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Review article

Nanosystem trends in drug delivery using quality-by-design concept

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ABSTRACT

Quality by design (QbD) has become an inevitable trend because of its benefits for product quality and process understanding. Trials have been conducted using QbD in nanosystems' optimization. This paper reviews the application of QbD for processing nanosystems and summarizes the application procedure. It provides prospective guidelines for future investigations that apply QbD to nanosystem manufacturing processes. Employing the QbD concept in this way is a novel area in nanosystem quality.

1. Introduction

Nanosystems are defined as vehicles with particle sizes of 10–100 nm, which compounds can be dissolved in, encapsulated in, or attached to for delivery [1]. With the ongoing development of this field, the definition has been extended when vesicles with one or more characteristic dimensions of up to 300 nm have been incorporated into the system [2]. Nanosystems have been developed continuously for more than 60 years. The first polymer-drug conjugate was synthesized in the 1950s [3]. And in 1964, the lecithin-cholesterol liposome was prepared, and its structure was observed by electron microscope [4]. In the 1970s, nanoparticles began to be synthesized and applied to the study of physiological activity [5,6]. Since then, different nanostructures have been studied, including nanoemulsions, nanoemulsions, nanomicelles, nanotubes and so forth.

Nanosystems have been subdivided into four categories according to function. The first type aims to enhance solubility and permeability in drug delivery. Moreover, nanosystems can entrap more than one compound simultaneously and achieve combined drug delivery. For example, Meng et al. encapsulated resveratrol and paclitaxel together in liposomes to reverse multidrug resistance in vivo [7]. The second category involves targeted delivery that aims to permeate physiological barriers (e.g. the blood-brain barrier), decrease toxicity, and increase efficacy, especially in curing cancer and brain diseases. Nanostructures are decorated with the ligands of receptors or antibodies of molecules overexpressed in focal sites, and the specific combination of ligands with their receptors promotes targeted delivery. Such decorations include folate [8], iron oxide [9], protein transferrin [10], and the antibodies of specific molecules. The third type is designed to achieve intra-and subcellular delivery and prevent nanosystems from being captured by immune cells [2]. Polyethylene glycol (PEG) and its derivatives are grafted onto the surface of the nanoparticles, avoiding clearance by the immune system and prolonging blood circulation time [11]. The fourth category involves intelligent nanosystems which are responsive to specific microenvironments and achieve targeted compound delivery [12]. These include low-pH triggered nanosystems in responding to acid environments in tumor sites [13], thermoresponsive delivery systems for the heat-sensitive properties of tumor [14], and redox-responsive systems for different redox potentials in extra- and intracellular spaces [15]. An individual nanoformulation usually represents a combination of the four above mentioned categories, not a single type. For example, Ngernyuang et al. formulated Au nanoparticles loaded with 5-fluorouracil and decorated with folic acid as the targeting agent and PEG as the protective material [16].

Apart from decorating nanosystems, the controls in their physicochemical properties also significantly improve their efficacy and decrease toxicity. These characteristics include particle size, polydispersity index (PDI), surface charge (in the form of zeta potential), and encapsulation efficiency (EE%). The enhanced permeability and retention (EPR) effect demonstrates that particle size plays a major role in particle accumulation through passive transport into tumor sites and inflammatory sites; this is because the sizes of capillary fenestrae in such sites are crucial factors [2]. The uniformity of nanomaterial size is emphasized because of its technological importance; also, a narrow size distribution ensures drug encapsulation uniformity [1] as well as nanoformulation stability and capability [17,18]. Surface charge affects the activities of nanoformulations. For example, nanoparticles' surface charges influence cellular uptake efficiency and their internalization

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into intracellular compartments [19]. Surface charge has also been found to govern electrolyte transport in carbon nanotubes and influence magnitude [20]. Regarding encapsulation efficiency, entrapping sufficient drugs in a nanocarrier is a major barrier in the nanosystems' development [11]. Precision in the amount of therapeutic agents in nanoformulations is essential for their efficacy and security.

Following several decades of development, some nanotechnology-based products (e.g. Doxil, a liposome dosage; Abraxane, a nanoparticle dosage; and Estrasorb, nanomicelle dosage [2]) were approved for clinical use. Currently, however, there are still many hurdles impeding the industrial production and clinical translation of nanoformulations. First, the factors that influence the physico-chemical characteristics of nanoformulations are not fully identified or their specific effects are not clearly illustrated. Second, problems still exist regarding particle size variability, low encapsulation efficiency, unsuitable surface charge and inhomogeneous shapes etc. These challenges limit industrial production, which must meet the reproducibility requirements and quality standards of the Good Manufacturing Practice (GMP) guidelines [21]. Third, the synthesis procedures for some formulations are far from simple, scalable, or cost-effective [11]. In particular, it's difficult to achieve a clinically meaningful manufacturing process for ligand-coated nanoformulations [21]. To overcome these obstacles, Formulation designs and processes need to be optimized through methods that are more scientific and systematic.

The concept of quality by design (QbD) was introduced in chemical manufacturing control in 2004. It has since gained increasing attention because of its expected benefits, as Janet Woodcock described it, for a maximally efficient, agile, and flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight [22]. In the ICH Q8 guideline, QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding, as well as process control, based on sound science and quality risk management [23].

Implementing QbD involves in identifying a quality target product profile (QTPP), critical quality attributes (CQAs), and critical process parameters (CPPs). It is based on risk identification, defining the design space after executing the design of experiment (DoE) and risk analysis. A control strategy is applied during the whole process to ensure that products have a consistent and predefined quality [24]. QTPP is a prospective summary of the ideal quality characteristics of a drug product that will be achieved to ensure the desired quality, taking into account the safety and efficacy of the product; CQAs are the physical, chemical, biological, or microbiological characteristics of drug substances, excipients, intermediates (in-process materials) and products that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Finally, CPPs are variable process parameters that affect CQAs and thus should be monitored or controlled to ensure the desired quality [23].

QTPP, CQAs and CPPs are usually identified using risk assessment tools, such as risk filtering, fishbone diagrams, and FMEA [25], as well as previous experience and knowledge gained from the literature [26]. When conducting risk analysis, analysis of variance (ANOVA) and multiple linear regression are generally applied to analyze the experimental results. ANOVA is used to determine the significance of each factor and the factor interactions while multiple linear regression is used to obtain the equation of the variables [27].

The design space is the multidimensional combination and interaction of this input variables (e.g., material attributes) and process parameters that have been shown to assure quality. Working within the design space is not considered a change. Moving out of the design space is considered a change that would normally initiate a regulatory approval change process [23].

Control strategy is a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to the drug substances, drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control [23]. Process analytical technology (PAT) is a significant tool for measuring these parameters and attributes timely [22]. Widely used PAT tools include near-infrared spectroscopy [28], infrared [29] and Raman spectroscopy [30], 2-D fluorescence spectroscopy [31], UV spectroscopy [32], real-time imaging [33] and mass spectrometry [34].

Pharmaceutical QbD has brought increasing benefits for pharmaceutical companies, administrative departments and patients. For pharmaceutical plants, design space optimization, PAT application and control strategies ensure product quality and facilitate quality monitoring, in-process materials to the final products. Enhanced product stability decreases the amount of rejected products and reduces costs. For patients, robust pharmaceutical products increase efficacy and minimize side effects. Meanwhile, it makes it easier for governments to implement management, regulation, and supervision in the research, development, manufacturing, storage and clinical use of drugs.

Process development for nanosystems is still in its early stages and applying QbD in this process is beneficial and necessary. The major barriers in the manufacture and clinical application of nanosystems include the destabilization of structures and an incomplete understanding of manufacturing processes. The QbD concept emphasizes understanding of products and processes, and aimsto controll product quality in accordance with standards. Applying QbD in the formulation design and manufacturing of nanosystems is encouraging and promising.

2. Nanosystems uing QbD

2.1. Nanoliosomes using QbD

A nanoliposome is a vehicle that is composed of a lipid bilayer, from natural or synthesized phospholipids, encapsulating an aqueous phase [35]. The structure is shown in Fig. 1.

Based on particle size, number of bilayers and preparation methods, a liposome can be divided into two types: unilamellar vesicle (ULV), multilamellar vesicle (MLV). A ULV is composed of a single phospholipid bilayer sphere while a MLV is composed of numerous concentric phospholipid bilayers with an “onion” structure [36]. A ULV can be

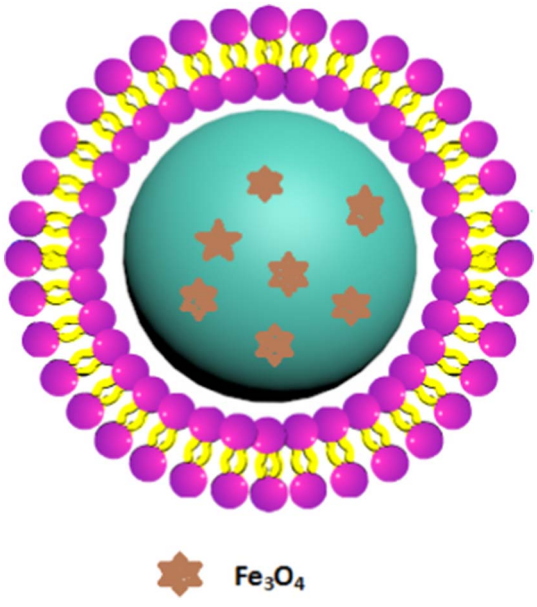

Fig. 1. Structure of nano-liposome.