



Quality by Design: A Methodical Approach in Development of Nano Delivery System

Priya S. Milmile*, Rasika J. Patil, Samiksha M. Nikam, Kamlesh J. Wadher, Milind J. Umekar
 Department of Quality Assurance, Smt. Kishoritai Bhoyar College of Pharmacy, Kampti, Nagpur, Pin-441002, India.
 *Corresponding author's E-mail: priyamilmile941997@gmail.com

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ABSTRACT

Pharmaceutical quality by design (QbD) is a methodical approach to development of drug which begins with predefined objectives and control based on scientific acumen and quality risk management. QbD in the field of pharmacy is based on the basic understanding of the quality profile of final products affects by materials and process parameters. The application of QbD in designing of drug delivery system is based on a sound understanding of the sources of variability and the manufacture process and parameters. Most of problems in quality in formulations are related to the way designing of pharmaceutical product was carried out. The most important element of QbD based drug delivery development is the risk assessment (RA) activity which is important aspect during the development process. This review article addressed various concepts and applications of QbD to optimize and develop various nano drug delivery systems such as, examples liposomes, proliposome, nanoliposomes, polymeric nanoparticles, microsponges, solid lipid nanoparticles, transgel. nanostructured lipid carriers, nano emulsions with the research published in recent years.

Keywords: Review, Quality by Design, Drug Delivery Systems, Nanocarrier, Risk Assessment.

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INTRODUCTION

Quality by Design (QbD) is a concept created by Dr. Joseph M. Juran, who believed in the importance of quality and also that method of designing a product is responsible for majority of problems associated with quality¹. The high-quality products should be free from contamination and provide the therapeutic advantage as claimed by the product². QbD is the modern approach for understanding quality of pharmaceutical product, which describes its use to ensure higher quality of Pharmaceuticals.

Nanotechnology has gained an implementation and advanced position in drug delivery approaches in the few decades. Enormous value over the considerate characteristics of the adapted therapeutics equally solubility, permeability and life hold on nano drug delivery system. Nanoparticulate for cancer targeting and controlled release functions these components allow the extended use. Many parenteral, oral, and topical nanoparticulate therapeutics are available on the market and clinical trial stages³⁻⁵. The term nanotechnology is also widely used and defined as the control and manipulation of matter at the nano-scale (10-100 nm). through, nanoparticles is size range of 1-1000nm then consider as the particles in practice. Nanoparticles are regarded as

special due to the fact that particles on the nanometer scale have unique optical, electronic, and structural/functional properties distinctive from the normal size. Moreover, nanosizing has a high permeability, a large surface to volume ratio, and higher mucoadhesion can be achieved a sequence⁶⁻⁷.

Nanoparticles can be classified into several groups such as polymeric nanoparticles, liposomes, proliposomes, nanoliposomes, polymeric nanoparticles, microsponges, solid lipid nanoparticles, transgel. nanostructured lipid carriers, nano emulsions, nano capsules are discussed. The nanoparticulate fabrication methods and the properties would also determine its application and utility. However, the type of nanoparticle used to different drug delivery systems of therapeutics has its own positive and negative influences.

The Quality by Design Approach

QbD brings a systemic approach to drug development that aims to ensure quality by applying analytical and risk management methodologies to the design, development and manufacturing new medication. QbD provides the tool to understand the way in which the quality of pharmaceutical formulations is influenced by the materials types, concentrations, and process variables; therefore, the quality of the product can be ensured by controlling the formulation input materials and the manufacturing process key variables. It involves designing a formulation to obtain a product with predetermined quality specifications. It also identifies characteristics that are significant to quality of the product and translates them into attributes that the drug should possess and process parameters can be varied to constantly produce a drug product with the desired characteristics⁸⁻¹⁰.



QbD in Nano Drug Delivery Systems

Nano drug delivery systems (Nano DDS) are the best approaches for delivery of targeting drugs, but the safety parameters and control of quality of nanocarrier DDS have become challenging task. The problems associated are, physicochemical characteristics, nonreproducibility, destabilization of structure, and cost of production of nano DDS. Hence, to prevail over these problems, nano formulation and process design need to be optimized using scientific methods¹¹. QbD is a systematic approach of predefined objectives, based on scientific and risk-based proactive method.

The objective of QbD in nanocarrier DDS is to establish safety, efficacy, and performance. It helps in investigation of variable factors involved and to enhance the process capability with less variability.

Transdermal drug delivery (TDD)

Liposomes

Pallagi E, adopted the QbD concept to the early development phase of a nanosized liposomal formulation for nasal administration with brain target. They focused on presents how to apply this risk focused approach and concentrates on the first four stages of the QbD implementation. The results showed that, QbD approach in liposome development can improve the formulation process¹².

The nanoparticles of meloxicam were produced by co-grinding method for nasal administration and studied according to the QbD policy and the QbD based risk assessment (RA) was also performed. The RA was able to predict and identify theoretically the factors such as sample composition, production method parameters which were found to have highest impact on the formulation quality¹³.

Xu X, et al applied QbD principles to liposomal formulation containing a hydrophilic drug to demonstrate both the feasibility and the advantages of applying QbD concepts to liposome based complex parenteral controlled release systems. The use of QbD in this study helped in identification of high-risk factors that impact liposome drug encapsulation efficiency and particle size¹⁴.

Proliposome

Chobisa et al. developed Organic solvent free nano-drug delivery system for parenteral delivery of Busulfan using QbD approach. They reported the Physicochemical stability of drug significantly higher in proliposomal formulation compared to marketed formulation¹⁵.

Patel et al. applied QbD principles for the development of proliposome of poorly soluble lopinavir. The result emphasized the potential of QbD as a simple and cost-effective approach to formulate proliposome systems with improved bioavailability¹⁶.

Patil-Gadhe et al. used QbD to the preparation, in-vitro and in-vivo performance of rifapentine loaded proliposomes for pulmonary inhalation. They applied QbD principles and design of experiment (DOE) approach to develop drug encapsulated proliposomes for inhalation by spray drying in single step¹⁷.

Nanoliposomes

Mahtab et al. applied Quality by design approach statistically for the optimization of the teriflunomide nanoliposomal formulation. The researcher found that Quality by design approach could improve therapeutic efficacy in the management of rheumatoid arthritis¹⁸.

Pandey et al. used QbD strategy for the fabrication of chitosan coated nanoliposomes encapsulating a hydrophilic drug. The QbD concept improved understanding of the process of preparing liposomes using the ethanol injection method. The researcher used QbD in correlation of the QAs of NLPs with pharmacokinetic studies, which can help enhance the efficacy of liposomal formulations¹⁹.

Polymeric nanoparticles

Soni et al. prepared polymeric nanoparticles prepared using high pressure homogenizer by application of QbD. Use of QbD approach in product design and manufacturing meets the quality of the product as well as the ease of manufacturing. QbD approach can be used for identifying the critical processing steps and suitability of characterization that confirms the reproducibility of the product²⁰.

Vuddanda et al. QbD based factorial design for optimization of formulation variables; drug to polymer ratio (X1) and surfactant concentration (X2) on entrapment efficiency (EE), particle size (PS) and polydispersity index (PDI) of the nanoparticles. The developed nanoformulations using QbD based factorial design would be useful to improve the bioavailability and improve the patient compliance²¹.

Troiano et al. used QbD technology to develop nanomedicine using a risk-based approach to identifying product attributes and process parameters. They confirmed that, a risk-based QbD development approach is the best way to effectively bring such novel products through the clinic and into commercial supply²².

Microsponges

Amrutiya N et al. developed and evaluated microspoon based topical formulation of mupirocin for sustained release and enhanced drug deposition in the skin²³.

The microsponges were prepared by the quasiemulsion diffusion method using, central composite design to investigate the effect of changes in various formulation and process parameters on critical product attributes²⁴.



Solid lipid nanoparticles

Himanshu Bhatt et al. optimized the nano-formulation by Quality by Design approach to understand the effect of various process parameters on various quality attributes, including drug loadability, particle size and polydispersity. The results provide a strong rationale for further exploration he researcher explored the developed SLN using Quality by Design approach to be utilized as a potent chemotherapeutic agent in cancer therapy ²⁵.

Mercuri et al. studied QbD approach for the formulation and manufacturing of solid lipid nanoparticles (SLN) for ocular applications. They also, stated that QbD could be the best approach used by pharmaceutical industries to improve the quality of the final product ²⁶. Shah et al. investigated QbD approach on the development and optimization of solid lipid nanoparticle (SLN) formulation of hydrophilic drug rivastigmine²⁷.

Nanostructured lipid carriers

Bhise et al. explained principles of QbD have to be used in development of many nanoparticles, such as, Nanostructured lipid carriers. The author reviewed the science behind development of NLCs using QbD approach as promising anticancer agents ²⁸.

Rathod et al. developed and optimized the Ibuprofen (IBU)-loaded nanostructured lipid carrier (IBU-NLCs) for sustained-release ocular drug delivery using a quality-by-design (QbD) approach. Quality-by-design (QbD) was successfully implemented in developing a robust ophthalmic formulation with superior physicochemical and morphometric properties ²⁹.

Nano emulsions

QbD approach used to optimize nanoemulsions using various mathematical models and statistical tests. Many researchers addressed the concepts and applications of QbD for the development of lipid-based nanosystems ³⁰. Negi et al. developed systematic optimisation and evaluation of nanoemulsions (NEs) of lidocaine and prilocaine, using the systematic approach of Quality by Design. The developed NE systems using Quality by Design found to be a promising carrier for topical delivery of lidocaine and prilocaine³¹.

Nano capsules

Marto et al studied the role of the different factors that affect the particle size distribution and zeta potential of NC prepared by the emulsification-solvent evaporation method was assessed using a quality by design approach³².

CONCLUSIONS

Development of nano delivery system has become an attractive strategy to overcome the problems associated with conventional therapy. Formulations of nano delivery includes various steps and multiple constituents which need to be addressed properly in order to develop stable and efficacious formulations. The application of quality by

design (QbD) approach can overcome the problems related to nanoformulation development and also provide broad acceptability for regulatory agencies Different optimization models have been used, regarding the parameters that influence the physical features of the resulting nano drug delivery systems such as, variations in types, composition and processing parameters. QbD also helps in exploration of variable factors with respect to excipients selection and process parameters which would augment the process capability with less variability.

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