

Explicating the Applications of Quality by Design Tools in Optimization of Microparticles and Nanotechnology Based Drug Delivery Systems

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Abstract: Quality by design (QbD) can also contribute to design, manufacturing, and producing highly finished goods. To better explain the manufacturing processes, the FDA focused QbD in the healthcare industry, based on a comprehensive understanding of how technology and design parameters affect the quality of the manufactured product. Various elements of QbD are critical quality attributes (CQA); critical material attributes (CMAs), and critical process parameters (CPPs). The tools generally applied in QbD are risk assessment, design of experiments, and process analytical technology. The various benefits of the QbD model are preventing sampling errors and variability in research studies, less experimentation, and enhanced productivity. Since the microparticles and nanotechnology-based formulations need complex experimentation and an extremely time-consuming process, the application of QbD tools in such investigations can intelligently conclude the research processes. This review article provides a brief outline of the fundamentals, elements, and tools of QbD. Furthermore, the recently published applications of QbD in the optimization of microparticles and nanotechnology-based drug delivery systems have been discussed in this review.

Keywords: quality by design; critical quality attributes; critical material attributes; critical process parameters; experimentation design; process analytical technology; microparticles; nanotechnology.

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1. Introduction

The primary purpose of drug manufacturing is to provide a higher quality-based product and ensure that acceptable quality is reliably produced. Technological expertise is required to access data collected from experimental studies and manufacturing to acknowledge design, specifications, and system control authenticity. Alterations in the manufacturing process and preparation and development are seen as opportunities to gain new knowledge or stimulate system design development [1-5]. Quality by design (QbD) is the science of developing and building formulations and product lines that meet predestined criteria [6-8]. Like other regulatory guidelines, for example, International Council for Harmonization (ICH) Q8, Q9, and Q10, and current guidance documents, current good manufacturing procedures (cGMP), food and drug administration (FDA), currently, the principles of QbD have gained popularity for several interventions in drug discovery in the twenty-first century [9-16]. Numerous

benefits of the QbD model are avoiding sampling errors and variability in investigations, escaping from prolonged experimentations, preventing complications with governing compliance, and enhancing production alternatives [17-19]. Figure 1 depicts the various processes required in the QbD model [20,21].

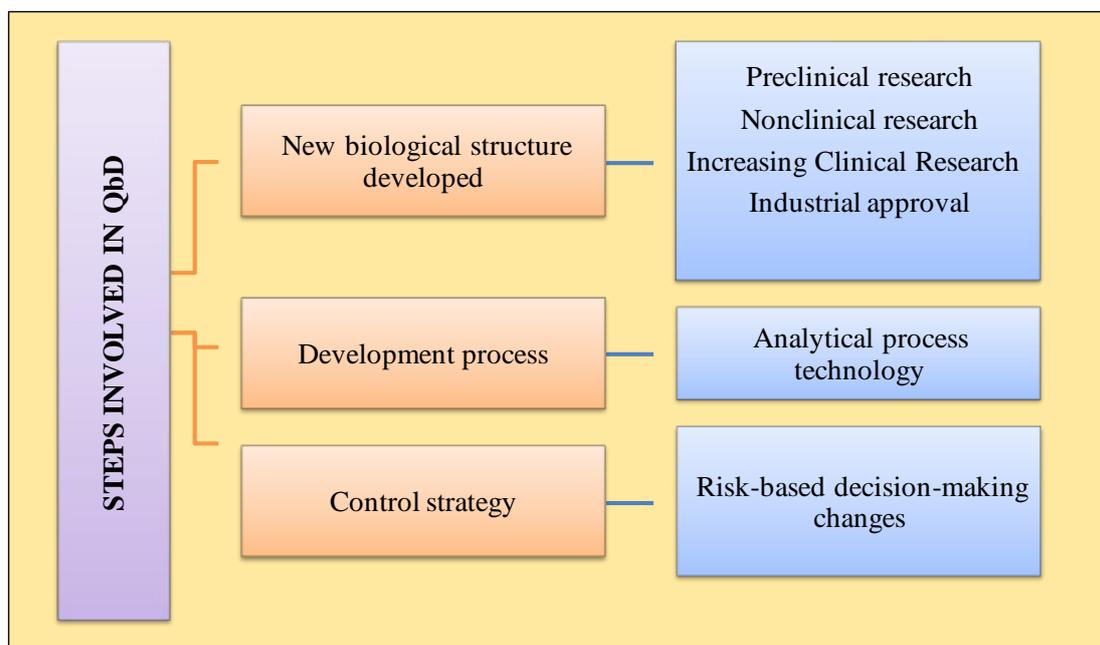


Figure 1. Pictorial representation of the progression of quality by design model.

The quality by test (QbT) approach maintains product quality through adopting a number of protocols, *i.e.*, raw material testing, the manufacturing cycle of defined pharmaceutical drugs, and finished product testing in anticipation to fulfill FDA requirements and certain additional conditions to bring the products into the industry for bulk manufacturing consequently. Due to the lack of knowledge of the procedure and uncertainty over it, the primary causes of failure have yet to be determined. Therefore, suppliers could subsequently regenerate the cycle before the underlying causes of inaccuracy are identified and treated, and furthermore, reevaluate that the inclusion process has been followed to surpass through unsuccessful conditions [21]. Table 1 shows a comparison of QbT and QbD [22].

Table 1. Comparison analysis between QbT and QbD.

Constraints	QbD	QbT	Interpretation
Product development process	The criteria concentrated on interpreting quality parameters	A norm depending on a batch's history	The QbT strategy is based on accuracy and also excludes or denied uncertainty. Flexible technique within the layout which enables long-term development in QbD system.
Validation	The model must be authenticated regularly	The focus is on reproducibility. Adaptable in the design field	In the QbT method, preliminary samples must be validated. The QbD technique emphasizes control policy.
Risk-based management	Power shifted dramatically; real-time issue	Changes in regulatory priority requirements Prior authorization	Value estimation is separated from research, and risk assessment has been carried out using the QbT method. In the QbD method, the decision was based on process identification and risk management.
Lifecycle based management	Constant adjustment within the process	Reacting to issues; space layout	Approval modifications are required in the QbT design, while change is made completely throughout the QbD model.

Constraints	QbD	QbT	Interpretation
Process control	Quality assurance is maintained on an ongoing basis	Go/No-Go, Tracking, Comprehensions, Evaluation	Surveillance and examination ensure performance in the QbT strategy. By definition, the QbD strategy is theoretically oriented.

2. Elements of QbD

In order to address GMP's limitations, the FDA introduced cGMP in the year 2002. According to cGMP, the focus on "software" throughout the production phase, especially at the managerial level, precisely defines the transparency of workers [23-26]. The ICH Q8 framework defines QbD as a systematic approach for development, which begins from predefined targets and emphasizes process and product evaluation with tracking, based on validated quality and process risk assessment [9]. The various research studies of drug development and industrial experience offer knowledge and experiences that help create quality standards and controls [27].

2.1. *Setting a goal.*

The quality goal profile (QTP) has been the center of QbD, which serves as the foundation for product design and development in respect to the initial target criteria stated within QbD definition. The quality target product profile (QTPP) establishes the quality of the finished product. In the case of analytic process development, this is frequently known as target product profile (TPP), as it includes an analytical target profile (ATP). TPP may play a significant part in all drug discovery procedures, including scheduling, choice, training, and execution of clinical research methods [28].

2.2. *Critical quality attributes (CQA) assessment.*

The CQAs are commonly related to the drug material, inert components, intermediate inputs (additives or excipients), and the dosage form itself. CQAs typically influence the characteristics of drug products, like particle sizes, drug release, solubility, zeta potential, entrapment efficiency, product yield, and drug loading [29]. The mechanical, physical, microbial, or biological characteristics or qualities of raw materials are described as critical material attributes (CMAs). CMAs are utilized during the context of a suitable range collection or production to assure that product content and excipients are consistent. This information serves as a foundation for applying the CQA to the product's effectiveness. The QbD paradigm is unique in that it uses rigorous risk assessment methods to identify CQAs. CQAs in large oral delivery forms typically affect drug release, quality, safety, and strength [9].

2.3. *Planning and implementing a control-based strategy.*

The goal of control-based planning is always to keep the product safe, and the system stays within the expected lowest and the highest limits. The factors and products are reviewed regularly during the production process, which ensures robustness. Typically, hit and trial frameworks are scaled up. Critical process parameters (CPPs) are parameters that influence CQAs and should therefore be monitored or controlled to ensure that the process produces the correct performance. Process robustness is defined as a system's ability to maintain rational effectiveness and efficiency while accepting input variance [30]. CQAs are concerned with

production parts, while CMAs are concerned with raw resources, like drug products and inert materials used in the manufacturing process. In general, QbD is used in practice to produce new pharmaceutical products at various levels, as shown in Figure 2 [9,31,32].

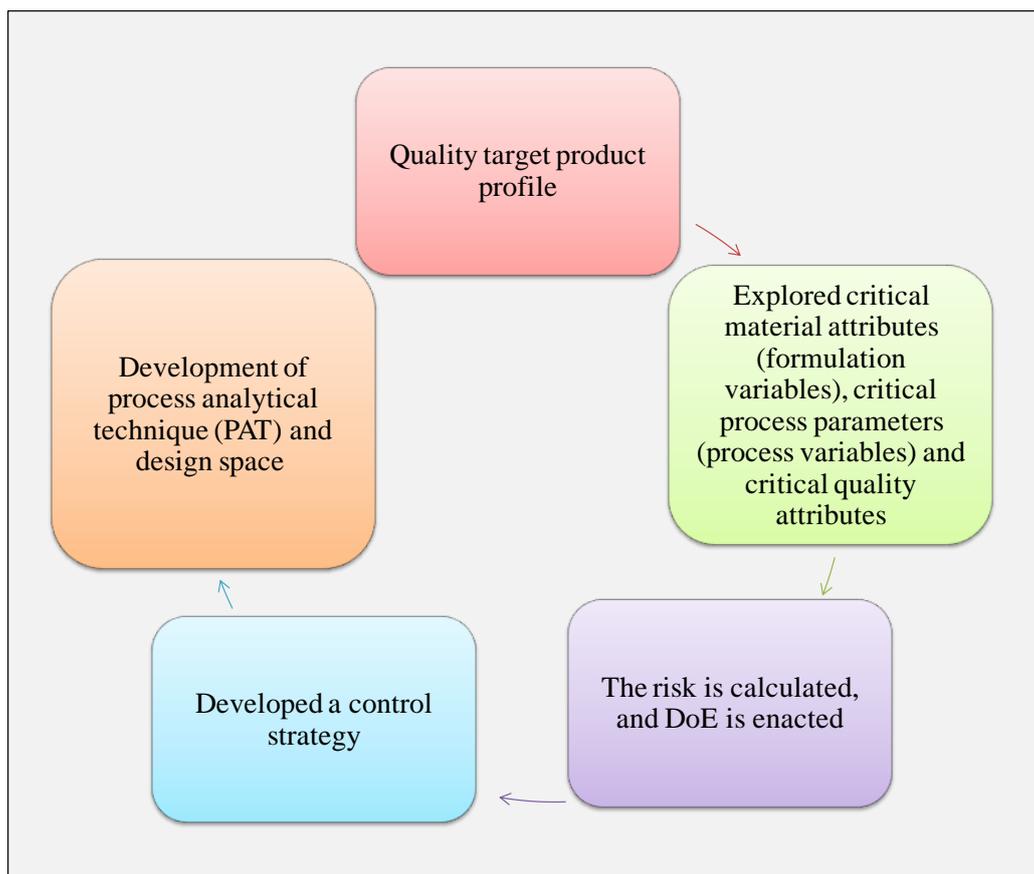


Figure 2. Steps indicating the approach of QbD.

2.4. Design layout.

As per ICH Q8 (R2), the design space has become a multidisciplinary framework and system of process parameters and manufacturing methods that have been shown to produce high-quality products. The developer recommends a design-based layout that is subjected to legal inspection and that is typically system and equipment-based; however, the design space chosen for the lab scale would not be applicable to commercially viable procedures. On a large level, design-space checking is therefore needed before it is established that the design space is self-contained [9]. The procedure for developing a design space for QbD elements includes providing input materials and processing of variables leading to the development of the product, followed by assessment and certification by regulatory bodies.

2.5. Elucidation of control strategy and continuous development.

Adjustments in the design space's layout, as in the QbD model, would not necessitate review or clearance. As a result, process improvements in terms of quality and performance can occur earlier in the product cycle, with fewer demands for post-approval. In relation to regulatory continuity, a better understanding of the manufacturing environment would aid in more efficient risk management in accordance with ICH Q9 criteria for the impact of perceived changes and production deviations on quality products [9].

3. Tools of QbD

For comprehending the aspects of QbD in the industrial paradigm, the implementation of successful QbD methods is essential, which include process analytical technology (PAT), risk evaluation, and design of experimentation (DoE) [9].

3.1. Risk assessment.

Risk evaluation is a method of organizing data to aid in risk decision-making in a risk mitigation environment. It entails detecting hazards as well as assessing and deciding exposure risks. This will be the first part of the quality-based risk management phase, followed by risk reduction and assessment stages. Risk management entails executing results to reduce or eliminate the risk and includes three components: risk identification, interpretation, and assessment. The risk management results should be reviewed in the final process to ensure that the basic tools and awareness are considered [33]. Historical facts, theoretical models, rational claims, and strategic choices are all used in the identification process to identify possible causes of hazards which led to the risk issue or challenge classification. Risk analysis needs to calculate risks based on the identified hazard; risk evaluation entails comparing the calculated risk to risk factors available through a qualitative or quantitative approach to determine the risk's significance.

ICH Q9 lists the following nine common risk management tools: (1) An evaluation of the basic risks (2) evaluation of the tree diagram (Ishikawa fishbone template, scatter diagrams, assess sheets); (3) facilitation strategies (4) initial risk analysis; (5) vulnerability scans with control laws; (6) an evaluation of malfunction and consequences; (7) review of failure, effects, and dissipation; (8) assessment of serviceability hazards; (9) statistical methods to assist. As part of the QbD implementation, risk assessment is prioritized through DoE. The techniques like Ishikawa fishbone and analysis of consequences/losses are widely used risk control approaches, either utilized separately or in combination [34-36].

3.2. Design of experimentation (DoE).

Initially, a risk-based assessment will be performed in addition to developing a research methodology. Testing design is an analytical, structured process to determine the relationship between process-related variables and DoE. DOE is a computational method being used to design and implement research and interpret the information generated from the experimental work. It is a type of computational modeling used to perform statistical analysis of a model, method, and material that controlled input parameters to analyze its influence on the calculated response variable. This is a wonderful tool that allows researchers to inspect variables according to a predetermined design. DoE is a practical technique for establishing relationships among process inputs and outputs in order to acquire a deeper knowledge of products and processes. It could assist in determining the ideal setting, CPPs, CMAs, and design space. This is recommended to build a design space by DoE for nonparametric exploration [31]. DoE was shown to be effective in developing different pharmacological therapies and operational conditions, and it can be used more extensively in the future years to ensure strong research performance with improved results. Various advantages of DOE are represented in Figure 3, and the classification of DOE techniques is illustrated in Figure 4.

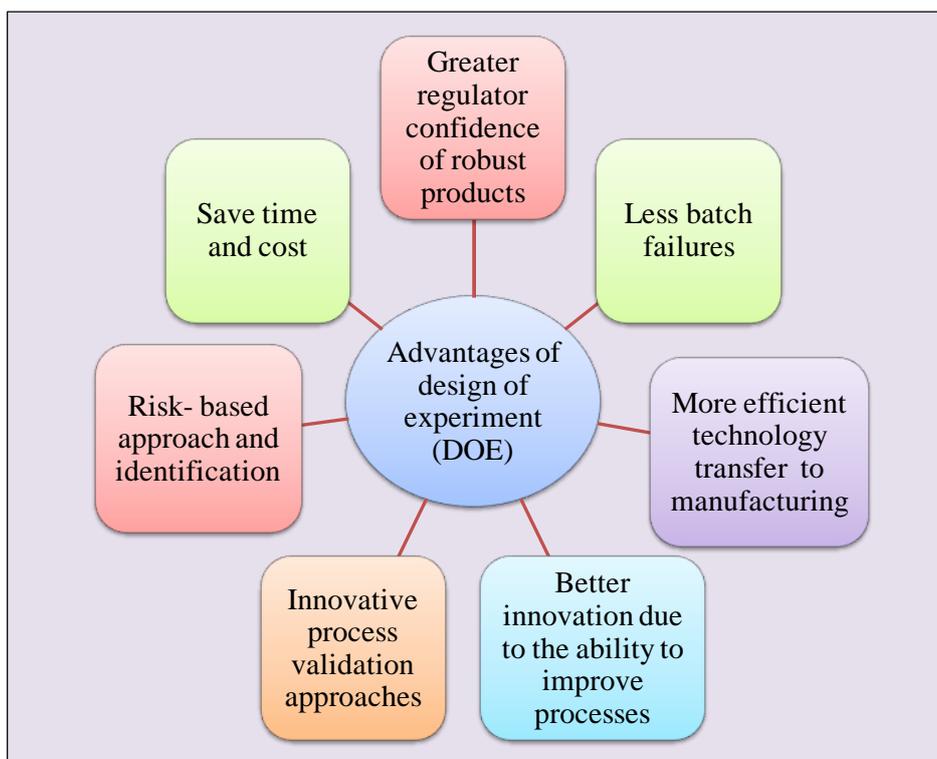


Figure 3. Advantages of design of experimentation techniques in pharmaceutical product optimization.

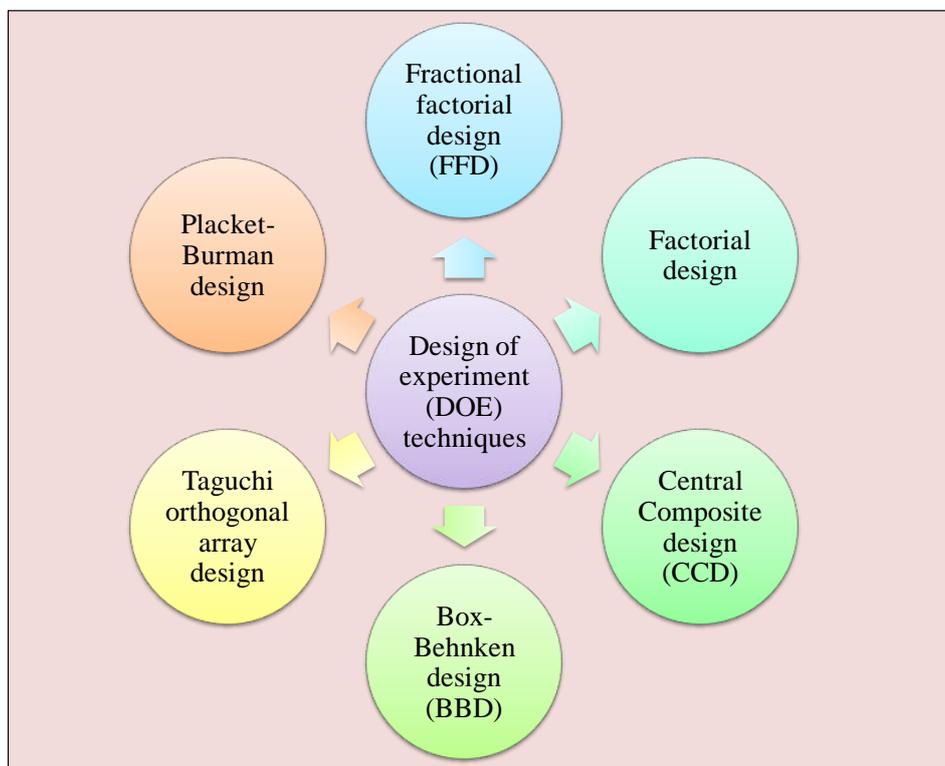


Figure 4. Classification of design of experiments techniques.

3.3. Process analytical technology (PAT).

PAT is described as a technique that uses actual variables throughout production to provide information to support optimized computing in order to produce a final product continuously in line with established quality and performance criteria [23]. ICHQ8 acknowledges the use of PAT to ensure cycle consistency in a design space that has already

been developed [31]. A system is considered developed from a PAT perspective when all important causes of variability are defined and described; the system handles variance; product equity's performance can be calculated effectively and accurately [34,37].

There is a three-step method of optimization of pharmaceutical preparations and production processes, which includes monitoring, study, and design, which is often used to compile literary works. In the monitoring stage, a performance measurement program allows real-time monitoring of all CPPs and CQAs by directly or indirectly systematic techniques and suitable analysis processes to investigate the identified quality attribute, required product attributes, and processing methods. During the design stage, experiments are carried out to determine which key variables are connected to a material's role, and the process conditions and input material properties may have a major effect on finished product quality [38,39]. This data is being used to identify the CQA, CPP, and QTPP requirements for establishing a PAT-based process control system [40].

As per FDA's PAT policy statement, process analysis could be characterized into three types: at-line, in-line, and online [13]. During at-line estimation, the sample is taken, extracted, and analyzed near the processing stream. Through online prediction, the specimens were removed from the apparatus and could be reintroduced into the flowing fluid. In the course of in-line estimation, the sample remains inside the processing stream and could be disruptive or intrusive. It is evident that PAT aids in the successful enforcement of QbD. It could perform real-time system monitoring without disruptions by bringing technological and systemic variables across online. PAT raises technology awareness which results in better quality control and register simplicity.

4. Applications of QbD in Optimization of Microparticles and Nanotechnology-Based Drug Delivery Systems

Nanomedicine has grown in popularity in recent decades, and research into the advancement of nanomaterials has been at the forefront of drug development. So many studies presented here indicated that microparticles, dendrimers, microemulsions, nanoemulsions, and micelles are successful drug delivery potential substitute's pharmaceutical formulations. The key benefits of these nanomaterials include increased bioavailability and sustained drug delivery, resulting in improved clinical outcomes and fewer adverse effects [41,42]. Controlling the efficiency and protection of micro- and nanomaterials is also critical. Furthermore, the large-scale transition of production processes is a barrier to industrial micro- and nanosystem development and clinical use. As a result, applying the QbD framework to develop nanomaterials is a strategic feature in deciding important production conditions and controlling variables that interact with the safety and quality of the finished products [43-45].

Many researchers have used this approach to evaluate CPPs, CQAs, design processes, CMAs, and quantitative strategies [46,47]. The present review discusses the most important studies that have reported the implementation of the QbD method to optimize nano- and microparticles-based systems, which commence the consistency and effectiveness of pharmaceutical products and allow for effective formulation optimization [48-51]. Raw material properties, product development, and manufacturing methods are examples of factors that require monitoring [52-54]. The specific QbD phases in the creation of micro- and nano-based systems are depicted in Figure 5. The QbD method relies on the prior recognition of critical research parameters.

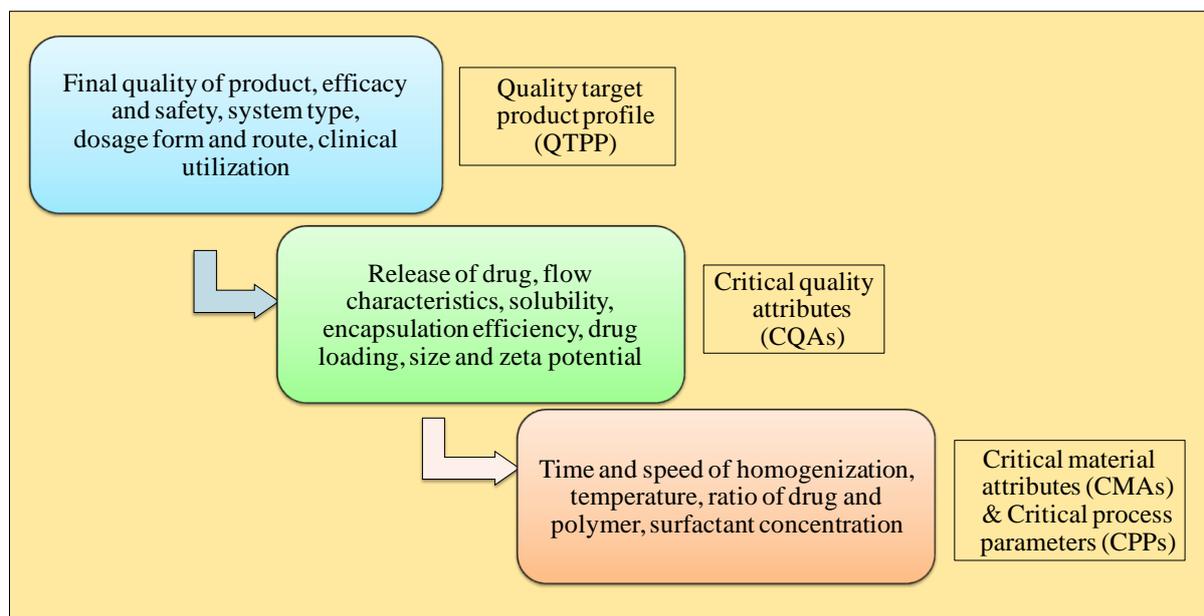


Figure 5. QBD approach steps in the micro and nanosystem implementation.

In the production of microparticles and nanotechnology-based drug delivery systems nanoparticle compositions, QbD has been used to promote effective drug release profile and targeting along with augmentation of pharmacodynamics, pharmacokinetics, and toxicity characteristics. DoE improves the consistency of the finished product by lowering the number of necessary experiments, which have been tested using various statistical formulas. There are several DoE design models that could help optimize the formulations of micro-and nanotechnology systems. Such examples of several researchers that utilized the approach of QbD in the optimization of micro-and nanoformulation are listed in Table 2.

Table 2. QbD for optimization of microparticles and nanotechnology-based drug delivery systems.

Formulation	QbD approach	Dependent variables	Independent variables	Ref.
Dexamethasone-polymeric nanoparticle	Multiple-level full factorial design	Zeta potential, particle size, %EE, PDI	Drug Concentration, Polymer concentration, Surfactant concentration	[55]
Curcumin loaded Polymeric Microparticulate	CCD	Particle size, drug loading, PDI, %EE, yield, drug release in 2, 4, 6, 12, and 24 h	Concentration of drug, Concentration of polymer, and Concentration of the polymer mixture (Eudragit FS and polycaprolactone)	[56]
Satranidazole based nanoparticle	2 ³ full factorial design	Particle size, %EE, zeta potential, dissolution efficiency	PVA concentration, Aqueous phase volume, Polymer concentration	[57]
Exemestane loaded vitamin E TPGS-nanoparticle	2 ³ factorial design	Particle size, %EE	Polymer concentration, Stirring speed, TPGS volume	[58]
Cyclosporine A-encapsulated nanoparticle	Plackett-Burman design	Zeta potential, particle size, dissolution efficiency, %EE, burst effect	Concentration of drug, Concentration of polymer, Concentration of emulsifier, Stirring speed, Solvent ratio, Organic to the aqueous phase	[59]
Docetaxel-encapsulated polyhydroxybutyrate-co-hydroxyvalerate nanoparticle	Plackett-Burman design for screening and BBD main design	Particle size, %EE, zeta potential	Homogenizer time, Polymer concentration, Homogenizer speed, Surfactant concentration, Ultra-sonication time	[60]

Formulation	QbD approach	Dependent variables	Independent variables	Ref.
Paclitaxel loaded nanoparticle	Plackett-Burman design, BBD	Zeta potential, %EE, particle size	Drug concentration, PLGA concentration, PLGA molecular weight, PLGA terminal group type, Surfactant type, Surfactant concentration, Homogenization rate, Homogenization time	[61]
Cetuximab loaded nanoparticle	3 ³ full factorial design	Particle size, %EE, zeta potential	Polymer concentration, Cross-linker concentration, Temperature	[62]
Quercetin-loaded nanoparticle	Fractional factorial design	Particle size, zeta potential, %EE, PDI	Polymer concentration, Stabilizer concentration, Stirring speed, Volumes of acetone: aqueous phase	[63]
Loratadine dry nanoparticles and nanosuspension	CCD	Particle size, polydispersity index, solubility, dissolution	Drug amount, Solvent to anti-solvent ratio, Stabilizer type, Stabilizer concentration, Sonication time, Sonication power	[64]
Sorafenib encapsulated nanoparticle	BBD	Size, Dissolution at 5min, 60 min, 180 min and max concentration of the drug, area under curve drug concentration	Concentration of HPMC, PVP concentration, Poloxamer concentration	[65]
Vildagliptin encapsulated Eudragit® microspheres	Plackett-Burman design	%EE and Dissolution rate	Eudragit RS-100 concentration, Span-80 amount, Volume of methanol, Volume of acetone, Stirring speed	[66]
Albendazole loaded chitosan microparticles	Plackett-Burman design	pH, yield, morphology, dissolution rate size, %EE	Stirring time, Stirring rate, Temperature, pH of an ionic solution, pH of chitosan solution, Chitosan concentration	[67]
Cefadroxil encapsulated Chitosan nanoparticle	2 ² full factorial design	PDI, zeta potential, %EE, Size,	Polymer weight, Polymer concentration	[68]
Pioglitazone Hydrochloride loaded polymeric nanoparticle	3 ² factorial design	Size, PDI, %EE, zeta potential	Stirring rate, Stirring time, Polymer concentration, Surfactant concentration, Amount of drug	[69]
Prednisolone loaded polymeric nanoparticle	2 ³ factorial design	Size, drug loading, Zeta potential	Drug to polymer ratio, Sonication time, PLGA concentration	[70]
Quercetin loaded polymeric nanoparticle	3 ² full factorial design	Size, drug release, encapsulation efficiency	Polymer concentration, Pluronic F-127 amount	[71]
Enoxaparin sodium encapsulated polymeric microspheres	CCD	%EE, Particle size	Eudragit FS-30D: Eudragit RS-PO, Polymer concentration, Sodium chloride concentration	[72]
Quetiapine fumarate loaded mucoadhesive microspheres	2 ⁵⁻² fractional factorial design	Particle size, drug release, percentage mucoadhesion behaviour	Ethyl cellulose concentration, Chitosan concentration, Stirring speed, Type of HPMC, HPMC concentration	[73]
Catechin hydrate polymeric nanoparticle	CCD	Zeta potential PDI, size	PLGA composition, PVA composition,	[74]

Formulation	QbD approach	Dependent variables	Independent variables	Ref.
			Temperature, Sonication time	
Piroxicam polymeric nanoparticle	CCD	Particle size, polydispersity index	The concentration of starch and drug	[75]
Zoledronic acid polymeric nanoparticle	CCD	Size PDI, %EE zeta potential	Zoledronic acid content, PLGA/Pluronic F68 ratio, Organic to aqueous phase ratio	[76]
Eflornithine hydrochloride solid lipid nanoparticle	CCD	Entrapment efficiency, drug loading, mean diameter, process yield	Drug: lipid, Surfactant concentration, Stirring time	[77]
Pentazocine microspheres	Three factors, three levels Box Behnken design	Size, dissolution rate, %EE	Polymer concentration, Stirring speed, Surfactant concentration	[78]
Metformin hydrochloride microparticles	BBD	Encapsulation efficiency, particle size, zeta potential	pH of the aqueous phase, Metformin in the inner aqueous phase, Amount of polyvinyl alcohol, Aqueous phase, Stirring rate	[79]
Theophylline microspheres	2 factor, 2 Level CCD	Size, %EE, Quantity of drug released	Starch: alginate Polymer: drug	[80]
Benzylisothiocyanate nanoparticles	CCD	Particle size, entrapment efficiency, drug release	Amount of polymer Concentration of surfactant	[81]
Epichlorohydrin microspheres	Two-level full factorial design	Cross-linking degree and drug release rate	Concentration of epichlorohydrin Duration of cross-linking	[82]
Nitazoxanide microbeads	CCD	Size, % yield, and %EE.	Percentage of chitosan, Percentage of sodium tripolyphosphate	[83]
Acyclovir emulgel	CCD	% Yield, size, %EE, % drug loading efficiency, drug release at 0.25 & 6 h	Homogenization speed, Drug/polymer ratio, PVA concentration	[84]
Ansamycin nanoparticles	CCD	%EE, Zeta potential, Size	The concentration of polymer, Concentration of surfactant The ratio of organic to aqueous phase	[85]
Clonazepam nanoparticle	3 ² full factorial design	%EE, size, % drug release	PLGA amount, Poloxamer 188 concentration	[86]
Clarithromycin nanoparticles	3 ² full factorial design	% Drug loading, size, %EE	Time of sonication Lipid amount	[87]
Vitamin B12 orodispersible films	BBD	Disintegration time, Tensile strength, Permeation, Dissolution rate	Amount of: Glycerine, Menthol, Polymer amount	[88]
Ketoconazole cubosomes	3 ² factorial design	Size, %EE, drug loading, PDI	Stabilizer, Surfactant amount	[89]
Efavirenz nanoparticles	Central composite rotatable design	Size, PDI, %EE	Solid lipid concentration, Concentration of stabilizer	[90]
Resveratrol polymeric micelles	CCD	Size, skin deposition and incorporation efficiency	Amount of Pluronic P123 %, Amount of Resveratrol amount	[91]
Clindamycin hydrochloride microsponges loaded topical gel	CCD	Particle size (D50 μ m), Span, Micro-sponge drug content	Water (ml), Amount of span, Acetone volume, Amount of ethylcellulose, Amount of drug and dichloromethane	[92]
Tazarotene nanoparticles	BBD	Size, %EE, drug release, and zeta potential	Amount of surfactant, Amount of lipid	[93]

Formulation	QbD approach	Dependent variables	Independent variables	Ref.
Resveratrol nanoparticles	CCD	Size, %EE, drug release, Zeta potential	Amount of Lecithin and Chitosan	[94]
Ibuprofen nanostructured lipid carriers	Plackett-Burman design followed by BBD	PDI, size, %EE, drug loading	The concentration of surfactant, Homogenization time, Concentration of lipid, Homogenization speed, Ultra-sonication time, The ratio of surfactant, Ultra-sonication frequency	[95]
L-arginine nanoparticles	2 ³ full factorial design	Size, %EE, and drug loading	Oleic acid concentration, Poloxamer 188 concentration, Sonication rate	[96]
Silver Sulphadiazine loaded egg oil organogel	Taguchi orthogonal array design	Release, size, viscosity, phase transition temperature	Organic phase ratio, Temperature, Phospholipids, Egg oil, Surfactant concentration, Surfactant type, Mixing time	[97]
Luliconazole lipid crystalline nanoparticles for topical delivery	Risk Estimation Matrix; CCD	Size, %EE, PDI, Zeta potential	Lipid content (glyceryl monooleate), Concentration of Poloxamer 407, Amount of co-surfactant (PEG 200)	[98]
Desoximetasone niosomes	CCD	Particle size, %EE	Amount of drug surfactant and cholesterol concentration, and lipids	[99]
Risedronate Sodium-Microspheres	Plackett-Burman design	Size, %EE, Zeta potential	Risedronate-chitosan ratio, Surfactant concentration, Homogenization time, Temperature, Homogenization speed	[100]
Curcumin loaded nanoemulsion	3 ² factorial design	Size, zeta potential, PDI	Surfactant mix concentration, Oil phase	[101]
Rivastigmine loaded nanostructured lipid carriers	Optimization of: Formulation variables by CCD, Instrumental parameters by BBD	Mean particle size, D50 nm, D90 nm, PDI, zeta potential, %EE	For CCD: Precirol® ATO 5: Vitamin E ratio, Tween® 80: Phospholipon® 90G concentration For BBD: Emulsification speed, high-pressure homogenization cycle, sonication amplitude	[102]
Erlotinib hydrochloride spray-dried microparticles	BBD	%EE, mean particle size, drug release in 168 hours	The concentration of polycaprolactone, Concentration of polyvinyl alcohol, Inlet temperature of spray dryer	[103]
Metronidazole nanoparticle	Fractional factorial design	Size, %EE	Concentration of chitosan, Acetic acid concentration, Concentration of tripolyphosphate	[104]

BBD: Box-Behnken design; CCD: Central Composite design; D50 nm: volume distribution (50% of particles with size equal or lower to the given value of D50); D90 nm: volume distribution (90% of particles with size equal or lower to the given value of D90); %EE: percentage entrapment efficiency; PDI: polydispersity index; TPGS: D- α -tocopheryl polyethylene glycol 1000 succinate.

5. Future Prospects

Nowadays, several firms are starting to engage with QbD principle and designing frameworks to help it, as shown by incorporating one or even more QbD components into the production, indicating a positive move into QbD as the future development model [105]. The primary reason for QbD acceptance is regulatory criteria. The medicinal company needs regulatory enforcement in order to obtain the goods approved for distribution. Even so, the QbD solution produces a high-quality service by using cost-effective techniques. By offering a design space model, QbD eliminates the commonly utilized frizzed method to system

development. Since it is not used among drug companies, it has a bright future when regulatory authorities require it. Due to the numerous benefits and flexibility of complying with regulatory bodies, companies can voluntarily follow this principle [106,107]. QbD enables the production of reproducible goods with the necessary quality characteristics. It is a method of developing biological that is systemic in order to avoid lot errors and reduce uncertainty in product consistency. Creating new drug formulations is a difficult task that costs a lot of money. Utilizing QbD guarantees production performance from the start, reducing costs in producing the ideal composition. As a result, it has a lot of potential in producing high-quality pharmaceutical drug products [108]. Multivariate Data Analysis (MVDA) tools like Partial Least Squares (PLS), and Principal Component Analysis (PCA) were viewed as important optimization methods for use in addition to DoE, assisting in reducing the number of variables being used in the DoE or exploring the research observations more thoroughly. It is often used to analyse data obtained through PAT tools in order to enhance production lines continuously. The combination of MVDA and PAT to monitor and adjust the system in response to materials or process fluctuations is the ideal future norm within the pharmaceutical sector [109,110].

6. Conclusions

The numerous advantages of QbD are deterrence of sampling errors and variability in research studies, the requirement of less experimentation, and improved productivity. The QbD is a cost-effective time-saving strategy that uses PAT, risk assessment, and DoE as tools to understand raw materials and process parameters better, making QbD a straightforward model for the development of pharmaceutical products for the healthcare sector. Quality by design (QbD) has the potential to contribute to design, manufacturing, and the ability to produce highly finished goods. The microparticles and nanotechnology-based formulations need complex experimentation and an extremely time-consuming process. Therefore, applying QbD tools to develop microparticles and nanotechnology-based formulations can conclude the research processes in proficient mode. QbD will progressively be recognized as an integral model for the effective development of nano-and micro-formulation and application of DoE in improving design process and risk management strategy. This review article highlighted the significance of QbD methodology in developing microparticles and nanotechnology-based formulations for achieving consistent efficacy and protection in pharmaceuticals.

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Conflict of Interest

The authors declare no conflict of interest.

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