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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 physico-chemical 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 into intracellular compartments [19]. Surface charge has also been found to govern electrolyte transport in carbon

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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 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 subdivided into two categories: small unilamellar vesicles (SUV), which are size less than 100 nm, and large unilamellar vesicles (LUV), which are larger than 100 nm [37].

The methods for preparing nanoliposomes include: the thin film evaporation method [36], reverse-phase evaporation method [38], solvent injection method [21], detergent depletion method [37], and supercritical fluid method [39]. Since it's easy to prepare MLVs, SUVs and LUVs are usually attained through the conversion of MLVs. Conversion methods include French press, sonication, homogenization and membrane extrusion [40].

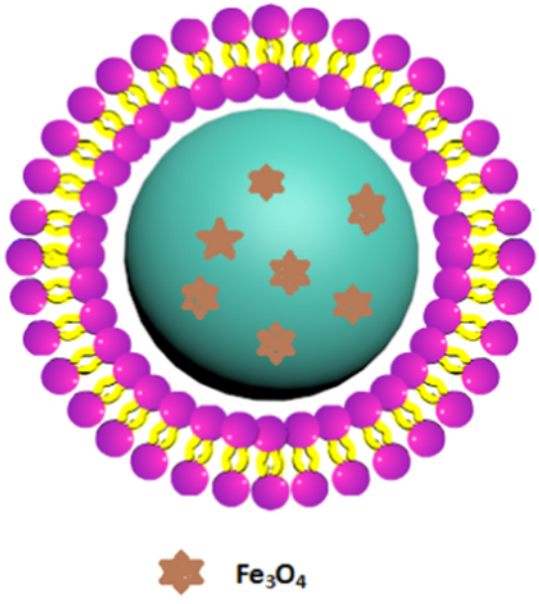

Fig. 1. Structure of nano-liposome.

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In exploring the application of QbD for nanoformulations, both microchemicals and macrocompounds have been investigated. In micromolecules, both hydrophilic and hydrophobic drugs have been considered as model drugs for improving their permeability or solubility. For macromolecules, proteins and RNA have been studied to enhance their stability and efficacy by being encapsulated in liposomes. Conventional optimization methods (e.g., the one-factor-at-a-time method), overlook the interaction of factors and possibly miss the best-optimized formulation [41]. DoE uses systematic experiments to evaluate the influences of all variables and their interactions; it achieves the maximal process understanding through minimal experiments and defines the design space [42].

2.1.1. Micromolecules in nanoliposomes using QbD

Hydrophilic drugs are linked to the hydrophilic parts of liposomes to enhance their permeability and bioavailability. Investigated drugs have included: doxorubicin [43], melittin [44], gemcitabine [45] and so on. Zhou et al. prepared the gefitinib liposome without considering the interactions of variables [46]. Costa optimized the process for freeze-thaw cycling while preparing the tenofovir liposome but without producing the design space [47].

Xu et al. applied the QbD concept in developing a liposome loaded with tenofovir using modified thin film hydration method to improve its absorption. To achieve enhanced intracellular transport and targeting, the particle liposome size and drug EE% were identified as CQAs [48]. A Plackett–Burman screening study was employed to screen the key variables influencing the EE%. The design space of EE% was defined based on selected variables, drug concentration and lipid concentration by using central composite design [49]. Pandey et al. prepared chitosan coated nanoliposomes containing tramadol using modified ethanol injection method based on QbD. They evaluated the effects of the variables on particle size, encapsulation efficiency, and coating efficiency. The results showed the suitability and robustness of the optimized design space for the formulation [50].

A hydrophobic drug with low solubility in aqueous solution, a short circulation time in the blood and limited absorption in the form of a free drug could improve its bioavailability by being entrapped in the lipid core of a liposome. Widely investigated lipophilic drugs have included benzocaine [51], curcumin [52], paclitaxel [53], cisplatin [54], Rhodamine B [55], quercetin and temozolomide [56]. Gharib et al. prepared a cyclodextrin liposome incorporating anethole based on conventional experimental methodology; however, the experiments did not consider the effects of the interactions of variables [57].

Some studies have applied QbD to prepare liposome loaded with hydrophobic drugs. Osama entrapped glimepiride (GMD) in liposome films (prepared using the phase evaporation/melting method) to enhance water solubility and gastrointestinal compliance. The defined CQAs were liposomal vesicular size, GMD entrapment capacity (GMD EC), and GMD release. Potential high-risk variables were divided into two groups. One group was the GMD-loaded liposome factors, including the concentrations of phosphatidylinositol and cholesterol, as well as drug and pH of the hydration medium. The other was the transdermal film factors, including HPMC, PG, and DMSO loading. NIR technology, as an important PAT, was applied to detect the contents of GMD in lyophilized liposome powders. Using Placket–Burmann design and risk assessment, the variables and their interactions were screened and evaluated for different CQAs [58]. Pall et al. defined the design space for spray drying process to engineer a liposome adjuvant of cationic adjuvant formulation 01 (CAF01) with trehalose as the stabilizing excipient. The identified CQAs were the mass median aerodynamic diameter (MMAD), particle size, PDI, moisture content, and yield. Based on a central composite face (CCF) centered fractional factorial design and risk analysis, the influences of the variables and their interactions on the CQAs were calculated. Finally, the optimal operation space for three CQAs (MMAD, liposome size ratio and yield) was shown in a four-dimensional modeling with regard to feedstock concentration and atomizing rate [41]. Sylvester et al. optimized the formulation of a long circulating liposome loaded with prednisolone. Using a D-optimal experimental design, the CQAs of drug concentration, EE%, and particle size have been evaluated with regard to six potential factors. The accuracy and robustness of an optimized design space has been confirmed in cell studies [59]. Zhao et al. optimized the preparation and process conditions for liposomes entrapping glycyrrhetinic acid (prepared using the film-dispersion method) based on a 3^3 factorial design and ANOVA [27].

2.2. Macromolecules in liposomes using QbD

Macromolecules referring to proteins, DNA, and RNA usually have low solubility in aqueous mediums and low permeability. Being entrapped into liposomes could improve their bioavailability and protect them from degradation. Investigated macromolecules have included: small interference RNA (siRNA) [60], oligodeoxynucleotide [61], plasmid DNA (pDNA) [62], bacteriophage [63], nitric oxide synthase [64], superoxide dismutase (SOD) [65] and bovine serum albumin [66] etc.

Kapoor et al. formulated an anionic liposome to deliver siRNA based on the conventional optimization method; the optimized variables were not shown in ranges but as specific values, which was not feasible to for manufacturing [67]. Vila-Caballer et al. prepared a bovine serum albumin liposome by evaluating the ratio of compositions without defining the design space [68].

Inspired by QbD thinking, studies have been conducted based on DoE and risk analysis in the design of liposomes containing macromolecules. Xu et al. developed an SOD liposome using film hydration method. In that study, the CQAs were defined as SOD EE%, particle size, and liposome stability. Based on a D-optimal design, the EE% response surfaces were exhibited with respect to lipid and cholesterol concentration. Only DPPC concentration was found to have a main influence on particle size. The properties of several variables affecting liposome carrier stability were considered, though no statistical design study was performed [69]. Elisabeth et al. reported a new microfluidics method for processing size-tunable liposomes containing DNA used for cell transfection. The CQAs were liposome size, polydispersity, and transfection efficiency, while the total flow rate (TFR) and flow rate ratio (FRR) were recognized as the risk variables. A DoE study was executed and then the response surface plots of the three CQAs with respect to TFR and FRR were established. Based on ANOVA, TFR and FRR both affected the size when FRR had a significant influence. For polydispersity and transfection efficiency, FRR was the only factor with significance [42].

For nanoliposomes, drugs that have been investigated using QbD include tenofovir, tramadol, glimepiride, CAF01, prednisolone, glycyrrhetinic acid, siRNA, SOD and DNA. The general procedure for implementing QbD in liposomes includes the following steps: (1) determine the entrapped compounds and their QTPPs (efficacy and stability). (2) define the formulation method and potential risk parameters (including formulation parameters such as the type and ratio of phospholipids and process parameters), (3) identify the CQAs (particle size, drug entrapment efficiency, zeta potential, and stability) of the liposomes and CPPs of specific processes based on previous knowledge and risk assessment,(4) establish the design space of the liposomes based on DoE, and (5) apply control strategy in all steps from the formulation design to the manufacturing process. Compared to liposome formulations that did not refer to the QbD concept, optimized formulations and procedures have shown more advantages. Firstly, the experimental design evaluated the influences of not only single variables but also the interactions between variables, such as the interaction between the content of different lipids. Secondly, ANOVA showed the importance of variables on the targeted product attributes and multiple linear regression obtained the formulation relationships between variables. Thirdly, drug encapsulation efficiency and stability were the two main limiting factors for liposomes. The formulations optimized by QbD exhibited enhanced drug entrapment efficiency and stability in long storing period. Fourthly, in some cases, the design space of one key process at a certain confidence level was exhibited in a specific operating area rather than a fixed process condition, which was favorable for ensuring targeted quality in manufacturing processes. Lastly, some studies took advantage of NIR for online detection, which was beneficial for continuous manufacturing processes.

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2.3. Nanoemulsions using QbD

Nanoemulsions are oil-in-water emulsions in nanoscale (average size 20–200 nm [70]), which are formed by an isotropic mixture (oil, surfactant, co-surfactant and drug) being introduced into water [71]. As a result of drugs being fused in the oil phase, nanoemulsions are widely used to deliver hydrophobic drugs, although hydrophilic drugs can also be loaded into the nanocarriers in the form of double nanoemulsions. Aside from the general advantages of nanoformulations, nanoemulsions have special benefits such as easy formulation, simple manufacturing processes, and thermodynamic stability [72]. In vivo studies have shown that nanoemulsions causeplasma concentration and drug bioavailability to reproduce well [73].

The general methods for developing nanoemulsions include the aqueous phase titration method [74], high-pressure homogenization method [75], microfluidization method, [76] solvent displacement method [72], and self-nanoemulsion method [77].

2.3.1. Micromolecules in nanoemulsions using QbD

Studied micromolecules in nanoemulsions were mainly hydrophobic compounds, including avanafil [78], ramipril [79], beta-carotene [80], and carbamazepine [81]. In preparing nanoemulsions via a new method of nonaqueous emulsification, Ding et al. investigated the factors influencing particle size, zeta potential, and transmission electron microscopy, though the interactions among factors were not considered [82].

With regard to applying QbD innanoemulsions, Zidan et al. studied thenanoemulsions loaded with cyclosporine A based on the QbD concept. A 3^3 DoE with a response surface methodology was employed to evaluate the effects of formulation variables on CQAs (particle size, nanoemulsion turbidity, amounts released after 5 and 10 min, emulsification rate and lag time) [83]. Shah et al. used a Box-Behnken DOE to conduct experiments and investigated the relevance between particle size and ultrasonic absorption. The high-level relevance between particle size and ultrasonic absorption suggested that ultrasonic measurement can be an effective PAT tool for directly and conveniently detecting particle size [71]. Poonam et al. prepared a lidocaine and prilocaine loaded nanoemulsion system employing QbD The CQAs screened by the Plackett–Burman design were particle size and PDI. Based on a 3^3 Box–Behnken design and risk analysis, the 2-D contour plots and 3-D response surface plots of the particle were established with regard to emulsifier concentration and homogenization pressure [70]. Shantanu et al. employed a holistic QbD strategy to optimize valsartan nanoemulsion systems. QTPP and CQAs (globule size, drug release in 10 min and amount permeated in 45 min) were defined and potential variables were screened based on preformulation experiments. A central composite design (CCD) was employed to study the influence of CPPs on the CQAs. The resulting design space showed its solubility and robustness in in vitro/in vivo studies compared to conventional marked formulation [84].

Innanoemulsions, micromolecular drugs, including cyclosporine A, lidocaine, prilocaine, and valsartan, have been investigated as model drugs based on QbD. The steps for applying QbD innanoemulsions include the following: (1) define QTPP based on the cargos' solubility and administration routes, (2) determine the suitable preparation method and specific parameters (formulation parameters such as the type and dosage of emulsifier and process parameters), (3) identify the CQAs (particle size, drug release, turbidity) and screen the CPPs based on prior knowledge and risk assessment, (4) conduct DoE to build design spaces, and (5) apply a process control strategy in the whole process. The benefit of using QbD in nanoemulsion preparation is that DoE offers more systemic and scientific methods for optimizing formulations. The uniformity of particle size, drug release rate and emulsification rate indicate the robustness of the defined design space.

2.4. Nanoparticles using QbD

Nanoparticles are particles in nanoscale, including nanospheres and nanocapsules. The structure of nanoparticles is shown in Fig. 2. A nanosphere is a solid matrix particle of 1–100 nm [85]. A nanocapsule is a nanoshell made from non-toxic polymer, that encapsulates an inner liquid or a semiliquid core at room temperature [86]. Compared to nanospheres, nanocapsules have high drug encapsulation efficiency due to the enhanced solubility of the drug in the core, also, their polymeric shells can reduce issue irritation and protect drug substances from degradation induced by pH and light [87].

Regarding the synthesis of nanospheres, there are two methods: the emulsion-solvent evaporation method [88] and the nanoprecipitation method [85]. For nano-capsules, there are mainly six methods, nanoprecipitation method, emulsion-diffusion method, double emulsification method, emulsion-coacervation method, polymer-coating method, and layer-by-layer method [87].

For the application of QbD in dosage forms, free nanoparticles and nanoparticles loaded with both micromolecules and macromolecules are explored.

2.4.1. Non-loaded in nanoparticles using QbD

Nanoparticles that do not incorporate chemical compounds are mainly used for diagnosis [89], charge transfer [90], catalysis [91] and so on. Investigated nanoparticles have Au nanoparticles [92], Fe_3O_4 nanoparticles [93], ZnO nanoparticles [94] and so on.

Molnar et al. investigated the effects of medium pH, the ratio of cross-linking and the molecular weight of poly(acrylic acid) on particle size but did not define the related design space [95]. After applying the QbD concept, Michael J et al. optimized the design space for a carbon dioxide-assisted nanosphere deposition process using the layers of experiment method with an adaptive combined design. The relationship between particle size and the variable, elevated temperature carbon dioxides, was evaluated [96]. Emmanuel et al. optimized the design space of PLLA nanoparticles and poly-ε-caprolactone-based nanoparticles based on a D-optimal mixture design and statistical analysis. The models (Scheffe polynomial) for particle size, percent yield of PLLA nanopar-

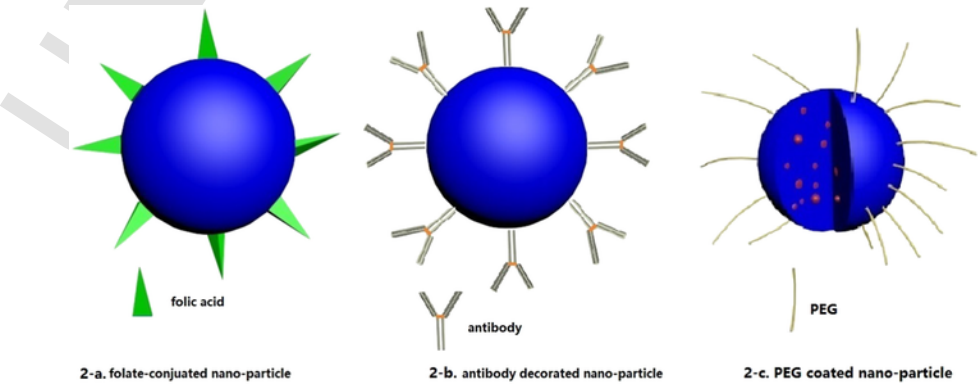

Fig. 2. Structures of nanoparticles.

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ticles, and negative surface potential of poly-ε-caprolactone-based nanoparticles were established respectively with respect to the compositions (crosslinking agent, initiator, stabilizer and macromonomer) [97].

2.4.2. Micromolecules in nanoparticles using QbD

Hydrophilic drugs, such as doxorubicin [98], glycyrrhizin [99], diclofenac sodium [100] and so on have been investigated to enhance their permeability.

Kim investigated the influence of hydrophilic additives on the supersaturation and dissolution rate when preparing dutasteride nanoparticles using a supercritical antisolvent process but without producing a design space [101]. Ali et al. evaluated the effects of variables on drug release and particle size when preparing simvastatin-tocotrienol lipid nanoparticles but without considering the interactions of variables [102].

Recently, great progress has been made in the QbD practices for preparing micromoelcules-loaded nanoparticles. As for hydrophilic drugs, Brijesh et al. prepared the solid nanoparticle of rivastigmine using homogenization and the ultrasonication method. Using a 3^3 factor design, multiple linear regression analysis and ANOVA, the influences of CPPs (lipid ratio, surfactant concentration, homogenization time) on CQAs (size, PDI, encapsulation efficiency) were investigated [103]. Joshi et al. optimized the formulation of rivastigmine loaded PLGA and PBCA nanoparticles (prepared using the nanoprecipitation technique) using factorial design, and the effects of key variables on particle size and drug entrapment percentage were studied [104]. Girotra et al. developed zolmitriptan nanoparticles (synthesized using modified double emulsion solvent diffusion technique) for brain delivery. A randomized 2^4 full factorial design was applied to optimize the conditions for achieving maximal encapsulation efficiency and minimal particle size. In vivo studies for evaluating brain uptake and pharmacodynamic studies have demonstrated the feasibility of optimized formulation [105].

For hydrophobic drugs, investigated compounds have included docetaxel [106], cisplatin [107], curcumin [108], paclitaxel [109] and so on. Das et al. investigated the optimized formulation of nanoparticles incorporating tretinoin. Product properties such as particle size, polydispersity index, zata potential and drug encapsulation were optimized based on conventional experiments without considering the interactions of variables [110].

Several examples employed QbD in nanoparticles loaded with hydrophobic drugs. For example, Se-Jin Park et al entrapped dutasteride in Eudragit E nanoparticles using the method of solvent displacement. A Plackett–Burman screening design and CCD were applied to screen CPPs and explore their specific influences on CQAs (particle size, polydispersity index and entrapment efficiency) [111]. Firat et al. optimized theoil-in-water (o/w) emulsification-solvent evaporation method for paclitaxel nanoparticles. Using a Plackett–Burman design and subsequent Box–Behnken design, the CPPs were identified and their influences on CQAs were studied [112]. Dinesh et al. prepared poly (caprolactone; PCL) nanoparticles to deliver quercetin using the nanoprecipitation method. The relationships between CQAs (particle size and polydispersity index, zata potential, in-vitro drug release) and CPPs (PCL amount and Pluronic F-127 amount) were investigated based on 3^2 factorial designs and the response surface methodology [113]. Fabrice et al. designed PLGA nanoparticles loaded with CAF01 adopting an oil-in-water single-emulsion method. The links between CPPs (acetone concentration in the water phase, stabilizer [polyvinylalcohol (PVA)] concentration, lipid-to-total solid ratio, and total concentration) and the CQAs (size, PDI, enthalpy of the phase transition and yield) were evaluated using a 2^4 factorial design and an optimal operation space was defined based on the statistical analysis [114].

Bansal et al. formulated paclitaxel nanoparticles using the desolvation technique based on a 3^2 full factorial design and response surface linear modeling was employed to predict the optimal condition [115]. Yin et al. optimized nanocapsules loaded with Lansiumamide B (prepared using the microemulsion polymerization method) via an orthogonal experiment design. However, the specific influences of variables on critical product properties were not analyzed and shown [116]. Marto et al. prepared starch-based nanocapsules loaded with coumarin-6, a hydrophobic drug using the method of emulsification solvent evaporation. Particle size and encapsulation efficiency were identified as CQAs when the influences of three-factor CCD was used to evaluate the effects of the variables on the CQAs [117]. George et al. evaluated the formulation of nanocapsules encapsulating carvedilol using a 3^2 factorial design and the effectiveness of QbD in formulation optimization was confirmed in the resulting product's properties and in vitro studies [118].

2.4.3. Macromolecules in nanoparticles using QbD

Nanoparticles have also been applied for delivering macromolecules, such as siRNA [119], DNA [120], bovine serum albumin [121] etc.

Cun et al. investigated the influences of different variables on particle size uniformity and encapsulation efficiency when preparing siRNA nanoparticles using the method of double emulsion solvent evaporation, however, the design space was not defined [122].

Dongmei also prepared PLGA nanocapsules containing siRNA using the method of double emulsion solvent evaporation. Particle size and encapsulation efficiency were identified as CQAs when the influences of five potential variables were evaluated using a 2^{5-1} fractional factorial design. Based on risk analysis, PLGA concentration had the most influence on particle size while encapsulation efficiency was affected mainly by PLGA concentration and volume ratio [123].

For nanoparticles, investigated drugs have included rivastigmine, zolmitriptan, dutasteride, quercetin, paclitaxel, CAF01, lansiumamide B, coumarin-6, and siRNA. The routine for implementing QbD in nanoparticles preparation is as follows: (1) determine the preparation method according to the cargo's property and the type of nanoparticles, (2) define the CQAs (particle size, PDI, encapsulation efficiency and drug release) of the formulation and the CPPs of the preparation process based on risk analysis under the guidance of the literature and prior experience, (3) establish a design space based on DoE, and(4) verify the feasibility and robustness of the built design space. Synthetic accessibility and robustness in preparing nanoparticles were achieved after using QbD in the process. When DoE is employed in designing nanoparticle formulation, formulation factors and process parameters are investigated more systematically, creating a more united particle size and improved encapsulation efficiency. Risk analysis determines the significance of every variable and provides evidence for monitoring critical parameters, such as the proportion ratio of surfactant, organic phase, and drug concentration etc. Moreover, using PAT in the process makes process control easier. The robustness of the design space helps minimize the difference between in batch and intra batch, which is favorable in manufacturing.

2.5. Nanomicelles using QbD

Nanomicelles are composed of amphiphilic surfactants or polymers that surround a hydrophobic core [2]. Nanomicelles have been developed extensively to deliver hydrophobic drugs with poor solubility. Studies have shown that the nanomicelles can be disassembled based on kinetically controlled mechanisms, which leads to a longer circulating time in the blood and reduced off-target toxicity due to decreased biodistribution [124]. Aside from this purpose, nanomicelles are also used in imaging by encapsulating contrast groups. They can be modified with aptamer to achieve the specific targeting of focal sites. For example, Jiangwei et al. designed a type of nanomicelle that was loaded with a fluorescent probe, NIR photosensitizer and cancer-specific ligand to target tumor sites and achieve NIR therapy [125]. Compared with other nanoformulations, nanomicelle is smaller, which is advantageous for transdermal drug delivery and crossing through leaky vasculature to tumor sites [126].

Micelles are formed at the critical micelle concentration (CMC) when the amphiphiles aggregate and self-assemble in the aqueous solution, along with the increase in concentration. Amphiphilic polymers have been preferred because of their low CMC, which keeps resulting micelle stable in the low polymer concentration resulting from the dilution by fluid, such as blood [126]. Block polymers have different types according to different arrangements: A-B type (biblock polymers), A-B-A type (triblock polymers) [127], and grafted

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polymers which consist of a linear backbone of one composition and randomly distributed branches of a different composition [128].

According to the physico-chemical properties of copolymers, there are different methods for preparing micelles. Micelles are generally formed by the self-assembly of amphiphilic polymers in the aqueous phase [127]. There are several methods for preparing nanomicelles according to the properties of polymers: direct dissolution for moderately hydrophobic copolymers [128], solvent removal method for amphiphilic polymers [127], thin film hydration when the organic phase is not soluble in water [129], and self-assembly method through ultrasonic emulsification [130].

2.5.1. Micromolecules in nanomicelles using QbD

Although the practices were limited in the micromolecules, nanomicelles have been developed using a QbD approach mainly for hydrophobic drugs such as mitoxantrone [131], gambogic acid [132], resveratrol [133], andrographolide [134], carbamazepine and nifedipine [135] etc.

Dai et al. studied the mechanism of ginsenoside Ro as a biosurfactant to enhance the solubility of saikosaponin-a. and developed self-assembly vehicles while not employing the QbD concept [136,137]. Fan et al. prepared the camptothecin nanomicelle to enhance its solubility; they evaluated the factors related to particle size, solubility, and micelle stability of micelles but didn't produce defined design space [138]. Dai et al. investigated platycodin as a potential carrier for preparing nanomicelles based on dissipative particle dynamics; however, they did not apply the QbD concept or produce a design space for the process [139].

Ravi et al. optimized two methods (film hydration and a new method) for preparing dexamethasone loaded nnaomicelles using the response surface methodology. The design space for drug solubility was established with respect to polymer amounts and dexamethasone amounts [140]. Kuchekar et al. developed a polymeric micelle encapsulating capecitabine based on a QbD approach. Significant process and formulation factors were evaluated and the suitability and robustness of the resulting design space was confirmed within different characterization parameters and in vitro studies [141]. Jinming et al. designed TPGS-g-PLGA/Pluronic F68 mixed micelles using thin film hydration to deliver tanshinone IIA and enhance its solubility and bioavailability. CCD and ANOVA were applied to investigate the effects of three CPPs on the CQAs (encapsulation efficiency and drug loading percentage). The optimized result showed in the response surfaces that the results of the overall desirability values of the two CQAs changed along with the three CPPs [142]. Ashwin et al. optimized the preparation conditions (eight formulation and process parameters) for capecitabine-loaded polymeric micelles using an o/w emulsion technique based on the Plackett-Burman design. The effects of these variables on the CQAs (drug content, entrapment efficiency, particle size and zeta potential) were shown in Pareto charts [143].

Investigated micromolecules in nanomicelles based on QbD concept have included dexamethasone, capecitabine, tanshinone IIA, and capecitabine. The procedures for using QbD in nanomicelles are as follows: (1) select the polymers and corresponding preparation method, (2) determine the CQAs of the nanomicelles (particle size, drug encapsulation efficiency, stability, etc.) and CPPs of the process based on prior knowledge and risk assessment, and (3) produce a design space and demonstrate its robustness and feasibility. Self-assembled polymeric micelles are formed gradually when the polymer concentration reaches CMC, whose destabilization in the dilution of blood is a major problem. Meanwhile, a small particle size is an advantage for the dosage form. Employing QbD in preparing nanomicelles provides holistic methods for screening and evaluating formulation and process parameters, which helps to obtain more stable micelles with minimal particle size and maximal drug encapsulation. Meanwhile, an effective and robust design space can help to minimize the differences between batches in the manufacturing process.

2.6. Nanosuspensions using QbD

Nanosuspensions are colloidal dispersions of drug particles stabilized in the presence of polymers, surfactants or both [144], which are used to deliver drug substances with poor solubility in aqueous and lipid solution [145]. Nanosuspensions have other benefits for nano-suspensions, such as application in intravenous administration to increase efficacy, pulmonary drug delivery to enhance deep-lung permeation, and ocular drug delivery for sustained release [145,146]. There are two main procedures for preparing nanosuspensions, which are the bottom-up process [147] and the top-down procedure [148]. Considering dosage stability and patent convenience, liquid nanosuspensions are often transferred to solid dosage forms.

In exploring QbD application in nanoformulations, nanosuspensions have been studied mainly for micromolecules, especially hydrophobic drugs such as isradipine [149], felodipine [150], olmesartan medoxomil [151], and paclitaxel [152] etc. Hsien studied the formulation of antimony-doped tin oxide nanosuspensions but did not investigate the specific influences of variables on critical properties, particle size or stability [86].

QbD application in nanosuspension has made progress in recent years. Sudhir et al. optimized the unit process for microfluidization in preparing indomethacin-loaded nano-suspensions using QbD. The identified CQAs were particle size, zeta potential, and the physical form of the drugs. A $2^{(5-1)}$ factorial design was performed, and multiple linear regression analysis and ANOVA were subsequently performed to analyze the influences of the variables on the CQAs [144]. Sumit et al. studied indomethacin crystalline nanouspension using the method of spray drying. The investigated CQAs were particle size, moisture content, percent yield and crystallinity. A full factorial design 2^3 was utilized and multiple linear regression analysis and ANOVA were conducted to evaluate the influences of the critical parameters. A design space of dry spraying to process the nanosuspensions was established [153]. Ghosh et al. optimized the formulation of a nanosuspension using the top-down media milling process. Based on DoE and risk analysis, the risk factors were evaluated and the optimized design space showed its suitability and consistency under different characterization parameters [154].

In summary, several compounds, such as indomethacin, have been studied using QbD thinking, such as, indomethacin. The procedure for implementing QbD in nanosuspensions includes the following steps: (1) determine the stabilizers and preparation method according to QTPP, (2) define the CQAs (particle size, stability etc.) and CPPs based on prior knowledge when conducting risk assessment, and (3) conduct DoE to build a design space and verify its feasibility and robustness. Using the QbD concept in the dosage form shows its advantages in comparison with traditional optimization methods. The benefits are reflected in the comprehensive and systematic considerations of influences from variables (e.g., type and amount of stabilizer), which is helpful for achieving minimal particle size, good crystallinity, and a high yield percentage. Identifying CPPs through risk analysis will provide reference for process monitoring in manufacturing. A robust and suitable design space ensures uniform product qualities (e.g., particle size, drug encapsulation efficiency, zeta potential.) between different batches.

3. Roadmap for implementing QbD for nanosystems

As shown in Fig. 3, the steps for applying QbD in nanosystems involve identifying QTPP, CQAs, and CPPs, as well as building a design space based on previous knowledge and research. Risk analysis and control strategies are conducted throughout the whole process. Finally, the design space is examined and adjusted to correspond to manufacturing needs.

(1) Identifying QTPP
Defining QTPP is based on prior scientific knowledge and in vivo relevance, which refers to dosage form, route of administration, therapeutic moiety release, pharmaceutical properties suitable for intended market product, etc. [22].
(2) Identifying CQAs
After identifying QTPP, the next step is to identify CQAs. CQAs are usually identified through risk identification based on prior knowledge and research experience. The most-determined CQAs for nanosystems include

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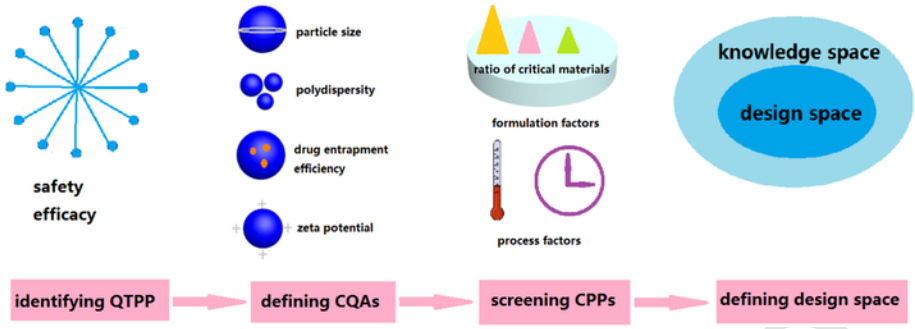

Fig. 3. Routine for implementing QbD in nano-systems. The identified QTPP was mainly about the safety and efficacy of the nano-medicines. The widely defined CQAs included vehicles' particle size, polydispersity, drug encapsulation efficiency as well as zeta potential. The CPPs investigated were divided into formulation factors and process factors. The formulation factors were mainly about the types of raw materials, such as surfactant and amphiphilic polymers; and the ratio among the critical materials. The process factors mainly referred to the process method, the temperature and time for preparing nano-systems. The design space was built based on the previous knowledge space and experiments.

particle size, polydispersity index, zeta potential, drug encapsulation efficiency and stability.

(3) Screening CPPs
Potential risk variables are usually screened using Placket–Burmann design followed by risk analysis.

(4) Defining the design space
The design space includes the product design space and process design space. The product design space is established with various CQAs as the dimensions. Once the variability of the CQAs is determined, the process design space can be formed which is exhibited as CQAs with respect to CPPs. The steps include the following: conduct DoE to study the process, perform risk analysis to identify the influences of variables on CQAs, and determine the operation region based on a predefined confidence level. It should be noted that determining the design space relies on multivariate experimentation that considers the main effects of factors and their interactions [22].

(5) Defining the control strategy
Compared with traditional control strategies, QbD control strategy is a dynamic strategy that usually combines two control levels. Level 1 is a real-time automatic control that monitors the CQAs of materials and automatically adjusts process parameters. Level 2 involves the reduced testing of end-products and adjusting CPPs and CQAs flexibly within the design space [24].

(6) Process validation and filling
Once the design space and control strategy are defined, it is necessary to examine whether a product processed within the design space meets the targeted quality criteria [155]. It is also necessary to confirm that the design space, at the lab or pilot scale, is suitable for application on a manufacturing scale [22]. The regulatory filling is then documented, which should include the design space with the defined range of CQAs and CPPs.

4. Conclusion

Nanomedicines have attracted extensive interest due to theirpromising application in curing intractable diseases (e.g., cancer, Parkinson's disease [156]), and in non-invasive diagnosis. However, nanoproduct instability, process uncertainty and manufacturing difficulties hinder their comprehensive application. The benefits of the QbD concept have been repeatedly confirmed in pharmaceutical manufacturing, and its procedures have reached to maturity stage. Its emphasis on process understanding and robust product quality provides a solution to the problems hindering nanomedicine production. QbD identifies critical product qualities and related influence factors and investigates the effects of factors based on scientific DoE and risk assessment.

Unlike traditional optimization methods, QbD considers the interaction of variables and clearly shows the optimized result in the form of a design space rather than a fixed process condition. It also emphasizes employing a control strategy to monitor product quality and variability in process parameters. Studies of nanomedicine employing QbD have succeeded in identifying CQAs and establishing design spaces for specific processes for specific type of nanomedicine. Despite such advances, there is still room for improvement. First, the application of QbD in nanomedicine processes is not comprehensive. For some dosages (e.g., nanocrystals, nanotubes and nanogels), there are few studies on QbD optimization. Second, the application of QbD in nanoformulations is still limited to simple nanostructures. Ligand or antibody coating nanostructures have yet to be investigated for optimization through QbD. Third, different CQAs have different optimized design spaces. How to combine these design spaces is a question that requires further investigation. Fourth, the use of PAT in preparing nanomedicine is insufficient. Employing PAT is a prerequisite for achieving dynamic control in manufacturing processes.

More systemic studies employing the QbD concept should be conducted in the future. More PAT tools for nanosystem manufacturing should be developed and applied. There is promise that nano-systems will achieve wide clinical application under the guidance of the QbD concept.

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Reference

[1] J. Jeevanandam, Y.S. Chan, M.K. Danquah, Nano-formulations of drugs: recent developments, impact and challenges, Biochimie 128–129 (2016) 99–112.
[2] Srinivas Ganta, Amit Singh, Timothy P. Coleman, David Williams, M. Amiji, Pharmaceutical Nanotechnology: Overcoming Drug Delivery Challenges in Contemporary Medicine, 2014196–200 (Chapter 10).
[3] J. H, An ein kolloidales blutplasmaersatzmittel (polyvinylpyrrolidon) gebundenes peptamin (glycyl L-leucyl-mezcalin) als neuartige depotform fur biologisch aktive primare amine (mezcalin), Z. Naturforsch. B 10 (1955) 27–31.
[4] A.D. Bangham, R.W. H., Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope, J. Mol. Biol. 8 (1964) 660–668.
[5] U. Scheffel, B.A. Rhodes, T.K. Natarajan, H.N. Wagner Jr., Albumin microspheres for study of the reticuloendothelial system, J. Nucl. Med. 13 (1972) 498–503.
[6] F. Vitek, T. Blazek, Z. Dienstbier, Double-tracer method for determining the proteolytical activity of RES in X-irradiated rats using 131I-labelled albumin microspheres, Strahlentherapie 148 (1974) 320–325.
[7] J. Meng, F.Q. Guo, H.Y. Xu, W. Liang, C. Wang, X.D. Yang, Combination therapy using co-encapsulated resveratrol and paclitaxel in liposomes for drug resistance reversal in breast cancer cells in vivo, Sci. Report. 6 (2016) 11.
[8] S.Y. Xiao, C.Y. Tong, X.M. Liu, D.M. Yu, Q.L. Liu, C.G. Xue, D.Y. Tang, L.J. Zhao, Preparation of folate-conjugated starch nanoparticles and its application to tumor-targeted drug delivery vector, Chin. Sci. Bull. 51 (2006) 1693–1697.
[9] S.S. Banerjee, D.H. Chen, Grafting of 2-hydroxypropyl-beta-cyclodextrin on gum arabic-modified iron oxide nanoparticles as a magnetic carrier for targeted delivery of hydrophobic anticancer drug, Int. J. Appl. Ceram. Technol. 7 (2010) 111–118.

UNCORRECTED PROOF

[10] Z.L. Chen, M. Huang, X.R. Wang, J. Fu, M. Han, Y.Q. Shen, Z. Xia, J.Q. Gao, Transferrin-modified liposome promotes alpha-mangostin to penetrate the blood-brain barrier, Nanomed. Nanotechnol. Biol. Med. 12 (2016) 421–430.
[11] F. Tang, L. Li, D. Chen, Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery, Adv. Mater. 24 (2012) 1504–1534.
[12] A. Albanese, P.S. Tang, W.C. Chan, The effect of nanoparticle size, shape, and surface chemistry on biological systems, Annu. Rev. Biomed. Eng. 14 (2012) 1–16.
[13] Y.F. Ye, X.H. Hu, A pH-sensitive injectable nanoparticle composite hydrogel for anticancer drug delivery, J. Nanomater. 8 (2016).
[14] X.J. Liu, Y. Chen, Q.L. Huang, W. He, Q.L. Feng, B. Yu, A novel thermo-sensitive hydrogel based on thiolated chitosan/hydroxyapatite/beta-glycerophosphate, Carbohydr. Polym. 110 (2014) 62–69.
[15] J. Li, M.R. Huo, J. Wang, J.P. Zhou, J.M. Mohammad, Y.L. Zhang, Q.N. Zhu, A.Y. Waddad, Q. Zhang, Redox-sensitive micelles self-assembled from amphiphilic hyaluronic acid-deoxycholic acid conjugates for targeted intracellular delivery of paclitaxel, Biomaterials 33 (2012) 2310–2320.
[16] N. Ngernyuang, W. Seubwai, S. Daduang, P. Boonsiri, T. Limpaiboon, J. Daduang, Targeted delivery of 5-fluorouracil to cholangiocarcinoma cells using folic acid as a targeting agent, Mater. Sci. Eng. C Mater. Biol. Appl. 60 (2016) 411–415.
[17] M. Gonzales-Weimuller, M. Zeisberger, K.M. Krishnan, Size-dependant heating rates of iron oxide nanoparticles for magnetic fluid hyperthermia, J. Magn. Magn. Mater. 321 (2009) 1947–1950.
[18] M. Nidhin, R. Indumathy, K.J. Sreeram, B.U. Nair, Synthesis of iron oxide nanoparticles of narrow size distribution on polysaccharide templates, Bull. Mater. Sci. 31 (2008) 93–96.
[19] S. Kralj, M. Rojnik, R. Romih, M. Jagodic, J. Kos, D. Makovec, Effect of surface charge on the cellular uptake of fluorescent magnetic nanoparticles, J. Nanopart. Res. 14 (2012) 14.
[20] J.M. Xue, P. Guo, Q. Sheng, Surface-charge-governed electrolyte transport in carbon nanotubes, Chin. Phys. B 24 (2015) 7.
[21] J.C. Kraft, J.P. Freeling, Z. Wang, R.J. Ho, Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems, J. Pharm. Sci. 103 (2014) 29–52.
[22] A.S. Rathore, Roadmap for implementation of quality by design (QbD) for biotechnology products, Trends Biotechnol. 27 (2009) 546–553.
[23] I.C.o. Harmonisation, ICH Harmonised Tripartite Guideline: Q8 (R1) Pharamaceutical Development, 2008.
[24] L.X. Yu, G. Amidon, M.A. Khan, S.W. Hoag, J. Polli, G.K. Raju, J. Woodcock, Understanding pharmaceutical quality by design, AAPS J. 16 (2014) 771–783.
[25] Jun Huang, Goldi Kaul, Chunsheng Cai, Ramarao Chatlapalli, Pedro Hernandez-Abad, Krishnendu Ghosh, A. Nagi, Quality by design case study an integrated multivariate approach to drug product and process development, Int. J. Pharm. 382 (2009) 23–32.
[26] E. Pallagi, R. Ambrus, P. Szabo-Revesz, I. Csoka, Adaptation of the quality by design concept in early pharmaceutical development of an intranasal nanosized formulation, Int. J. Pharm. 491 (2015) 384–392.
[27] X. Zhao, J. Liu, Y. Hu, Y. Fan, D. Wang, J. Yuan, L. Xu, L. Cui, Z. Jing, Optimization on condition of glycyrrhetinic acid liposome by RSM and the research of its immunological activity, Int. J. Biol. Macromol. 51 (2012) 299–304.
[28] Z.S. Wu, Y.F. Peng, W. Chen, B. Xu, Q. Ma, X.Y. Shi, Y.J. Qiao, NIR spectroscopy as a process analytical technology (PAT) tool for monitoring and understanding of a hydrolysis process, Bioresour. Technol. 137 (2013) 394–399.
[29] Z. Rahman, A.S. Zidan, M.J. Habib, M.A. Khan, Understanding the quality of protein loaded PLGA nanoparticles variability by Plackett-Burman design, Int. J. Pharm. 389 (2010) 186–194.
[30] H.Q. Wu, M.A. Khan, Quality-by-Design (QbD): an integrated Process Analytical Technology (PAT) approach for real-time monitoring and mapping the state of a pharmaceutical coprecipitation process, J. Pharm. Sci. 99 (2010) 1516–1534.
[31] G.A. Lott, A. Perdomo-Ortiz, J.K. Utterback, J.R. Widom, A. Aspuru-Guzik, A.H. Marcus, Conformation of self-assembled porphyrin dimers in liposome vesicles by phase-modulation 2D fluorescence spectroscopy, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 16521–16526.
[32] P. Billot, M. Couty, P. Hosek, Application of ATR-UV spectroscopy for monitoring the crystallisation of UV absorbing and nonabsorbing molecules, Org. Process. Res. Dev. 14 (2010) 511–523.
[33] C. Zhang, C.H. Li, L.H.V. Wang, Fast and robust deconvolution-based image reconstruction for photoacoustic tomography in circular geometry: experimental validation, IEEE Photonics J. 2 (2010) 57–66.
[34] Mathieu Streefland, Dirk E. Martens, E. Coen Beuvery, R.H. Wijffels, Process analytical technology (PAT) tools for the cultivation step in biopharmaceutical production, Eng. Life Sci. 13 (2012) 212–223.
[35] Y. Malam, M. Loizidou, A.M. Seifalian, Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer, Trends Pharmacol. Sci. 30 (2009) 592–599.
[36] Abolfazl Akbarzadeh, Rogaie Rezaei-Sadabady, Soodabeh Davaran, Sang Woo Joo, Nosratollah Zarghami, Younes Hanifehpou, Mohammad Samiei, Mohammad Kouhi, K. Nejati-Koshki, Liposome: classification, preparation, and applications, Nanoscale Res. Lett. 8 (2013) 102.
[37] B. Maherani, E. Arab-Tehrany, M.R. Mozafari, C. Gaiani, M. Linder, Liposomes: a review of manufacturing techniques and targeting strategies, Curr. Nanosci. 7 (2011) 436–452.
[38] J. Huang, G.J. Gou, B. Xue, Q.S. Yan, Y. Sun, L.E. Dong, Preparation and characterization of "dextran-magnetic layered double hydroxide-fluorouracil" targeted liposomes, Int. J. Pharm. 450 (2013) 323–330.
[39] W.-C. Tsai, S.S.H. Rizvi, Liposomal microencapsulation using the conventional methods and novel supercritical fluid processes, Trends Food Sci. Technol. 55 (2016) 61–71.
[40] Y.P. Patil, S. Jadhav, Novel methods for liposome preparation, Chem. Phys. Lipids 177 (2014) 8–18.
[41] P.T. Ingvarsson, M. Yang, H. Mulvad, H.M. Nielsen, J. Rantanen, C. Foged, Engineering of an inhalable DDA/TDB liposomal adjuvant: a quality-by-design approach towards optimization of the spray drying process, Pharm. Res. 30 (2013) 2772–2784.
[42] E. Kastner, R. Kaur, D. Lowry, B. Moghaddam, A. Wilkinson, Y. Perrie, High-throughput manufacturing of size-tuned liposomes by a new microfluidics method using enhanced statistical tools for characterization, Int. J. Pharm. 477 (2014) 361–368.
[43] L.M. Kaminskas, V.M. McLeod, B.D. Kelly, G. Sberna, B.J. Boyd, M. Williamson, D.J. Owen, C.J.H. Porter, A comparison of changes to doxorubicin pharmacokinetics, antitumor activity, and toxicity mediated by PEGylated dendrimer and PEGylated liposome drug delivery systems, Nanomed. Nanotechnol. Biol. Med. 8 (2012) 103–111.
[44] L. Zhou, G. Narsimhan, X.Y. Wu, F.P. Du, Pore formation in 1,2-dimyristoyl-sn-glycero-3-phosphocholine/cholesterol mixed bilayers by low concentrations of antimicrobial peptide melittin, Colloids Surf. B Biointerfaces 123 (2014) 419–428.
[45] J.P. May, E. Undzys, A. Roy, S.D. Li, Synthesis of a gemcitabine prodrug for remote loading into liposomes and improved therapeutic effect, Bioconjug. Chem. 27 (2016) 226–237.
[46] X.J. Zhou, B. Yung, Y.F. Huang, H. Li, X.M. Hu, G.Y. Xiang, R.J. Lee, Novel Liposomal Gefitinib (L-GEF) formulations, Anticancer Res. 32 (2012) 2919–2923.
[47] A.P. Costa, X.M. Xu, D.J. Burgess, Freeze-anneal-thaw cycling of unilamellar liposomes: effect on encapsulation efficiency, Pharm. Res. 31 (2014) 97–103.
[48] X.M. Xu, M.A. Khan, D.J. Burgess, A quality by design (QbD) case study on liposomes containing hydrophilic API: I. Formulation, processing design and risk assessment, Int. J. Pharm. 419 (2011) 52–59.
[49] X. Xu, M.A. Khan, D.J. Burgess, A quality by design (QbD) case study on liposomes containing hydrophilic API: II. Screening of critical variables, and establishment of design space at laboratory scale, Int. J. Pharm. 423 (2012) 543–553.
[50] A.P. Pandey, K.P. Karande, R.O. Sonawane, P.K. Deshmukh, Applying quality by design (QbD) concept for fabrication of chitosan coated nanoliposomes, J. Liposome Res. 24 (2014) 37–52.
[51] P. Mura, F. Maestrelli, M.L. Gonzalez-Rodriguez, I. Michelacci, C. Ghelardini, A.M. Rabasco, Development, characterization and in vivo evaluation of benzocaine-loaded liposomes, Eur. J. Pharm. Biopharm. 67 (2007) 86–95.
[52] L. Li, F.S. Braiteh, R. Kurzrock, Liposome-encapsulated curcumin - in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis, Cancer 104 (2005) 1322–1331.
[53] T. Yang, F.D. Cui, M.K. Choi, J.W. Cho, S.J. Chung, C.K. Shim, D.D. Kim, Enhanced solubility and stability of PEGylated liposomal paclitaxel: in vitro and in vivo evaluation, Int. J. Pharm. 338 (2007) 317–326.
[54] L.Z. Feng, M. Gao, D.L. Tao, Q. Chen, H.R. Wang, Z.L. Dong, M.W. Chen, Z. Liu, Cisplatin-prodrug-constructed liposomes as a versatile theranostic nanoplatform for bimodal imaging guided combination cancer therapy, Adv. Funct. Mater. 26 (2016) 2207–2217.
[55] B.K. Kim, Y.B. Seu, J.S. Choi, J.W. Park, K.O. Doh, Synthesis and validation of novel cholesterol-based fluorescent lipids designed to observe the cellular trafficking of cationic liposomes, Bioorg. Med. Chem. Lett. 25 (2015) 3893–3896.
[56] J. Hu, J.J. Wang, G. Wang, Z.J. Yao, X.Q. Dang, Pharmacokinetics and antitumor efficacy of DSPE-PEG2000 polymeric liposomes loaded with quercetin and temozolomide: analysis of their effectiveness in enhancing the chemosensitization of drug-resistant glioma cells, Int. J. Mol. Med. 37 (2016) 690–702.
[57] R. Gharib, H. Greige-Gerges, A. Jraij, L. Auezova, C. Charcosset, Preparation of drug-in-cyclodextrin-in-liposomes at a large scale using a membrane contactor: application to trans-anethole, Carbohydr. Polym. 154 (2016) 276–286.
[58] O.A. Ahmed, M. Kurakula, Z.M. Banjar, M.I. Afouna, A.S. Zidan, Quality by design coupled with near infrared in formulation of transdermal glimepiride liposomal films, J. Pharm. Sci. 104 (2015) 2062–2075.
[59] B. Sylvester, A. Porfire, D.-M. Muntean, L. Vlase, L. Lupuţ, E. Licarete, A. Sesarman, M.C. Alupei, M. Banciu, M. Achim, I. Tomuţă, Optimization of prednisolone-loaded long-circulating liposomes via application of Quality by Design (QbD) approach, J. Liposome Res. (2016) 1–13.
[60] P.Y. Xie, X.C. Meng, Z.Y. Zhou, MRI-visible liposome for targeted therapy in combination with sorafenib and MAPK14 siRNA aimed at overcoming resistant hepatocellular carcinoma, Hepatology 63 (2016) 269A–270A.
[61] S.D. Li, L. Huang, Targeted delivery of antisense oligodeoxynucleotide and small interference RNA into lung cancer cells, Mol. Pharm. 3 (2006) 579–588.
[62] S.C. Hyde, I.A. Pringle, S. Abdullah, A.E. Lawton, L.A. Davies, A. Varathalingam, G. Nunez-Alonso, A.M. Green, R.P. Bazzani, S.G. Sumner-Jones, M. Chan, H. Li, N.S. Yew, S.H. Cheng, A.C. Boyd, J.C. Davies, U. Griesenbach, D.J. Porteous, D.N. Sheppard, F.M. Munkonge, E. Alton, D.R. Gill, CpG-free plasmids confer reduced inflammation and sustained pulmonary gene expression, Nat. Biotechnol. 26 (2008) 549–551.
[63] S. Singla, K. Harjai, K. Raza, S. Wadhwa, O.P. Katare, S. Chhibber, Phospholipid vesicles encapsulated bacteriophage: a novel approach to enhance phage biodistribution, J. Virol. Methods 236 (2016) 68–76.
[64] R.H. Perera, P.M. Peiris, S.F. Peteu, M. Bayachou, Nitric oxide synthase encapsulation in liposomes: a potential delivery platform to (nitric oxide)-deficient targets, Electroanalysis 24 (2012) 37–41.
[65] S. Zhang, Y. Cao, L. Xie, D.R. Qiao, Y. Cao, Effect of superoxide dismutase-entrapped liposomes and protein transduction domain-superoxide dismutase on human umbilical vein endothelial cells, Mol. Med. Rep. 9 (2014) 1427–1433.
[66] W.L. Liu, A.G. Ye, W. Liu, C.M. Liu, J.Z. Han, H. Singh, Behaviour of liposomes loaded with bovine serum albumin during in vitro digestion, Food Chem. 175 (2015) 16–24.
[67] M. Kapoor, D.J. Burgess, Efficient and safe delivery of siRNA using anionic lipids: formulation optimization studies, Int. J. Pharm. 432 (2012) 80–90.
[68] M. Vila-Caballer, G. Codolo, F. Munari, A. Malfanti, M. Fassan, M. Rugge, A. Balasso, M. de Bernard, S. Salmaso, A pH-sensitive stearoyl-PEG-poly(methacryloyl sul-

UNCORRECTED PROOF

fadimethoxine)-decorated liposome system for protein delivery: an application for bladder cancer treatment, J. Control. Release 238 (2016) 31–42.
[69] X.M. Xu, A.P. Costa, M.A. Khan, D.J. Burgess, Application of quality by design to formulation and processing of protein liposomes, Int. J. Pharm. 434 (2012) 349–359.
[70] P. Negi, B. Singh, G. Sharma, S. Beg, O.P. Katare, Biocompatible lidocaine and prilocaine loaded-nanoemulsion system for enhanced percutaneous absorption: QbD-based optimisation, dermatokinetics and in vivo evaluation, J. Microencapsul. 32 (2015) 419–431.
[71] R.B. Shah, A.S. Zidan, T. Funck, M.A. Tawakkul, A. Nguyenpho, M.A. Khan, Quality by design: characterization of self-nano-emulsified drug delivery systems (SNEDDs) using ultrasonic resonator technology, Int. J. Pharm. 341 (2007) 189–194.
[72] A. Qadir, M.D. Faiyazuddin, M.D. Talib Hussain, T.M. Alshammari, F. Shakeel, Critical steps and energetics involved in a successful development of a stable nanoemulsion, J. Mol. Liq. 214 (2016) 7–18.
[73] S. Shafiq, F. Shakeel, S. Talegaonkar, F.J. Ahmad, R.K. Khar, M. Ali, Development and bioavailability assessment of ramipril nanoemulsion formulation, Eur. J. Pharma. Biopharm. 66 (2007) 227–243.
[74] F. Shakeel, M. Iqbal, E. Ezzeldin, Bioavailability enhancement and pharmacokinetic profile of an anticancer drug ibrutinib by self-nanoemulsifying drug delivery system, J. Pharm. Pharmacol. 68 (2016) 772–780.
[75] A. Ali, G. Mekhloufi, N. Huang, F. Agnely, Beta-lactoglobulin stabilized nanemulsions-formulation and process factors affecting droplet size and nanoemulsion stability, Int. J. Pharm. 500 (2016) 291–304.
[76] L. Bai, S.Q. Huan, J.Y. Gu, D.J. McClements, Fabrication of oil-in-water nanoemulsions by dual-channel microfluidization using natural emulsifiers: saponins, phospholipids, proteins, and polysaccharides, Food Hydrocoll. 61 (2016) 703–711.
[77] H.S.S. Qhattal, S. Wang, T. Salihima, S.K. Srivastava, X.L. Liu, Nanoemulsions of cancer chemopreventive agent benzyl isothiocyanate display enhanced solubility, Dissolution, and Permeability, J. Agric. Food Chem. 59 (2011) 12396–12404.
[78] K.A. Soliman, H.K. Ibrahim, M.M. Ghorab, Formulation of avanafil in a solid self-nanoemulsifying drug delivery system for enhanced oral delivery, Eur. J. Pharm. Sci. 93 (2016) 447–455.
[79] S. Shafiq, F. Shakeel, S. Talegaonkar, F.J. Ahmad, R.K. Khar, M. Ali, Development and bioavailability assessment of ramipril nanoemulsion formulation, Eur. J. Pharm. Biopharm. 66 (2007) 227–243.
[80] C. Qian, E.A. Decker, H. Xiao, D.J. McClements, Physical and chemical stability of beta-carotene-enriched nanoemulsions: influence of pH, ionic strength, temperature, and emulsifier type, Food Chem. 132 (2012) 1221–1229.
[81] R.G. Kelmann, G. Kuminek, H.F. Teixeira, L.S. Koester, Carbamazepine parenteral nanoemulsions prepared by spontaneous emulsification process, Int. J. Pharm. 342 (2007) 231–239.
[82] F.C. Ding, Y.J. Tong, X.L. Luo, H.M. Guan, B.H. Hu, Preparation, characterization, and properties of polyamic acid nano-emulsion, Polym. Adv. Technol. 22 (2011) 2633–2637.
[83] A.S. Zidan, O.A. Sammour, M.A. Hammad, N.A. Megrab, M.J. Habib, M.A. Khan, Quality by design: understanding the formulation variables of a cyclosporine a self-nanoemulsified drug delivery systems by Box-Behnken design and desirability function, Int. J. Pharm. 332 (2007) 55–63.
[84] S. Bandyopadhyay, S. Beg, O.P. Katare, G. Sharma, B. Singh, QbD-oriented development of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) of valsartan with improved biopharmaceutical performance, Curr. Drug Deliv. 12 (2015) 544–563.
[85] C. Vauthier, K. Bouchemal, Methods for the preparation and manufacture of polymeric nanoparticles, Pharm. Res. 26 (2009) 1025–1058.
[86] Q. Tan, G. Yu, Y. Liao, B.N. Hu, X.Y. Zhang, Preparation of stable aqueous suspensions of antimony-doped tin oxide nanoparticles used for transparent and thermal insulation fluorocarbon coating, Colloid Polym. Sci. 292 (2014) 3233–3241.
[87] C.E. Mora-Huertas, H. Fessi, A. Elaissari, Polymer-based nanocapsules for drug delivery, Int. J. Pharm. 385 (2010) 113–142.
[88] R.H. Staff, D. Schaeffel, A. Turshatov, D. Donadio, H.J. Butt, K. Landfester, K. Koynov, D. Crespy, Particle formation in the emulsion-solvent evaporation process, Small 9 (2013) 3514–3522.
[89] J.H. Choi, H.S. Kim, J.W. Choi, J.W. Hong, Y.K. Kim, B.K. Oh, A novel Au-nanoparticle biosensor for the rapid and simple detection of PSA using a sequence-specific peptide cleavage reaction, Biosens. Bioelectron. 49 (2013) 415–419.
[90] J.H. Shu, W. Qiu, S.Q. Zheng, Polyaniline/gold nanoparticle composites, Prog. Chem. 21 (2009) 1015–1022.
[91] N. Udawatte, M. Lee, J. Kim, D. Lee, Well-defined Au/ZnO nanoparticle composites exhibiting enhanced photocatalytic activities, ACS Appl. Mater. Interfaces 3 (2011) 4531–4538.
[92] Y. Zhang, V. Suryanarayanan, I. Nakazawa, S. Yoshihara, T. Shirakashi, Electrochemical behavior of Au nanoparticle deposited on as-grown and O-terminated diamond electrodes for oxygen reduction in alkaline solution, Electrochim. Acta 49 (2004) 5235–5240.
[93] P. Torruella, R. Arenal, F. de la Pena, Z. Saghi, L. Yedra, A. Eljarrat, L. Lopez-Conesa, M. Estrader, A. Lopez-Ortega, G. Salazar-Alvarez, J. Nogues, C. Ducati, P.A. Midgley, F. Peiro, S. Estrade, 3D visualization of the iron oxidation state in FeO/Fe3O4 core-shell nanocubes from electron energy loss tomography, Nano Lett. 16 (2016) 5068–5073.
[94] H.Q. Bian, S.Y. Ma, A.M. Sun, X.L. Xu, G.J. Yang, S.H. Yan, J.M. Gao, Z.M. Zhang, H.B. Zhu, Improvement of acetone gas sensing performance of ZnO nanoparticles, J. Alloys Compd. 658 (2016) 629–635.
[95] R.M. Molnar, M. Bodnar, J.F. Hartmann, B. Janos, Preparation and characterization of poly(acrylic acid)-based nanoparticles, Colloid Polym. Sci. 287 (2009) 739–744.
[96] Michael J. Casciato, Sungil Kim, J.C. Lu, Dennis W. Hess, M.A. Grover, Optimization of a carbon dioxide-assisted nanoparticle deposition process using sequential experimental design with adaptive design space, Ind. Eng. Chem. Res. 51 (2012) 4363–4370.
[97] Emmanuel O. Akala, Simeon Adesina, O. Ogunwuyi, Computer optimization of biodegradable nanoparticles fabricated by dispersion polymerization, Int. J. Environ. Res. Public Health 13 (2016) 47.
[98] J.H. Maeng, D.H. Lee, K.H. Jung, Y.H. Bae, I.S. Park, S. Jeong, Y.S. Jeon, C.K. Shim, W. Kim, J. Kim, J. Lee, Y.M. Lee, J.H. Kim, W.H. Kim, S.S. Hong, Multifunctional doxorubicin loaded superparamagnetic iron oxide nanoparticles for chemotherapy and magnetic resonance imaging in liver cancer, Biomaterials 31 (2010) 4995–5006.
[99] R. Rani, N. Dilbaghi, D. Dhingra, S. Kumar, Optimization and evaluation of bioactive drug-loaded polymeric nanoparticles for drug delivery, Int. J. Biol. Macromol. 78 (2015) 173–179.
[100] D.F. Liu, L. Chen, S.M. Jiang, S.N. Zhu, Y. Qian, F.Z. Wang, R. Li, Q.W. Xu, Formulation and characterization of hydrophilic drug diclofenac sodium-loaded solid lipid nanoparticles based on phospholipid complexes technology, J. Liposome Res. 24 (2014) 17–26.
[101] M.S. Kim, Influence of hydrophilic additives on the supersaturation and bioavailability of dutasteride-loaded hydroxypropyl-beta-cyclodextrin nanostructures, Int. J. Nanomedicine 8 (2013) 2029–2039.
[102] H. Ali, A.B. Shirode, P.W. Sylvester, S. Nazzal, Preparation, characterization, and anticancer effects of simvastatin-tocotrienol lipid nanoparticles, Int. J. Pharm. 389 (2010) 223–231.
[103] Brijesh Shah, Dignesh Khunt, Himanshu Bhatt, Manju Misra, H. Padh, Application of quality by design approach for intranasal delivery of rivastigmine loaded solid lipid nanoparticles: effect on formulation and characterization parameters, Eur. J. Pharm. Sci. 78 (2015) 54–66.
[104] S.A. Joshi, S.S. Chavhan, K.K. Sawant, Rivastigmine-loaded PLGA and PBCA nanoparticles: preparation, optimization, characterization, in vitro and pharmacodynamic studies, Eur. J. Pharm. Biopharm. 76 (2010) 189–199.
[105] P. Girotra, S.K. Singh, G. Kumar, Development of zolmitriptan loaded PLGA/poloxamer nanoparticles for migraine using quality by design approach, Int. J. Biol. Macromol. 85 (2016) 92–101.
[106] O.C. Farokhzad, J.J. Cheng, B.A. Teply, I. Sherifi, S. Jon, P.W. Kantoff, J.P. Richie, R. Langer, Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 6315–6320.
[107] X.P. Duan, C.B. He, S.J. Kron, W.B. Lin, Nanoparticle formulations of cisplatin for cancer therapy, Wiley Interdiscip. Rev.-Nanomed. Nanobiotechnol. 8 (2016) 776–791.
[108] H. Shen, X.Y. Hu, M. Szymusiak, Z.J. Wang, Y. Liu, Orally administered nanocurcumin to attenuate morphine tolerance: comparison between negatively charged PLGA and Partially and fully PEGylated nanoparticles, Mol. Pharm. 10 (2013) 4546–4551.
[109] P. Manivasagan, S. Bharathiraja, N.Q. Bui, I.G. Lim, J. Oh, Paclitaxel-loaded chitosan oligosaccharide-stabilized gold nanoparticles as novel agents for drug delivery and photoacoustic imaging of cancer cells, Int. J. Pharm. 511 (2016) 367–379.
[110] S. Das, W.K. Ng, P. Kanaujia, S. Kim, R.B.H. Tan, Formulation design, preparation and physicochemical characterizations of solid lipid nanoparticles containing a hydrophobic drug: effects of process variables, Colloids Surf. B Biointerfaces 88 (2011) 483–489.
[111] Se-Jin Park, Gwang-Ho Choo, Sung-Joo H., M.-S. Kim, Quality by design: screening of critical variables and formulation optimization of Eudragit E nanoparticles containing dutasteride, Arch. Pharm. Res. 36 (2013) 593–601.
[112] F. Yerlikaya, A. Ozgen, I. Vural, O. Guven, E. Karaagaoglu, M.A. Khan, Y. Capan, Development and evaluation of paclitaxel nanoparticles using a quality-by-design approach, J. Pharm. Sci. 102 (2013) 3748–3761.
[113] V.D. Kumar, P.R.P. Verma, S.K. Singh, Development and evaluation of biodegradable polymeric nanoparticles for the effective delivery of quercetin using a quality by design approach, LWT Food Sci. Technol. 61 (2015) 330–338.
[114] F. Rose, J.E. Wern, P.T. Ingvarsson, M. van de Weert, P. Andersen, F. Follmann, C. Foged, Engineering of a novel adjuvant based on lipid-polymer hybrid nanoparticles: a quality-by-design approach, J. Control. Release 210 (2015) 48–57.
[115] A. Bansal, D.N. Kapoor, R. Kapil, N. Chhabra, S. Dhawan, Design and development of paclitaxel-loaded bovine serum albumin nanoparticles for brain targeting, Acta Pharma. 61 (2011) 141–156.
[116] Y.H. Yin, Q.M. Guo, Y. Han, L.J. Wang, S.Q. Wan, Preparation, characterization and nematicidal activity of lansiumamide B nano-capsules, J. Integr. Agric. 11 (2012) 1151–1158.
[117] J. Marto, L.F. Gouveia, L.M. Goncalves, D.P. Gaspar, P. Pinto, F.A. Carvalho, E. Oliveira, H.M. Ribeiro, A.J. Almeida, A Quality by design (QbD) approach on starch-based nanocapsules: a promising platform for topical drug delivery, Colloids Surf. B: Biointerfaces 143 (2016) 177–185.
[118] J.K. George, S.K. Singh, P.R.P. Verma, Morphological and in vitro investigation of core–shell nanostructures of carvedilol using quality by design, J. Pharm. Invest. 45 (2015) 561–578.
[119] M.E. Davis, J.E. Zuckerman, C.H.J. Choi, D. Seligson, A. Tolcher, C.A. Alabi, Y. Yen, J.D. Heidel, A. Ribas, Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles, Nature 464 (2010) 1067–U1140.
[120] A.S. Levina, M.N. Repkova, N.A. Mazurkova, V.F. Zarytova, Nanoparticle-mediated nonviral DNA delivery for effective inhibition of influenza a viruses in cells, IEEE Trans. Nanotechnol. 15 (2016) 248–254.
[121] Y. Hu, S.S. Ma, Z.H. Yang, W.Y. Zhou, Z.S. Du, J. Huang, H. Yi, C.Y. Wang, Facile fabrication of poly(L-lactic acid) microsphere-incorporated calcium alginate/hydroxyapatite porous scaffolds based on Pickering emulsion templates, Colloids Surf. B Biointerfaces 140 (2016) 382–391.
[122] D.M. Cun, C. Foged, M.S. Yang, S. Frokjaer, H.M. Nielsen, Preparation and characterization of poly(DL-lactide-co-glycolide) nanoparticles for siRNA delivery, Int. J. Pharm. 390 (2010) 70–75.
[123] D.M. Cun, D.K. Jensen, M.J. Maltesen, M. Bunker, P. Whiteside, D. Scurr, C. Foged, H.M. Nielsen, High loading efficiency and sustained release of siRNA encapsulated in

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PLGA nanoparticles: quality by design optimization and characterization, Eur. J. Pharm. Biopharm. 77 (2011) 26–35.
[124] V.P. Torchilin, Micellar nanocarriers: pharmaceutical perspectives, Pharm. Res. 24 (2007) 1–16.
[125] J. Tian, L. Ding, H. Ju, Y. Yang, X. Li, Z. Shen, Z. Zhu, J.S. Yu, C.J. Yang, A multifunctional nanomicelle for real-time targeted imaging and precise near-infrared cancer therapy, Angew. Chem. 53 (2014) 9544–9549.
[126] C. Oerlemans, W. Bult, M. Bos, G. Storm, J.F. Nijsen, W.E. Hennink, Polymeric micelles in anticancer therapy: targeting, imaging and triggered release, Pharm. Res. 27 (2010) 2569–2589.
[127] G. Gaucher, M.H. Dufresne, V.P. Sant, N. Kang, D. Maysinger, J.C. Leroux, Block copolymer micelles: preparation, characterization and application in drug delivery, J. Control. Release 109 (2005) 169–188.
[128] A.B.E. Attia, Z.Y. Ong, J.L. Hedrick, P.P. Lee, P.L.R. Ee, P.T. Hammond, Y.Y. Yang, Mixed micelles self-assembled from block copolymers for drug delivery, Curr. Opin. Colloid Interface Sci. 16 (2011) 182–194.
[129] T. Thambi, V.G. Deepagan, C.K. Yoo, J.H. Park, Synthesis and physicochemical characterization of amphiphilic block copolymers bearing acid-sensitive orthoester linkage as the drug carrier, Polymer 52 (2011) 4753–4759.
[130] X.B. Fang, J.M. Zhang, X. Xie, D. Liu, C.W. He, J.B. Wan, M.W. Chen, pH-sensitive micelles based on acid-labile pluronic F68-curcumin conjugates for improved tumor intracellular drug delivery, Int. J. Pharm. 502 (2016) 28–37.
[131] Y.L. Liu, Y.Q. Xu, M.H. Wu, L.J. Fan, C.W. He, J.B. Wan, P. Li, M.W. Chen, H. Li, Vitamin E succinate-conjugated F68 micelles for mitoxantrone delivery in enhancing anticancer activity, Int. J. Nanomedicine 11 (2016) 3167–3178.
[132] S.P. Wang, Y. Yang, Y.T. Wang, M.W. Chen, Gambogic acid-loaded pH-sensitive mixed micelles for overcoming breast cancer resistance, Int. J. Pharm. 495 (2015) 840–848.
[133] S.P. Wang, R. Chen, J. Morott, M.A. Repka, Y.T. Wang, M.W. Chen, mPEG-b-PCL/TPGS mixed micelles for delivery of resveratrol in overcoming resistant breast cancer, Expert Opin. Drug Deliv. 12 (2015) 361–373.
[134] J.M. Zhang, Y.B. Li, W. Gao, M.A. Repka, Y.T. Wang, M.W. Chen, Andrographolide-loaded PLGA-PEG-PLGA micelles to improve its bioavailability and anticancer efficacy, Expert Opin. Drug Deliv. 11 (2014) 1367–1380.
[135] M. Maswal, A.H. Pandith, N. Islam, A.A. Dar, Co-solubilization of the hydrophobic drugs carbamazepine and nifedipine in aqueous nonionic surfactant media, J. Solut. Chem. 42 (2013) 1374–1392.
[136] X.X. Dai, X.Y. Shi, Q.Q. Yin, H.O. Ding, Y.J. Qiao, Multiscale study on the interaction mechanism between ginsenoside biosurfactant and saikosaponin a, J. Colloid Interface Sci. 396 (2013) 165–172.
[137] X.X. Dai, X.Y. Shi, Y.G. Wang, Y.J. Qiao, Solubilization of saikosaponin a by ginsenoside Ro biosurfactant in aqueous solution: mesoscopic simulation, J. Colloid Interface Sci. 384 (2012) 73–80.
[138] N.Q. Fan, K.R. Duan, C.Y. Wang, S.Y. Liu, S.F. Luo, J.H. Yu, J. Huang, Y.P. Li, D.X. Wang, Fabrication of nanomicelle with enhanced solubility and stability of camptothecin based on alpha, beta-poly (N-carboxybutyl)-L-aspartamide-camptothecin conjugate, Colloids Surf. B Biointerfaces 75 (2010) 543–549.
[139] X.X. Dai, H.O. Ding, Q.Q. Yin, G. Wan, X.Y. Shi, Y.J. Qiao, Dissipative particle dynamics study on self-assembled platycodin structures: the potential biocarriers for drug delivery, J. Mol. Graph. 57 (2015) 20–26.
[140] R.D. Vaishya, M. Gokulgandhi, S. Patel, M. Minocha, A.K. Mitra, Novel dexamethasone-loaded nanomicelles for the intermediate and posterior segment uveitis, AAPS PharmSciTech 15 (2014) 1238–1251.
[141] A.B. Kuchekar, A.P. Pawar, Capecitabine loaded polymeric micelles: formulation, characterization and cytotoxicity study, In: International Conference on Advanced Nanomaterials & Emerging Engineering Technologies, 2013, pp. 412–415.
[142] J. Zhang, Y. Li, X. Fang, D. Zhou, Y. Wang, M. Chen, TPGS-g-PLGA/pluronic F68 mixed micelles for tanshinone IIA delivery in cancer therapy, Int. J. Pharm. 476 (2014) 185–198.
[143] Ashwin B. Kuchekar, A.P. Pawar, Screening factors using Plackett Burman design in the preparation of capecitabine-loaded nano polymeric micelles, Int J Pharm Pharm Sci 6 (2014) 489–496.
[144] S. Verma, Y. Lan, R. Gokhale, D.J. Burgess, Quality by design approach to understand the process of nanosuspension preparation, Int. J. Pharm. 377 (2009) 185–198.
[145] V.R. Patel, Y.K. Agrawal, Nanosuspension: an approach to enhance solubility of drugs, J. Adv. Pharm. Technol. Res. 2 (2011) 81–87.
[146] Ang Chen, Ye Shi, Zhiqiang Yan, Hongxun Hao, Yong Zhang, Jian Zhong, H. Hou, Dosage form developments of nanosuspension drug delivery system for oral administration route, Curr. Pharm. Des. 21 (2015) 1–11.
[147] H.S.M. Ali, P. York, N. Blagden, Preparation of hydrocortisone nanosuspension through a bottom-up nanoprecipitation technique using microfluidic reactors, Int. J. Pharm. 375 (2009) 107–113.
[148] S. Verma, R. Gokhale, D.J. Burgess, A comparative study of top-down and bottom-up approaches for the preparation of micro/nanosuspensions, Int. J. Pharm. 380 (2009) 216–222.
[149] T.T.D. Tran, P.H.L. Tran, M.N.U. Nguyen, K.T.M. Tran, M.N. Pham, P.C. Tran, T.V. Vo, Amorphous isradipine nanosuspension by the sonoprecipitation method, Int. J. Pharm. 474 (2014) 146–150.
[150] B.P. Sahu, M.K. Das, Preparation and in vitro/in vivo evaluation of felodipine nanosuspension, Eur. J. Drug Metab. Pharmacokinet. 39 (2014) 183–193.
[151] Z. Attari, A. Bhandari, P.C. Jagadish, S. Lewis, Enhanced ex vivo intestinal absorption of olmesartan medoxomil nanosuspension: preparation by combinative technology, Saudi Pharm. J. 24 (2016) 57–63.
[152] Y. Li, X.H. Zhao, Y.G. Zu, Y. Zhang, Preparation and characterization of paclitaxel nanosuspension using novel emulsification method by combining high speed homogenizer and high pressure homogenization, Int. J. Pharm. 490 (2015) 324–333.
[153] S. Kumar, R. Gokhale, D.J. Burgess, Quality by Design approach to spray drying processing of crystalline nanosuspensions, Int. J. Pharm. 464 (2014) 234–242.
[154] I. Ghosh, D. Schenck, S. Bose, F. Liu, M. Motto, Identification of critical process parameters and its interplay with nanosuspension formulation prepared by top down media milling technology–a QbD perspective, Pharm. Dev. Technol. 18 (2013) 719–729.
[155] A.S. Rathore, R. Branning, D. Cecchini, Design space for biotech products, Biopharm. Int. 20 (2007) 36.
[156] G.H. Hawthorne, M.P. Bernuci, M. Bortolanza, V. Tumas, A.C. Issy, E. Del-Bel, Nanomedicine to overcome current Parkinson's treatment liabilities: a systematic review, Neurotox. Res. 30 (2016) 715–729.

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