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Review Article

Advancing Nanoparticle Production: Scaling Up Techniques, Challenges, and Future Perspectives in Pharmaceutical Applications

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Abstract

Background: Nanoparticles (NPs) have transformed pharmaceutical sciences by enhancing drug delivery, solubility, and absorption. However, scaling up NP production from laboratory settings to industrial capacities is facing immense challenges due to process difficulties, consistency issues, and high costs.

Objectives: This review discusses recent progress, challenges, and critical process parameters (CPPs) in scaling up different NP preparation methods. It highlights sustainable strategies, process limitations, and future opportunities in pharmaceutical nanoparticle production.

Methods: A systematic review was conducted using international databases such as (Scopus, PubMed, Web of Science, Google Scholar) between 2012 and 2024. The keywords used in the primary search included scale-up, challenges, limitations, critical process parameters, and nanoparticles. This study considered conventional and novel methods for preparing nanoparticles, including thin film hydration, ethanol injection, ultrasonication, spray drying, and high-pressure homogenization.

Results: This review outlines and discusses critical process parameters such as mixing speed, temperature control, choice of solvent, and flow rate that impact NP size, morphology, and stability during scale-up. Advanced techniques such as microfluidics and ethanol injection allow one to control the characteristics of nanoparticles with precision, while high-pressure homogenization ensures particle-size consistency. More importantly, environmentally friendly synthesis approaches are a useful route toward sustainable production practices.

Conclusions: Scaling up NP production requires optimization of process parameters, equipment design, and a focus on reproducibility and cost-efficiency. While challenges persist, adopting green synthesis methods and developing regulatory frameworks will enhance clinical translation and commercial viability of NP-based drug delivery systems.

1. Introduction

The majority of traditional drug delivery systems possess an instant elevated level of drug release following administration, therefore leading to high administration frequency [1]. Nanotechnology is an evolving, unique technology performed at the nanoscale. "Nan" is a word that is taken from the Latin word, which refers to "dwarf" [2]. Nanotechnology has developed into an actual and revolutionary force that has an impact on a variety of scientific and technical sectors and additionally [3,4].

Nanoparticles (NPs) show particular or enhanced attributes depending on their size, shape, and structure at the nanoscale. NPs are utilized in various applications, including drug delivery and more [5,6]. In the past decade, drug-delivery NPs have received significant advancements, leading to the development of sophisticated and smart drug-delivery systems designed to overcome complex obstacles in the treatment of challenging diseases [7,8]. NPs can serve as carriers to deliver drugs to specific cells or tissues in the body. They can also be engineered with particular surface properties that enable them to selectively target diseased cells, enhancing effectiveness and minimizing drug side effects [9]. In oncology, NPs are used to transport chemotherapy directly to tumor sites, boosting effectiveness while reducing side effects on healthy tissues. Also, antibody-drug conjugates make use of NPs for targeted treatment, allowing for accurate delivery of drugs to cancer cells. In gene therapy, NPs assist in delivering nucleic acids such as DNA and RNA into cells, which facilitates the treatment of genetic disorders [10,11]. Vaccines advantage from NPs technology, as they can enhance immune reactions and improve stability and delivery of antigens. Furthermore, in antibiotic delivery, NPs can help defeat bacterial resistance by allowing the targeted release of antimicrobial agents [12]. Additionally, NPs are investigated in neurodegenerative diseases for transporting drugs across the blood-brain barrier, addressing challenges in treating conditions like Alzheimer's and Parkinson's disease. Overall, the different applications of NPs in drug delivery highlight their potential to develop treatment concepts across various therapeutic areas [10,13,14].

Moreover, NPs can be designed to release their content in a controlled manner, allowing for sustained drug delivery over time [3,15]. Additionally, NPs can significantly enhance the solubility and bioavailability of poorly soluble drugs. Their small size increases the surface area, allowing better dissolution and absorption in the body. This characteristic is particularly favorable for drugs that traditionally have low bioavailability [16]. NPs also play a vital role in improving diagnostic techniques. NPs can be used as contrast agents in imaging, providing better visualization of tissues and tumors. Furthermore, they can assist in early disease detection, enhancing the effectiveness of treatment approaches [17,18].

Finally, the quality of human life is continuously enhanced by the successful applications of nanotechnology in medicine involving drug manufacturing, designing, conjugation, and efficient delivery options with advances in nano-based genomics, tissue engineering, and gene therapy [19,20].

Thus, many studies have been conducted worldwide focusing on developing pharmaceutical NPs for translation into products manufactured by local pharmaceutical companies [1]. There is an enormous potential in research & development that includes modelling, imaging, measuring, etc. [2]. There are different nanomaterials such as dendrimers, micelles, carbon-based, metal-based, and lipids are very used in the pharmaceutical industry and can be manufactured by various methods [21,22]. NPs are categorized into particular categories based on their morphology, which refers to their structure, size, and shape.

NPs are divided into two categories: organic and inorganic. Inorganic NPs include silver, gold, palladium, titanium, zinc, copper NPs etc.

The effectiveness of drug delivery using inorganic NPs is influenced by two main factors: (i) the design of these NPs to achieve gradual and prolonged drug release and (ii) their capacity to transport therapeutic agents precisely to target locations [4]. NPs can have their surfaces modified to target specific structures, enhancing their applicability across various delivery systems due to their targeting capabilities [23].

Inorganic NPs face certain limitations. The safety and risk assessment for both patients and manufacturers remains ambiguous. Moreover, the risk/benefit analysis encounters difficulties because a robust evaluation framework has not been established. For nano-based products to be viable, developing detailed preclinical and clinical testing guidelines is essential. Although nanoscience has recently advanced in drug delivery, significant research is still

needed to fully understand the toxicity, pharmacology, and immune responses associated with these nano-products [24].

Organic NPs involve various categories, including micelles, dendrimers, liposomes, nanogels, polymeric nanoparticles, and layered biopolymers. Notably, some of these, like micelles and liposomes, own a hollow spherical structure and are characterized by their non-toxicity and biodegradability. These features make organic nanoparticles a promising solution for drug delivery applications [25]. Due to their numerous merits, the current review focuses on the scale-up of these NPs.

Conventional preparation methods of NPs on a lab scale

Thin film hydration method (TFH):

TFH method is a simple technique often used to prepare NPs. During this process, membrane forming materials are dissolved in an organic solvent (OS) within a round bottom rotary evaporator flask. Then after that the OS is evaporated, resulting in a dried thin film forming on the bottom of the flask. After that, an aqueous medium is added to the film at a temperature for a specific period under constant condition (mild agitation). Drugs to be in capsulated form are dissolved either in aqueous or organic phase depending on their solubility. This technique is usually followed by sonication to allow the NPs formed in homogenous size distribution [26].

The limitations of the TFH method for formulating NPs are low encapsulation efficiency, difficulty scaling up, difficulty of organic solvent removal, formation of large particles, and time consumption [27]. The low Encapsulation efficiency may be attributed to the fact that this method relies on the passive diffusion of drugs into lipid vesicles during hydration, also there are difficulty in controlling the hydration temperature, the agitation speeds during the hydration step leading to in-consistent drug loading [28-30].

Ethanol injection method

Schubert first reported the ethanol injection method used for preparing NPs. This method involves the injection of a lipid solution of ethanol into an aqueous solution [31]. The ratio between both the organic solvent and the aqueous solutions depends on individual experimental protocols as determined by the original researchers. The aqueous phase is prepared using a surfactant or a surfactant mixture of water. Then, a needle introduces the organic phase to the aqueous phase under mechanical stirring. After injection, two main mechanisms occur. First, the solvent disuses out of the droplets into the aqueous phase, leading to droplet size reduction. Therefore, lipid concentration in these droplets increases, forming local supersaturated zones stabilized by surfactant in the aqueous phase [32]. Second, the surfactant decreases the interfacial tension between water and solvent, and this leads to the formation of small solvent-lipid droplets at the injection spot, which further fuse to form NPs structures after evaporation of ethanol. The NPs can be finally obtained [31].

One limitation of the ethanol injection method is the remaining ethanol; it could be challenging to remove the remaining ethanol due to the low solubility of some lipids in ethanol, and the instability of certain drugs as well, as the ethanol injection method necessitates the consumption of large amounts of hydrophilic drugs for correct entrapment; therefore the low volumes of ethanol used in this method would lead to some troublesomeness with the end-product [31]. However, it is possible to get rid of residual ethanol using dialysis or rotary evaporation.

Ultrasonication

Ultrasonication is a specialized technique for homogenization, applied in various fields. This process breaks down larger particles into smaller fragments and ensures more uniform particle sizes within the base fluid [33,34]. Sonication of nanofluids is accomplished by applying sound energy to agitate the nanoparticles within the suspension [35-37]. The most commonly used devices, like ultrasonic probes and ultrasonic cleaning baths, function at frequencies ranging from 20 to 40 kHz. However, the latter lacks adjustable power and has complexities regarding temperature control, which does not support nanoparticle generation. As a result, the probes that enable the selection and regulation of these parameters are preferred for developing nanocarriers [38]. The key factors to manage during ultrasonication are sonication power and duration, as these

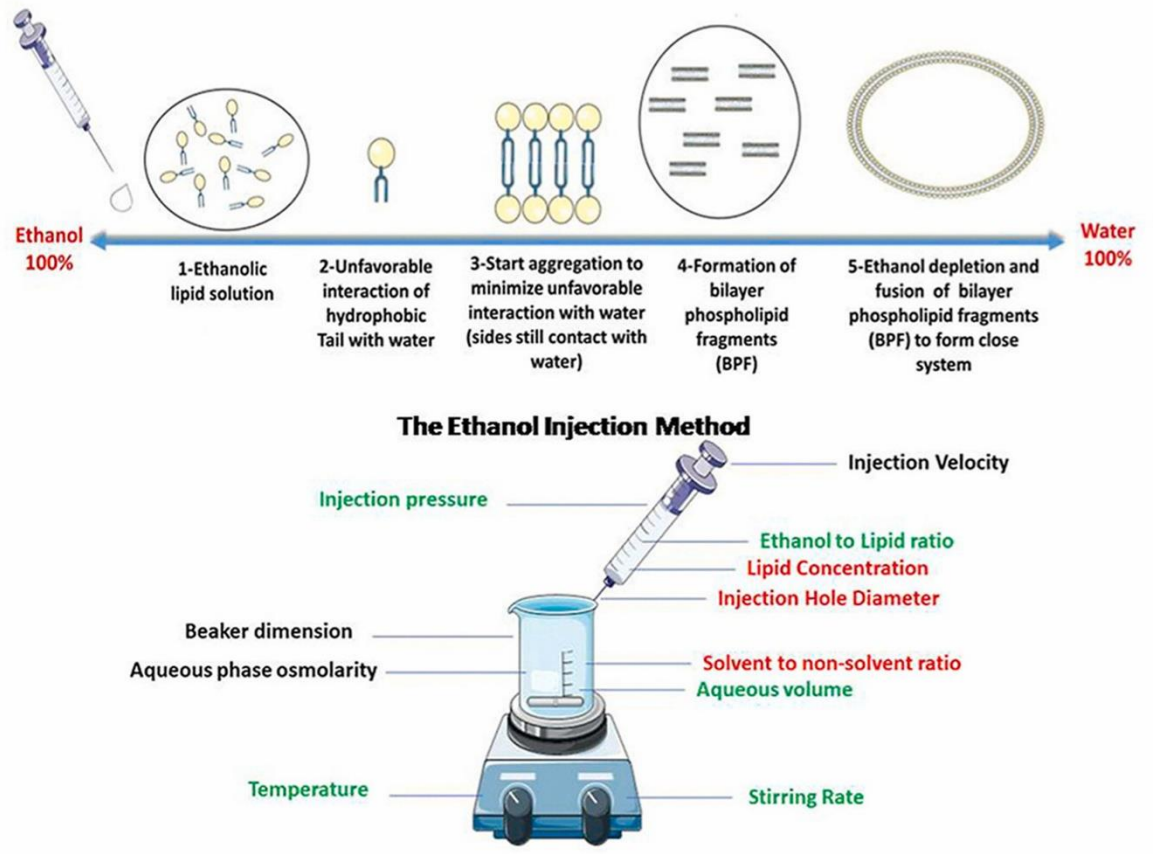

Figure 1: Schematic diagram for ethanol injection method [31].

can significantly influence the characteristics of the produced NPs. If sonication is excessively intense or prolonged, it may potentially impacting the efficiency of the process [40].

Limitation:

The outcomes of sonication can frequently be inconsistent, making it challenging to create quantitative models. This is important because the success of sonication is influenced by both the device's settings and the particle dispersion's physicochemical properties. As a result, sonication generally shows low reproducibility [41].

Homogenization

The cornerstone of high-pressure homogenization (HPH) technique is reducing the size of droplets and particles under high-pressure conditions [23]. It entails pushing a blend of the active pharmaceutical ingredient and other components through a homogenizer nozzle, utilizing substantial motor power and cavitation [42]. This method effectively disintegrates agglomerates, clusters, or immiscible materials, as a result the dispersion becomes more uniform and the quality of the product improved. The particle size scale and distribution can be accurately regulated by optimizing some conditions such as pressure, passes number and concentration of sample [25]. HPH encompasses two approaches: cold and hot homogenization [42]. HPH is a widely utilized method that is effective for the controlled synthesis of several NPs, including:

1. Liposomes, which are spherical vesicles formed of lipid bilayers.
2. Nanoemulsions are characterized by stable, finely dispersed emulsions that can be either oil-in-water or water-in-oil, with particles at the nanometer range.
3. Nanocrystals, which are submicron at size crystalline particles with a significant surface area;
4. Lipid- based NPs, spherical NPs with a diameter between 10 and 1000 nm which use lipids as the core structural element. Lipid-based NPs can be classified according to their structure and

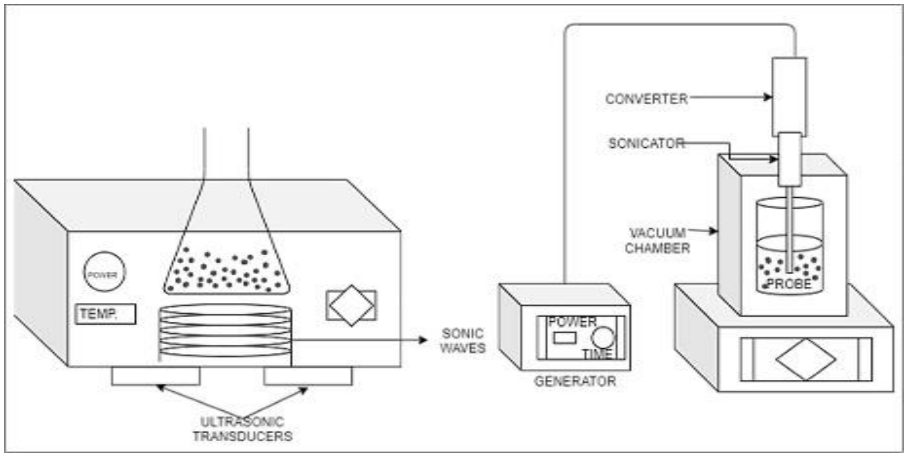

Figure 2: Types of Sonication instruments bath type (left) and probe sonicator (right) [39].

composition. The common types are Lipid nanoparticles, Solid lipid nanoparticles, Nanostructured lipid carriers, and Lipid drug conjugates [43].

5. Nanosuspensions, which are colloidal drug particles dispersed in a liquid medium.

These examples demonstrate the versatility of HPH in attaining specific size and dispersion of NPs [25,27,31,44].

Limitations:

HPH creates heat because of the excessive shearing forces included. The temperature increased during the process resulting in thermal degradation or compromise the stability of heat-sensitive materials [24,29]. Additionally, the method demands substantial energy consumption, and the accompanied costs, including those for the specific equipment and maintenance, should be factored into its application [24,30].

Spray drying in lab scale:

Spray drying is a rapid and single step method for converting liquid feeds (such as aqueous and organic solutions, suspensions, and emulsions) into powders. This technique is widely employed for micro encapsulating purposes. The encapsulation process using a traditional spray dryer includes emulsifying the active components using a high shear mixer, homogenizer, or ultrasonication, after that using spray dryer to dry the emulsion. According to their size, the particles produced from encapsulation can be categorized as macro (>5 mm), micro (1 µm–5 mm), and nano (<1 µm) encapsulation [45].

Particles generated by traditional spray drying generally fall within the micrometer range, resulting in lower absorption rates, solubility, controlled release, and targeting precision, leading to reduced bioavailability of the core compounds compared to NPs. Therefore, there is a growing necessity to enhance the conventional spray drying method for traditional microencapsulation to reach the 'nanometer' scale. However, traditional atomization techniques (such as rotary, pressure, and pneumatic atomization), inefficient powder recovery systems, and turbulence within the drying chamber limit the effectiveness of traditional spray dryers in NPs production [46].

Thus, nanoencapsulation using nano spray drying presents a promising solution to address the limitations of conventional spray drying techniques. The nano spray dryer B-90, developed by BUCHI Labortechnik AG in 2009, was designed to extend the capabilities of spray drying to produce NPs. This technique enables high particle recovery rates, achieving milligram quantities of powder with particle sizes ranging from 300 nm to 5 µm [47].

2. Materials and Methods

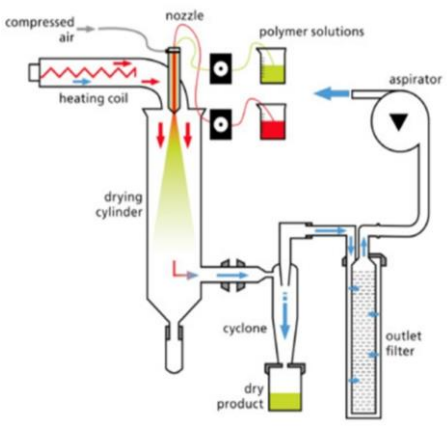

Figure 3: Spray drying primarily involves three key operational steps: (1) atomization of liquid feed, (2) drying of the atomized droplets, and (3) separation

This article presents an in-depth review of the recently investigated methods for scaling up NPs and the critical attributes during manufacturing.

Search strategy

Data were collected from four international databases, including Scopus, Pubmed, Web of Science, and Google Scholar, from 2012 to 2024. The search keywords used were scale-up, challenges, limitation, critical process parameters and nanoparticles. A study selection flow diagram is shown in Figure 4.

3. Results and Discussion

Nanoprecipitation:

Nanoprecipitation, also known as solvent displacement or interfacial deposition, is among the earliest techniques developed for encapsulating drug molecules. This method was introduced by Fessi et al. in 1989. It requires the preparation of solvent and nonsolvent phases, followed by adding one phase to the other under moderate magnetic stirring. The evaporation of the organic solvent at ambient temperature or using a rotary evaporator result in a suspension of NPs in water. Aqueous phase removal can be achieved through ultracentrifugation or freeze drying. The solvent phase typically contains (film forming material, one or more drug molecules, a lipophilic surfactant, and organic solvents). The solvent phase is referred to organic phase while nonsolvent phase is referred to aqueous phases. Film forming materials can include (natural, synthetic, or semi-synthetic) polymers. Surfactants can also be incorporated into the formulation to prevent NP aggregation [24].

Since its inception, this technique has been extensively utilized for encapsulating hydrophobic drugs, primarily nanocapsules or nanospheres. A variety of polymers have been employed for this purpose, particularly biodegradable polyesters such as poly(lactide), poly(lactide-co-glycolide) (PLGA), and poly(ε-caprolactone) [25].

Nanoprecipitation offers several benefits compared to alternative encapsulation methods, including its simple process, scalability, and high reproducibility. It minimizes the use of large quantities of toxic solvents, allows for the production of submicron particles with a narrow size distribution, and does not require high energy inputs.

During the process of mixing a drug and polymer solution with water, both the polymer nanoparticles (NPs) and the drug may precipitate. This precipitation depends on the solubility of the components involved. In the case of the polymer, precipitation is typically rapid. However, the precipitation of the drug relies on its solubility within the changing solvent system, which is affected by the addition of the drug/polymer solution. Additionally, the solubility of the drug in the modified solvent and the kinetics of the process play significant roles [32]. The key formulation parameters that influence the formation of nanoparticles using the nanoprecipitation technique include the polymer concentration, solvent ratios, stirring speed, injection flow rate, and the properties of the non-solvent phase [33].

Microfluidic

Microfluidic technology has become an essential instrument in NP synthesis, transforming traditional techniques by providing greater control and precision. This method allows for efficient preparation of NPs in a reproducible and controllable way. When compared to conventional approaches, microfluidics enhances the uniformity and controllability of NPs drug delivery systems. The rapid mixing and laminar flow characteristics within the microchannels can adjust the physicochemical properties of NPs, such as particle size, distribution and morphology, leading to a restricted distribution of particle size and an increased drug-loading capacity [26, 27,48].

A significant advancement is the development of microfluidic systems, which can be optimized through a computational tool-assisted approach. In scaling up liposome production, careful adjustments to microfluidic channel design, flow rate, feed ratio, concentration, and temperature have made it possible to leverage laminar flow and adjustable mixing for both laboratory and industrial applications. This method proves to be more efficient than traditional techniques like thin-film hydration and reverse-phase evaporation [28]. Microfluidic systems are particularly beneficial for high-throughput formulation design and large-scale manufacturing, making them an important consideration. Various commercially available setups facilitate the transition from microliter to liter-scale production of nanocarriers. By employing microfluidic systems, scaling up synthesis becomes more feasible for specific

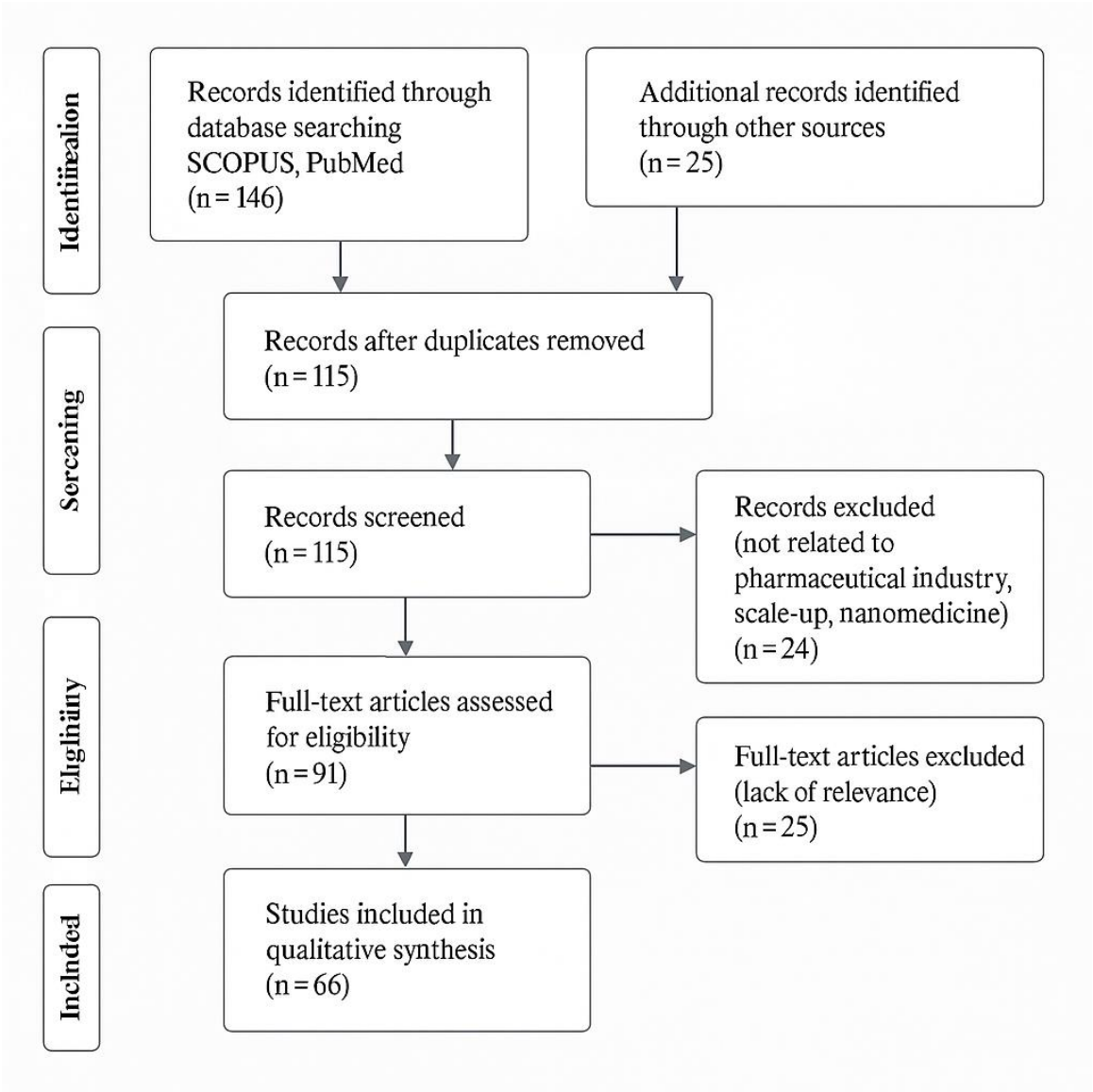

Figure 4: The study selection flow diagram

nanocarriers, especially liposomes, solid lipid nanoparticles, and certain inorganic/organic hybrid carriers [27,49].

The fabrication of microfluidic devices is achieved through high-precision micro-machining processes [29]. Several factors, including temperature, precursor concentration, time, and pH, influence microfluidic NPs' properties. Additionally, the continuous flow nature of microfluidics introduces other variables such as total flow rate (TFR), flow rate ratio (FRR), the shape of the main channel, and residence time, all of which affect the physicochemical characteristics of the NPs. Parameters like flow rate (FR), TFR, and FRR reflect the combined flow rates of organic and aqueous phases in the main mixing channel and the ratio of these two phases [30,31]

Active microfluidic synthesis of NPs provides enhanced process control. The cost of a more complex system configuration may require additional modules, such as signal generators and piezoelectric actuators, for effective mixing within microchannels. Conversely, passive microfluidic systems typically consist of microchannels connected to one or more pumping units, with operational flexibility limited to modulating flow rates only [30].

There are numerous challenges to implementing microfluidics in the pharmaceutical sector, including the materials used for constructing microchannels, their design, the associated equipment like pumps, and the materials utilized in fabricating nano systems [31].

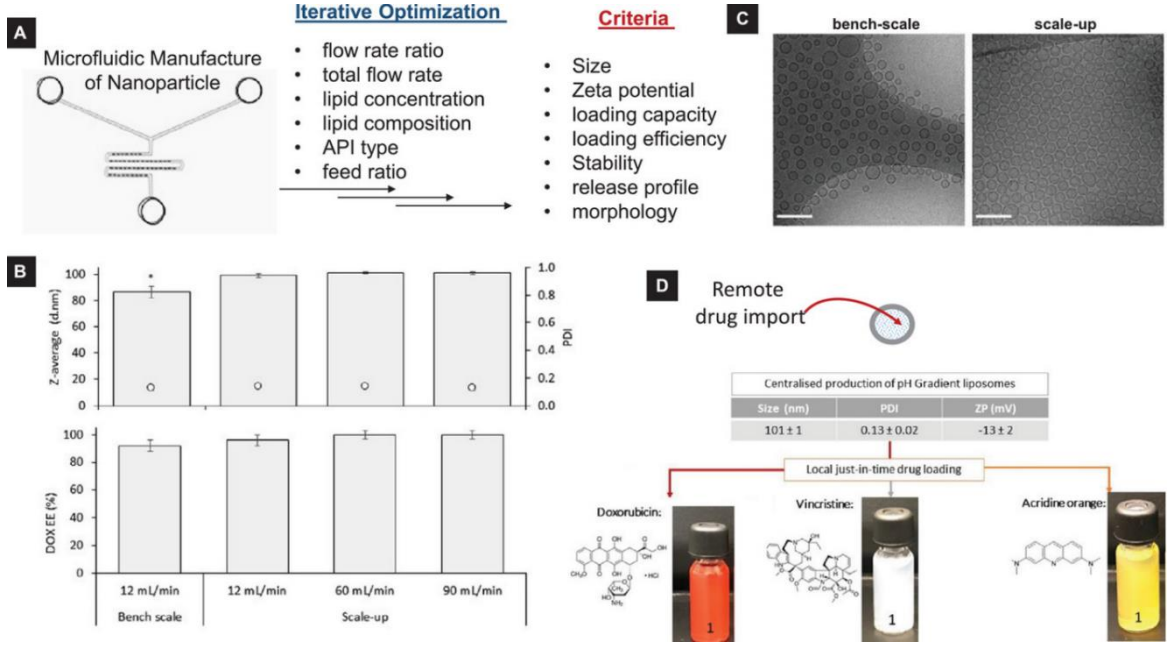

Figure 5: NPs scale-up synthesis by microfluidic technique. (A) Design and control of microfluidics system for making high-quality NPs. (B) Liposomes of stable quality created by microfluidics system from batch scale to scale-up. (C) Liposome cryo-EM images done with microfluidics system from batch scale to scale-up. (D) The microfluidic system usage to create trapping agent-laden liposomes can be used as a "just-in-time" personalized nanomedicine method, in which various drugs can be loaded before the usage [50].

Ethanol injection method

Scaling up the ethanol injection method necessitates changes in both injection devices and process conditions to ensure uniformity in large batches. For example, Charcosset et al. assessed various configurations, including syringe-based and membrane injection setups. They found that pilot-scale implementations utilizing tubular systems enable consistent NPs formation for volumes exceeding 3 liters. Furthermore, automated systems that incorporate pipetting robotics and dynamic light scattering tools have been created to enhance production efficiency [32].

Also, a crossflow injection method was specifically developed for the mass production of liposomes. This setup features two stainless steel tubes arranged in a cross shape, with a small injection hole at their intersection. An ethanolic solution containing lipids is introduced into a buffer solution through this crossflow tube by adjusting the pressure of a nitrogen regulator, resulting in liposome formation [16].

Recent studies also underscore the flexibility of ethanol injection for various lipid compositions and drug encapsulations. For instance, the application of SPG membrane technology improves lipid mixing efficiency, leading to more homogeneous lipid nanoparticle populations crucial for drug delivery applications. In the context of gene therapy, ethanol injection proves effective in encapsulating nucleic acids, benefiting from the versatility of lipid nanoparticles for different molecular payloads [33].

Additionally, ethanol injection facilitates quick adjustments in formulation conditions, aiding continuous manufacturing processes in the pharmaceutical industry. Lombardo and Kiselev highlighted that continuous-flow systems equipped with T- or Y-mixers improve mixing rates, ensuring the nanoscale uniformity necessary for commercial scalability. As a result, the ethanol injection method continues to be a promising strategy in nanomedicine manufacturing, bolstered by ongoing advancements that tackle significant production challenges [34].

High-pressure homogenization (HPH)

High-pressure homogenization (HPH) generates intense localized stresses, resulting in a significant decrease in particle size. Its ability to produce continuously on a large scale makes the technology ideal for scaling up [42]. To achieve a consistent and fine droplet size in suspensions or emulsions, pre-homogenization is crucial [51].

The homogenizer consists of essential components like pumps, pistons, valves, and narrow gaps responsible for reducing droplet size. During operation, HPH creates high pressure through the acceleration of the piston pump, which forces the liquid from the inlet chamber to the outlet chamber through the narrow gap [42].

High-pressure pumps are activated to control and force the premix under the required pressure. These pumps typically feature 3 to 5 pistons, with lab-scale HPH systems having a single piston, while production and pilot-scale models are equipped with 3 to 5 pistons [52]. The required capacity and pressure are determined by selecting the suitable piston diameter. A piston pump with a larger diameter provides a high-capacity machine with moderate pressure, while a smaller diameter piston results in a high-pressure machine with moderate capacity [42].

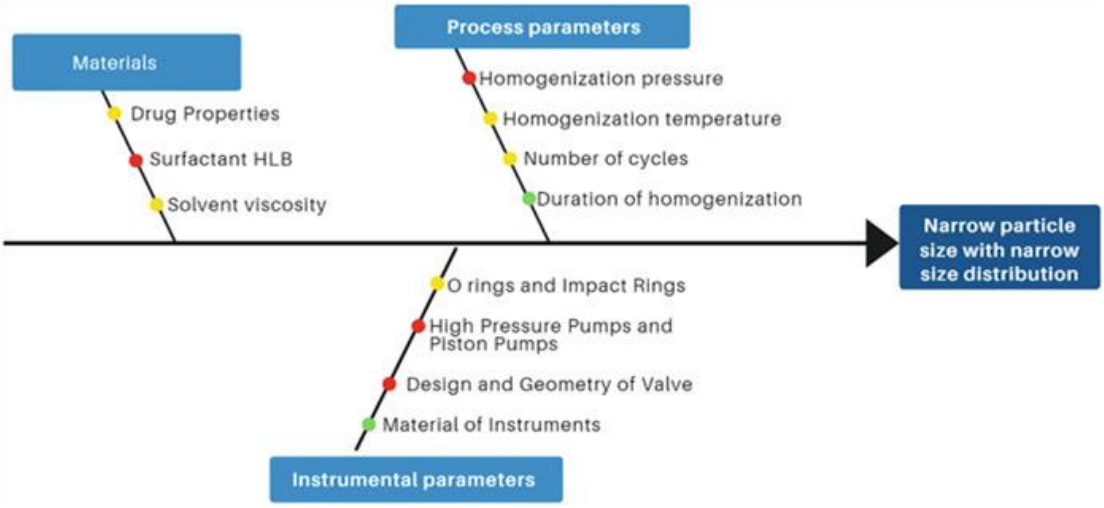

Figure 6: Diagram for HPH technique [53].

High-pressure homogenization generally results in a narrow distribution of particle sizes and modifies the drug's properties, including its shape, size, and even its chemical characteristics (amorphization) [53].

Process parameters that need to be considered while using a high-pressure homogenizer

When operating a high-pressure homogenizer, several process parameters must be taken into account. The valve geometry is designed to disrupt fluid flow, creating turbulence that enhances the homogenization mechanism. [53] An increase in pressure leads to a greater pressure drop, effectively surpassing Laplace's pressure and facilitating size reduction. Consequently, higher pressure can reduce the mean droplet diameter to a certain extent, influenced by the emulsion formulation method, polymer combinations, and the drug quantity [54].

A cycle is considered complete when the collected premix is recirculated through a narrow gap under defined pressure conditions. Increasing the cycle count will further decrease droplet size, depending on the emulsion's material characteristics while maintaining constant pressure [37,47,55].

The process temperature is determined by the materials subjected to high-pressure homogenization. Cold homogenization is preferred for substances with low melting points or thermal sensitivity, whereas hot homogenization is utilized for materials with significant lipid content or when the drug needs to be encapsulated in lipids. Therefore, high-pressure homogenization can be categorized into hot and cold processes based on temperature considerations [53].

The influence of factors other than cooling and heating rates can significantly affect particle formation and the narrow particle size distribution achieved. Due to the minimal factors requiring control during the entire procedure, this technique is relatively straightforward to scale up [53].

Critical Process Parameters for Scaling up Nanoparticles

The critical process parameter is a term used in the pharmaceutical field to identify process variables that impact the critical quality approach of a process [56]. For example, critical process parameters (CPPs) are essential for developing PLGA nanoparticles through the double emulsion process. Key CPPs include the rate of addition of the aqueous phase to the organic phase, stirring time, stirring speed, and temperature, as these significantly influence particle size distribution, homogeneity, and stability. Factors like stirring/sonication speed and solvent evaporation temperature must be controlled meticulously for optimal results [57,58].

Moreover, ensuring consistency in these parameters helps maintain reproducibility across batches, which is critical for industrial-scale production. Adjusting these CPPs directly affects NPs characteristics, such as encapsulation efficiency and drug release profiles, which are crucial for achieving desired therapeutic outcomes in drug delivery applications [57].

Scaling up Nps production poses challenges, including maintaining size, distribution, and morphology. Important CPPs identified include mixing speed, solvent choice, temperature, and pressure in high-pressure homogenization, which are critical in achieving a uniform size and distribution. Process stability and reproducibility are essential for successful scale-up and ensuring quality consistency [53].

Another critical consideration in scaling up is the equipment used for manufacturing. For instance, maintaining uniform heat distribution and efficient solvent removal becomes more challenging as the production scale increases, which can impact NPs properties and efficacy. Such factors must be optimized to produce consistent and therapeutically viable nanoparticles at larger scales [53].

It is also important to control CPPs like thermal gradient, mixing time, and solvent dynamics to ensure particle size and quality consistency. These parameters are crucial in minimizing batch variability and maintaining drug release efficacy, which is paramount for therapeutic applications [59].

Table 1: Challenges and limitations of scaling up the process of NPs manufacturing.

Limitation	No of studies	Brief description
Reproducibility	13 studies [60-73]	many nanotherapeutics do not successfully reach the market due to challenges in achieving reproducibility and meeting the requirements for scalable synthesis.
Complexity	8 studies [56,60,61,64,66,67,69,74]	The manufacturing of nanoparticles (NPs) for large-scale drug preparations is challenging due to their complexity. The manufacturing process of NPs usually requires multiple unit operations. Further, the complexity increases as every unit operation requires in-process quality control, making it a long and labour-intensive process.
Consistent stability	14 studies [22,60-65, 67-69, 75-78]	Scaling nanomedicine is challenging due to the necessity of maintaining consistent physicochemical properties across different batches. Minor variations in production methods or composition can greatly influence the structure and function of the nanomedicine. This is particularly complicated because the manufacturing process can alter properties that distinguish nanoparticles from their bulk counterparts, such as colloidal stability, drug loading capacity, mean particle size, morphology, and surface characteristics.
Cost	7 studies [61,62,75,76,79-81]	In large-scale production, it's essential to factor in the costs of raw materials and the requirement for countless multistep processes, leading to significant time and financial expenses in the industrial manufacturing of nanomedicines.
Regulatory aspects	8 studies [11,64,76,77,81-83].	The lack of regulatory frameworks and standards governing manufacturing practices, quality control, safety, and efficacy assessment presents a significant barrier to the developing of nanotherapeutics. currently, there are no globally recognized regulatory standards specifically designed for the clinical translation of these nanomedicinal products.

Additionally, scaling up necessitates thoroughly understanding material interactions and environmental conditions during production. Parameters such as NPs surface charge and colloidal stability in physiological conditions can drastically affect in vivo performance, making monitoring these aspects rigorously during the manufacturing process essential [59].

Challenges and limitations:

There are several challenges and limitations facing scale up of NPs, several studies have discussed these limitations, as shown in Table 1.

Future perspective:

Embracing green eco-friendly synthesis techniques and sustainable manufacturing practices is crucial for decreasing the dependance on hazardous substances and lowering waste production. A safe-by-design strategy that incorporates safety factors from the initial phases of nanoparticle (NP) development successfully meets this objective. This strategy includes the use of environmentally safe solvents, renewable energy sources, and encourages recycling and waste minimization [84]. Green synthesis refers to the use of clean, safe, and eco-friendly methods, including natural extracts from plants, microbes, biopolymers, and biowastes. Its goal is to reduce the harmful impacts typically linked to traditional chemical and physical methods for producing nanoparticles [85,86].

Advantages of green synthesis:

1-Sustainability: green methods typically need less energy, enhancing the sustainability of the synthesis process.

2- Biosafety: their non-toxic nature makes them appealing for various uses, including medical applications. Research has shown that green nanoparticles are less likely to have toxic residues or by-products, enhancing their biosafety and making them particularly suitable for biomedical and pharmaceutical purposes.

3-Biocompatibility: recent research has shown that nanoparticles created through biological methods tend to be naturally biocompatible, making them ideal for a range of biomedical uses, including drug delivery, imaging, and diagnostics [5,87,88].

Conclusion

Scaling up nanoparticle production continues to be a major challenge, even with significant progress in formulation techniques and manufacturing processes. Techniques like high-pressure homogenization, ethanol injection, and microfluidics have demonstrated strong potential for large-scale production while maintaining particle size, morphology, and drug encapsulation efficiency. Nevertheless, obstacles such as process complexity, high production costs, and the absence of clear regulatory guidelines remain barriers to widespread commercial implementation.

Addressing these issues is crucial to facilitate the transition of nanoparticle production from the laboratory to an industrial scale. Green synthesis methods offer a

promising solution by reducing environmental impact and improving biosafety through sustainable practices.

Looking ahead, collaborative efforts across disciplines, the integration of advanced technologies, and the implementation of rigorous quality control systems will be key. Further research should prioritize scalable and cost-efficient production strategies, explore the intricate behavior of nanoparticles, and establish regulatory pathways to support the commercialization of nanoparticle-based pharmaceuticals.

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Data Availability Statement

This study is a review article and does not include any primary data. All data generated or analyzed during this study are derived from previously published articles, which are cited appropriately in the references section.

Ethics approval

Not Applicable

Conflict of interest

The authors report no conflict of interest.

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