Enhancing Therapeutic Outcomes with Novel Drug Delivery Systems: Challenges and the Role of Quality by Design

K Selvakumar[1], J.Joysa Ruby[2], Payel Pramanick[1], D Shanthini[1]

{selvakumark@acharya.ac.in[1]}

[1]Department of Quality Assurance, Acharya & BM Reddy College of Pharmacy, Soladevanahalli, Bengaluru – 560107, Karnataka, India

[2]Department of Pharmaceutics, Acharya & BM Reddy College of Pharmacy, Soladevanahalli, Bengaluru – 560107, Karnataka, India

Abstract. Novel Drug Delivery Systems (NDDS) have significantly improved pharmaceutical science by addressing the drawbacks of traditional drug delivery methodssuch as low bioavailability, ineffective targeted delivery and rapid degradation. These advanced systems like nanoparticles, liposomes, micelles, and nanocapsules enable drug release in controlled manner, enhanced stability, and precise targeting to specific tissues or cells, thereby better therapeutic efficacy and patient compliance. The complex and multivariate nature of NDDS development demands a systematic approach to ensure consistent quality and optimal performance. QbD offers a science-based framework that integrates risk management, understanding the process, and control of CQAs and CPPs throughout the lifecycle of the product. By incorporating tools such as DoE and PAT, that facilitates robust formulation and manufacturing processe while reducing development time and costs. This review highlights the role of QbD in overcoming the challenges associated with NDDS, illustrates its application across various drug carriers and its impact on enhancing drug delivery efficiency, safety, and regulatory compliance. The integration of QbD into NDDS development promises to advance personalized medicine and promote innovation in pharmaceutical therapeutics.

Keywords: Novel Drug Delivery System (NDDS), Critical Quality Attributes (CQA), Critical Process Parameters (CPP), Design of experiments (DoE).

1. Introduction

The drug delivery system plays important role in determining a medication's therapeutic efficacy. Many drugs exhibit a desired concentration range for maximum effectiveness; deviations from this range may result in lowered efficacy or harmful effects. Improvement in life-threatening disease treatment options have draw attention to the rising demand for integrated strategies that promote drug targeting within tissues. This resulted in the development of novel drug delivery systems (NDDS), which are designed to aim regulate

FPCS 2024, November 13-14, Bengaluru, India

DOI 10.4108/eai.13-11-2024.2355678

pharmacokinetics and, pharmacodynamics, as well as overall therapeutic effects. These systems represent a multidisciplinary approach, integrating, pharmaceutical development, bio-conjugate, and molecular-biology.[1] A range of specialized drug delivery systems has been created to reduce drug degradation and its loss, minimize unwanted effects, improve bioavailability, and improve accumulation of drug at the intended site of action. Examples of drug carriers include soluble polymers, micelles, cells, liposomes, lipoproteins and microparticles made from biodegradable synthetic and natural polymers.[2] Drug carriers can be engineered to degrade gradually, respond to environmental factors like temperature or pH, or specifically target desired sites, for instance, by conjugating them with antibodies that recognize specific markers of the target area. Targeting refers to the capability to manage a drug-encapsulated system precisely to its specific site of action.[3] Two primary strategies for targeted drug delivery are namely passive and active targeting. In passive targeting, chemotherapeutic drugs tend to accumulate in solid tumors due to the improved vascular permeability of tumor tissues compared to healthy tissues. This phenomenon allows for selective drug accumulation at the tumor site.[4]

The regulation of drug release and absorption is crucial for the creation of effective pharmaceutical formulations. Possible release mechanisms includingthe release of drugs that have been adsorbed, diffusion through the carrier matrix, the desorption of adsorbed drugs, diffusion via the carrier matrix wall, breakdown of the carrier matrix, or a combination of breakdown and diffusion. The mode of drug delivery can determine the success or failure of a therapy, as it significantly influences the drug's selection and therapeutic performance [5]. In sustained (or continuous) drug release, polymers are used to deliver the drug at a specified rate, either by diffusion out from the polymer matrix or by gradual polymer decomposition over the course of time. Pulsatile delivery, which mimics the body's natural rhythmic release of hormones like insulin, is a widely used drug delivery strategy. It typically involves drug-loaded polymers that respond to light, pH changes, or temperature shifts [6]. For over 20 years, researchers have recognized the importance of nanotechnology to bring significant advancements in drug delivery and therapeutic targeting. Improved delivery technologies offer substantial benefits to both patients and the pharmaceutical industry by reducing toxicity and enhancing drug efficacy [7]. Other drug delivery approaches focus on identifying suitable alternative routes for administering protein-based drugs bypassing the gastrointestinal tract, where they are prone to degradation or on overcoming physical barriers to improve targeting and therapeutic effectiveness [8].

2. Novel Drug Delivery System

NDDS carriers used include micelles, nanoparticles, niosomes, nanocapsules, nanospheres, liposomes, liquid crystals, and nanogels. [9]

2.1 Micelles:

A micelle is an aggregate of surfactant molecules distributed within a liquid, creating a colloidal suspension[10]. In pharmaceutical delivery applications, micelles created through the self-assembly of amphiphiliccopolymers in water typically ranging from 5 to 50 nm sizes are of particular interest. These copolymer micelles can physically entrap drugs which are hydrophobic within its core, enabling the delivery of drugs at higher concentrations than their

intrinsic water solubility.[10] The manufacturing and scale-up of micelle formulations can be challenging, often affecting product consistency and increasing production costs.[11,12]

2.2 Nanoparticles:

Nanoparticles are particles ranging from 10nm to 1000 nm size. Drugs can be dissolved, entrapped, encapsulated, or adsorbed onto the nanoparticle matrix. For instance, nanoparticles like nanospheres and nanocapsules sized 10 and 200 nm and exist in a solid state either classified as either amorphous or crystalline[13]. Nanospheres that contain the drug evenly dispersed within the polymer, whereas nanocapsules, in which the drug is trapped within a cavity surrounded by a distinct polymer membrane. Both biodegradable and non-biodegradable polymers may be utilized in nanoparticles intended for delivering various drug delivery. [14]. The reliable manufacturing of nanomaterials heavily relies on thorough characterization and a clear understanding of their behavior. Process nanometrology plays a key role in this regard, utilizing highly sensitive and precise instruments capable of measuring features at or below the nanometre scale [15]. Furthermore, the application of DoE methodologies such as factorial designs and response surface methods provides a systematic approach to optimizing both formulation and manufacturing processes by evaluating the influence of various CMAs and CPPs.[16]

2.3 Niosomes

Niosomes represent a unique technology in drug delivery, encapsulating medications within vesicles made of a bi-layer of non-ionic surfactants. These vesicles are typically nanometric in size and, though structurally same as liposomes, offer several advantages over them. Recent studies have demonstrated that niosomes significantly enhance trans-dermal delivery which can be effectively employed for drug targeting, making them a promising area for NDD strategies [17]. Also referred to as non-ionic surfactant vesicles, niosomes share many features and components with liposomes [18]. They are highly organized microscopic vesicles from 10 to 1000 nm in diameter ranges. Drugs with intermediate log P values distribute evenly within the hydrophilic core and the hydrophobic bilayer [19].

Niosomes have drawn considerable attention in the field of topical and transdermal drug delivery due to their non-toxicity, biodegradability, amphiphilic nature, non-immunogenicity, and ability to modify drug bioavailability. They enhance penetration of drug, provide a solubilizing matrix, and form a localized reservoir, within the deeper layers of the skin, a sustained release is achieved. Furthermore, by acting as a rate-limiting membrane, niosomes prolong drug presence in the stratum-corneum and epidermis, thereby improving skin deposition while restricting systemic absorption [20].

The effect of the final niosome formulation can be affected by various formulation as well as process variables during preparation. Investigating the factors is essential to deepen scientific understanding of these carriers [21]. Applying a QbD approach allows the simultaneous analysis of numerous key factors via a minimal quantity of trials, significantly reducing the duration and expenses associated with drug development and manufacturing. Moreover, QbD

helps identify the optimal formulation composition and provides a comprehensive understanding of both product and process characteristics [22].

2.4 Nano-Capsules

Nanocapsules, a distinct class of nanoparticles, consisting of one or more active materials (core) enclosed within a protective matrix or shell that confines the therapeutic agent [23]. Broadly, they can be described as nano-vesicular systems with characteristic core-shell configuration, in which the drug is localized within a reservoir or coating. The core may include the active pharmaceutical ingredient in either solid or liquid state, or as a molecular dispersion.Depending on the method of preparation and the raw materials utilized, the reservoir possesses a lipophilic nature. Additionally, considering the practical limitations of preparation techniques, nanocapsules may also carry the active ingredient on their surface or embedded within the polymeric membrane [24]. Despite their promising potential as drug delivery systems, nanocapsules face several formulation challenges to be addressed [25].

2.5 Liposome

A liposome is a spherical vesicle made up of one or more lipid bi-layers. Liposomes serve as versatile drug delivery vehicles for administering nutrients and pharmaceutical agents, including lipid nanoparticles used in mRNA and DNA vaccines. They are prepared by disrupting biological membranes, for instance, through sonication [26]. Owing to their structural resemblance to biological membranes and their capacity to encapsulate a wide range of substances, liposomes are considered nearly ideal drug carriers [27]. For instance, Perkins et al. illustrated that paclitaxel nanospheres coated with PEG 5000 and distearoyl phosphatidylethanolamine significantly prolonged their circulation time in the body [28]. However, liposome formulation presents several challenges.

2.6 Nanospheres

These are solid particles with 10 to 200 nm diameters. They can be either crystalline or amorphous and offer protection to drugs for combating enzymatic and chemical degradation. However, the hydrophobic surfaces of nanospheres are highly prone to opsonization and subsequent clearance by the reticuloendothelial system (RES). Unlike vesicles, which are microscopic capsules that store drugs, nanospheres are solid matrix structures [29]. Commonly, nanospheres have been fabricated from polymers such as PLGA and poly (D, L-lactic acid). Numerous research have effectively developed paclitaxel-loaded nanospheres utilizing biodegradable polymers that are coated with phospholipids, cholesterol, and vitamin E TPGS (tocopherol polyethylene glycol succinate) [29]. Compared to polyvinyl alcohol (PVA), TPGS shown significant improvement in paclitaxel encapsulation efficiency in PLGA nanospheres. Moreover, Perkins et al. illustrated the coating of paclitaxel nanospheres with distearoyl phosphatidylethanolamine and PEG 5000 improved their circulation time in vivo. [30].

3. QbD Approach

Pharmaceutical product development has evolved significantly over the past few decades, shifting from an empirical approach to a more organized and science-driven process [37]. The

latest ICH guidelines emphasize the importance of such systematic methodologies and provide detailed guidance on their implementation [37]. Regulatory authorities now consider QbD an essential component of pharmaceutical development for the consistent delivery of high standard products. As per the guidelines ICH Q8 (R2), a systematic, scientific, risk-based approach to pharmaceutical development is QbD that starts with predefined objectives that emphasizes a thorough comprehension and management of both the product and the process. [38,39].

In QbD-guided pharmaceutical development context, the target product profile (TPP) along with its related quality attributes referred as QTPP. Defining the QTPP is the critical initial step, as QbD begins by specifying the intended product characteristics. The QTPP outlines the quality attributes necessary to ensure the desired therapeutic performance of the product [39]. Following this, factors influencing the QTPP are identified, with particular focus on those having a significant impact. These key factors are known as CQAs. Additionally, CMAs of excipients and CPPs involved in product manufacturing must be controlled to ensure consistent product quality [39,40].

A fundamental component of QbD-aided development is risk assessment (RA), which systematically identifies material attributes and process variables that could affect the CQAs [40]. RA supports effective risk management by prioritizing factors that require close monitoring. To establish the design space, those variables with a high impact on product quality are analyzed and optimized to ensure robust performance with minimal variability. In accordance with ICH Q8, the design space is defined as the multi-dimensional combination and interaction of input variables such as critical material attributes and process parameters that influence product quality [40]. A summary of various NDDS and related QbD parameters is presented in **Table 1**.

Table 1: Various novel drug delivery systems and their QbD parameters

S.No	System	Description	Formulation Attributes	Critical Quality Attributes (CQAs)	Process Parameters	DoE Approach
1	Micelles	Self-assembled structures of amphiphilic block copolymers (5–50 nm) in aqueous media; widely explored for drug delivery.	-Indication -Route of administration -Target patients -Site of activity -Absorption feature -Dissolution profile	-Particle size -Solubility -Dissolution time -Wettability -Stability	-Composition -Time of Mixing -Rotation speed and pressure -Temperature & speed	Central composite design[31]
2	Nanoparticles	Amorphous or crystalline nanoparticles are both in the solid state. The dimensions of nanospheres and	- Dosage form& design -Route of administration -Dose strength	-Particle size - distribution -Dissolution zeta potential	-Mixing time -Mixing speed -Size reduction -Sonication	Box-Behnken design[32]

		nano-capsules range from 10 to 200 nm.				
3	Niosomes	Highly ordered microscopic drug-containing vesicles that are in the rangeof size from 10 to 1000 nm.	-Dosage form and dosage design -Route of administration -Dose strength	-Particle size & distribution -Dissolution -Zeta potential	-Mixing time -Mixing speed -External phase temperature -External phase volume	Fractional factorial design central composite design[33]
4	Nano-capsules	A harmless polymer is used to create a tiny shell known as a nano-capsule. They are vesicular structures comprised of a polymeric membrane that encloses a nanoscale liquid core.	-Route of administration -Dose -Stability	-Particle size -Particle shape -Dissolution	-Mixing speed -Size reduction -Mixing time	Central composite design[34]
5	Liposomes	A spherical vesicle is usually known as liposome which have at least one lipid bilayer.	-Dosage form -Dosage design -Administration route -Dose strength	-Drug content -Drug release -Degradation products	-Rotatory evaporator speed -Rotatory evaporator time	Plackett-Burmendesign[35]
6	Nanospheres	Solid, spherical polymeric particles (10–200 nm) exhibiting size-dependent properties advantageous for drug delivery applications.	-Dosage form -Dosage design -Route of administration -Dose strength	-Particle size -Particles size distribution -Dissolution	-Freeze drying time -Freeze drying temperature	Central composite design[36]

Drug formulation and process development are inherently complex and multivariate, making it difficult to establish a design space using the convention change one factor at a time (OFAT) approach [41]. Instead, statistical DoE and other multivariate methods are employed to systematically explore the relationships between multiple formulation and process variables and quality attributes [41]. DoE is a cost-effective and efficient tool that minimizes the number of experiments needed while rationalizing the effects of input factors on product quality. Additionally, DoE can predict potential interactions among factors across a broad range of conditions without the need to test every possible combination directly [42]. This comprehensive understanding of variability sources enables the effective use of PAT tools to monitor and control the manufacturing process more precisely [42].

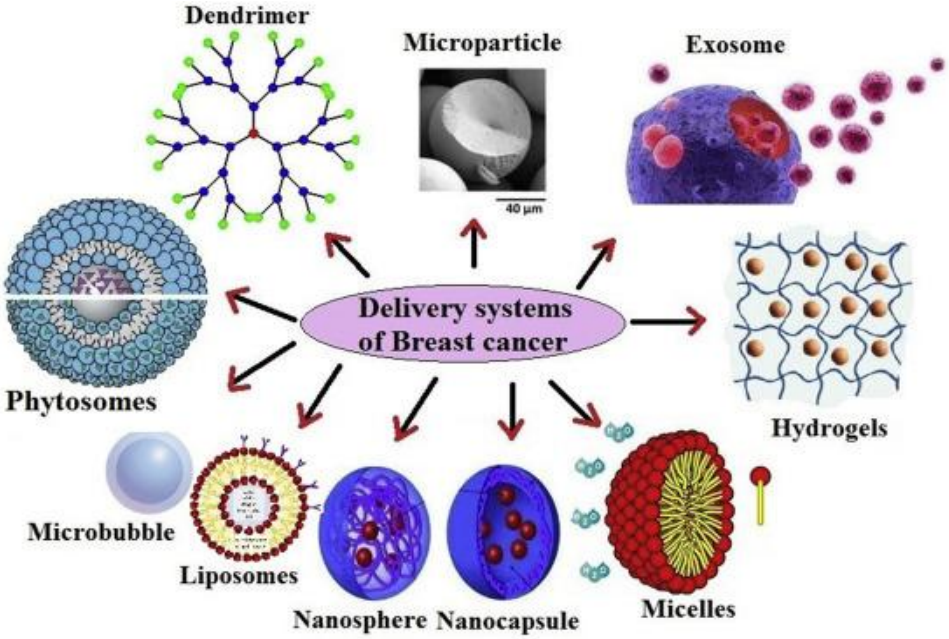

Fig 1: Novel drug delivery systems[43]

.

4. Conclusion

Quality by Design is essential in the processes of development and optimization of NDDS. Its primary advantage lies in embedding quality into the development process right from the beginning, rather than depending solely on end-product testing. QbD enables the design of robust and sustainable drug delivery systems by emphasizing key elements such as DoE, CPPs, and CQAs. This approach enhances control over drug release, bioavailability, and targeting efficiency, addressing the unique challenges posed by advanced formulations like nanoparticles, liposomes, micelles, and nanocapsules. In conclusion, QbD is reshaping the NDDS landscape by providing a comprehensive framework that ensures consistent product quality, optimizes therapeutic outcomes, and supports market growth. Its continued integration into pharmaceutical development is expected to drive innovation, making drug delivery technologies more effective and safer.

References

[1] Bassi da Silva J, Ferreira SB, de Freitas O, Bruschi ML. A critical review about methodologies for the analysis of mucoadhesive properties of drug delivery systems. Drug development and industrial pharmacy. 2017 Jul 3;43(7):1053-70.

[2] Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. Pharmacognosy reviews. 2010 Jan;4(7):27.

[3] Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. Drug delivery systems: An updated review. International journal of pharmaceutical investigation. 2012 Jan;2(1):2.
[4] Robinson DH, Mauger JW. Drug delivery systems. American journal of hospital pharmacy. 1991 Oct 1;48(10_suppl):S14-23.
[5] Kapoor DN, Bhatia A, Kaur R, Sharma R, Kaur G, Dhawan S. PLGA: a unique polymer for drug delivery. Therapeutic delivery. 2015 Jan 1;6(1):41-58.
[6] Singh R, Lillard Jr JW. Nanoparticle-based targeted drug delivery. Experimental and molecular pathology. 2009 Jun 1;86(3):215-23.
[7] Klose D, Siepmann F, Elkharraz K, Siepmann J. PLGA-based drug delivery systems: importance of the type of drug and device geometry. International journal of pharmaceutics. 2008 Apr 16;354(1-2):95-103.
[8] Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers. 2011 Aug 26;3(3):1377-97.
[9] Luu YK, Kim K, Hsiao BS, Chu B, Hadjiargyrou M. Development of a nanostructured DNA delivery scaffold via electrospinning of PLGA and PLA–PEG block copolymers. Journal of controlled release. 2003 Apr 29;89(2):341-53.
[10] Kiss T, Alapi T, Varga G, Bartos C, Ambrus R, Szabó-Révész P, Katona G. Interaction studies between levodopa and different excipients to develop coground binary mixtures for intranasal application. Journal of Pharmaceutical Sciences. 2019 Aug 1;108(8):2552-60.
[11] Pallagi E, Jójárt-Laczkovich O, Németh Z, Szabó-Révész P, Csóka I. Application of the QbD-based approach in the early development of liposomes for nasal administration. International journal of pharmaceutics. 2019 May 1;562:11-22.
[12] Katona G, Balogh GT, Dargó G, Gáspár R, Márki Á, Ducza E, Sztojkov-Ivanov A, Tömösi F, Kecskeméti G, Janáky T, Kiss T. Development of meloxicam-human serum albumin nanoparticles for nose-to-brain deliveryvia application of a quality by design approach. Pharmaceutics. 2020 Jan 25;12(2):97.
[13] Croy SR, Kwon GS. Polymeric micelles for drug delivery. Current pharmaceutical design. 2006 Dec 1;12(36):4669-84.
[14] Kanazawa T, Taki H, Tanaka K, Takashima Y, Okada H. Cell-penetrating peptide-modified block copolymer micelles promote direct brain delivery via intranasal administration. Pharmaceutical research. 2011 Sep;28:2130-9.
[15] Si PZ, Li D, Choi CJ, Li YB, Geng DY, Zhang ZD. Large coercivity and small exchange bias in Mn3O4/MnO nanoparticles. Solid state communications. 2007 Jun 1;142(12):723-6.
[16] Berkowitz AE, Rodriguez GF, Hong JI, An K, Hyeon T, Agarwal N, Smith DJ, Fullerton EE. Monodispersed MnO nanoparticles with epitaxial Mn3O4 shells. Journal of Physics D: Applied Physics. 2008 Jun 19;41(13):134007.
[17] Sun X, Frey Huls N, Sigdel A, Sun S. Tuning exchange bias in core/shell FeO/Fe3O4 nanoparticles. Nano letters. 2012 Jan 11;12(1):246-51.
[18] Zeng H, Sun S, Li J, Wang ZL, Liu JP. Tailoring magnetic properties of core⁄ shell nanoparticles. Applied physics letters. 2004 Aug 2;85(5):792-4.
[19] Smit J, Wijn HP. Ferrites, Philips Technical Library, Eindhoven. The Netherlands. 1959;151:157-8.
[20] Makovec D, Drofenik M. Non-stoichiometric zinc-ferrite spinel nanoparticles. Journal of Nanoparticle Research. 2008 Dec;10:131-41.

[21] Gyergyek S, Makovec D, Kodre A, Arčon I, Jagodič M, Drofenik M. Influence of synthesis method on structural and magnetic properties of cobalt ferrite nanoparticles. Journal of Nanoparticle Research. 2010 May;12:1263-73.
[22] Ammar S, Jouini N, Fievet F, Stephan O, Marhic C, Richard M, Villain F, dit Moulin CC, Brice S, Sainctavit P. Influence of the synthesis parameters on the cationic distribution of ZnFe2O4 nanoparticles obtained by forced hydrolysis in polyol medium. Journal of non-crystalline solids. 2004 Oct 15;345:658-62.
[23] Sato T, Haneda K, Seki M, Iijima T. Morphology and magnetic properties of ultrafine ZnFe 2 O 4 particles. Applied Physics A. 1990 Jan;50:13-6.
[24] Kamiyama T, Haneda K, Sato T, Ikeda S, Asano H. Cation distribution in ZnFe2O4 fine particles studied by neutron powder diffraction. Solid state communications. 1992 Feb 1;81(7):563-6.
[25] Haroun M, Elsewedy HS, Shehata TM, Tratrat C, Al Dhubiab BE, Venugopala KN, Almostafa MM, Kochkar H, Elnahas HM. Significant of injectable brucine PEGylated niosomes in treatment of MDA cancer cells. Journal of Drug Delivery Science and Technology. 2022 May 1;71:103322.
[26] Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. European journal of pharmaceutics and biopharmaceutics. 2019 Nov 1;144:18-39.
[27] Shaker DS, Shaker MA, Hanafy MS. Cellular uptake, cytotoxicity and in-vivo evaluation of Tamoxifen citrate loaded niosomes. International journal of pharmaceutics. 2015 Sep 30;493(1-2):285-94.
[28] Mohamed HB, El-Shanawany SM, Hamad MA, Elsabahy M. Niosomes: a strategy toward prevention of clinically significant drug incompatibilities. Scientific reports. 2017 Jul 24;7(1):6340.
[29] Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: a controlled and novel drug delivery system. Biological and Pharmaceutical Bulletin. 2011 Jul 1;34(7):945-53.
[30] Yang H, Deng A, Zhang J, Wang J, Lu B. Preparation, characterization and anticancer therapeutic efficacy of cisplatin-loaded niosomes. Journal of microencapsulation. 2013 May 1;30(3):237-44.
[31] Sharma V, Anandhakumar S, Sasidharan M. Self-degrading niosomes for encapsulation of hydrophilic and hydrophobic drugs: an efficient carrier for cancer multi-drug delivery. Materials Science and Engineering: C. 2015 Nov 1;56:393-400.
[32] Sezgin-Bayindir Z, Antep MN, Yuksel N. Development and characterization of mixed niosomes for oral delivery using candesartan cilexetil as a model poorly water-soluble drug. AAPS pharmscitech. 2015 Feb;16:108-17.
[33] Duong VA, Nguyen TT, Maeng HJ. Preparation of solid lipid nanoparticles and nanostructured lipid carriers for drug delivery and the effects of preparation parameters of solvent injection method. Molecules. 2020 Oct 18;25(20):4781.
[34] Guideline IH. Impurities: guideline for residual solvents. InInternational Conference on Harmonisation Q3C, Geneva 1997 Jul 17 (pp. 1-16).
[35] Schubert MA, Müller-Goymann CC. Solvent injection as a new approach for manufacturing lipid nanoparticles–evaluation of the method and process parameters. European journal of pharmaceutics and biopharmaceutics. 2003 Jan 1;55(1):125-31.

[36] Ritwiset A, Krongsuk S, Johns JR. Molecular structure and dynamical properties of niosome bilayers with and without cholesterol incorporation: A molecular dynamics simulation study. Applied surface science. 2016 Sep 1;380:23-31.
[37] Tabatabaei Mirakabad FS, Akbarzadeh A, Milani M, Zarghami N, Taheri-Anganeh M, Zeighamian V, Badrzadeh F, Rahmati-Yamchi M. A Comparison between the cytotoxic effects of pure curcumin and curcumin-loaded PLGA-PEG nanoparticles on the MCF-7 human breast cancer cell line. Artificial cells, nanomedicine, and biotechnology. 2016 Jan 2;44(1):423-30.
[38] Lalatsa A, Schatzlein AG, Uchegbu IF. Strategies to deliver peptide drugs to the brain. Molecular pharmaceutics. 2014 Apr 7;11(4):1081-93.
[39] Van Hoesen GW, Hyman BT, Damasio AR. Entorhinal cortex pathology in Alzheimer's disease. Hippocampus. 1991 Jan 1;1(1):1-8.
[40] Teskač K, Kristl J. The evidence for solid lipid nanoparticles mediated cell uptake of resveratrol. International journal of pharmaceutics. 2010 May 5;390(1):61-9.
[41] Szabó-Révész P. Modifying the physicochemical properties of NSAIDs for nasal and pulmonary administration. Drug Discovery Today: Technologies. 2018 Jul 1;27:87-93.
[42] Kürti L, Gáspár R, Márki Á, Kápolna E, Bocsik A, Veszelka S, Bartos C, Ambrus R, Vastag M, Deli MA, Szabó-Révész P. In vitro and in vivo characterization of meloxicam nanoparticles designed for nasal administration. European Journal of Pharmaceutical Sciences. 2013 Sep 27;50(1):86-92.
[43] Hani U, Rahamathulla M, Osmani RA, Kumar HY, Urolagin D, Ansari MY, Pandey K, Devi K, Yasmin S. Recent advances in novel drug delivery systems and approaches for management of breast cancer: A comprehensive review. Journal of Drug Delivery Science and Technology. 2020 Apr 1;56:101505.