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DESIGN, DEVELOP AND OPTIMIZE NANOPARTICLES USING QUALITY BY DESIGN STRATEGY

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Abstract

Quality by design (QbD) may aid in all three stages of product development, from conceptualization through fabrication to final assembly. The Food and Drug Administration has given QbD in the healthcare industry high priority in order to better explain manufacturing processes, based on a complete understanding of how technology and design variables effect quality in production. Quality by design (CPD) encompasses CQA, CMA, and CPP, or critical quality, critical material, and critical process aspects, respectively. Among the many tools utilized in Quality by Design (QbD) are risk analysis, experimental design, and process analytical technologies. The QbD approach has several advantages, including less experimentation, increased productivity, and the elimination of sample mistakes and unpredictability in scientific investigations. Use of QbD techniques in such inquiries may intelligently finish the research procedures, since evaluating microparticles and nanotechnology-based formulations requires specialized equipment and a lengthy process.

Key words: microparticles, nanotechnology, Quality, healthcare, manufacturing, Risk

INTRODUCTION

In the pharmaceutical sector today, Quality by Design is a crucial component. As a product is being designed, developed, or manufactured, it is utilized to maintain a certain quality standard. Risks in product development may be identified and a more scientific approach to optimization can be attained with its help. Products are designed to last as long as feasible, and their specifications are set according to how well they must perform.

Manufacturers using the Quality by Design methodology for developing pharmaceuticals focus on establishing a relationship between critical material attributes (CMAs), critical process parameters (CPPs), and critical quality attributes (CQAs) to ensure the reliability of drug product quality. By altering the drug's dissolving profile, bioavailability may be increased, and SLNs can be used for targeted drug administration, making them promising drug-delivery systems for controlled drug delivery. The primary goal of this research was to develop a more efficient method for producing solid lipid nanoparticles and to determine the effect various production variables had on key quality indicators (QbD). To consistently and reliably generate a medicine of acceptable quality is the fundamental goal of the drug manufacturing process. In order to verify design, requirements, and system control, it is necessary to have access to data acquired through experimental research and production. Alterations to the production procedure and its precursors are seen as potential educational opportunities and sources of innovation for the underlying system design. Developing and constructing formulas and product lines that match predefined requirements is the scientific discipline known as "quality by design" (QbD). QbD's many advantages include reduced risk of experimental variability and sample mistake, shorter experimentation times, simpler regulatory compliance, and more flexible manufacturing options. The steps involved in the QbD model are shown in Figure 1.

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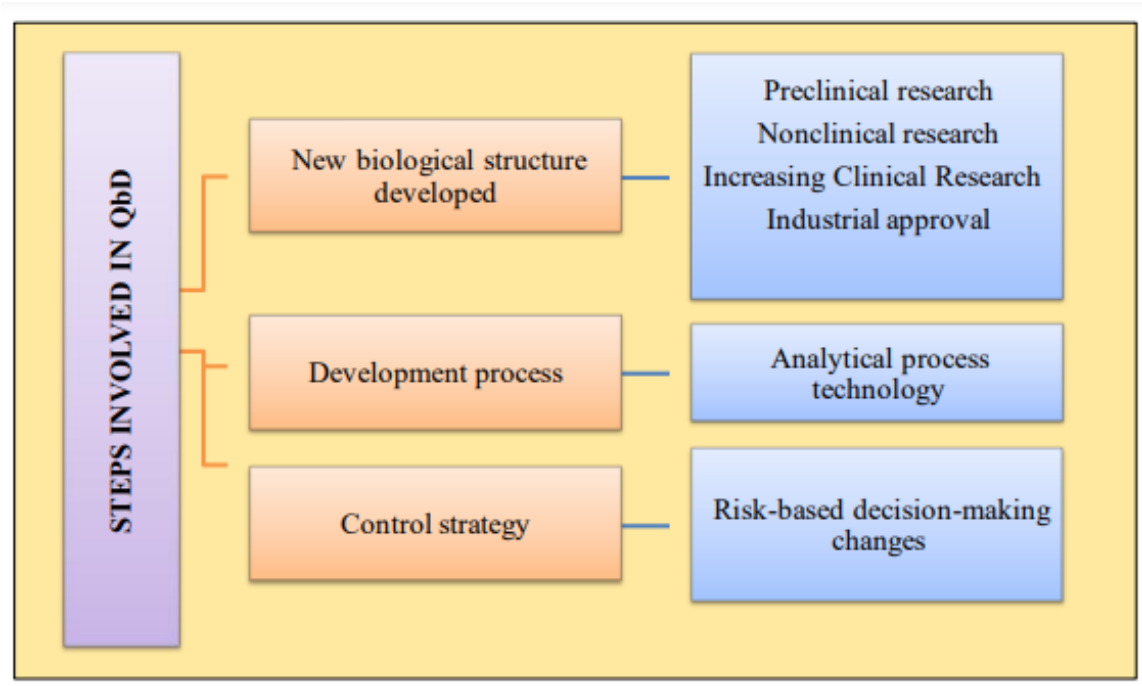

Figure 1: Pictorial representation of the progression of quality by design model

Raw material testing, the production cycle of specified pharmaceutical pharmaceuticals, and final product testing are all part of the QbT strategy to maintaining product quality in preparation for meeting FDA standards and other criteria to introduce the goods into the industry for bulk manufacture. The main reasons for the procedure's failure are still unknown because of the lack of information about it and the uncertainties surrounding it. To ensure the inclusion procedure has been followed to overcome failed circumstances, providers might assess the situation and restart the cycle before the root causes of inaccuracy have been found and corrected.

LITERATURE REVIEW

Patra, J.K., Das, G., Fraceto, L.F. et al. (2018), Nano delivery systems are a relatively new but quickly developing topic of study in which materials on the nanoscale are employed as diagnostic tools or to provide medicinal chemicals to precisely specified regions. The targeted and precise distribution of drugs is one of nanotechnology's numerous benefits in the treatment of chronic human diseases. In recent years, nanomedicine has been put to excellent use in the delivery of chemotherapeutic, biological, and immunotherapeutic drugs, among other treatments, for a wide range of disorders. Nanomedicines are explored, along with the advantages and disadvantages of using them to transport drugs from synthetic and natural sources for therapeutic use. We have also provided data on future developments and trends in the field of nanomedicine.

Ruba Ismail; et al. (2019), The goal of this study was to develop and stabilize orally bioavailable PLGA NPs loaded with Liraglutide. To find the best way to make PLGA NPs using the double emulsion solvent evaporation method, we employed a Plackett-Burman screening design with 7 parameters and 2 stages of optimization. Encapsulation efficiency was 51.81%, and the resultant NPs were spherical in shape with a particle size of 188.95 nm. Encapsulation of liraglutide into the NPs was effective, and the drug retained both its amorphous form and its structural integrity.

Bing Cao, et al. (2018), The majority of materials science advancements have been achieved by trial-and-error experimentation, usually by changing one variable at a time. Materials-based systems, on the

other hand, have complex and interconnected properties. Because of the interconnected nature of the many components and processing conditions of a device like an organic photovoltaic, for example, a little shift in any one of them may have far-reaching consequences. Planning tests according to the principles of Design of Experiments (DoE) allows one to test and optimize numerous variables concurrently, discovery and optimization may be accelerated, saving time and money in the lab in the process. Consideration of one's data in this way, in conjunction with machine learning, offers a new vantage point from which to optimize and discover, like climbing out of the valley of serial testing and finding yourself on top of a mountain with a panoramic vista in every way.

D. Panigrahi; P.K. Sahu; S. Swain. QbD allows pharma researchers to reduce the time and effort spent on experiments, as reported by et al. (2019). The double emulsion method for creating PLGA nanoparticles, which might be utilized to encapsulate hydrophilic pharmaceuticals, has received a lot of interest. When two distinct emulsification processes must be performed in order to create a double emulsion, the procedure naturally increases in complexity. Because to the wide variety of formulations and process parameters, it is yet unclear how long-lasting nanoparticles created by the double emulsion approach will be. At present, the Quality by Design method may be used in conjunction with PLGA-based nanoparticles generated using a double emulsion methodology as an alternate pharmaceutical production procedure. Particle size distribution, encapsulation efficiency, etc. are all crucial qualities of a therapeutic product, and this review has explored the QbD aspects that provide light on how material properties, formulation, and process factors affect these qualities. In this analysis, we have covered in depth the composition of a double emulsion, as well as the properties of the medications, polymers, and stabilizers utilized.

(I.) Gessner. (2016), The demand for more secure and effective treatments, as well as more sensitive and speedy diagnostics, has accelerated the development of nanomedicine in recent years. Nanoparticles have unquestionable advantages in diagnostic and therapeutic applications, but there have been barriers to their use in clinical practice. These include issues with toxicity, half-life, blood-circulating time, clearance, stability, and reproducibility in the lab and in vivo. The future of nanomedicine is uncertain, but researchers may shape it by creating novel multifunctional compounds and tailoring the material design to specific needs. Finding the optimal degree of functionality without increasing the system's complexity is the ultimate aim. This article's goal is to bring attention to the promise and difficulties of nanoparticle-based medicinal treatments, and to show how careful and purposeful material design may assist to address many of the obstacles holding nanoparticles back from their full potential in the clinic.

METHODOLOGY

Materials used:

MSN Laboratories of Hyderabad, India, generously donated linagliptin. We got our hands on some stearic acid from Loba chemie in Mumbai and some Pluronic F-68 from Sigma-Aldrich. All other compounds used were of analytical reagent quality.

Method:

Quality by Design (QbD):

Quality by design is a strategy for minimizing product defects and maximizing product quality throughout the product's life cycle by identifying and analyzing the factors that have the greatest impact on product quality.

After the QTPP has been determined, the characteristics that have the most significant impact on the

QTPP, the CQAs of the formulation, may be identified. Risk assessment is the cornerstone of the quality by design methodology (QbD), and it is a method that is grounded in science (Quality risk management). Following a preliminary risk assessment, the elements that will have the greatest influence on the CQAs of the formulation are identified and the design space is established.

Quality target product profile:

It is the first stage in developing a new formulation, and it is what establishes the scope of the project. Each formulation must adhere to this Quality characteristic if the desired product profile is to be realized. Since they are crucial to the formulation process, assay, impurities, drug loading and drug release, and stability testing were all included in the Quality target product profile.

Quality target product profile was the first stage in implementing quality by design, and it contains details such medicine delivery method, dosage form, dose strength, route of administration, and so on.

Identification of Critical Quality Attributes:

Step two of quality by design is settling on what features of Solid Lipid Nanoparticles are most crucial. These features are what prove the formulation works. All of them stemmed from a high-caliber profile for the ideal product.

Initial risk assessment:

Risk assessment was described as taking into account the likelihood, frequency, and impact of potential dangers. This must be done before the formulation phase can begin so that it is clear what research are needed and what factors are essential and which are not. Using a fishbone or Ishikawa diagram to assess potential dangers. In order to generate optimal solid lipid nanoparticles, an Ishikawa diagram was built to highlight the impact of important material qualities and critical process factors.

Experimental Design and statistical analysis:

With design expert® Software, we optimized both important material qualities and critical process parameters (StatEase, Inc., USA). Two independent variables were linked at three levels (-1, 0, +1) such as low, medium, and high using a 3 level factorial design using a response surface approach. X1: Lipid Content Particle size, entrapment efficiency, and in-vitro drug release were chosen as responses, with X2: surfactant concentration as the independent variable. Response surface methodology allows for the prediction of the interaction between each component and its effect on dependent variables (responses).

Preparation of Linagliptin Solid Lipid Nanoparticles:

Solid lipid nanoparticles were produced using a thermal homogenization method. The drug (5mg) was dispensed in a lipid melt made by melting a measured amount of stearic acid and ethanol together in a water bath. Before being injected into the aqueous phase which contains a specific amount of surfactant the organic phase was homogenized at 3000rpm for 1 hour. Coarse emulsion was obtained after three cycles of continuous homogenization. The ultimate suspension was achieved after further emulsion sonication using a probe sonicator for 10 minutes. The final suspension was centrifuged for 30 minutes at 10,000 rpm. A freeze dryer was used to freeze dry the suspension after it was filtered.

Quality Target Product Profile:

It is the first stage in developing a new formulation, and it is what establishes the scope of the project. Each formulation must adhere to this Quality characteristic if the desired product profile is to be

realized. Considering the safety and effectiveness of Solid lipid nanoparticles, A quality target product profile defines the characteristics of a drug that must be met throughout its manufacture.

Table 1: QTPP for Linagliptin loaded Solid Lipid Nanoparticles

Attributes	Target	Justification	
A. Physical Attributes			
Type of drug delivery	Lipid based system	It helps in getting better absorption of drug and it leads to increase the bioavailability of a drug	
Dosage form	Solid Lipid nanoparticles	Lipid based vascular system. It helps in increasing the bioavailability of a drug	
Dosage strength	50 mg	Requires same strength as that of reference product	
Route of Administration	Oral route	Highly recommended route for SLN administration and commercially available formulations also intended for oral route only	
B. Chemical Attributes			
	Test	**Result**	**Specification**
I.	Identification by		
	• Infrared Absorption	The IR absorption spectrum matches with standard spectrum	The infrared absorption spectrum of the sample shall be concordant with that of Linagliptin standard spectrum
	• HPLC	Sample RT matches with standard RT	The major peak retention time of the sample shall match with major peak retention time of the Linagliptin standard, as obtained in the chiral purity by HPLC
II.	Assay by HPLC	99.5 % w/w	Needed for clinical effectiveness
III.	Diffusion Profile	Media:6.8 buffer, 45 ml	Needed for clinical effectiveness
IV.	Residual solvents	0.06 % w/w	Not more than 0.10%
V.	Water content by KFR	0.49 % w/w	Not more than 1%
C. Packaging and Storage related			
Packaging	Capsules	The SLN's can be easily delivered by filling in capsules with improved patient compliance and manufacturing ease	
Stability	At least 6 months at room temperature	To retain therapeutic potential of the drug during storage	

Quality-by-Design Methods and Their Use in Improving Drug Delivery Vehicles Based on Nanotechnology and Microparticles

Nanoparticle research has been on the cutting edge of drug development, and nanomedicine has been more popular over the last several decades. Pharmaceutical formulations such as microparticles, dendrimers, microemulsions, nanoemulsions, and micelles have been shown to be effective drug delivery alternatives in several investigations. Increased bioavailability and prolonged drug administration are two of the main advantages of these nanomaterials, leading to better therapeutic results with fewer side effects. Maintaining command over the effectiveness and safety of micro- and nanoparticles is also essential. Extensive changes in manufacturing processes are impeding industrial micro and nanosystem development and clinical use. Hence, using the QbD framework to create safe and high-quality nanomaterials is a key factor in determining crucial manufacturing conditions and managing variables.

This technique has been used for assessing CPPs, CQAs, design processes, CMAs, and quantitative approaches. Nanoparticle and microparticle-based systems, the foundation for repeatability and potency in pharmaceuticals, have been the focus of studies describing the QbD approach's usage to enhance these systems, are discussed in this review. Factors including raw material qualities, product development, and production procedures should all be tracked. Figure 2 shows the sequential QbD

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steps required to build micro and nanoscale devices. Identifying key research parameters is fundamental to the QbD approach.

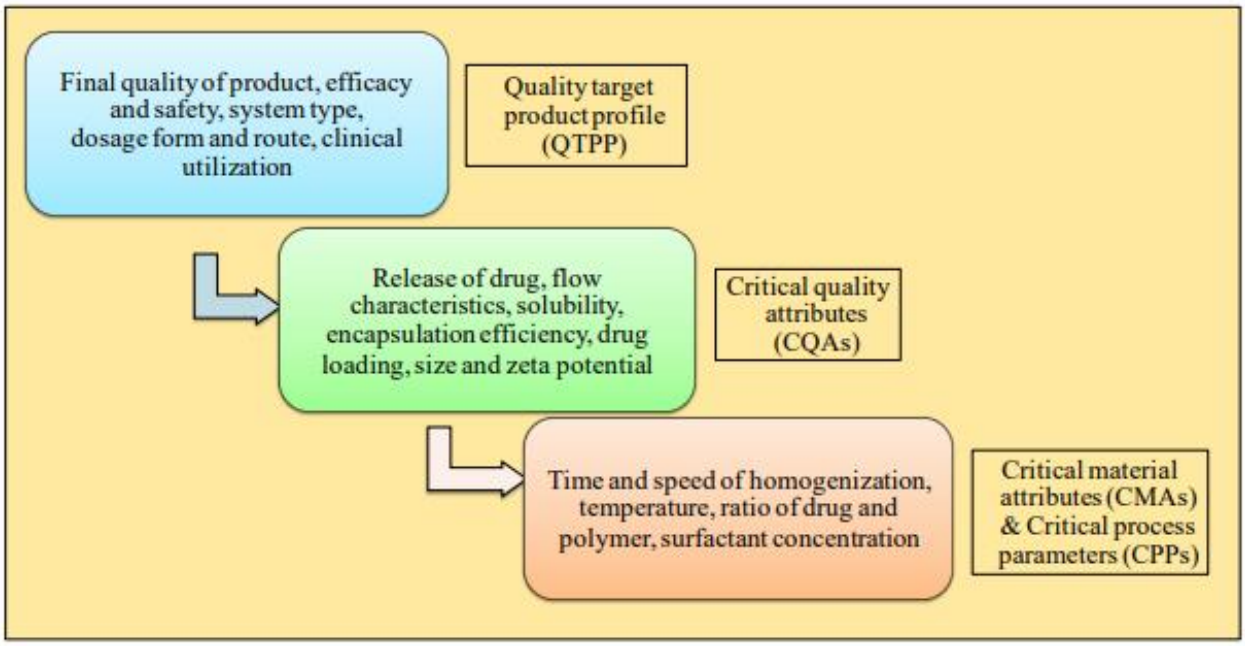

Figure 2: QBD approach steps in the micro and nanosystem implementation.

Effective drug release profile and targeting, as well as enhancement of pharmacodynamics, pharmacokinetics, and toxicity characteristics, have all been achieved by the use of QbD in the creation of microparticles and nanotechnology-based drug delivery systems nanoparticle compositions. DoE reduces the amount of tests that must be conducted to ensure quality in the final output, and this theory has been validated by many statistical methods. Multiple DoE design models exist, and they may be used to better formulate micro- and nanotechnology-based systems. Table 2 provides a few instances of how QbD has been used to optimize micro- and nano-formulation by various researchers.

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

Formulation	QbD approach	Dependent variables	Independent variables
Dexamethasone-polymeric nanoparticle	Multiple-level full factorial design	Zeta potential, particle size, %EE, PDI	Drug Concentration, Polymer concentration, Surfactant concentration
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)
Satranidazole based nanoparticle	2^3 full factorial design	Particle size, %EE, zeta potential, dissolution efficiency	PVA concentration, Aqueous phase volume, Polymer concentration
Exemestane loaded vitamin E TPGS-nanoparticle	2^3 factorial designs	Particle size, %EE	Polymer concentration, Stirring speed, TPGS volume
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
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

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
Cetuximab loaded nanoparticle	3^3 full factorial design	Particle size, %EE, zeta potential	Polymer concentration, Cross-linker concentration, Temperature
Quercetin-loaded nanoparticle	Fractional factorial design	Particle size, zeta potential, %EE, PDI	Polymer concentration, Stabilizer concentration Stirring speed, Volumes of acetone: aqueous phase
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
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
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

Future Prospects

Incorporating one or more QbD components into production demonstrates a good shift towards QbD as the future development paradigm, and many companies are beginning to interact with the QbD idea and design frameworks to aid it. QbD is widely used because it meets regulatory requirements. The pharmaceutical firm requires regulatory enforcement to get its products approved for sale. Nonetheless, the QbD solution generates high-quality service by using efficient methods. QbD gets rid of the sloppy approach to system development by providing a design space model. Since pharmaceutical businesses are not already making use of it, its future prospects are excellent once it is mandated by authorities. Companies might voluntarily adhere to this approach due to the various advantages and adaptability of cooperating with regulatory authorities. QbD allows for the mass manufacture of consistent products that meet all quality standards. It's a systematic approach to generating biological products that helps guarantee consistent quality from batch to batch. Developing novel medication formulations is a time-consuming and expensive process. Using QbD ensures performance in production from the outset, cutting down on expenses while creating the optimal composition. Therefore, it has great promise for

manufacturing effective pharmaceuticals. Partial Least Squares (PLS) and Principal Component Analysis (PCA) are two examples of multivariate data analysis (MVDA) tools that can be used in conjunction with DoE to further optimize your research. These methods can help you narrow down the number of variables you're testing for in your DoE or dig deeper into your research observations. It is often used to analyze PAT tool data for the purpose of making steady improvements to manufacturing processes. The pharmaceutical industry's desired future standard will include the use of MVDA and PAT together to monitor and alter the system in response to variations in materials or processes.

CONCLUSION

In this research, we were able to determine the optimum conditions for the creation of solid lipid nanoparticles using the solvent injection method, as well as determine which elements of the manufacturing process and which characteristics of the raw materials had the greatest impact on the product's quality. Optimization was achieved by using a desirability strategy, after the Quality target product profile had been defined and a response surface technique and regression methods had been used to characterize the relationship between the dependent and independent variables. Quality by design (QbD) has the potential to improve product development, production processes, and the end-product itself. Formulations based on nanotechnology or microparticles need extensive research and development time. Therefore, research procedures may be concluded effectively by using QbD technologies to generate microparticles and nanotechnology-based formulations. QbD will be widely acknowledged as a crucial paradigm for enhancing the design process and risk management approach, especially in the context of nano- and micro-formulation development and the use of DoE. This review paper focused on how QbD technique is used to create microparticles and nanotechnology-based formulations that consistently provide effectiveness and safety in the pharmaceutical industry.

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