenomenon. It should be understood, therefore, the importance of joining the AI technology with the scientific understanding. Also, the issue of reproducibility is another important aspect that should be addressed when

introducing a new tool to a production process. Differences in data quality and training protocols may affect the final result. Another matter that should not be ignored is principles. It includes several problems like the duty of using the software and the data privacy issues. The technology has many additional benefits. So there is a need to marry data driven approaches with scientific understanding.

12. CONCLUSION

The combined use of Artificial Intelligence (AI) with Quality by Design (QbD) has established a novel approach in the pharmaceutical manufacturing process, especially in the area of topical nanoparticles drug delivery systems. AI approaches have proven considerable promise in improving formulation design, predicting design spaces, real-time quality monitoring, and process optimization. But, there are problems and limitations that must be addressed in the use of AI. These include limited data availability, issues with model explainability, ambiguous regulations, and high implementation costs. Integration of the AI technologies with QbD principle offers modern strategy to improve formulation development and quality assurance.

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