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Review

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C. Camacho Vieira, L. Peltonen, A.P. Karttunen, A.J. Ribeiro

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Is it advantageous to use Quality by Design (QbD) to develop nanoparticle-based dosage forms for parenteral drug administration?

Camacho Vieira, C. [1], Peltonen, L. [2], Karttunen, A.P.[2], Ribeiro, A. J.[1,3], *

[1] Universidade de Coimbra, Faculdade de Farmácia, 3000-148 Coimbra, Portugal;

[2] Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland;

[3] i_3S, IBMC, Rua Alfredo Allen, 4200-135 Porto, Portugal.

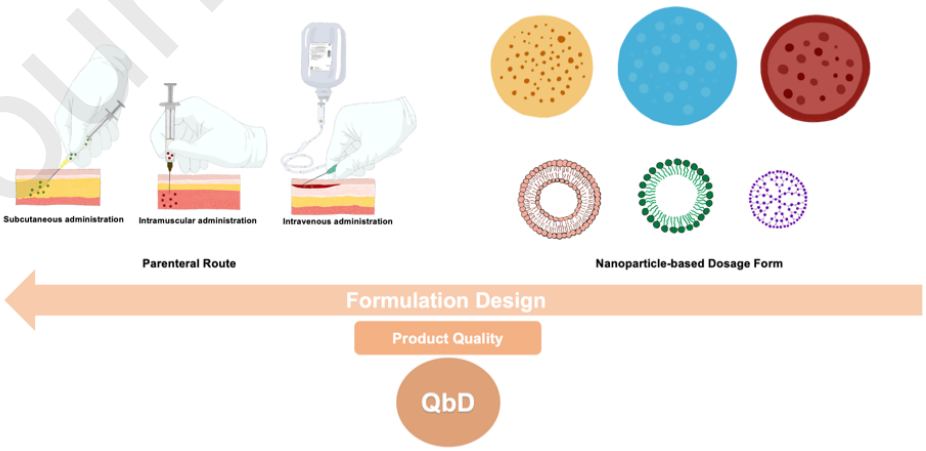
* Corresponding author:

António J Ribeiro

Universidade de Coimbra

Faculdade de Farmácia, Portugal.

E-mail address: aribeiro@ff.uc.pt



Declaration of interests

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Abstract

Parenteral administration is one of the most commonly used drug delivery routes for nanoparticle-based dosage forms, such as lipid-based and polymeric nanoparticles. For the treatment of various diseases, parenteral administration include intravenous, subcutaneous, and intramuscular route. In drug development phase, multiparameter strategy with a focus on drug physicochemical properties and the specificity of the administration route is required. Nanoparticle properties in terms of size and targeted delivery, among others, are able to surpass many drawbacks of conventional dosage forms, but these unique properties can be a bottleneck for approval by regulatory authorities.

Quality by Design (QbD) approach has been widely utilized in development of parenteral nanoparticle-based dosage forms. It fosters knowledge of product and process quality by involving sound scientific data and risk assessment strategies. A full and comprehensive investigation into the state of implementation and applications of the QbD approach in these complex drug products can highlight the gaps and challenges. In this review, the analysis of critical attributes and Design of Experiment (DoE) approach in different nanoparticulate systems, together with the proper utilization of Process Analytical Technology (PAT) applications are described. The essential of QbD approach for the design and development of nanoparticle-based dosage forms for delivery via parenteral routes is discussed thoroughly.

Keywords: Nanotechnology; QbD; Parenteral route; Process analytical technology; Continuous manufacturing.

Abbreviations

API(s) active pharmaceutical ingredient(s); BBD Box-Behnken design; CCC central composite circumscribed; CCD central composite design; CCF central composite face centered; CCI central composite inscribed; CJM coaxial jet mixer; CM continuous manufacturing; CMA(s) critical material attribute(s); CPP(s) critical process parameter(s); CQA(s) critical quality attribute(s); DLS dynamic light scattering; DoE design of experiments; DS design space; EE entrapment efficiency; EMA European medicines agency; EU European union; FDA food and drug administration; FDLCI Fourier domain low-coherence interferometry; FFD full factorial design; FrFD fractional factorial design; GMP good manufacturing practices; HME hot-melt extrusion; ICH international council for harmonization; IM intramuscular; IV intravenous; LCI low-coherence interferometry; MD(s) mixture design(s); mRNA messenger ribonucleic acid; NFS nanoflow sizer; NIR near infrared; NNI national nanotechnology institute; NP(s) nanoparticle(s); OD optimal design; OF2i optofluidic force induction; PAT process analytical technology; PbD Placket-Burman design; PDI polydispersity index; PDW photon density wave spectroscopy; PLGA poly(D,L-lactide-co-glycolide); PS particle size; QbD quality by design; QTPP(s); quality target product profile(s); RA risk assessment; SC subcutaneous; TD Taguchi design; TUS turbidity spectrometry; ZP zeta potential.

1. Introduction

Derived from the Greek words “para” (besides) and “enteron” (the intestine), the term parenteral can be transcribed as “outside the digestive tract”. Accordingly, it includes administration routes, which are not intestinal nor duodenal, and it usually refers to subcutaneous (SC), intramuscular (IM), or intravenous (IV) administration of drugs. When we administer the drug through the parenteral route, we have an immediate therapeutic effect that is useful in emergency situations. Some drugs can’t be administered via non-injectable routes due to their poor bioavailability, such as paclitaxel (Yerlikaya et al., 2013). Disadvantage of parenteral administration is infection risk on the administration site when the body's natural barriers are bypassed. Further, in the case of dosing error, it is difficult to reverse the effect. Due to the stringent requirements of parenteral dosage forms, including sterility, there is a need to develop alternative delivery systems that ideally overcome the multiparametric manufacturing challenges while providing quality, efficacy, and safety (Nema and Ludwig, 2019).

Nanomedicines are the applications of nanotechnology in drug discovery and delivery. The use of nanoparticles offers several advantages, including drug stability, enhanced drug release, and drug cellular uptake. The concept was introduced by the United States government in 2000 with the creation of a new initiative called the National Nanotechnology Initiative (NNI). From the beginning, nanomedicines have focused almost exclusively on tumor-targeted drug delivery, which has many advantages (Park et al., 2022), but the applications of nanoparticle-based drug delivery systems have also faced challenges (Wang et al., 2021).

Anticancer nanoformulations have been developed for intravenous use and, alternatively, for intradermal, subcutaneous, and oral use since the administration route determines the biodistribution pattern of drugs (Wang et al., 2021). Over the years, successful commercial nanoparticle-based anticancer dosage forms have been developed, including Mylotarg®, Doxil®, and Abraxane®, among others (Park et al., 2022).

The use of nanotechnology has some advantages and disadvantages in many fields and in various nanoparticle-based dosage forms. The main advantages include prevention of degradation of the loaded drug, specificity and targeted delivery, and improved bioavailability and efficiency (Adepu and Ramakrishna, 2021) (Pozharov and Minko, 2023). However, we also find some disadvantages, such as the high value of their production, the unexpected diffusion of these nanoparticle-based dosage forms into the lungs and some body barriers, which may lead to toxicity, and the special storage conditions of lipid-based nanoparticles (Adepu and Ramakrishna, 2021) (Pozharov and Minko, 2023).

Formulation design is an essential step in the development of nanoparticle-based dosage forms, and the scale-up of lab-scale preparation methods to industrial production scale is a barrier to bringing nanotherapeutics to market, and there is still a large gap between the progress made in research and in the clinic (Villa nova et al., 2015). Large amounts of financial resources are usually devoted to drug development studies. Therefore, maintaining quality attributes at an affordable cost within a short period of time has become important to both academia and the pharmaceutical industry, and consequently, the implementation of the Quality by Design (QbD) approach has received much attention (Barbalata et al., 2022). The elements and the QbD approach are detailed in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, such as ICH Q8, Q9, Q10, Q11, Q12, and more recently Q13 (Grangeia et al., 2020).

The elements of QbD include the description of the Quality Target Product Profile (QTPP), in particular the ideal parameters that the product should achieve, the identification of characteristics in the formulation named Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), the results of the Risk Assessment (RA), which is the crucial step because it supports the impact of the CQAs and the CPPs on the target product profile, key points of the Design of Experiments (DoE), and the definition of Design Space (DS) (Németh et al., 2022). This approach has been proven successful in oral drug delivery systems, using different experimental designs that resulted in improved bioavailability and stability (Beg et al., 2019c).

This review aims to identify the predominant elements of QbD in nanoparticle-based parenteral drug delivery dosage forms and their importance in achieving the ideal final product.

It aims to help understand and improve preparation processes and operations, accelerate pharmaceutical development, shorten the time between research and clinical applications, and propose a strategy to overcome key obstacles. At the end of the review, we also cover highlights of Process Analytical Technology (PAT) and Continuous Manufacturing (CM), which support the inclusion of QbD and vice versa.

2. Parenteral Administration

As described earlier, parenteral administration, and thus the parenteral route, refers to the administration of drugs bypassing the gastrointestinal system. There are several parenteral routes of drug administration, such as subcutaneous, intravenous, intramuscular, intravitreal, intradermal, intra-articular, intrathecal, intra epidural, intracisternal, intra-arterial, intracardiac, intrapleural, intraperitoneal and intraosseous routes, but the most commonly used routes are intravenous, intramuscular, and subcutaneous (Nema and Ludwig, 2019).

2.1 Reasons for choosing parenteral administration

The oral route is usually preferred by many patients because of the convenience of storage and administration of drug dosage forms, but in some cases, the parenteral route is the only possible route. There are some examples of drugs, such as liposomal formulations, which need to be administered parenterally to ensure the efficacy of therapeutic agents; aminoglycoside antibiotics, such as gentamicin; and biologic drugs, due to their susceptibility to proteolytic degradation, poor permeability, and delicate assembly of various structures. Over the years, some studies have developed oral formulations for some biological drugs, such as insulin, but subcutaneous administration is still the preferred route (Nema and Ludwig, 2019) (Elsayed et al., 2023).

Parenteral administration is not only used in cases, where it is the only possible route, but it is also sometimes preferred instead of other routes of administration. It has high bioavailability, drug acts in seconds, drug is delivered directly to the bloodstream, localized effect in a specific area or organ can be reached, and administration to unconscious patients or patients with gastrointestinal tract disease that prevents absorption of both drugs, nutrients as well as vitamins is possible (Zhang et al., 2017).

Nevertheless, compared to oral administration, parenteral administration is more invasive, occasionally painful, and it is associated with lower safety. Parenteral preparations are more expensive to produce. Parenteral forms, such as injections, require a sterile, controlled, and specialized environment for their production, and these processes and requirements can turn their production more expensive (Cyriac and James, 2014).

We have some safety concerns related to parenteral administration, especially regarding the risk of infection and tissue damaging. There are some preventative measures and best practices to reduce these risks and ensure the safe and effective administration of medicines to patients. These are listed in "WHO best practices for injections and related procedures toolkit" instructions for healthcare professionals involved in the administration of parenteral medicines. Instructions include appropriate injection techniques, criteria for the selection of the administration site and protocols for post-administration monitoring (WHO, 2010).

2.2 Routes of parenteral administration and facts to consider when selecting the different routes

The route of administration imposes certain requirements and limitations on formulations and the devices used to administer the dosage forms. A growing number of drugs must be administered parenterally, i.e., intravenously, intramuscularly, or subcutaneously (Figure 1). These parenteral routes of administration may obey different requirements, and they influence the designing of novel dosage forms in order to ensure the efficacy of therapeutics. There are some important principles associated with the choice of injection route, such as safety, efficiency, patient preference, and pharmacoeconomics. In addition to these four principles, there are also some other factors that matters: factors related to patient characteristics, such as age and body mass index; factors related to drug administration, such as dose and formulation characteristics; and health care staff/institution-related factors (Nema and Ludwig, 2019).

2.2.1 Intramuscular (IM) route

Intramuscular route and, therefore, intramuscular injections are administered into a relaxed muscle, preferably at muscle sites such as buttock, thigh, or shoulder muscles. They may be aqueous or oily solutions or suspensions. The rate of absorption is slow compared to the IV route. The injection volume can be up to 4 mL, given that a large bolus of injected drug can cause local damage and muscle infarction, causing an increase in the serum levels of muscle enzymes and a sterile abscess. If rapid absorption in the deltoid muscle is desired, low-volume injections can be used. This route is particularly suitable for pediatric patients (Nema and Ludwig, 2019) (Ogston-Tuck, 2014).

2.2.2 Subcutaneous (SC) route

In the subcutaneous route, administration of drug is made to the abdomen at the level of the umbilicus, the upper back, the upper arms, and the upper hip. Compared to the oral route, the SC route absorbs drugs in a faster and more predictable way. However, compared to the IM route, and given that the muscles have different vascularities, the absorption in the SC administration is slower and less predictable. In the SC route, suspensions and aqueous

solutions are administered in volumes ranging from 1 to 2 mL. Alkaline, highly acidic, and irritating medications should not be administered via SC route, because they can cause inflammation, necrosis, and pain. The use of the route can cause infections, which are more prevalent in self-administration, mainly when patients have poor level of hygiene. Other than IV infusion, hypertonic solutions are normally used in the IM and SC routes since they assist in absorption due to local effusion of tissue fluids (Nema and Ludwig, 2019) (Usach et al., 2019).

2.2.3 Intravenous (IV) route

Intravenous injections and infusions are usually administered to the peripheral veins in arm or, when they are unavailable, the leg and dorsal foot veins can be used. Dosage forms administered in this route cannot be suspensions or water-in-oil emulsions, because of the possible blockage of blood capillaries, the pH and isotonicity of the solutions can also damage the cells at the edge of the vein. They can reach volumes from 1 mL to several liters, and rapidly increase the drug concentration in plasma (Nema and Ludwig, 2019) (Aulton and Taylor, 2018).

Considering Table 1, in nanoparticle-based dosage forms of QbD papers, the most commonly used route of administration is IV. IM and SC are also used, especially for slow drug release, mostly SC, due to the presence of fewer blood vessels than muscles (Rama and Ribeiro, 2023).

Figure 1 Different parenteral routes. Intramuscular (volumes up to 4 mL can be administered, hypertonic solutions are often used and isotonicity is not needed, the solutions can be oily, co-solvent, suspensions and emulsions and the administration sites can be the buttock, thigh, or shoulder muscles). Subcutaneous (volumes up to 4 mL can be administered, hypertonic solutions are often used, isotonicity is also not needed, the solutions can be oily, solvent, suspensions and emulsions and the administration sites can be the abdomen at the level of the umbilicus, the upper back, the upper arms, and the upper hip) and intravenous (volumes of 1 mL up to several liters through infusion

can be administered, isotonicity is important unless the administration is slow enough to permit dilution or adjustment in the blood, it is restricted to dilute aqueous solutions and can be administered in the peripheral veins)

3. Parenteral Administration, Nanotechnology and Application of QbD in Parenteral Nanopharmaceutical Development

QbD concept was created in the early 1970s by an American engineer, J.M. Juran, with the release of his book "Juran on Quality by Design". The concept was applied in diverse areas and later adopted in 2004 by the pharmaceutical industry with a focus on improving the standards of pharmaceutical manufacturing by the United States Food and Drug Administration (FDA) (Beg et al., 2019b) (Mahtab et al., 2019).

3.1 Drugs and nanoparticle-based dosage forms

Over the years, several nanoparticle-based dosage forms have been developed for the treatment of various diseases and disorders. Both benefits and disadvantages exist for nanoparticle-based dosage forms. Benefits include their size, large surface area, and prevention of their destruction in the interstitial fluid and blood. They can diminish immune responses, prolong drug release, and have surface properties that improve the ability to pass the barriers, making them safer than conventional therapy and helping reduce the dose and dosing frequency. Some disadvantages, such as high cost in development and manufacture, scale-up, technology transfer, and quality control, can be a challenge in these particles more than in conventional forms. The special storage conditions under which these nanoparticle-based dosage forms need to prevent disintegration make their approval more difficult (Rapalli et al., 2019) (Pozharov and Minko, 2023) (Lou et al., 2022).

Nanoparticle-based dosage forms greatly expand the options available for treating cancer. There is an expanded platform in the field of anticancer therapies, with several benefits in treatment, such as tumor tissue accumulation through passive targeting, improved penetration, and prolonged systemic circulation time (Bhatt et al., 2021). In the literature, for the development of nanoparticle-based dosage forms using the QbD approach, the most studied drugs are related to cancer treatment, as shown in Table 1, such as doxorubicin (Shaik, 2017), docetaxel (Rafiei and Haddadi, 2019) (Yadav et al., 2015), and paclitaxel (Anwar et al., 2016) (Jeswani et al., 2021) (Mittal et al., 2019). Nanoparticle-based dosage forms for IV administration for some other diseases, such as rheumatoid arthritis, have been studied and developed, and liposomes have been shown to be the most suitable (Mahtab et al., 2019). As shown in Table 1, the most prevalent nanoparticle-based dosage forms are liposomes and PLGA nanoparticles.

3.2 Recent research findings and emerging technologies in parenteral drug delivery systems

In recent years, there have been some new discoveries and technologies in the field of parenteral drug delivery, such as some new long-acting parenteral drug delivery systems. These systems have improved existing treatments for some diseases, e.g., AIDS, tuberculosis and malaria, many of which are being tested in clinical trials, while others are already approved (Jindal et al., 2023). Injectable hydrogels have also been developed, particularly in the field of cancer therapy. However, there have been some difficulties, and further efforts are needed to move these formulations into clinical trials (Mfoafo et al., 2023). Further, ultrathin needles have been developed for insulin injections, enabling insulin delivery with minimal invasion (Sparre et al., 2023).

There are recent studies that deal with the transdermal administration of drugs, more precisely with microneedle-based drug delivery systems. These systems have been fabricated from diverse materials, and using a variety of fabrication methods, they also have different applications (Luo et al., 2023). Microneedles tend to have excellent patient acceptance since they are simple and adaptable systems for painless noninvasive administration of medication. This is an attractive delivery system, because it can overcome needle phobia since it is minimally invasive, reduces the frequency of administration and increases patient compliance. Some of them are already being tested in clinical trials for various diseases and for pain management (Starlin Chellathurai et al., 2024) (Priya and Singhvi, 2022). In patients with diseases such as diabetes mellitus, patient adherence is important given the frequency of insulin administration. In cancer, especially in the treatment of melanoma, they can be used to deliver therapeutic agents as they are minimally invasive (Starlin Chellathurai et al., 2024) (Martins et al., 2024).

3.3 Application of QbD in nanoparticle-based dosage form

QbD has become synonymous with pharmaceutical improvement. Pharmaceutical companies for product development and process understanding have embraced QbD principles and approaches. Nevertheless, although the industry may still aspire to fully embrace these ideas, efforts to gradually introduce the QbD approach are still the goal, given the regulatory benefits (Rapalli et al., 2019). Formulations such as lipid-based nanoparticles and polymeric nanoparticles, among others, have been developed using QbD principles. Their introduction helps to improve the product, process, and therapeutic performance and overcome the problems associated with conventional delivery systems, such as low bioavailability, non-specificity, burst release, low stability, and several side effects (Beg et al., 2019a).

Table 1: Quality by Design (QbD)-based development of nanotechnology-based systems for parenteral administration of drugs with disclosure of the type of nanoparticle and drug, disease application and experimental design.

Nanoparticle (encapsulated)	Administration Route	QTPP	Therapeutical purpose	RA (qualitative or quantitative)	DoE (screening or optimization) (design, number of experiments)	References
SLN (salmon calcitonin)	Subcutaneous	No	Osteoporosis	No	Optimization (3^3,17)	(Wang et al., 2019)
HA (teriflunomide and methotrexate)	Subcutaneous	No	Rheumatoid arthritis	No	Optimization (3^3,17)	(Pandey et al., 2018)
PLGA	Subcutaneous, oral, nasal, or intramuscular	No	Hepatitis B	No	Optimization (3^4,30)	(Dewangan et al., 2018)
PLGA (Olanzapine)	Intramuscular	No	Schizophrenia	No	Optimization (3^2,11)	(Joseph et al., 2018)
Zein (Glimepride)	Intramuscular	No	Type 2 diabetes	No	Optimization (5^2,16)	(Ahmed et al., 2016)
Liposomes (a-galactosidase A enzyme)	Parenteral[a]	No	Fabry disease	Qualitative	Optimization (2^4,10)	(Merlo-Mas et al., 2021)
Liposomes and Niosomes (Tenoxicam)	Parenteral[a]	No	NSAID (anti-inflammatory drug)	No	Optimization ($2^2.3^1$. 12)	(Ammar et al., 2018)
Transferrin- conjugated PLGA (Docetaxel)	Parenteral	No	Cancer	No	Optimization (3^2,13)	(Jose et al., 2019)
PLGA (Doxorubicin)	Parenteral	Yes	Cancer	Qualitative	Optimization (3^4,27)	(Shaikh et al., 2017)
PLGA	Parenteral	No	Intracellular delivery	No	Optimization (2^4,10)	(Sahin et al., 2017)
PLGA (Hyaluronidase)	Parenteral	No	Cancer	No	Optimization (2^5,8)	(Narayanan et al., 2014)
Hyaluronic acid coated PLGA (Raloxifene Hydrochloride)	Parenteral	No	Cancer	No	Screening (2^3,15)	(Bhatt et al., 2021)
Hyaluronic acid coated PLGA (Raloxifene Hydrochloride)	Parenteral	No	Cancer	No	Optimization (3^2,13)	(Bhatt et al., 2021)
PLGA (Photosensitizer meso-tetrakis (3-hydroxyphenyl) chlorin (mTHPC))	Intravenous	No	Cancer	No	Optimization (2^4,17)	(Villa Nova et al., 2015)
PLGA (Photosensitizer meso-tetrakis (3-hydroxyphenyl) chlorin (mTHPC))	Intravenous	No	Cancer	No	Optimization (5^2,10)	(Villa Nova et al., 2015)
Lyotropic liquid crystals (Temozolomide)	Intravenous	Yes	Cancer	Qualitative	Optimization (3^3,10)	(Waghule et al., 2022)
Ultrasmall nanostructured lipid carriers	Intravenous	No	Cancer	Qualitative	Optimization (3^2, 9)	(Mendes et al., 2020)

SLN (Apocynin)	Intravenous	No	Neurodegenerative	No	Optimization (2^4,16)	(Aman et al., 2018)
PLGA (Docetaxel)	Intravenous	No	Cancer	No	Optimization (2^4,4^2, 16)	(Rafiei and Haddadi, 2019)
PEGylated lipid nanocapsules (Paclitaxel)	Intravenous	No	Cancer	No	Optimization (3^3,17)	(Anwar et al., 2016)
Liposomes (Teriflunomide)	Intravenous	No	Multiple sclerosis	No	Optimization (2^3,17)	(Mahtab et al., 2019)
Eudragit/PLGA (Paclitaxel)	Intravenous	No	Cancer	No	Optimization (3^3,21)	(Jeswani et al., 2021)
Phospholipid (Docetaxel)	Intravenous	No	Cancer	No	Optimization (3^2,13)	(Yadav et al., 2015)
Polycaprolactone (Oxaliplatin)	Intravenous	No	Cancer	No	Optimization (3^3,27)	(Esim et al., 2020)
PLGA (Paclitaxel)	Intravenous	No	Cancer	No	Optimization (3^3,17)	(Mittal et al., 2019)
SLN (Curcumin)	Intravenous	No	Alzheimer's	No	Optimization (2^3,17)	(Malvajerd et al., 2019)
PLGA (Meso-tetraphenylporphyrin metal complex)	Intravenous	No	Cancer	No	Optimization (2^3,17)	(Mollaeva et al., 2021)
Liposomes (Coloading of Simvastatin and Soxorubicin)	Intravenous	No	Cancer	No	Optimization (3^3,17)	(Barbalata et al., 2022)
Selenium-plated novasomes (Quercetin)	Intravenous	No	Cancer	No	Optimization (3^3,15)	(Aboud et al., 2022)
Lipid-polymer hybrid	Intravenous	No	Brain Delivery	No	Optimization (2^3,8)	(Ishak et al., 2017)
Agarose based liposomes (Sorafenib tosylate)	Intravenous	No	Cancer	No	Optimization (2^3,8)	(Dhawan et al., 2022)
Liposomes	Intravenous	No [b]		Qualitative	Optimization (3^2,9)	(Németh et al., 2022)
PEGylated PLGA (Brucine)	Intravenous	No	Cancer	No	Optimization (3^2,9)	(Elsewedy et al., 2020)
PEGylated PLGA (Gallium phthalocyanine)	Intravenous	No	Alzheimer	No	Optimization (2^3,10)	(Lorenzoni et al., 2019)
Biodegradable PLGA (Stavudine)	Intravenous	No	AIDS	No	Optimization (2^2,6)	(Ghosh et al., 2017)
Protein-functionalized PLGA (Lamotrigine)	Intravenous	No	Neuropathic pain	No	Optimization (3^3,27)	(Lalani et al., 2015)
PLGA (Amphotericin B)	Intravenous	No	Fungal infections	No	Optimization (2^2 x 3^1.12)	(Carraro et al., 2016)

[a] (no parenteral route was discriminated), [b] (not available), AIDS (acquired immune deficiency syndrome), HA (hydroxyapatite), PEG (polyethylene glycol), PLGA (poly-D,L-lactide-co-glycolide), SLN (solid lipid nanoparticle)

4. QbD elements and parenteral route of administration

Although QbD is not a new approach, it has only recently been considered in the pharmaceutical industry. The ICH, US FDA, EMA, and some pharmaceutical companies have collaborated in the development of pharmaceutical guidelines such as ICH Q8 (R2) for pharmaceutical development, ICH Q9 for risk management, and ICH Q10 for pharmaceutical quality systems to ensure the quality of pharmaceutical products (Grangeia et al., 2020) (ICH Q8 (R2), 2009) (ICH Q9, 2006) (ICH Q10, 2008). To better understand how a particular process or material can affect the quality profile of a pharmaceutical product, we first need to define some basic QbD elements. As shown in Figure 2, to obtain product quality, QbD and therefore its elements must be used.

4.1 Quality Target Product Profile (QTPP)

As defined in the guideline ICH Q8, the QTPP is "a prospective summary of the quality characteristics of a drug product that are ideally achieved to ensure the desired quality, taking into account safety and efficacy of the drug product" (ICH Q8 (R2), 2009). As a key element of the QbD approach, it plays a critical role in defining the objectives of the development of a drug product, such as its clinical use, route of administration, dosage form, and delivery systems, as well as its pharmacokinetics and the criteria that affect quality, in establishing targeted and efficient formulation strategies that result in a product that meets the needs of patients (ICH Q8 (R2), 2009) (Yu et al., 2014). Consequently, the QTPP is considered to form the basis for the design of a drug product, because it is related to predefined objective criteria and defines the expectations of the final product (Sangshetti et al., 2017).

The purpose of pre-development use of Risk Assessment (RA) is to identify process variables as potentially high-risk formulations that could affect the quality of the drug product. There are many tools for conducting RA studies, such as the Ishikawa diagram, C&E matrices, decision tree analysis, and others, as mentioned in ICH Guideline Q9 (ICH Q9, 2006). The results of the study determine, which variables are potentially critical, and which are not critical, leading to the identification of variables that need to be studied experimentally (Yu et al., 2014). In some experimental works relating to nanoparticle-based dosage forms for parenteral administration, QTPP (Shaikh et al., 2017) (Németh et al., 2022) (Waghule et al., 2022) was used, as well as also RA (Merlo-Mas et al., 2021) (Waghule et al., 2022) (Mendes et al., 2020).

4.2 Critical Quality Attributes (CQAs)

CQAs are often considered offshoots of QTPP elements. They are identified first from QTPPs, taking into account their impact on the safety and efficacy of the product and the severity of harm to the patient. They are defined in ICH Q8 R2 as "a physical, chemical,

biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" and consequently have a direct impact on the efficacy and safety of the drug product (ICH Q8 (R2), 2009) (Beg et al., 2019a).

CQAs are also an essential component of manufacturing control strategies. They include attributes of the drug product, drug substance, active raw materials, excipients, and packaging materials and they must be identified in the early stages of development (Beg et al., 2019a). They depend on the type of nanoparticles, route of administration and disease/treatment, e.g., for a colloidal drug delivery system for tumor targeting, encapsulation efficiency, particle size and polydispersity index are key quality attributes (Shaikh et al., 2017). As shown in Table 2, for lipid-based and polymeric nanoparticles, the particle size, entrapment efficiency, and zeta potential are the most predominant attributes (Esim et al., 2020).

4.2.1 Particle Size (PS) and Polydispersity Index (PDI)

As the name "nano" implies, nanoparticle-based dosage forms can have a size from 1 nm to <1000 nm (Taha et al., 2020). Larger particles, larger than 150 nm, tend to accumulate in the lungs, liver, and spleen. Nanoparticles smaller than 5 nm are excreted through the kidneys (Talegaonkar and Bhattacharyya, 2019). For some therapeutics and applications, size is the most important attribute. It is the key attribute for successful drug delivery and affects drug loading, release behavior, particle pharmacokinetics and biological fate, although the desired size may vary depending on the application (Taha et al., 2020).

Described as the degree of non-uniformity of the size distribution, the PDI is a representation of the PS distribution of a given sample varying from 0.0 when the size is uniform to 1.0 when the sample is highly polydisperse (Danaei et al., 2018). Concerning liposomal drug products, the FDA´s "guidance for industry" highlights the PS and PDI being CQAs and as such to be essential components of stability studies of these products (FDA, 2018).

4.2.2 Entrapment Efficiency (EE)

Defined as the percentage of drug entrapped in the nanoparticle-based dosage form matrix relative to the total drug supply, the entrapment efficiency is a crucial attribute that should be considered in the quality evaluation and art of production during storage. The EE calculation is crucial because it affects the drug dose and the screening of formulations (Lv et al., 2018). In lipid-based nanoparticles, depending on the hydrophobicity of the drug, Active Pharmaceutical Ingredients (APIs) can be encapsulated, if there is no disturbance of the lipid structure (Fan et al., 2021). The hydrophobicity of the polymer and the drug are the main challenges in the production of polymeric nanoparticles with the desired EE (Kolate et al., 2015).

4.2.3 Zeta Potential (ZP)

The electrokinetic potential in colloidal dispersions, also known as the zeta potential, is the potential at the slipping plane/area of a particle moving under an electric field; in other words, it is the electrostatic measure of repulsion or attraction between particles (Bhattacharjee, 2016). The ZP is the best criterion for the stability of a colloid since high zeta potential values should be achieved, either negative or positive, to maintain excellent stability and avoid aggregation of the particles (Shah et al., 2014).

As shown in Table 2, PS is the most prevalent CQA in lipid-based nanoparticles and polymeric nanoparticles, followed by EE, ZP and PDI. Although these CQAs are the most common, there are also other less common ones. However, the ones mentioned here should receive more attention due to for example stability and drug release reasons, as shown in Table 3.

4.3 Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)

CMAs and CPPs are the independent parameters and the input variables associated with the quality of the formulation and process performance (Mahtab et al., 2019). According to ICH Q8 (R2), a CPP is "a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality". A CMA is "a physical, chemical, biological, or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired product quality" (ICH Q8 (R2), 2009).

In some experimental work, and as shown in Table 2, lipid-based nanoparticles and polymeric nanoparticles have some CPPs and CMAs that are equal, such as drug concentration, and also the same CQAs that they should have. However, there are also many CPPs and CMAs that are different. This can be explained by their different preparation methods and formulations, e.g., in lipid-based nanoparticles as CPPs and CMAs, we have the lipid and phospholipid-to-cholesterol ratio (Mahtab et al., 2019) (Dhawan et al., 2022), respectively, and in polymeric nanoparticles, we have the polymer concentration and the emulsifier concentration (Esim et al., 2020).

4.4 Design of Experiments (DoE)

Being a structured, organized method for determining the relationship between input factors and output responses, affecting a process and the output of that process, the DoE is an excellent tool that enables the manipulation of factors according to a prespecified design (Yu et al., 2014). The nature of the experiments, such as factor optimization, screening and characterization, are important factors for the selection of experimental design. Other considerations, such as the number of factors and sample size, the choice of an appropriate

execution order for the experimental trials, and whether blocking or other randomization constraints determine the choice of experimental design. This selection also depends on the choice of empirical models used to describe the statistical cause–effect relationship (Beg et al., 2019c). For the selection of the experimental design, normally, major impact key parameters on product characteristics are identified, and preformulation studies are conducted since the number of parameters in the experimental design increases the number of experiments (Villa Nova et al., 2015). Experimental designs are used to reduce the number of experiments needed and therefore directly or indirectly reduce the costs, but still provide the highest level of information. This depends on the number and levels of variables to be investigated (Rapalli et al., 2019). The experimental design is grouped into two types: screening designs and response surface designs (Beg et al., 2019c).

4.4.1 Screening Designs

The word "screening" describes an experimental strategy aimed at isolating a small number of important factors from a long list of possible factors. Screening designs are quick and efficient ways to find these significant main effects of factors. Rather than focusing on interaction effects, a screening approach is usually used to find important main effects. Screening experimental designs include Fractional Factorial Design (FrFD), Taguchi Design (TD) and Plackett–Burman Design (PbD) (Beg et al., 2019c).

4.4.1.1 Fractional Factorial Design (FrFD)

FrFDs are usually used for factor screening. The notation $X^{k\ p}$ is used, where X is the number of levels, k is the number of factors, and p is the size of the full factorial fraction used (Beg et al., 2019c) (Hibbert, 2012) (Dangat et al., 2021).

Studies have shown that FrFD can be a suitable choice for the preparation and optimization of nanoformulations. However, this method is less economical and requires a significant amount of experimentation depending on the number of factors chosen. Increasing the number of levels, usually from "high" to "low" for each variable, leads to higher complexity of the technique (Rapalli et al., 2019).

FrFD has been found to be more widespread for lipid-based nanoparticles than for polymeric nanoparticles, as shown in Table 4.

4.4.1.2 Taguchi Design (TD)

Proposed by a Japanese engineer, the Taguchi Design utilizes two-, three-, and mixed-level fractional factorial designs. Being a design that ensures good performance in the product processes of the design stage within minimum time and cost effectiveness, it relies on the fact that not all the factors that cause variability can be controlled. It starts with a minimum of three

factors and produces four experimental runs at two levels, primarily relying on the use of orthogonal arrays and maintaining the equilibrium of equally weighted factor levels (Rapalli et al., 2019) (Beg et al., 2019c).

4.4.1.3 Plackett–Burman Design (PbD)

PbD is used for screening experiments, when a complete understanding of the system is not available in the early stages of development. It has also been applied to identify the most important formulation or process factors, to identify the main effects and to generate minimal experimental runs. The run numbers are multiples of 4, and the PbD starts with 11 factors and produces 12 experimental runs. When two-way interactions are anticipated to be minimal, PbD should be utilized to explore the primary impacts (Rapalli et al., 2019) (Beg et al., 2019c).

4.4.2 Response Surface Designs

Being particularly useful for optimizing the factors identified from screening designs or risk assessments, these experimental designs produce enough runs to identify both interaction effects and the main effects of the factors and to identify and monitor the levels of CMAs at high, medium, or low levels. Full Factorial Design (FFD), Central Composite Design (CCD), Box-Behnken Design (BBD), Optimal Design (OD), and Mixture Design (MD) are the most often utilized designs used for response surface optimization (Beg et al., 2019c).

4.4.2.1 Full Factorial Design (FFD)

Also called a fully crossed design, the FFD consists of two or more factors with possible values or levels, X^k, where X indicates the factor and k indicates the level. The FFD shows all the possibilities of combining the levels of each element with those of the other. With this kind of design, the investigator may examine how each component affects the response variables individually as well as how those interactions affect the response variables. An experiment is said to be fully factorial, if it has two or more components in its design, each of which has distinct potential values or “levels”, and if the experimental units can combine these levels in any way. They show all possibilities of combining the levels of each element with those of the others (Rapalli et al., 2019) (Beg et al., 2019c). As shown in Table 4, FFD is the most commonly used DoE in polymeric nanoparticles.

4.4.2.2 Central Composite Design (CCD)

A CCD is a statistical design that can be used to select the most important parameters and interactions in an investigation. It is useful in three-level factorial experiments, it provides information exclusively on the effect of experimental variables and it is widely used for response surface optimization. CCDs are classified into three different types: Central Composite Circumscribed (CCC), Inscribed (CCI) and Face Centered (CCF). A second-order

(quadratic) model can be used in response surface optimization without using a complete three-level factorial experimental design. It is used when factorial designs find curvature in the data, necessitating a change from an earlier linear design to a quadratic response surface design. A CCD can be seen to be an improved version of a three-level factorial design combined with axial or star points (Dewangan et al., 2018) (Rapalli et al., 2019) (Dangat et al., 2021).

4.4.2.3 Box-Behnken Design (BBD)

BBD is an independent quadratic design, and it consists of duplicate center points and a set of points located in the middle of each cube surface, which defines the area of interest. Simulating first- and second-order response surface designs is more efficient than the three-level full factorial design, especially if there are many input variables. The BBD helps in understanding the quadratic response surfaces and reduces the number of potential runs with more than 3 independent variables. It requires three levels for each factor (Rapalli et al., 2019) (Beg et al., 2019c) (Dangat et al., 2021).

The literature has revealed the vast application of BBD in the development of robust nanoparticle-based dosage forms, such as lipid-based nanoparticles, inorganic nanoparticles, and others, using complex variables and it is the most widely used design, as shown in Table 4 (Shaikh et al., 2017).

4.4.2.4 Mixture Design (MD) and Optimal Design (OD)

The MDs can be of different types (simplex-lattice designs, simplex-centroid designs, and optimal designs), and they have been used for the selection of an appropriate nanoparticle-based dosage form development composition and to study the different effects of several formulation variables. The OD is the most commonly used MD, especially for factor optimization studies. There are several types of ODs, such as D-optimal, L-optimal, and A-optimal, and these designs utilize three levels for each of the selected factors. The optimality of a design is evaluated in terms of a statistical criterion that is connected to the estimator´s variance matrix, which depends on the statistical model (Rapalli et al., 2019).

4.5 Design Space (DS)

DS is determined by ICH Q8 (R2) as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality” (ICH Q8 (R2), 2009). It is constituted by an integration of mathematical levels, allowing us to obtain a multidimensional graphic representation that will let us modify a factor and will let us know the impact of that change. It assures that when working in that region, we guarantee all the quality characteristics and therefore the product quality. The DS can be submitted for regulatory validation and approval, both as mathematical and graphical approaches by the applicant. Once approved by regulatory authorities, working

inside this design space is ideal, and working outside the approved design space is no longer seen as ideal and requires regulatory approval (Beg et al., 2019b) (ICH Q8 (R2), 2009). Different variants of Design Space can be possible, including at the laboratory scale, pilot scale and commercial scale, and each pharmaceutical product can have more than one DS (Beg et al., 2019b).

There are various ways to create a DS, and it can be in the form of graphical or mathematical representations. Product quality is important, as creating a DS will limit CPPs from achieving the defined CQAs (Peltonen, 2018a). At the laboratory scale, it is also important to use this technique, because it is an important tool for visualizing, comparing, and interpreting the data. There are various mathematical models and representations that are frequently presented in the literature, but not as frequently as graphical representations. 3D response surface plots are the most common, while overlay plots are not common (Manzon et al., 2020). These plots are crucial since they help to visualize the range of viable response values. As shown in Figure 3a and 3b, Shaikh et al. and Waghule et al. used appropriate software to create an overlay plot that allows the identification of, by the yellow region, the DS with viable response values (Shaikh et al., 2017) (Waghule et al., 2022).

From our point of view, creating a DS at all scales is important since it helps to gain insight into process behavior, ensure consistent product quality and risk management, optimize process parameters and ensure regulatory compliance.

4.6 Control Strategy

In order to guarantee the consistency in product quality, the control strategy is defined by ICH Q10 as “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 drug substance and 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” (ICH Q10, 2008). As a dynamic element of QbD, a control strategy must start after the product development phase is completed and, unlike a DS, can evolve and change over time, so it is conceptualized in a meaningful way to enable continuous improvement across the whole product development cycle (Beg et al., 2019a) (Beg et al., 2019b).

Table 2: Typical Input Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and Critical Quality Attributes (CQAs) (by order of prevalence) of Pharmaceutical Unit Operations

Type of nanoparticle/Delivery System	CQAs	CMA/CPP
Lipid-based Nanoparticles	PS, EE, ZP, PDI, DR, Yield, Stability, Uni-lamellarity Mean dissolution time	Drug amount, lipid amount, phospholipid/cholesterol, stirring rate, internal phase/external phase, and surfactant amount.
Polymeric Nanoparticles	PS, EE, ZP, PDI, DR, Yield, RE and PVA residual	Drug amount, polymer amount, polymer MW, surfactant amount, aqueous phase/organic phase, drug/polymer, sonication time, homogenization time and emulsification time.
Inorganic Nanoparticles	PS, PDI	Precursors pH and amount of calcium and molar concentration
Others	PS, PDI, ZP, EE and DL	GMO concentration, surfactant concentration and PEG concentration

CMAs (critical material attributes), CPPs (critical process parameters), CQAs (critical quality attributes), DL (drug loading), DR (drug release), EE (entrapment efficiency), GMO (glyceryl monooleate) MW (molecular weight), PEG (polyethylene glycol), PDI (polydispersity index), PS (particle size), RE (recovery efficiency), ZP (zeta potential).

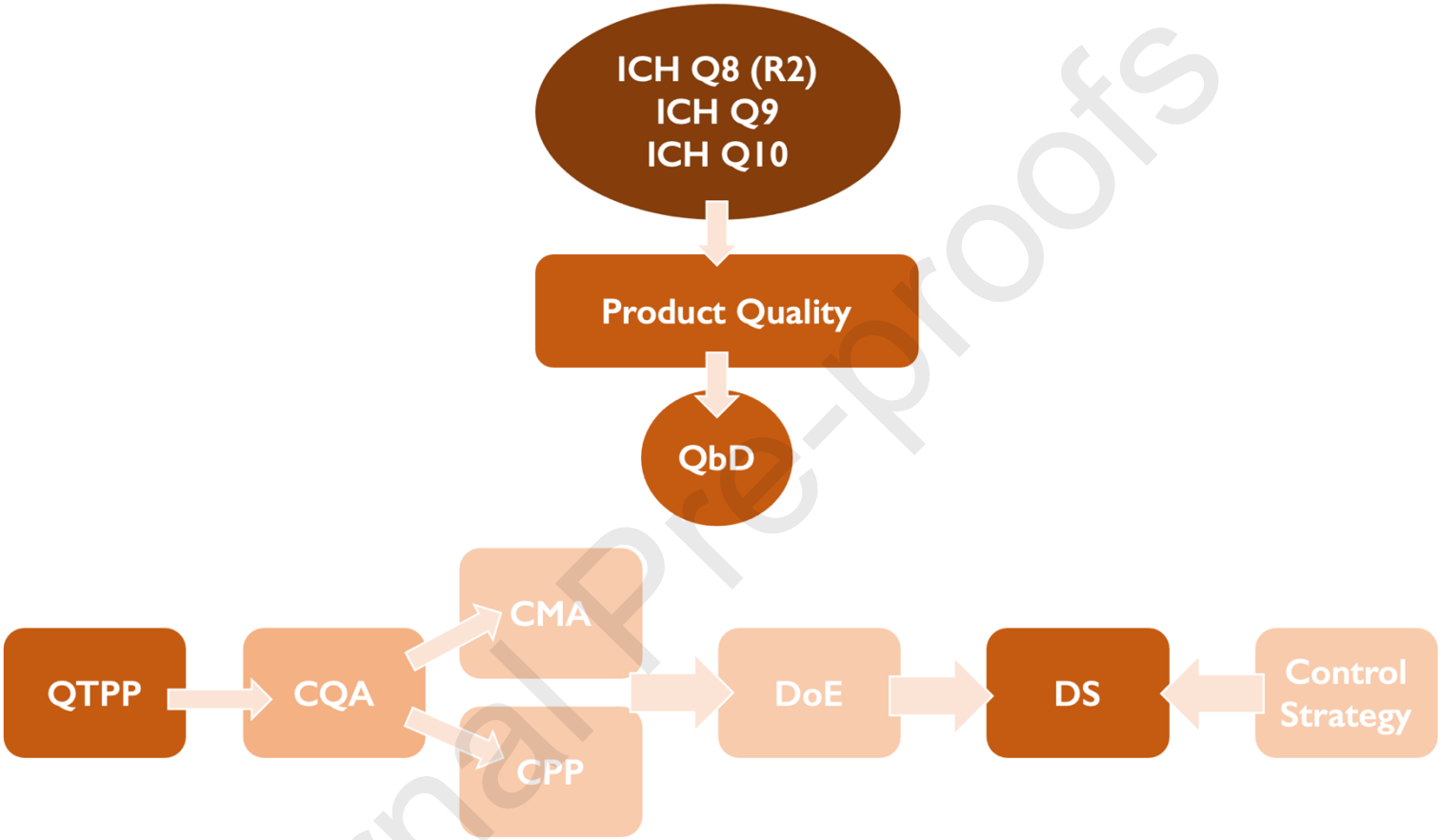

Figure 2 ICH Q8, ICH Q9 and ICH Q10 are pharmaceutical guidelines that were created to ensure the quality of pharmaceutical products and therefore the product quality. Product quality can be obtained by using the Quality by Design (QbD) approach, which has the following elements: QTPP (Quality Target Product Profile), CQAs (Critical Quality Attributes), CMAs (Critical Material Attributes), CPPs (Critical Process Parameters) and DoE (Design of Experiments), which are used to obtain a DS (Design Space). Control strategy ensures the process control and product quality. .

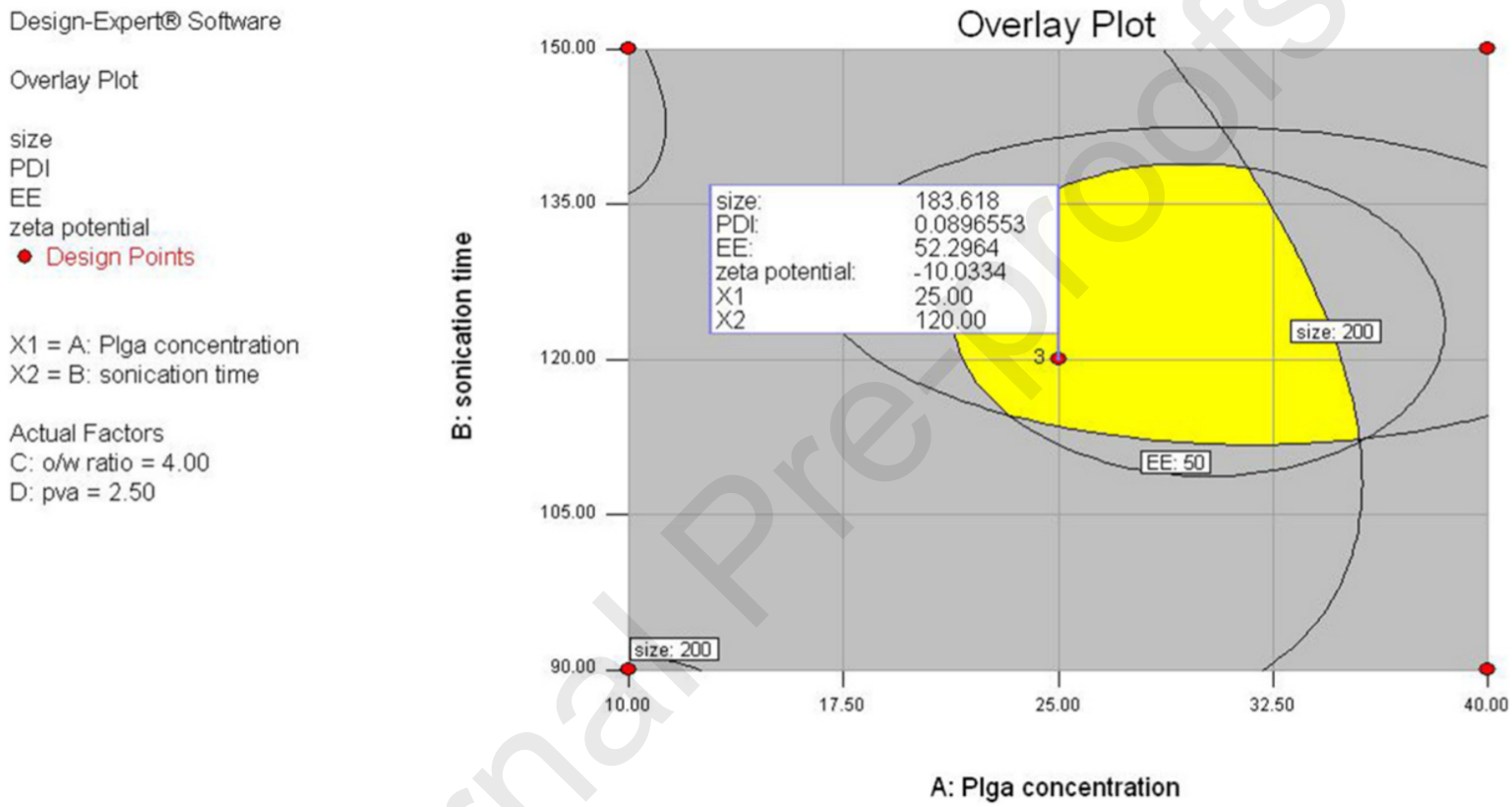

Figure 3a Overlay plot. According to the "Formulation and optimization of doxorubicin loaded polymeric nanoparticles using Box–Behnken design: *ex vivo stability* and *in vitro* activity" by Shaikh et al, 2017, 100, p. 266, Figure 3 (https://10.1016/j.ejps.2017.01.026)

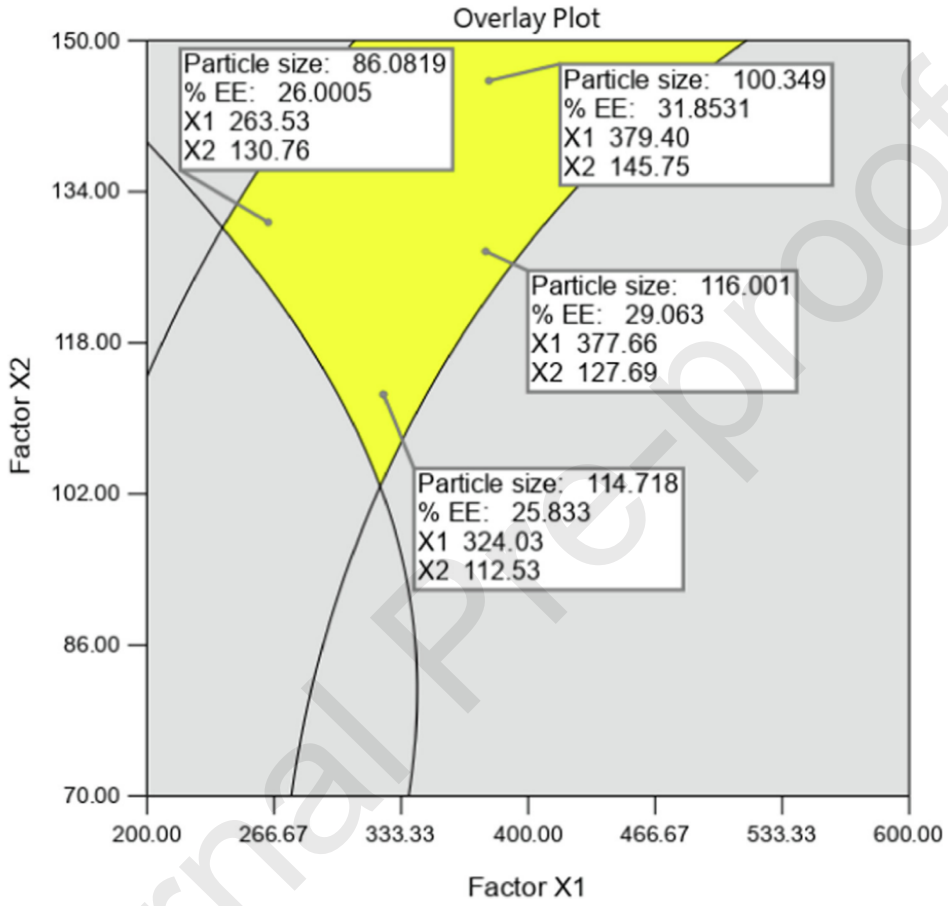

Figure 3b Overlay plot. The "Quality by design assisted optimization of temozolomide loaded PEGylated lyotropic liquid crystals: Investigating various formulation and process variables along with *in vitro* characterization" by Waghule et al., 2022, 352, p. 9, Figure 2 (https://10.1016/j.molliq.2022.118724)

Table 3: Potential Quality Attributes (QAs) to consider in the formulation development of nanoparticle-based dosage forms for parenteral administration.

Quality Attributes (QAs)	Justification	References
Stability	The physical and chemical stability in lipid nanoparticle formulations must be monitored to meet the criteria for good product practice The nanoparticle stability describes preservation of nanoparticle-based dosage forms qualities, such as composition, shape, size, and surface chemistry In nanoparticle-based dosage forms for intravenous administration, nanoparticles that have been shown to be stable in aqueous suspensions may behave differently in physiological fluids	(Rapalli et al., 2019) (Fan et al., 2021) (Phan and Haes, 2019) (Peltonen, 2018b) (Taha et al., 2020)
Drug Release (DR)	Drug release kinetics is an important feature of the formulation and a quality control one It has an essential role in the determination of the pharmacological effect Its prediction of in vivo release by using in vitro methods and in vitro-in vivo correlation (IVIVC), are essential in preclinical development and will serve as the basis for evaluation of drug formulations and regulatory approvals	(Fan et al., 2021) (D'Souza, 2014)

DR (drug release), IVIVC (*in vitro-in vivo* correlation)

Table 4: Selected literature case studies on Design of Experiments (DoE)-based optimization of nanotechnology-based systems for parenteral administration of drugs with disclosure of experimental design for each study and a focus on the effect of several Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) on Critical Quality Attributes (CQAs).

Nanoparticle-based dosage form	Experimental design with supporting bibliographic references	DoE Outputs with supporting bibliographic references
Lipid-Based Nanoparticles	**BBD** (Wang et al., 2019) (Anwar et al., 2016) (Mahtab et al., 2019) (Aboud et al., 2022) **FrFD** (Merlo-Mas et al., 2021) **FFD** (Ammar et al., 2018) (Mendes et al., 2020) (Aman et al., 2018) (Ishak et al., 2017) (Dhawan et al., 2022) **CCD** (Yadav et al., 2015) (Barbalata et al., 2022) **D-OD** (Malvajerd et al., 2019)	Longer homogenization time decreased PS but a negative effect of it on the stability of NP may occur (Wang et al., 2019) Effect of biological drug amount on PS and aggregation of NP, lipid amount's influence on PS, stability of NP, and pegylation improved stability and circulation time (Merlo-Mas et al., 2021) Both the effect of surfactant and its ratio with cholesterol had a significant effect on PS (Ammar et al., 2018) Optimized NP were supported on low amount of solid lipid, high amount of surfactant and both ultrasonication and high-pressure homogenization methods (Mendes et al., 2020) All the independent variables except sucrose mono palmitate had positive effect on EE and interactions among independent variables was found to be relevant (Aman et al., 2018) PS and EE decreased as surfactant amount, HPH pressure and HPH cycles increased (Anwar et al., 2016) Liposomal formulations were successfully developed with low PS and PDI, and high EE and improved DR characteristics (Mahtab et al., 2019) Interaction between drug amount and stirring rate was found to have influence on PS while EE was affected by stirring rate (Yadav et al., 2015) PS and EE of NP were optimized, and the cost, time and number of experiments was reduced (Malvajerd et al., 2019) Development of an optimal formulation that meets the QTPP and most critical factors were PL, SIM, and drug amount (Barbalata et al., 2022) Optimum NP exhibited small PS no aggregation behavior and prolonged in vitro release profile (Aboud et al., 2022) NP were developed using the desirability function and the optimized CPP were employed for replacing Tween® 80 with other PEG-SAA, TPGS, and Solutol® (Ishak et al., 2017) Phospholipid/cholesterol ratio, targeting ligand and drug amount were found the most critical factors on the PS, EE, ZP and stability of NP (Dhawan et al., 2022)

		The FrFD determined cholesterol, phosphatidylcholine, and SA/DCP molar ratios for liposomes with characteristics satisfying the formulation requisites. The polynomials describing the effects on the ZP were calculated and the prepared liposomes exhibited adequate ZP for stable formulations (Németh et al., 2022)
Polymeric Nanoparticles	**FFD** (Joseph et al., 2018) (Jose et al., 2019) (Sahin et al., 2017) (Bhatt et al., 2021) (Villa Nova et al., 2015) (Esim et al., 2020) (Németh et al., 2022) (Elsewedy et al., 2020) **BBD** (Dewangan et al., 2018) (Shaikh et al., 2017) (Mittal et al., 2019) (Mollaeva et al., 2021) (Lorenzoni et al., 2019) **SLMD** (Jeswani et al., 2021), **TRD** (Rafiei and Haddadi, 2019), **FrFD** (Ahmed et al., 2016) (Narayanan et al., 2014) (Bhatt et al., 2021) **CCD** (Villa Nova et al., 2015)	Higher amount of PLGA and aqueous/organic ratio decreased the PS, and interaction found between PLGA and PVA (Dewangan et al., 2018) Effect of polymer and surfactant amount rather on PS than on EE (Joseph et al., 2018) Effect of zein, drug amount and stabilizer on PS, ZP and DR and interaction between zein and drug amount was relevant (Ahmed et al., 2016) PS and EE decreased as aqueous phase/organic phase ratio and sonication time increased (Jose et al., 2019) Sub200 nm NP with narrow size distribution and a negative ZP were optimized using BBD to select CMAs such as PLGA and oil/water ratio and CPP sonication time (Shaikh et al., 2017) PLGA amount and higher volume of organic phase were the CMAs most affecting PS (Sahin et al., 2017) No significant effect of homogenization speed and internal phase/eternal phase ratio on PS was found but the design was useful in analyzing interactions among independent variables (Narayanan et al., 2014) Both the PS and EE decreased as the aqueous phase/organic phase ratio increased; PS and EE increased as the polymer amount and volume of aqueous phase increased (Bhatt et al., 2021) Effect of surfactant and PLGA-PEG on PS and EE, respectively, and upon CCD the EE increased from 66 to 83%. (Villa Nova et al., 2015) Taguchi robust method was used for optimization of PLGA nanoparticles loaded with docetaxel and type of PLGA and nanoparticle preparation method were the factors that significantly influence nanoparticle-important characteristics (Rafiei and Haddadi, 2019) NP with a PS less than 220 nm, cumulative drug release greater than 50% at 15 days, and percent hemolysis less than 10% were developed upon simplex lattice mixture design of experiment to study the influence of formulation polymers with focus on polymer (Jeswani et al., 2021) Homogenization speed and surfactant ratio were the main factors influencing PS and PDI and did not seem to depend on the PCL ratio (Esim et al., 2020) Increased polymer amount increased EE up to a certain amount of organic solvent and a sufficient high surfactant was required to form NP with adequate PDI and EE (Mittal et al., 2019) Positive and negative effect of o/w ratio and PLGA and surfactant amount, respectively, on EE and interaction among factors was found to be relevant (Mollaeva et al., 2021)

		PLGA NPs were developed using a modified solvent evaporation technique and confirmed that PLGA and surfactant concentration play greater roles in determining NPs characteristics for intravenous administration (Elsewedy et al., 2020) PEG-PLGA-NPs and the individual and combinatory effects of the emulsification time, the method used for the nanoparticle preparation and the temperature of the aqueous phase was successfully evaluated on the PS,EE, efficacy of nanoparticle recovery, residual PVA and ZP (Lorenzoni et al., 2019)
Inorganic Nanoparticles	**BBD** (Pandey et al., 2018)	Higher pH and calcium amount decreased PS and increased ZP (Pandey et al., 2018)
Others	**BBD** (Waghule et al., 2022)	Positive and negative effect of lipid and surfactant amount, respectively, and PDI was mostly dependent of PEG and surfactant amount (Waghule et al., 2022)

BBD (box–behnken design), CCD (central composite design), CMAs (critical material attributes), CPPs (critical process parameters), CQAs (critical quality attributes), D-OD (D-optimal design), DR (drug release), EE (entrapment efficiency), FrFD (fractional factorial design), FFD (full factorial design), HPH (high-pressure homogenizer), NP(s) (nanoparticle(s)), PCL (polycaprolactone), PDI (polydispersity index), PEG-SAA (PEG-based surface-active agents), PLGA (poly-D,L-lactide-co-glycolide), PS (particle size), PVA (polyvinyl alcohol), QTPP (quality target product profile), SA/DCP (stearylamine/dicetyl phosphate), TPGS (d-α-tocopherol polyethylene glycol 1000 succinate) and ZP (zeta potential)

5. PAT framework applications in nanotechnology-based products

During the last two decades, the regulatory and industrial operators in pharmaceutical area have recognized the urgent need to improve the quality of pharmaceutical manufacturing processes by engaging the Process Analytical Technologies (PAT) throughout the manufacturing chains of pharmaceutical products (FDA, 2004) (Rathore et al., 2010). Utilization of PAT in all the processes improves the continuous real-time process control, which assures the high quality of the end-product. PAT also increases the level of process understanding and, hence, typically fastens the process development step. PAT concept is readily connected with QbD approach, where qualified production is ensured by systemic approach based on the thorough product and process understanding combined with relevant process control systems (Ferreira and Tobyn, 2014). For PAT, it is important to recognize the vital product-quality attributes, CQAs and identify the critical variables, CPPs and CMAs affecting the determined CQAs. Further, the analytical methods determining CQAs, CPPs and CMAs should be found, and the analytical information should be available in such a timeframe that real-time decisions and changes to the process can be made.

In pharmaceutical research, PAT concept has been studied during the last couple of decades, and for example in fluid bed granulation it has been utilized in modeling, control, and as an endpoint detection tool (Burggraeve et al., 2013), or in freeze-drying of parenterals for the controlling of the freezing and drying parameters, as well as the end-product properties like residual water level (Sharma et al., 2021) (Patel and Pikal, 2009) (Read et al., 2009). In biotherapeutics, in-line or near-line probes have been utilized in process control for parameters like temperature, pressure, redox potential, pH, gas phase and dissolved gas, etc. (Maruthamuthu et al., 2020). For nanoformulations its utilization has just recently started (Nanopat, 2023) (PAT4nano, 2023). The challenge here is that thermodynamical principles are not valid with nanosized materials and their physical properties like solubility etc. are size related. With nanomaterials the reliable PS, size deviation and shape information are the most important properties for production of high-quality nanosystems. But, due to the nanoscale the applied analytical techniques also differ from normal bulk materials.

As mentioned above, the most important properties of nanoparticle-based dosage forms are PS and size deviation (EMA, 2021). Also, according to the European Pharmacopoeia, parenteral preparations for injections, which contains dispersed particles (the case with nanosystems), PS should be controlled in the manufacturing, so that it is suitable for intended use. However, while various drug nanosystems have been studied a lot during the last decades, the risk of failure is still considerably high when translating research to a marketed product. Accordingly, there are more and more interest on precise control of quality attributes during the

manufacturing process, and international bodies like EU have raised the interest to fund PAT research in nanosystems. For example, EU-funded NanoPAT project (Nanopat, 2023) (PAT4nano, 2023) is studying three new analytical real-time techniques, Photon Density Wave spectroscopy (PDW), Optofluidic Force Induction (OF2i) and Turbidity Spectrometry (TUS) in PAT applications for nanosystems. Besides, the real time analysis of nanoparticles during the process requires further new data analysis methods.

Nanoparticle-based dosage forms sizing for process control purposes has been performed traditionally by Dynamic Light Scattering (DLS) techniques, which is challenging technique in PAT application. This is due to the fact that dispersion turbidities are often too high in process environment, flow or mixing disturbs the measurement and the measurement time frame is not suitable for PAT purposes. Besseling et al. (Besseling et al., 2019) developed NanoFlowSizer (NFS), which utilizes Fourier Domain Low-Coherence Interferometry (FDLCI) in particle sizing. In this technique, LCI illuminates the sample by low coherence light. Backscattered light and light split from the source interfere with a certain optical path length, and Fourier analysis enables almost instantaneous path length analysis. Measurements are done with microseconds intervals. The technique was tested for different kind of nanodispersions to validate the technique. Even highly turbid nanodispersions, which were not suitable for traditional DLS equipment, were measured successfully with the technique. However, some limitations were found. High flow lowered the accuracy of the technique for large particles. Besides, the size range was limited by the spectral acquisition rate, and with the used system, the lower limit was 15nm. The upper limit was several micrometers.

When thinking of PAT framework applications in nanoparticle-based dosage forms, certain process control measurements, e.g., moisture determination, temperature measurement, for nanomaterials do not differ from those used for macroscale particles and formulations. However, the small PS of nanomaterials poses great deal of limitations to use existing PAT techniques for their characterization, especially for the measurement of size and size distribution. Likewise, some of the used PAT techniques such as Near Infrared (NIR) for concentration can’t be used as the wavelength exceeds the PS of nanoparticles.

6. View on Continuous Manufacturing (CM) for Nanoparticles

CM is a modernization to conventional pharmaceutical batch-wise manufacture with the aim of coupling the different manufacturing unit operations together instead of performing them separately one by one. The key benefits, highlighted several times in review articles, commentaries and original articles, include shorter lead time in manufacturing, smaller equipment footprint, flexibility with batch sizes, reduced waste and enhanced control over the

process (Lee et al., 2015) (Rantanen and Khinast, 2015) (Nasr et al., 2016) (Badman et al., 2019) (Fisher et al., 2022). One clear benefit from the perspective of patient is the enhanced quality of manufacture that can eliminate certain drug shortages that in the past have resulted due to issues with the manufacturing processes (Lee et al., 2015) (Fisher et al., 2022). If initially the drug manufacturers were at the forefront to drive this development, the regulatory bodies have also expressed their endorsement for the positive development (FDA, 2023). Furthermore, there now exists also an ICH guideline for instructing the viewpoint of the marketing approval givers on what needs to be proven different/additional to that previously with batch processes (ICH Q13, 2021). The processes can be fully continuous, or some unit operations are operated in continuous mode and some in batch. Furthermore, the process can comprise both drug substance and drug product manufacture in one end to end process, or CM can be applied to only one part of the process, e.g., manufacture of final dosage form. Equipment design as well as raw material characteristics and requirements can be different from previous batch processes due to the altered manufacturing process. With CM processes some steps, such as purification, might become obsolete, if e.g., certain impurities are not created in the process anymore. This with the abovementioned shorter lead times and smaller processes can lead to substantial process intensification.

PAT tools are usually exploited in development and process control in the context of CM (Lee et al., 2015) (Rantanen and Khinast, 2015) (ICH Q13, 2021) (De Beer et al., 2011). It could be argued that the full potential of PAT, especially as the continuous process control, can be fully exploited when it comes to CM processes (Rathore et al., 2010). The development and transition of CM processes has gone already a long way for oral solid dosage forms. One additional feature, when it comes to designing continuous processes for parenteral products, is the requirement of sterility (EMA, 2023). This needs to be considered when implementing the new equipment trains in GMP manufacture. Possibility for terminal sterilization, or alternatively aseptic process and sterile filtration are required. However, it needs to be pointed out that even if the final terminal sterilization would be done as batch process for the whole batch, converting the preceding manufacture into continuous mode most probably still provides clear benefits for the overall manufacturing process.

CM of nanoparticle-based dosage forms for parenteral administration utilizes microfluidics in majority of cases. The technique has also been used for the manufacture of BioNTech-Pfizer Covid-19 vaccine Comirnaty® (Sealy, 2021). To the best of our knowledge, this is the first commercialized nanotechnology product produced with a continuous process. The concept of microfluidics is not entirely new anymore and several well written reviews on the basic principles exist already, such as those by Colombo et al (Colombo et al., 2018), Liu

et al (Liu et al., 2022), Osouli-Bostanabad et al (Osouli-Bostanabad et al., 2022) and Shepherd et al (Shepherd et al., 2021). In general, microfluidics exploits flow inside small tubing/capillaries that have inner diameter less than or equal to 1000µm. In ultimate case, the volumes are in only picolitre scale but depending on the source can range to microliters/min. However, in some of the more recent articles, authors have described their systems as microfluidics even though the flow rates have been clearly on mL/min scale (Chiesa et al., 2022) (Desai et al., 2021) (Nag et al., 2022).

Due to the greatly reduced geometries and flow rates, the flow patterns are considered to be laminar, and the flow resistance is minimal (Colombo et al., 2018) (Liu et al., 2022) (Osouli-Bostanabad et al., 2022) (Shepherd et al., 2021). The major benefits are better control over the system, fast mixing, short reaction kinetics, possibility of parallelization of the individual small volume process flows and coupling of sequential processing steps. It has also been argued that CM for this type of flow manufacturing provides larger process enhancement potential than oral solid form manufacturing, where CM has been a hot topic for at least a decade (Colombo et al., 2018). Likewise, the coupling of the QbD paradigm into these processes can provide the most meaningful outcomes due to enhanced process understanding and controllability of the process. To scale up the very small-scale manufacturing to commercial volumes, parallelization can be utilized. This was also the case to produce the Comirnaty® vaccine. This chapter now focuses on some of the case studies of microfluidics from recent years.

Some of the recent NP systems manufactured with microfluidics include lipid-based nanoparticles (Desai et al., 2021) (Nag et al., 2022) (Dimov et al., 2017), polymeric nanoparticles (Chiesa et al., 2022) (Desai et al., 2021) (Operti et al., 2022), block copolymer micelles (Bresseleers et al., 2019) and metallic NPs (Desai et al., 2021). The flow rates in the system in these studies ranged from 1 mL/min up to 50 mL/min (without parallelization), so it can be argued that these systems are not purely microfluidic systems but could be described as millifluidic. Nevertheless, they seem to employ the same principles and benefits as previously described for pure microfluidic systems. In essence, all the different microfluidic systems can be described as precipitation methods where two or more phases (containing the starting materials) are mixed to form the nanoparticles. The type of the system regarding the mixing of the phases and some other downstream processing steps, however, were different.

Desai et al (Desai et al., 2021) used a self-designed microfluidic cartridge in two different sizes employing fluidic traps to create chaotic mixing. They manufactured different types of NPs with their system, i.e., liposomes, PLGA particles and zinc oxide and iron oxide NPs. Chiesa et al (Chiesa et al., 2022) used somewhat similar approach and utilized microfluidic

cartridge that bases the mixing of phases on passive staggered Herringbone Mixer, which is a common mixing tool in microfluidic systems. They produced PLGA nanoparticles and tested loading them with curcumin as model API. Same staggered Herringbone type mixer was also used by Dimov et al (Dimov et al., 2017) for microfluidic production of liposomes. In this study, as well as in the one by Desai et al, the possibility for scaling up through parallelization was highlighted. Nag et al (Nag et al., 2022) as well as Operti et al (Operti et al., 2022) used an approach to combine microfluidics with sonication at the end to control the PS of the resulting NPs. Nag et al produced lipid NPs containing mRNA Covid-19 vaccine and Operti et al PLGA NPs containing ritonavir or celecoxib. In these studies, the sterility requirement of parenteral NPs was also considered. Nag et al employed sterile filtration and Operti et al considered sterilization but also replacement of piping between different products. In the study of Bresseleers et al (Bresseleers et al., 2019), a rather simple T-mixer was used for the production of docetaxel-loaded block copolymer micelles. This system was also regarded as scalable one that could potentially be transferred into GMP level manufacture. Although the microfluidic systems are usually precipitation (i.e., bottom-up) techniques, there is also the possibility for a top-down technique to decrease PS into nanoscale using high pressure homogenization by z-shape interaction chamber that creates high shear forces that break particles into smaller ones (Choi et al., 2020).

One alternative design to microfluidic systems is Coaxial Jet mixer (CJM). In this design the mixing of the phases and nanoparticle precipitation takes place when a jet is formed as the non-aqueous phase is jetted into the aqueous phase (Costa et al., 2016) (Sheybanifard et al., 2022). In these two studies, liposomes with well controlled and robust PS were produced. Same production process was used by Gupta et al (Gupta et al., 2020) to produce block co-polymer micelles containing curcumin as model API. They also compared the quality to corresponding batch process, showing enhanced NP quality with the continuous process. Similar approach was also used by Bovone et al (Bovone et al., 2019) to produce variety of block copolymer NPs and finally a polymeric nanoparticle gel for administration by injection. In all the studies, it was demonstrated how the NP size was able to be controlled through process parameters in a stable manner, highlighting the control over the continuous system and ability for reaching desired quality, i.e., promoting the QbD paradigm.

Another example of continuous biomanufacturing was described for continuous in vitro transcription of mRNA of Comirnaty® vaccine and packing into lipid-based nanoparticles (Schmidt et al., 2022) (Hengelbrock et al., 2023). In these studies, a slug flow system was utilized for the generation of flexible batch sizes ranging from 1000 to 10 million doses. This

eliminates scale-up issues as the amount of mRNA needed to produce can be controlled by the size of the slugs generated into the continuous flow of immiscible phase.

Experimental designs were used in all these studies, and results clearly show that essentially in all cases the particle (or in vitro transcription) characteristics could be fine-tuned and controlled through right processing conditions. This underlines the statement by the exceptional potential of CM for microfluidic systems to enhance process quality (Colombo et al., 2018). Furthermore, this was proven here for all these continuous systems, microfluidic or not. An often-stated hurdle for commercial implementation of NP production process has been batch-to-batch variation in batch processes. The studies presented here have all addressed this challenge by the robust and controllable NP quality.

Alternatively, Hot-Melt Extrusion (HME) (Patil et al., 2014) or HME coupled with high pressure homogenization (Khairnar et al., 2022) can also be used for continuous manufacture of NPs. Although perhaps usually seen more as a manufacturing means for oral solid dosage forms, HME could be used to produce NPs with parenteral administration as long as the sterility requirements are met. The product would in this case be solid NPs that would need to be suspended with a suitable vehicle before administration. However, the stability of liquid formulations is not always sufficient (at least without freeze storage) and solid nanoparticles or drying for storage might need to be considered. Continuous drying techniques do exist such as spin freeze drying, continuous freeze drying of suspended vials or more advanced drying technique called PRINT® that utilizes micromolding (Sharma et al., 2021). One can of course not disregard conventional option of spray drying (Schiller et al., 2020).

7. Conclusion

Intravenous administration is the most commonly used parenteral route for the delivery of nanoparticle-based dosage forms. The application of QbD in pharmaceutical manufacturing has become an essential approach for the pharmaceutical industry to ensure the efficacy and safety of pharmaceutical products, and its implementation in manufacturing is important because, as with any dosage form, it must meet quality parameters to be therapeutically effective and safe.

Without the implementation of QbD, the production of nanoparticle-based dosage forms will take more time to achieve quality and will therefore eventually be more expensive. However, the QbD approach has not been widely used in their development, and compared to conventional dosage forms, it is more challenging because size, charge, and aggregation are important quality attributes to consider. The implementation of QbD in these dosage forms is

essential to ensure the properties of the final product and the intended therapeutic and safety profiles.

With the goal of developing a safe and effective treatment and possible cure and considering its high market value, the most studied drugs and consequently the most studied disease in the implementation of QbD into nanoparticle-based dosage forms is cancer.

Lipid-based and polymeric nanoparticles are the most studied nanoparticle systems, and BBD is the most widely applied DoE. The CQAs PS, PDI, EE and ZP were the most commonly used, although others are less common and should receive more attention for various reasons, such as stability and DR, as shown in Table 3. Given its importance, the QTPP, an important but often neglected QbD element, has been established in very few published works on the parenteral route, and it should appear more often. Choosing the most appropriate DoE for any formulation depends on several factors, but BBD's advantages of avoiding extreme values of the factors and requiring fewer runs than a FFD or a CCD can be determinant. The largest part of the designs are optimizations, which can be explained by these designs having a higher variety of factor values expressed in a wide range. There are still a few nanoparticle-based dosage forms for disclosing design spaces, and this can be explained by the minor role of QbD in drug product development overall. Nevertheless, a benefit of space planning and design to increase human resource efficiency by understanding the unique needs of the intervenient in each role is still a challenge.

The concepts of PAT and CM are fully aligned with the QbD approach and vice versa. The synergy of these three paradigms together enhances the product and process understanding during pharmaceutical development, and ultimately the product quality.

The number of papers on other routes of administration such as oral administration is greater than that on parenteral administration. Therefore, research focused on parenteral administration routes seeking more specific CQA is needed, as closer collaboration among academic researchers, industry, and regulators is needed to overcome challenges and uncertainties and to decrease barriers in the regulatory approval of nanoparticle-based dosage forms developed using QbD.

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