ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

Quality By Design (QBD) Approach in Processing of Nanoparticles Loading Antifungal Drugs

Received: 24 October 2022, **Revised:** 25 November 2022, **Accepted:** 28 December 2022

Soundarya R[1], Praveen Halagali[2], Preethi S[1]*, Hemanth P. R Vikram[3,4], Seema Mehdi[5], Rohan Singadi[6]

[1]Department of Pharmaceutical Quality Assurance, JSS College of Pharmacy, JSS Academy of Higher Education and Research (JSSAHER), Mysuru-570015, Karnataka, India

[1*,2]Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research (JSSAHER), Mysuru-570015, Karnataka, India

[3]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education and Research (JSSAHER), Mysuru-570015, Karnataka, India

[4]Xenon Healthcare Pvt.Ltd, #318, Third floor, US Complex, Jasola, New Delhi-110076

[5]Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education and Research (JSSAHER), Mysuru-570015, Karnataka, India

[6]Assistant professor, Department of Pharmaceutical Chemistry, KLE College of Pharmacy, KLE Academy of Higher Education and Research, Belagavi-590001, Karnataka, India

*Author for Correspondence: Preethi S: preethis@jssuni.edu.in

Keywords

Quality by design, Product quality, Nanoparticles, antifungal

Abstract

"Quality by Design" (QbD) is a strategic process for development and manufacturing, it is aimed to make sure that a final pharmaceutical product performs as expected, both in terms of purity and efficacy. To achieve this, QbD implementation in the manufacturing process must be done clearly with defined objectives and proper risk management. Considering that it provides drug developers with a better understanding of manufacturing processes, reduces the frequency of batch failures, and therefore is data-driven, the QbD methodology contributes to the progressive manufacturing environment and provides a higher return on investment. Applying QbD in nano formulation can greatly impact advanced drug delivery. Particles with a diameter of less than 100 nm are known as nanoparticles, are extensively studied in nanotechnology, and have wide application in novel drug delivery systems, targeted sites, and dosing regimens. Controlling particle size, surface characteristics, and the release of pharmacologically active substances are the main criteria when formulating nanoparticles as a delivery system. As fungal infections are increasing rapidly which affect the skin, hair, nails, or mucous membranes and can also infect the lungs or other parts of your body, implementing QbD in the processing of nanoparticles loading antifungals might be of great need.

1. Introduction

"In a product, Quality cannot be tested; it must be built" there are various perceptions on this remark, making it necessary to present an arrangement to dispel confusion. Pharmaceutical industry can produce reliable products while considering every element of quality in the method of preparation of formulation. All pharmaceutical companies comply with different types of ICH guidelines. The phrase "Quality by Design" is very much needed in guidance materials for the pharmaceutical sector to acquire the most desired product with appealing features and simultaneous facilitation of governmental barriers [1]. The components of quality by design are discussed in ICH Q8: Pharmaceutical

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Development. These together with the enablers form the cornerstone of the QbD development methodology. A visual illustration of the usual QbD elements is shown in **Figure 1** [2].

Figure 1: Elements Of Quality by Design (QbD)

The undefined parameters that appear during the formulation development process have a rationale provided by a subset of QbD known as the Design of Experiments (DoE). The application of DoE also helps the manufacturer identify critical materials attributes (CMAs) and critical process parameters (CPPs) to fit within the desired critical quality attributes (CQAs) inside the design space [3]. Application of the QbD approach is so important that even final product quality testing may be neglected [4]. Aspects of the Quality Target Product Profile (QTPP) would be the first stage in the product development cycle in a QbD strategy to ensure the desired qualities. This step entails making good assignments. QbD is an overview of drug development with a primary focus on safety and efficacy provided in terms of labelling concepts which include description, clinical pharmacology, indications, and usage, contraindications, warning, drug abuse and dependence, precautions, adverse reactions, how it is supplied, dosage and administration, clinical studies, overdosage, animal pharmacology/ toxicology. CQAs in QTPP become a subcategory that specifies a few CPPs involved in developing a product. CPPs that are likely to change are illustrated in **Figure 2**. To guarantee that a pharmacological product remains within safe and reliable boundaries, it must be observed and assessed throughout the product development period [5].

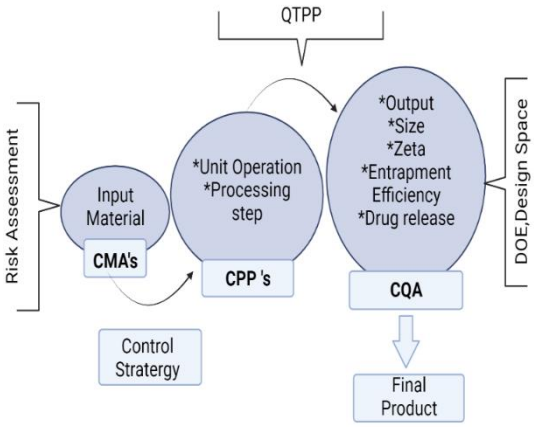

Figure 2: A cycle of QbD in Product Development

The features and attributes of the materials that are used in the process technology play a crucial part in any high-quality product. For instance, the input materials must be noted as Qualities of Critical Material (CMAs). Materials' in-process characteristics are CMAs for a one-step process and are then considered as CQAs in the downstream production procedure. Identifying Critical Processes CPPs are added to production process parameters. Finally, product development is influenced by risk assessment [6]. The current review analysis emphasizes the various challenges experienced while scaling up polymeric nanoparticles in these aspects and the viability of overcoming such challenges[7]. The research has been developed at the atomic, molecular, or macromolecular levels referred to as nanotechnology. Particles with a diameter of less than 100 nm are known as nanoparticles, are extensively studied in nanotechnology, and have wide application in novel drug delivery systems, targeted sites, and dosing regimens [8,9]. Controlling the size of particles, surface characteristics, and the release of pharmacologically active substances are the main criteria when formulating nanoparticles as a delivery system. Types of nanomaterials: carbon-based, metal-based, dendrimers, and nanocomposites, a brief explanation is given in **Figure 3** [10,11]. The main characteristics of nanoparticles are explained in **Table 1** [12].

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

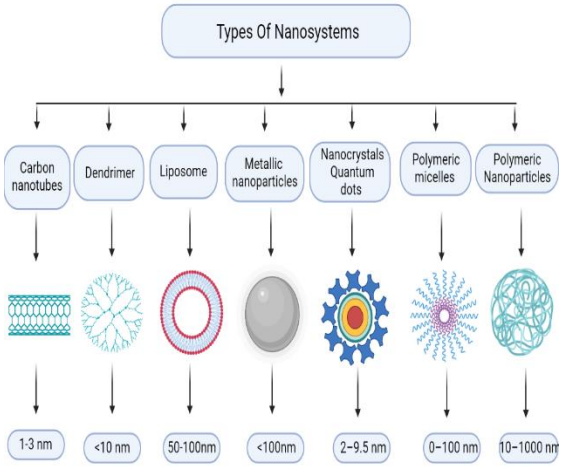

Figure 3: Types of Nanosystems

Table 1: Characteristics of nanoparticles

Types of Nanoparticles	Characteristics	Applications
Carbon Nanotubes	Carbon sheets are available as SWNT and MWNT in their allotropic crystalline form. Crystals are extremely strong. Special electrical characteristics	Enhance solubility Penetration into Cytoplasm Nucleus
Dendrimer	Highly branched Nearly monodispersed polymeric system	Long-term circulation Enhance the release of bioactive substances under control
Liposomes	Phospholipid vesicle Biocompatible Versatile	Long circulatory Offers active and passive delivery for genes, and protein.
	Improved entrapment	
Metallic nanoparticles	Gold and silver colloids with a high surface area are extremely small Stable	Gene delivery Radiotherapy
Nanocrystal Quantum dots	Semi-conductive substance Bright fluorescence Narrow emission Highly photostable	Liver cancer cell long-term multiple-color imaging hybridization of DNA Immunoassay
Polymeric Micelles	High drug entrapment Biostability Block amphiphilic copolymer micelles	Long term circulation Target-specific drug delivery through active and passive methods
Polymeric nanoparticles	Biocompatible Biopolymer Complete protection of drugs Incorporates both lipophilic and hydrophilic drugs	Excellent for sustained, controlled drug delivery Stealth and surface altering

Carbon nanotubes (CNTs) have been successfully used in pharmacy and medicine because of its large surface area and ability to adsorb or conjugate with a range of medicinal and diagnostic substances, (drugs, genes, vaccines, antibodies, biosensors, etc.). Pure carbon atoms

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

are bound together in the shape of hexagons and pentagons to form the soccer-ball-like molecule C60. In addition to diamond, graphite, and C60, multi-walled carbon nanotubes (MWNT) are another form of carbon that was initially identified by Iijima et al., in 1991 in carbon-soot created using the arc-discharge technique. After two years, he made observations of SWNT [13]. An SWNT is a graphene sheet that has been folded over into a cylinder with a typical diameter of the order of 1.4 nm and is made of cylinders with an interlayer spacing of 3.4Å and a diameter that is typically in the range of 10-20 nm. According to important prior research, carbon nanotubes' distinctive structural, electrical, mechanical, and chemical characteristics may be the main use for them. [14]. Novel pharmaceutical formulations known as nanostructured lipid carriers (NLCs) are made up of lipids that are physiological and biocompatible as well as surfactants and co-surfactants. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers are the two primary types of lipid-based nanoparticles (NLCs). SLNs were developed to address the drawbacks of conventional nanocarriers, such as emulsions, liposomes, and polymeric nanoparticles, by providing advantages such as a high-release profile and tailored drug delivery with remarkable physical stability. (109). Cholesterol and natural, non-toxic phospholipids can be used to make the small, spherical vesicles known as liposomes. Liposomes are promising drug delivery devices because of their size, hydrophobic and hydrophilic nature, and biocompatibility. Initially, liposomes were given through the oral route only because of their high compatibility they can now be given in other different routes. Liposomes have been used to deliver anticancer agents in order to reduce the toxic effects of the drugs when given alone or to increase the circulation time and effectiveness of the drugs [15]. Polymeric nanoparticles (PNPs) have generated much interest due to their distinct characteristics like high mechanical strength, electrical conductivity, optical and thermal properties [16]. Nanoparticles have a major application, in targeted drug delivery, biocompatibility, biocatalysts, antigen detection, etc [17]. The merits of PNPs include carriers for controlled release, combining both therapeutic and imaging agents (Theranostics), and enhancing therapeutic index [18,19]. It can be made of various materials, such as lipids, polymers, and copolymers. Compared to other nanoparticles, Polymeric Nanoparticles have distinct properties due to their versatility in exhibiting a range of surface-attached ligands, stability in loading therapeutic compounds at high levels, control over drug release, and a long history of safe use in humans. [20]. The drug can be maintained inside or adsorbed onto the surface of nanospheres thanks to their continuous polymeric network [21]. PNPs like nanospheres (matrix system) and nanocapsules (reservoir system) are included under the term “nanoparticle” umbrella. This is shown in **Figure 4** [22]. Nano capsule size ranges from 10-1000 nm. Depending on the preparation and use the size will be more specific . Nano capsule consists of a nano vesicular system formed in a shell arrangement and the shell is made from a polymeric membrane or coating [23]. The drug is dissolved in an oily nanocapsule core, encased in a polymeric shell that regulates the drug's release profile (36). Encapsulation depends on the drug substance's requirement and on the physicochemical properties of the wall material, core material, and required size. Nanocapsules can be prepared by nano preparation, solvent evaporation, and emulsion diffusion. Nanosphere size ranges from 10-200nm. They are homogenous matrix systems in which active compounds are dispersed, adsorbed, or entrapped within the polymeric matrix [24]. Nanospheres can be prepared by emulsification-evaporation and nanoprecipitation methods and they play a major role in fungal infection [25].

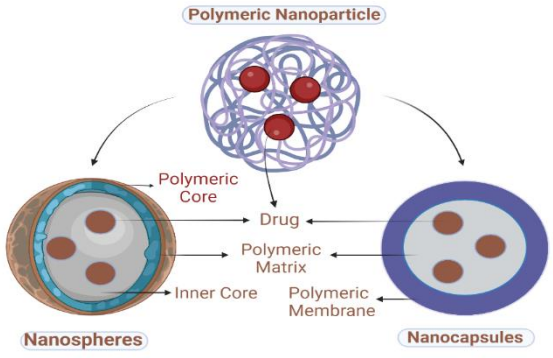

Figure 4: Forms of Polymeric Nanoparticles

2. Fungal Infection

Infections of the skin and mucous membranes as well as more serious invasive infections of the internal organs can be brought on by fungi. (1).

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Patients' visits to dermatologists are frequently caused by superficial fungal infections i.e., Chronic fungal infections of the Subcutaneous tissues and skin caused by various fungal agents (2). Some of the infections are shown in **Figure 5**

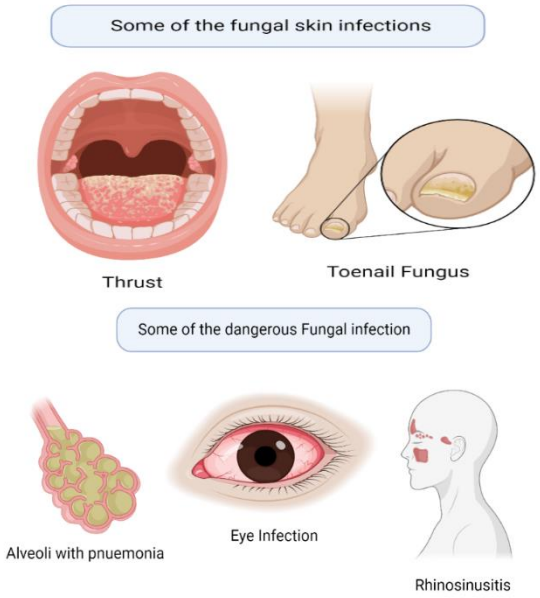

Figure 5: Some of the skin and dangerous fungal infections [26].

Approximately, 20–25% of people worldwide are having superficial mycoses (3). Invasive fungal infections are a major source of morbidity and mortality for people with AIDS, hematologic malignancies, aplastic anaemia, and myelodysplasia, impaired immune system individuals, and people undergoing organ transplants, infants (0-1 years), and the elders (>65 years) (4). In the 1990s, the introduction of first-generation azole medications, such as fluconazole and itraconazole, and second-generation azole medications, such as aripiprazole, olanzapine, clozapine, etc were introduced after this (5). The newly developed antifungal agents like voriconazole, Posaconazole, and ravuconazole can overcome the limits relating to their pharmacokinetics, drug-drug interactions, physicochemical and biological properties, and pharmacodynamic characteristics (6). The potential ability of these therapeutic agents is utilized to enhance the efficacy, safety profile, and reduce the side effects of antifungal medicines, many novel drug delivery methods have been developed. Nanoparticles (NPs) have emerged and aims to target drug delivery by minimizing undesirable side effect (7). The drugs that will kill or inhibit the growth of fungi that causes infections it is also called antimycotic agents. In the 1990s researchers discovered and developed novel antifungals; hence, it is deemed as the "Golden era" of antifungal drugs. Since then the discovery of Antifungal agents became stagnant, its been two decades since the discovery of echinocandins, the newest class of antifungal drugs. Currently, four classes of antifungal medications are FDA-approved. are shown in **Figure 6** [27,28].

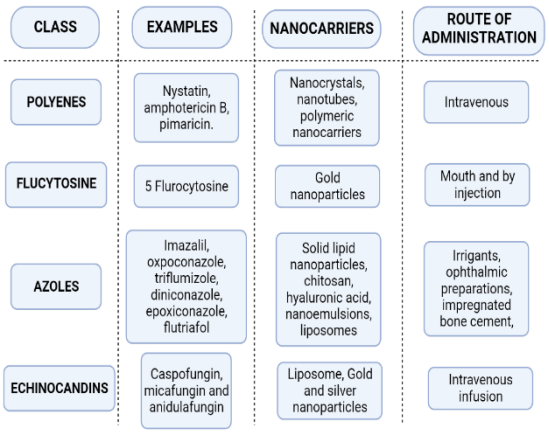

Figure 6: Class of antifungal drugs.

Polyenes were the broad-spectrum antifungals for humans discovered in the 1940s and 1950s with the first ever FDA- approved antifungal drug Amphotericin B and it remained as standard for many years in the treatment of mycoses. Amphotericin B lipid complex (ABLC), Liposomal amphotericin B (LAmB), and amphotericin B colloidal dispersion(ABCD), and having low toxicity were developed as amphotericin B had been showing toxicity, especially nephrotoxicity which can lead to kidney failure [29,30]. In 1957, Since being created as a possible anti-tumor agent, 5-fluorocytosine was granted human antifungal authorization. It is a pyrimidine (heterocyclic nitrogenous base found in the nucleic acids DNA and RNA). Flucytosine cannot be used in monotherapy, it is always used in combination with other antifungals as it can develop resistance, this is one of the major drawbacks of using flucytosine. In addition to this, they are associated with hepatotoxicity and hemotoxicity as the common adverse event [31–33]. Despite being discovered in the 1940s, azoles were not licensed for usage in humans until the late 1950s and early 1960s. Numerous azoles are fungistatic and have a relatively wide range of activity. As a result of its fungistatic properties, resistance development happens

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

frequently. The most used azole for treating systemic infections is fluconazole. The development of triazoles created a revolution in treating fungal infections [34–38]. The FDA has approved the class of antifungals known as echinocandins. It was not introduced in the market till the 2000s though it was discovered in the 1970s. They were initially used for the treatment of aspergillosis infection. The first approved echinocandin in humans was caspofungin. Later on, micafungin and anidulafungin were discovered in 2005 and 2006 respectively. Resistance is rare as the consequence of drug exposure increases [39–43]. **Figure 7** shows the structure of a fungal cell and the different classes of antifungals acting on them. The mechanism of action is explained in **Table 2,**

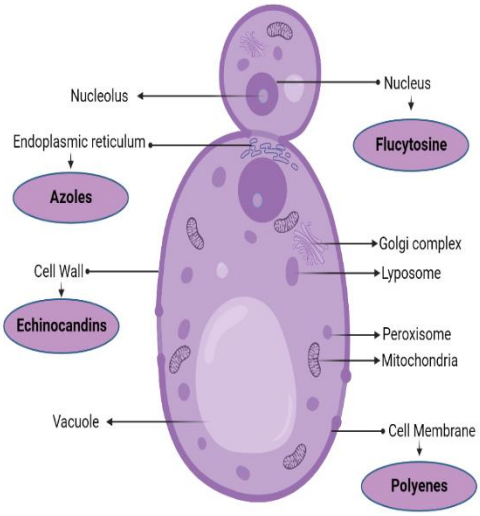

Figure 7: Fungal Cell

Table 2: Mechanism of action

POLYENES	FLUCYTOSINE	AZOLES	ECHINOCANDINS
Amphotericin B extracts sterols from fungi's cell membrane via binding to ergosterol. By acting as a sponge Which leads to a weakened cell membrane leading to death [44–46].	5 Flucytosine is converted into 5 Fluorouracil Which is phosphorylated and incorporated into RNA Inhibits thymine methyl synthase [47].	Azoles inhibit cytochrome P450(14 α demethylases) which is necessary for ergosterol synthesis, which is a major component of fungal membrane Which is alter membrane permeability and disrupts its function [42].	Echinocandins' primary target is 1,3-D glucan synthase. It is an enzyme responsible for making 1,3-D glucan. It is one of the primary elements of the fungal wall's structural framework [48].

To improve patient compliance and reduce variability, pharmaceutical companies have recently been devoting a large portion of their resources to developing better carrier systems [49]. These systems must be able to deliver the drugs continuously for an extended period with fewer side effects possible. Polymer-based drug delivery systems are being evaluated as a viable substitute for traditional carrier systems due to their variety of functions and characteristics [50].

3. QbD approach

To include quality in the product from the start of manufacturing, QbD and process analytical technology (PAT) were introduced by the FDA in 2003 [51]. In the olden days, the quality by testing (QbT) method assesses the quality of a product at the very end of the manufacturing process by comparing it against the accepted regulatory criteria. Scaling up a product from research to manufacturing size is very unpredictable, and the causes of failure are frequently unknown. If products do not meet their standards, the batch will either be rejected or need to be reworked, increasing the cost and regulatory responsibility. Post-approval changes of noncritical behavior should also be pre-approved by the regulatory authorities. If a batch of a critical product is

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

wasted, it may be difficult for a pharmaceutical company to remain competitive in the market. Because of this, there is a significant communication gap between regulatory organizations and industrial businesses, which emphasizes the need for strong regulations and supervision. The QbD principles promote product innovation and continuous development to achieve predetermined quality goals. Novel risk-based strategies are used in the product and process design by consequently meeting the regulatory requirements and patient needs at an affordable price (81). In the initial stages, it enlists the CQA and CPP that directly affect the product's quality. The research findings can be more successfully incorporated into the development phase if the design and testing of pharmaceuticals are based on the QbD technique. QTPP is the first step in QbD, which is the objective of development. The following stages are to determine CQA, CMA, and CPP, and thereafter risk assessment is used to choose the parameters that could potentially affect the quality of the product [52]. Although the QbD technique is a novel way of creating medications, it can be difficult for developers to implement because the QbD principle is different in each formulation.[49]. Manufacturing problems are crucial and require rapid response to avoid damaging the company's reputation and financial losses. A very important strategy for maintaining and continuously enhancing product quality is quality management, which is composed of quality assurance and quality control. The Ishikawa diagram is one of the methods used to increase quality and decrease rejection that is well known and widely applied. It is highly helpful for identifying problems from many angles and is hence called a cause-and-effect diagram (CED). It is also called a fishbone diagram as the shape of the diagram is like a fishbone depicted in **Figure 8** which helps us to identify the root cause of the problem [53].

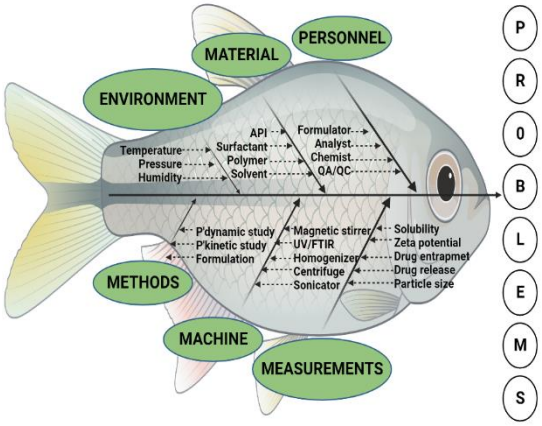

Figure 8: Fishbone diagram [54,55]

The field of drug delivery has been transformed by nanoparticles (NPs), which are created by combining biodegradable and/or biocompatible polymers, particularly in the treatment of cancer. NPs have demonstrated excellent capability in improving the therapeutic effects of drugs while reducing their toxicity. Although some NP-based polymeric Cytotoxic drug formulations are still in the design stages, many have already reached clinical trials [56]. From to several studies, incorporating antifungal medications inside nanospheres and nanocapsules maintained sustained release, increased antifungal activity, and decreased toxicity.

4. QbD approach to polymeric nanoparticles loaded antifungal drugs [57]

Vinam Puri et al., conducted a study on Qbd the synthesis of terbinafine hydrochloride PNPs utilizing a nano gel formulation to treat onychomycosis. Infections caused by fungi are the most type of skin illness in the world, with superficial infections ranking among the ten most common. Onychomycosis is the most common nail problem and the most challenging superficial fungal infection to treat [58,59]. The popular oral and topical formulation of the broad-spectrum allylamine antifungal terbinafine is available [60,61]. Numerous topical formulations using PNs have shown prolonged and efficient drug delivery. The objective of his project was to create terbinafine hydrochloride (TBH)-containing polymeric antifungal nanospheres for topical nail drug delivery containing TBH gel. Topical formulations have been

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

effectively produced to meet the quality target product profile, it was done by improving the process and material variables that affected CQA. The TBH Nanospheres were prepared by dissolving polymer and drug in Dichloromethane (DCM) and then the organic phase was mixed with Polyvinyl alcohol (PVA) solution using a magnetic stirrer at 450 rpm for 10 mins, After centrifuging the samples at 20,000 rpm for 15 minutes at 18 degrees, discarding the supernatant layer, and collecting the pellet, the emulsion was then converted to an aqueous suspension of the drug-loaded nanospheres by stirring at 450 rpm when it was room temperature to allow the solvent to evaporation. Cause and effective diagram were employed to ensure the possible risk. 2^4 full factorial designs were employed. PVA concentration and Drug-to-polymer ratio were the material attributes, and mixing period after emulsion formulation and ultrasonication time were the process variables. To investigate the independent factors, preliminary tests, like particle size and polydispersity index were employed. Based on these findings, the EPV to IPV ratio was investigated using a secondary fractional factorial design for this series of studies, which continued to use particle size and PDI response. In combination with a strong set of procedures and material characteristics, 2% PVA by weight and a drug-to-polymer ratio of 1:4 created nanoparticles measuring 108.7 nm with a polydispersity index (PDI) of 0.63 and a recovery rate of 57.43%. Ex vivo nail permeation research and *in vitro* drug release testing (IVRT) was used to analyze this investigation. Compared to the control gel, TBH nanosphere-containing gel exhibited a slower and more controlled drug release profile., as well as more effective nail delivery [62].

5. QbD approach to Nano lipid carriers (NLC) loaded antifungal drugs [63]

Tejashree Waghule et al., in their study, said that in clinical research, voriconazole has many adverse effects, including nausea, vomiting, and other gastrointestinal problems. A topical formulation with embedded nanostructured lipid carriers (NLCs) was created to distribute voriconazole to reduce the both the probability and severity of the related adverse effects at the topical site. The formulation of voriconazole-loaded NLCs was carried out in this research using the QbD (Quality by Design)-based risk analysis. NLCs were developed using a hot-melt emulsification process, by ultrasonication. In a brief, liquid lipid and solid lipid were mixed in a 3:7 ratio. The co-surfactant and surfactant were dissolved in five ml of Milli-Q to create the aqueous phase. These two phases were kept at a constant 75 °C. In order to create a homogeneous emulsion, voriconazole (20 mg) was added to the melted lipid mixture after being mixed with 0.4 mL of acetone. Acetone was then continuously evaporated while the lipid mixture was being stirred, and then the aqueous phase was added drop by drop and stirred continuously at 600rpm. The resulting primary emulsion underwent six minutes of ultrasonication (30 s of "ON" time and four s of "OFF" time with a 25% amplitude. The resultant solution was diluted with 5 mL of ice-cold water and stirred on a magnetic stirrer at room temperature for 15 minutes. (99,100). Characterization was done by conducting spreadability, viscosity, extrudability, an assay of gel, Ex-vivo skin permeation study. Optimization and risk assessment for different formulations and CPPs were done using the Box-Behnken design. To achieve this purpose, two central points were used. The formulation had a average size of 107.7 ± 8 nm, an entrapment efficiency of 70.52 ± 5%, and a drug loading of 6.59%. An *in-vitro* drug release investigation said that voriconazole released slowly over a 10-hour period. The chosen formulation was added to the Carbopol gel, and in comparison, to free drug-based gel, *ex-vivo* permeation experiments using NLCs-loaded gel revealed better penetration (66.45%) and sustained release for up to 11 h. The NLC gel keep drug in the skin layers, indicating that systemic circulation was decreased, could lessen the side effects brought on by drugs. The zone of inhibition for the NLCs formulation in *in-vitro* antifungal research on Aspergillus flavus culture was 22.5 ± 0.5 mm, whereas the zone for the free drug was only 14.5 ± 0.5 mm. The QbD assimilation approach for formulation optimization helped to understand the connections between process and formulation parameters. The prepared NLCs gel may therefore target skin and be a new potential option for the treatment of topical fungal infections in the future

6. QbD approach to Cubosomes loaded antifungal drugs [64]

Vamshi krishna rapali et al., wanted to develop a topical hydrogel based on qbd that contained cubosomes loaded with ketoconazole in their

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

investigation. Monoglycerides were emulsified in water at a high temperature to create cubosomes that were loaded with ketoconazole. which was previously used by esposito et al and morsi [14,54]. The fats employed in this work was glycerol monooleate (GMO). At various concentrations, PVA and Poloxamer 407 were utilized as stabilizers and surfactants, respectively. Poloxamer 407 (in an amount ranging from 200 to 400 mg) was added to melted 2g of GMO at 85 °C temperatures, and then it was stirred at 700 RPM on a magnetic stirrer until clear solution of the surfactant was formed in the oily mass. This molten lipid mass received 100 mg of ketoconazole, which was then agitated into complete solubilization. A little amount of PVA (between 0 and 5% of the weight of the GMO utilized) was gently added to the preheated aqueous dispersion with the lipidic mass until an emulsion was produced. The heated emulsion was then agitated for a short period of time at a comparable RPM until it reached room temperature. The volume was then increased to 50 mL by adding the pre-emulsion while continuously stirring (at 500 RPM). On constant stirring, a cubosomal dispersion stable emulsion is produced. To separate the cubosomal dispersion from the unentrapped drug and extra lipid, the generated dispersion was centrifuged at 5000 RPM for 5 minutes. The screening was done after the risk assessment was completed and 3^2 factorial designs were used with Design-Expert® software to optimize the results. As it was expected following the completion of the (DoE) research, large scale batches were made while maintaining a constituent combination same as the optimal batches. The 3^2 factorial design model was used to estimate the composition of the optimal formulation. Different mathematical models were used to carry out and analyze an in vitro drug release investigation. Goat ear skin was used to investigate an *ex vivo permeation* study. The optimized drug had a 24-hour cumulative release of 67% ketoconazole and a release pattern like the Korsmeyer-Peppas model. In an ex vivo permeation research, hydrogel containing ketoconazole-loaded cubosomes with a 92.73% 24-hour release rate through goat ear skin was found to have a sustained release pattern. Ketoconazole-loaded cubosomes had a 198 nm particle size and a 45% entrapment efficiency, according to scale-up batches experiments that supported the results of the post-characterization investigations.. Topical drug administration is achievable using this hydrogel that contains cubosomes that are loaded with ketoconazole [65–68].

7. QbD approach to Liposome loaded antifungal drugs [69]

An attempt has been made to use the QbD technique to create nanoliposomes (NLs) with a long retention time by controlled release of the antifungal medication fluconazole (FCZ). A low partition coefficient antifungal drug called FCZ (logP 0.5) with reduced bioavailability as a result of tear fluid washing it off needs giving doses repeatedly, which reduces patient compliance. Thin-film hydration-based liposomes containing FCZ were created using the Box-Behnken design, which included the lipid content, sonication time, and hydration time as independent parameters.. The FCZ-loaded NLs (FCZ-NLs) have an optimum PS (268 3.6 nm), potential (23.15 3.12 mV), and EE (69.75 4.4%). Also, For lyophilization, the amount of cryoprotectant was modified.. FCZ-NLs demonstrated higher ex-vivo penetration rates and zero-order release kinetics that closely matched the data when compared to the commercial formulation. Eye pain and hemolysis were not noted in preclinical studies. The FCZ-NLs' AUC (0-), MRT, and drug availability above the MIC were 2.36, 3.05, and 4.57 times higher than those of the commercial formulation. The enhanced FCZ-NLs may one day be employed as a method of delivering eye medications.

8. Conclusion

Applying qbd in manufacturing is creating a good impact on the quality of the product and adopting qbd can prevent a company's reputation and financial loss. As the number of antifungal cases is increasing massively adopting qbd and implementing it in our manufacturing process can lead to a good quality product and helps us in understanding the risk associated with it along with creating a quality target product profile. In the current review it was found that there was less number of research article on the qbd approach in processing nanoparticles loading antifungals, the articles which were found were majority from the azoles group and so increasing the number of research related to this topic, and working on other class of antifungals may help the other researchers

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

to have an idea in the field of manufacturing and can have a good number of product meeting the quality requirements.

References

[1] Kim JY. Human fungal pathogens: Why should we learn? J Microbiol. 2016;54(3):145–8.
[2] Lockhart SR, Diekema DJ, Pfaller MA. The epidemiology of fungal infections. Clin Mycol with CD-ROM. 2009;1–14.
[3] Rudramurthy SM, Shaw D. Epidemiology of superficial fungal infections in Asia. Clin Pract Med Mycol Asia. 2019;9–37.
[4] Vallabhaneni S, Mody RK, Walker T, Chiller T. The Global Burden of Fungal Diseases. Infect Dis Clin North Am. 2016;30(1):1–11.
[5] Nett, J.E., Andes DR. Antifungal agents: spectrum of activity, pharmacology, and clinical indications.
[6] Lewis RE. Current concepts in antifungal pharmacology. Mayo Clin Proc. 2011;86(8):805–17.
[7] Zazo H, Colino CI, Lanao JM. Current applications of nanoparticles in infectious diseases. J Control Release. 2016;224:86–102.
[8] Roco MC. Broader societal issues of nanotechnology. J Nanoparticle Res. 2003;5(3–4):181–9.
[9] Saltzman W. Drug delivery: engineering principles for drug therapy. Drug Deliv Eng Princ Drug Ther [Internet]. 2001;235–63. Available from: http://books.google.com/books?hl=en&lr=&id=Z5UDv8pCprUC&oi=fnd&pg=PA1&dq=Drug+Delivery:+Engineering+Principles+for+Drug+Therapy&ots=luKr8IJeCk&sig=jOin-nsVBzl2c89z6Yj6uWGnGFM
[10] Vila A, Sánchez A, Tobío M, Calvo P, Alonso MJ. Design of biodegradable particles for protein delivery. J Control Release. 2002;78(1–3):15–24.
[11] Mu L, Feng SS. A novel controlled release formulation for the anticancer drug paclitaxel (taxol ®): PLGA nanoparticles containing vitamin E TPGS. Chemother Eng Collect Pap Si-Shen Feng - A Tribut to Shu Chien His 82nd Birthd. 2013;246–305.
[12] Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nat Biotechnol. 2009;27(1):26–34.
[13] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771–83.
[14] Charoo NA, Shamsher AAA, Zidan AS, Rahman Z. Quality by design approach for formulation development: A case study of dispersible tablets. Int J Pharm. 2012;423(2):167–78.
[15] Soni G, Yadav KS, Gupta MK. Design of Experiments (DoE) Approach to Optimize the Sustained Release Microparticles of Gefitinib. Curr Drug Deliv. 2018;16(4):364–74.
[16] Leuenberger H, Puchkov M, Krausbauer E, Betz G. Manufacturing pharmaceutical granules: Is the granulation end-point a myth? Powder Technol. 2009;189(2):141–8.
[17] Miller CE. Chemometrics and NIR: A match made in heaven,.
[18] Incecayir T, Sun J, Tsume Y, Xu H, Gose T, Nakanishi T, et al. Carrier-Mediated Prodrug Uptake to Improve the Oral Bioavailability of Polar Drugs: An Application to an Oseltamivir Analogue. J Pharm Sci. 2016;105(2):925–34.
[19] Belasco JM. Target product profile: beginning drug development with the end in mind. Udate Rep. 2007;1:36–9.
[20] Nahar M, Dutta T, Murugesan S, Asthana A, Mishra D, Rajkumar V, et al. Functional polymeric nanoparticles: An efficient and promising tool for active delivery of bioactives. Crit Rev Ther Drug Carrier Syst. 2006;23(4):259–318.
[21] Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009;3(1):16–20.
[22] García-Corvillo MDP. Polymeric nanoparticles for drug delivery to the central nervous system via nasal route. Ars Pharm. 2016;57(1):27–35.
[23] Lin G, Zhang H, Huang L. Smart polymeric nanoparticles for cancer gene delivery. Mol Pharm. 2015;12(2):314–21.
[24] Zhong Y, Meng F, Deng C, Zhong Z. Ligand-directed active tumor-targeting polymeric nanoparticles for cancer chemotherapy. Biomacromolecules. 2014;15(6):1955–69.
[25] Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: Design, development and clinical translation. Chem Soc Rev. 2012;41(7):2971–3010.
[26] Krasia-Christoforou T, Georgiou TK. Polymeric theranostics: Using polymer-based systems for simultaneous imaging and therapy. J Mater Chem B. 2013;1(24):3002–25.
[27] Schaffazick SR, Pohlmann AR, Dalla-Costa T, Guterres SS. Freeze-drying polymeric colloidal suspensions: Nanocapsules, nanospheres and nanodispersion. A comparative study. Eur J Pharm Biopharm. 2003;56(3):501–5.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[28] Crucho CIC, Barros MT. Polymeric nanoparticles: A study on the preparation variables and characterization methods. Mater Sci Eng C. 2017;80:771–84.
[29] Guterres SS, Alves MP, Pohlmann AR. Polymeric Nanoparticles, Nanospheres and Nanocapsules, for Cutaneous Applications. Drug Target Insights. 2007;2:117739280700200.
[30] Christoforidis JB, Chang S, Jiang A, Wang J, Cebulla CM. Intravitreal devices for the treatment of vitreous inflammation. Mediators Inflamm. 2012;2012.
[31] Nagavarma BVN, Yadav HKS, Ayaz A, Vasudha LS, Shivakumar HG. Different techniques for preparation of polymeric nanoparticles- A review. Asian J Pharm Clin Res. 2012;5(SUPPL. 3):16–23.
[32] Mora-Huertas CE, Fessi H, Elaissari A. Polymer-based nanocapsules for drug delivery. Int J Pharm. 2010;385(1–2):113–42.
[33] Ezhilarasi PN, Karthik P, Chhanwal N, Anandharamakrishnan C. Nanoencapsulation Techniques for Food Bioactive Components: A Review. Food Bioprocess Technol. 2013;6(3):628–47.
[34] Charrueau C, Zandanel C. Drug Delivery by Polymer Nanoparticles: The Challenge of Controlled Release and Evaluation. Polym Nanoparticles Nanomedicines. 2016;439–503.
[35] Nicolas J, Mura S, Brambilla D, Mackiewicz N, Couvreur P. Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. Chem Soc Rev. 2013;42(3):1147–235.
[36] Odds, F.C.; Brown, A.J.; Gow N. Antifungal agents: Mechanisms of action.
[37] ALrawashdeh I, Qaralleh H, Al-limoun M, Khleifat K. Antibactrial Activity of Asteriscus graveolens Methanolic Extract: Synergistic Effect with Fungal Mediated Nanoparticles against Some Enteric Bacterial Human Pathogens. J Basic Appl Res Biomed. 2019;5(2):89–98.
[38] Vera-González N, Bailey-Hytholt CM, Langlois L, de Camargo Ribeiro F, de Souza Santos EL, Junqueira JC, et al. Anidulafungin liposome nanoparticles exhibit antifungal activity against planktonic and biofilm Candida albicans. J Biomed Mater Res - Part A. 2020;108(11):2263–76.
[39] Mahmood A, Rapalli VK, Waghule T, Gorantla S, Singhvi G. Luliconazole loaded lyotropic liquid crystalline nanoparticles for topical delivery: QbD driven optimization, in-vitro characterization and dermatokinetic assessment. Chem Phys Lipids. 2021;234.
[40] Spósito PÁ, Mazzeti AL, Faria C de O, Aurbina J, Pound-Lana G, Bahia MT, et al. Ravuconazole self-emulsifying delivery stem: In vitro activity against Trypanosoma cruzi amastigotes and in vivo toxicity. Int J Nanomedicine. 2017;12:3785–99.
[41] Liu M, Chen M, Yang Z. Design of amphotericin B oral formulation for antifungal therapy. Drug Deliv. 2017;24(1):1–9.
[42] Odds, F.C.; Brown, A.J.; Gow NA. Antifungal agents: Mechanisms of action.
[43] Janknegt R, de Marie S, Bakker-Woudenberg IAJM, Crommelin DJA. Liposomal and Lipid Formulations of Amphotericin B: Clinical Pharmacokinetics. Clin Pharmacokinet. 1992;23(4):279–91.
[44] Vermes A, Guchelaar HJ, Dankert J. Flucytosine: A review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. J Antimicrob Chemother. 2000;46(2):171–9.
[45] Ashe, W.D. J. VR. D.E. 5-fluorocytosine: A brief review.
[46] Larsen RAF. In Essentials of Clinical Mycology; Kauffman, C.A., Pappas, P.G., Sobel, J.D., Dismukes, W.E.,.
[47] Viviani MA. Flucytosine—What is its future?
[48] Chang YL, Yu SJ, Heitman J, Wellington M, Chen YL. New facets of antifungal therapy. Virulence. 2017;8(2):222–36.
[49] Pianalto KM, Alspaugh JA. New horizons in antifungal therapy. J Fungi. 2016;2(4).
[50] Martínez-Matías N, Rodríguez-Medina JR. Fundamental concepts of azole compounds and triazole antifungals: A beginner's review. P R Health Sci J. 2018;37(3):135–42.
[51] Peyton, L.R.; Gallagher S. H. M. Triazole antifungals: A review.
[52] Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of antifungal drug resistance. Cold Spring Harb Perspect Med. 2015;5(7).
[53] Cappelletty D, Eiselstein-McKitrick K. The echinocandins. Pharmacotherapy. 2007;27(3):369–88.
[54] Johnson MD, Perfect JR. Caspofungin: First approved agent in a new class of antifungals. Expert Opin Pharmacother. 2003;4(5):807–23.
[55] Chen SCA, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: A comparison.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Drugs. 2011;71(1):11–41.
[56] Sucher AJ, Chahine EB, Balcer HE. Echinocandins: The newest class of antifungals. Ann Pharmacother. 2009;43(10):1647–57.
[57] Patil A, Majumdar S. Echinocandins in antifungal pharmacotherapy. J Pharm Pharmacol. 2017;69(12):1635–60.
[58] Ia IA. Practice guidelines for the diagnosis and management of aspergillosis. 2021;62(10):1282–7.
[59] Aigner M, Lass-Flörl C. Treatment of drug-resistant Aspergillus infection. Expert Opin Pharmacother. 2015;16(15):2267–70.
[60] Te Welscher YM, Van Leeuwen MR, De Kruijff B, Dijksterhuis J, Breukink E. Polyene antibiotic that inhibits membrane transport proteins. Proc Natl Acad Sci U S A. 2012;109(28):11156–9.
[61] Anderson TM, Clay MC, Cioffi AG, Diaz KA, Hisao GS, Tuttle MD, et al. Amphotericin forms an extramembranous and fungicidal sterol sponge. Nat Chem Biol. 2014;10(5):400–6.
[62] Gray KC, Palacios DS, Dailey I, Endo MM, Uno BE, Wilcock BC, et al. Amphotericin primarily kills yeast by simply binding ergosterol. Proc Natl Acad Sci U S A. 2012;109(7):2234–9.
[63] Hope WW, Tabernero L, Denning DW, Anderson MJ. Molecular mechanisms of primary resistance to flucytosine in Candida albicans. Antimicrob Agents Chemother. 2004;48(11):4377–86.
[64] Whaley SG, Berkow EL, Rybak JM, Nishimoto AT, Barker KS, Rogers PD. Azole antifungal resistance in Candida albicans and emerging non-albicans Candida Species. Front Microbiol. 2017;7(JAN).
[65] Nayak AK, Ahmad SA, Beg S, Ara TJ, Hasnain MS. Drug delivery: Present, past, and future of medicine. Appl Nanocomposite Mater Drug Deliv. 2018;255–82.
[66] Singhvi G, Rapalli VK, Nagpal S, Dubey SK, Saha RN. Nanocarriers as Potential Targeted Drug Delivery for Cancer Therapy. 2020;51–88.
[67] Yu LX. Pharmaceutical quality by design: Product and process development, understanding, and control (Pharmaceutical Research DOI: 10.1007/s11095-007- 9511-1). Pharm Res. 2008;25(10):2463.
[68] Falusi F, Budai-Szűcs M, Csányi E, Berkó S, Spaits T, Csóka I, et al. Investigation of the effect of polymers on dermal foam properties using the QbD approach. Eur J Pharm Sci. 2022;173.
[69] Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. J Am Acad Dermatol. 2019;80(4):853–67.