Consideration for the scale-up manufacture of nanotherapeutics—A critical step for technology transfer

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Abstract
While nano-enabled biotechnology is offering great promise, in certain areas providing fundamental paradigm shift for disease management, we are rapidly moving into a new era of nanotechnology developmental stage, in which chemistry, manufacturing, and controls of nanotherapeutics (nano-CMC) become a critical step for translational nanomedicine. This is not a trivial task, in fact, nano-CMC requires a long list of considerations. Minimally, it includes raw materials, scale-up synthesis routes, batch sizes, stability check, analytical methods, and documentation. The growing items on the list could collectively ensure the reproducible production of nanotherapeutics that are safe and efficacious and meet new drug application (NDA) specifications. This article begins from the lesson learned from liposome, such as Doxil® and other FDA-approved liposomes, then continues to provide a literature summary on the scale-up synthesis of nanoparticles that were designed for therapeutic or diagnostic purposes. We outlined the key challenges during the scale-up activities, followed by the case studies to illustrate the impact of emerging strategies that may improve the reproducible synthesis of large-batch nanoparticles. The availability of quality-controlled large-batch size opens the possibility to conduct robust preclinical studies and clinical trials. This includes the recent advances of using microfluidics system, implementation of multiparameters iterative CMC optimization, and use of computer software, allowing the successful preparation of different organic and inorganic nanoparticles at desired batch sizes. The authors also share personal insights with respect to how nano-CMC research would facilitate “personalized and just-in-time” nanomedicine.

KEYWORDS
microfluidics system, nano-CMC, nanomaterials, nanomedicine, scale-up synthesis

1 INTRODUCTION
Generally speaking, the production of nanomaterials (NMs) is a challenging task in terms of reproducibility and quality control (QC). Preparation of pharmaceutical-grade NMs, that is, nanotherapeutics, could be even more difficult. While people have penetrated through the journey of chemistry, manufacturing and controls (CMC)
for the traditional nanoformulation, such as liposome, the nano-CMC for emerging nanotherapeutics still requires intensive basic and translational studies. The key considerations, such as the rational choice of raw materials, standardized and facile scale-up synthesis protocol, design of appropriate batch sizes, stability check, and analytical methods for emerging NM’s physicochemical properties, and standard documentation, are of great importance for the nanotherapeutics of different chemical composition.[2]

This manuscript begins from the discussion about the lesson learned from Doxil®, the first FDA-approved liposome that is highly successful but undergoes supply shortage at certain point. Then, the scope moves beyond liposomes to cover the recent advancement on scale-up synthesis of therapeutic or diagnostic nanoparticles including the key challenges during the nano-CMC activity. Several case studies are provided to illustrate the impact of the emerging strategy that may improve the reproducible synthesis of large-batch nanoparticles. The clear pathway on nano-CMC is expected to foster the performance of robust preclinical studies, big animal toxicity studies, and clinical trials. The outcome of nano-CMC research has promoted the authors to contemplate “personalized and just-in-time” nanomedicine including overcoming the time-sensitive public health crisis.

2 | LESSONS LEARNED FROM THE CMC ACTIVITY FOR LIPOSOMAL FORMULATIONS

Liposome, a spherical vesicle that consist of one or more lipid bilayer, is recognized as nanocarrier for delivery of different drugs or active pharmaceutical ingredients (APIs).[13] Although phospholipid made liposome is approximately 40-year old technology, it does not become a barrier innovation wise[4]; in fact, the integrated formulation design and nano-/biodiscovery processes yield new nanomedicine candidates, leading to the most robust clinical trials globally, that is, approximately 500 active studies according to clinicaltrials.gov (searched on 20 November 2020). During this journey, reproducible and QC-controlled CMC for the innovative liposomal vehicles is a frequent practice by pharma, which continues to make clinical success in the past decades, exemplified by the success of Doxil®, Onivyde®, and Vyxeos® among others.[4-6,7] Without CMC, however, it would be impossible to make advances clinically because of the inadequate supply of new and chemically distinct nanocarriers that have to undergo rigorous preclinical and clinical investigation. The family of liposome includes variety of subcategories such as stealth liposome, targeted liposome, pH-sensitive liposome, temperature-sensitive liposome, reverse-phase evaporation liposome, charge reversion liposome, immunoliposome, prodrug liposome, etc.[4,7] Ample evidences suggested that upgrade of research-grade liposome to well-controlled and IND-enabling batches at industrial scale is a challenging step. This is partially because of the lack of appropriate methods to produce large and reproducible quantities that can fit into different developmental stages.[18] One example is the film rehydration method for liposome synthesis.[8]

While the popularity of this method in research originates from composition-independent lipid mixing, ease of particle encapsulation, and high lipid working concentration, a major pitfall is the difficulty of scaling-up beyond milliliter volume in order to obtain homogeneous and desired particle size when lipid film is involved.[4,8,9] Alternative protocols have been developed, such as ethanol injection method and reverse-phase evaporation method, which is relatively easy to practice but generates new challenges such as size, homogeneity, removal of organic solvent, and sometimes detergent.[4] In order to reduce liposome size, different technologies have been developed, that is, sonication, extrusion, and homogenization, with a view to obtain size controlled unilamellar and/or multilamellar liposomes.[3-5,8] So far, the most well-established approach is pore extrusion using polycarbonate membrane.[10] Different setup, ranging from “minieextruder” (that produces milliliters volume) to equipment that can handle several liters of samples, are commercially available to make liposomes from approximately 25 nm to several hundred nanometers size range with low polydispersity index (PDI).[10] Most extruders contain a temperature controlled unit (allowing the operation above the transition temperature or Tc), however, the preparation process is time consuming and frequently suffers from membrane clogging, especially for the rigid liposomes with high % cholesterol or charge-conversion lipid compositions.[4,10] Recently, microfluidics-based production rapidly emerged as a major breakthrough for liposome and other lipid-based formulations,[11] which will be discussed later.

In addition to the batch size, a list of FDA expected information, such as source of raw materials, stability, and product releasing criteria (QC), collectively impact the success of nano-CMC for liposome. For a pharmaceutical good manufacturing practice-grade product, it is important to control the batch from a regulatory perspective. Noteworthy, even for the most cited liposome, Doxil®, suffered supply shortages at certain point when the FDA found huge manufacturing and sanitary issues, leading it to intermittently halt production, according to a news report (https://www.fiercepharma.com/m-a/updated-j-j-s-doxil-shortage-to-last-until-at-least-end-of-2014). The shortage prompted an expedited approval of a generic Doxil® by Sun Pharmaceutical Industries and other
vendors.\cite{12} Although it is not possible to provide a universal strategy on how to develop liposome CMC because each formulation is different, a FDA document (April 2018 version, https://www.fda.gov/media/70837/download) indeed outlines the recommendation on liposomal new drug applications (NDA). In addition to the International Conference on Harmonization guideline on new drug,\cite{13} extra attentions are required in terms of physicochemical parameters, batch-to-batch varies, quantitative analysis on encapsulated versus nonencapsulated API(s), lipid components, lipid peroxidation, degradation products, and in vitro release data. This document also contains information about pharmacokinetics and bioavailability, that is, distinguish between encapsulated and nonencapsulated drug, in vivo integrity, stability, liposome/protein interaction (eg, lipoproteins in the blood stream), and safety.

3 | KEY CHALLENGES DURING THE SCALE-UP ACTIVITY OF EMERGING NANOMEDICINE

Having demonstrated that nanoenabled products for certain disease of interest is no longer an unusual activity in academic research laboratory, one of the key tasks now becomes CMC related. That said, it is important to show the capability to transfer the technology in a developmental facility or contract manufacturing organization, where a cost-effect, well-controlled, and scalable procedure can be established to produce large-batch sizes under good laboratory practice and ultimately GMP conditions. In terms of scale-up synthesis, a recent literature search led to very few hits about this topic,\cite{2,14} while the large majority of articles document the proof-of-principle studies using milligram or subgram quantity of NMs that were tested in tissue culture or at intact animal level.\cite{15} Despite the promise of using nanotherapeutics with different chemical composition, we expect, unfortunately, considerable amount of platforms will be “triaged” along the evolution simply because of the failure of nano-CMC. From this perspective, the key challenges, in our opinion, that need early attention include:

- Introduction of difficult-to-remove catalysts, solvents, and impurities during nano-CMC may prevent the pharmaceutical utilization of nanoparticles.
- Super sensitive synthetic parameters during nano-CMC may lead to batch-to-batch and facility-to-facility differences.
- Utilization of closed systems and/or automation to reduce cost, improve safety, and reduce the possibility of making errors.
- Establishment of rigorous general and nano-specific QC such as quantitative in-the-process control and sample releasing tests.
- Instead of using green chemistry, involvement of inflammable or toxic raw materials may complicate nano-CMC.
- Nano safety risk and risk assessment during large-batch manufacturing.
- Endotoxin contamination.
- Delineation of hazardous potentials associated with unique nanosurface property and reactivity.
- Nano-specific consideration on stability, shelf-life, and degradation.
- Composition-specific technological hurdles. For example, specific consideration on short shelf-life, temperature-sensitive, and radioactive nanomedicine may demand deliberate process design.
- Specific consideration on nano-CMC that involves biological elements such as antibody, protein, cell product, etc.
- Cost-effectiveness.

4 | PLAN A SUCCESSFUL NANO-CMC PROCESS

While it is not possible at this stage to provide a detailed blueprint of how to develop a fully matured nano-CMC, the field begins to appreciate the infrastructural needs to build such a guideline.

4.1 | Simple yet transitionally attractive

While multifunctionality has been advocated as a key feature of the next-generation of nanomedicine, it sets a higher bar from a nano-CMC perspective. Take proof-of-principle cancer nanomedicine research, for example, it is helpful to investigate, individually or in an integrated fashion, the versatile nanocharacteristics such as high drug loading, passive and/or active targeting, efficient tumor penetration and intratumoral distribution, autonomous or on-demand release, imaging, synergistic codelivery, and photodynamic/photothermal
therapy for research purpose. However, in order to perform advanced preclinical and clinical study, critical decision-making is needed in order to identify the “leading candidate” in the pipeline that requires to be manufactured in a controlled large batch. Are all the design features clinically feasible or just an academic exercise? While the answer is case-specific, we advocate a simple yet transitionally attractive design approach. Take liposome, for example, the vast majority of clinically tested liposomes have simple design. Most of them are primarily designed for intravenous injection exemplified by lipoplatin (cisplatin liposome for non-small cell lung cancer) or ThermoDox (doxorubicin liposome for hepatocellular and certain breast cancer), with exception such as amikacin aerosol delivery liposome for lung infection disease. Noteworthy, ThermoDox, which is a thermosensitive liposomal doxorubicin whose novel mechanisms include passive targeting and heat (40°C)-triggered release, failed to delay the regrowth of liver tumors, and recently is combined with radiofrequency ablation therapy (https://www.globenewswire.com/news-release/2020/06/25/2053369/0/en/Celsion-Affirms-July-Timing-for-Second-Interim-Analysis-of-the-Phase-III-OPTIMA-Study-of-ThermoDox-in-Primary-Liver-Cancer.html).

Almost all the liposomes contain one type of API, except Vyxeos that carries ratiometrically designed daunorubicin and cytarabine for the treatment of acute myeloid leukemia. Another important caveat is that only small portion of the liposome formulations contain so-called active targeting, that is, antibody or peptide, putatively due to the complexities that are involved during storage and protein/peptide conjugation, and limited efficacy improvement.

The successful large-quantity preparation of nonliposomal platforms is rapidly emerging. Take metal and metal oxide (eg, Fe, MnO, and CoO), for example, a pioneer study demonstrated the feasibility on the large-scale synthesis of monodisperse nanocrystals, which involves the use of metal-oleate precursors, in an inexpensive fashion (Figure 1). Efforts were also devoted to large-scale synthesis of many other types of nanoparticles for biomedical application such as polymer nanoparticles, solid lipid nanoparticles (LNPs), gold/silver nanoparticles, silica nanoparticles, carbon dots, metal-organic frameworks (MOFs), etc. While multiple specific inorganic nanoparticles have been successfully moved into clinical studies, such as C-dots (Cornell dots, <10 nm ultrasmall inorganic hybrid silica nanoparticles for imaging and treatment purpose) MOFs, nanoscale coordination polymers, and gold nanoparticles (human tumor necrosis factor alpha (rhTNF) binding gold nanoparticles (CYT-6091) and gold-silica nanoshells (AuroShell)), the detailed scale-up synthesis of these nanoformulations were generally not disclosed. Moreover, for the emerging new functional NMs, such as two-dimensional nanosheets, comprehensive characterization methods (eg, HR-TEM, nanozyme assay, EPR, DCF assay) should be performed to look at the surface activities (eg, catalytic activity, oxidative activity) during the scale-up process.

Noteworthy, it would be also helpful to consult NM literature in the field of nonbiomedicine research, such as catalysis and energy storage, which is inspiring in terms of how to upgrade the synthetic condition from a conventional flask reactor (capable of producing $\leq$1 g quantity) to a continuous large batch synthesis approaches.

### 4.2 Multiparameter and iterative optimization

For nano-CMC, it is almost certain that multiple factors will affect the synthesis quality, quantity, and physicochemical characteristics of the final products. Usually, these factors include the amount and feed ratio of raw materials, reaction temperature, pH, choice buffer.
solution, energy input, catalyst, pressure, impurity removal, and sterilization, etc. In order to determine the best condition for the big batch synthesis, an engineering approach is required. A linear ramp-up activity, that is, simply increase the reactor size and feed materials while keep the reaction parameters the same, is unlikely to be optimal. Ample evidence reveals that a multiparameter iterative optimization process should be considered during the scale-up synthesis of NMs.\[2,28,38,39\] It is important to establish a “tuning toolbox” using small reactors with a view to systematically dissect how the parameters of interest impact the scale-up activity. While it is somewhat time consuming, these activities, in return, would significantly increase the yield, quantity, quality, and reproducibility of the nanoparticles through less consumption of time in the long run. For example, we are encouraged by the proof-of-principle study of our chemo drug-laden nanocarrier,\[40\] that is, irinotecan-laden lipid coated mesoporous silica nanoparticles (a.k.a. silicasome), which can now make at approximately 100 g quantity batch.\[38\] This involved a multiround optimization to look at each parameters during synthesis, that is, reaction temperature, reaction time, stirring speed, and the ratio of silica precursor (tetraethyl orthosilicate, TEOS) versus the organic base (triethanolamine) and templating agent (cetyltrimethylammonium chloride).\[38\] After experimenting with more than 70 synthetic conditions in an iterative fashion, it was possible to accomplish approximately 100 g batch sizes in approximately 18-L reaction volume.\[38\] Another major upgrade was to introduce a flow through sonication system which allowed the mixing of silica nanoparticle with lipid ethanol solution with controlled energy input, leading to highly uniform and intact coating on the particle surface.\[38\] The particles, which were fully characterized with the expected particles size, morphology, surface area, and pore volume (Figure 2), are subjected to the robust translational research. Moreover, we were able to demonstrate a novel synergy using the big batch irinotecan silicasome in combination with anti-PD-1 antibody, leading to an improved survival outcome through a chemoimmunotherapy response in an orthotopic Kras-dependent pancreatic cancer mouse model.\[41\] In addition to our data, a recent report for hollow mesoporous silica microparticles demonstrated that reactor mixing was the most important parameter as confirmed by computational fluid dynamics and experimental analysis.\[39\] The particles made from volume- and concentration-based scale-up approaches exhibited different physicochemical properties due to different velocity profiles in the mixing system (Figure 3),\[39\] which may lead to different behaviors (eg, loading capacity, drug release profile, colloidal stability) when used as drug delivery carrier in biological system.
FIGURE 3  Use of a chemical engineering approach for scale-up synthesis of dense and hollow mesoporous silica microspheres. (A) The cited study reported the results of an experimental and computational study of batch scale-up for dense and hollow mesoporous silica microparticles, which were conceptualized in the scheme. (B) Volume and concentration-based scale-up approaches have been investigated and systematically compared using a similarity index that included parameters related to the particle size distribution and pore structure. The particle size distribution was found to be dependent mainly on the hydrodynamic conditions, expressed by the homogenization time, while the pore structure and the overall yield of the process were found to depend mainly on the CTAB/TEOS ratio (B). Reproduced with permission from Ref. [39]. Copyright 2018, Elsevier

4.3 | Advanced technologies such as microfluidic and AI pave the way for a smoother nano-CMC development

We have discussed the roles of multiparameters during nanoparticle synthesis, which may require an exhaustive amount of experimentation and/or empirical design to understand how the multivariable nano-CMC impacts the final products. With the rapid development of artificial intelligence (AI), it was possible to use computational approach, including machine learning, to determine the optimal engineering parameters.[42–44] (Figure 4). Moreover, it is advantageous to consider the orthogonal design of experiments (DOE), which ensures that all the parameters of interest may be estimated without the need to experimentally explore every single possibility.[45] More specifically, DOE process includes the design step and the analysis step. For the former, the goal is to decide which parameter settings are selected for the experiments. For the latter, the analysis step aims to reduce the number of experimental runs and at the same time ensure the maximum information from the experimental results, which collectively contribute to the identification of the optimal nano-CMC condition. Another exciting progress is the introduction of microfluidic system, which can be optimized using a computational tool-assisted approach.[46] In the case of liposome scale-up production, through careful controls on microfluidics channel design, flow rate, feed ratio, concentration and temperature, it was possible to utilize laminar flow and tunable mixing for both lab scale and industrial development, which is more efficient than the traditional methods such as thin-film hydration and reverse-phase evaporation (Figure 5).[47] Microfluidic systems, which could be highly advantageous
FIGURE 4  Combined use of multiobjective machine learning optimization, high yield microreactors, and high throughput analysis to facilitate the big batch synthesis of nanoparticles. (A) Development methodology utilizing multiple acceleration tools (a) and an agile development strategy (b), illustrated schematically in (c). (B) Potential variables in a scale-up scenario, comparing batch stirred reactors and annular microreactor synthesis (AMS). Reproduced under the terms of the CC BY-NC-ND 4.0 license. Copyright 2020, chemrxiv.org

FIGURE 5  Microfluidic system for translational nanoparticle scale-up synthesis. (A) Design and control of microfluidics system to make high quality nanoparticles for nanomedicine. (B) Stable quality of liposomes made by microfluidics system from batch scale to scale-up. (C) Cryo-EM images of liposomes made by microfluidics system from batch scale to scale-up. (D) The use of microfluidic system to make trapping agent-laden liposome can serve as a “just-in-time” personalized nanomedicine approach, in which different drugs can be onsite loaded before use. Reproduced with permission from Ref. [47]. Copyright 2020, Elsevier
during the high-throughput formulation design/selection and big batch manufacture, should be strongly considered. In this regard, there are commercially available setups, which hold advantage with respect to scaling-up nanocarriers production from microlitres volume to litre volume. Through the use of microfluidic system, the scale-up synthesis becomes more practical for certain nanocarriers particularly liposome, solid lipid nanoparticle, and certain inorganic/organic hybrid carrier. [11,17,22,42,48]

5 | CONCLUSION REMARK AND PERSPECTIVE

Despite the intensive investigation of various nanomedicine or nanoenabled products are frequently reported in the literature, nano-CMC requires immediate attention from the tech-transfer point of view. An ideal CMC process should involve automatic and continuous production process, which can be applied in different facilities under QC control. Although the L-scale production or sub-Kg quantity is likely below the ultimate large-scale manufacture in pharma, the intermediary upgrade activity that is originated from a proof-of-principle research laboratory would provide key information to plan the QC-controlled nano-CMC. Particularly, it is important to consider the advanced chemical engineering approach, such as multiparameter iterative optimization, CDF analysis, orthogonal DOE design, and AI, which facilitate the paradigm shift from an empirical approach to the rational CMC approach. Moreover, a timely comment is that the readiness of CMC would allow rapid nano-enabled resolution for a public health crisis (i.e., lipid-based COVID19 vaccination development) or contemplate so-called “just-in-time” personalized nanomedicine. [47,49] For the former, the microfluidic system was demonstrated to be a powerful tool to optimize the LNP formulations with multiparameters for making efficient mRNA vaccines (Figure 6). [50,51] Recently, Moderna developed mRNA vaccine (mRNA-1273) relies on a CMC-ready LNP platform, which encapsulates nucleoside-modified mRNA that encodes the SARS-CoV-2 spike (S) glycoprotein. [52] This nanoenabled mRNA vaccine led to a 94.5% effectiveness in big Phase 3 trials according to a recent news release (https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy). For the “just-in-time” personalized nanomedicine, use of microfluidic system to make trapping agent-laden liposome is a good example. This CMC-ready approach could be standardized,
enabling a bedside mix-and-match strategy, allowing an experimental-based combination therapy in cancer and other disease (Figure 5D).[47]

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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