

Recent Advances in Different Nanoprecipitation Methods for Efficient Drug Loading and Controlled Release

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Abstract

Nanoprecipitation has emerged as a versatile and efficient technique for formulating nanoparticles, providing significant advantages in drug delivery applications. Nanomaterials, particularly polymer nanoparticles (PNPs), play a crucial role in encapsulating and controlling the release of drug molecules, serving as an alternative to traditional drug delivery methods. Various types and morphologies of PNPs have been synthesized using different nanoprecipitation methods that are being used as drug carriers, demonstrating superior performance in targeted drug delivery with controlled release compared to conventional methods. This review highlights recent advances in preparing diverse PNPs through different nanoprecipitation techniques, emphasizing improvements in drug loading capacity and controlled release profiles under various physicochemical conditions. Initially, the general principles of nanoprecipitation for synthesizing nanoparticles are discussed. This is followed by an overview of the different methods used in nanoprecipitation to synthesize PNPs of varying sizes and morphologies. Numerous examples have been given to understand the applications of PNPs synthesized via nanoprecipitation for loading and releasing various types of drugs. Additionally, a comparison of the effectiveness of PNPs synthesized through different nanoprecipitation methods is provided. This article outlines the latest methodologies in nanoprecipitation for synthesizing various PNPs and suggests future directions for translating nanoprecipitation technology into clinical applications.

Keywords: Nanoprecipitation, Drug, Nanomaterials, Polymer, Solvent, Anti-Solvent

Introduction

Drugs are any substance or materials used to prevent, diagnose, cure, or relieve symptoms of a disease or any abnormal conditions. Various methods are followed to administer the drugs inside the body, such as oral, nasal, injection, etc. [1]. One of the main intentions of using drug molecules or substances is that they can target the site infected with the disease and controllably release or deliver the drug molecules to the specific cells or tissues in the affected area without or with minimal effect on the healthy cells. However, in many cases, the targeting of the drug is not entirely attained [2]. To attain specific targeting of the infected area and complete delivery of drugs, various drug delivery systems such as liposomes and nanoparticles have been developed in the past few decades [3,4]. The drug delivery systems can target the specific infected area and have control or systematic release of the drug molecules. This process of

targeted drug delivery and systematic release of the drug molecules enhances the efficiency of the drugs.

Various drug delivery systems have been developed in the past few decades, and nanoparticles have played a prominent role in them [3-6]. Nanomaterials are prepared through various routes, among which the solution-based approach of nanoprecipitation plays an important role owing to its easy implementation, simple methodology, minimal input energy, reproducibility, etc. [7-9]. It is a simple, efficient, and scalable approach for synthesizing polymer nanoparticles (PNPs) [10]. This method also offers a simple, scalable, and cost-effective method for drug encapsulation and controlled release. Its advantages include but are not limited to its easy implementation, reproducibility, and tuneability. The main advantage of nanoprecipitation involves preparing nanoparticles without using surfactant [11-13], which in many cases causes toxicity inside the body. Nanoparticles

synthesized through nanoprecipitation are used for drug delivery and in biosensors, bio-imaging, bio-catalysis, etc.

Different nanoprecipitation approaches, including conventional, flash, and microfluidic, offer unique advantages for fine-tuning particle characteristics that could be used for drug release applications [14,15]. While conventional nanoprecipitation provides easy operation and reproducibility, emerging techniques such as flash and microfluidic nanoprecipitation (MNP) deliver superior control over particle size distribution and batch-to-batch consistency. Additionally, recent developments in scalable manufacturing and continuous processing technologies address the growing demand for industrial-scale production of nanoparticle-based therapeutics. This method offers several advantages and influences both drug loading and delivery in multiple ways that include but are not limited to enhanced drug loading efficiency, improved drug stability, tunable drug release, scalable and reproducible process, etc. However, it also has many challenges to be overcome for its effective implementations such as proper selection of the solvents, controlling burst release of the drug, and optimizing the process, etc.

Nanoprecipitation techniques have enabled precise control over nanoparticle size and morphology that enable enhanced drug loading and controlled release kinetics [16,17]. Advancements in nanoprecipitation techniques result in the synthesis of many complex nanostructures that further improve the efficiency of biomedical applications. Different polymers, such as chitosan, polycaprolactone, PCL, PLGA-PEG, PLA-PEG, gelatin, and dextran, have been used to prepare PNPs. Various types of PNPs with complex structures have also been produced using nanoprecipitation, such as solid nanoparticles [18], drug nanoparticles [19], bio-PNPs [20-

25], porous nanoparticles [26], liposome particles [27], PNPs [28,29], etc. The synthesized PNPs possess unique properties that have been exploited to develop numerous potential applications [30,31].

Review articles on the bio-medical applications of nanoparticles using different nanoprecipitation methods have been published [1-4,32]. This review aims to provide a comprehensive overview of recent advances in various nanoprecipitation techniques for preparing PNPs for efficient drug loading and controlled release. First, the preparation of PNPs using different nanoprecipitation methods is explained. Then, the application of the synthesized PNPs for the loading and controlled release of the drugs is explained. The role of some important parameters in the nanoprecipitation methods that alter the properties of the synthesized PNPs and, thereby, its capacity for loading drug and encapsulation percentage is also discussed. Since this area of drug-loading and controlled release using nanoparticles has rapidly expanded in the past few decades, comprehending all the work is impossible in this review. However, some of the very important work in each nanoprecipitation technique could be beneficial in getting much better ideas to expand future studies on this topic.

General Principles of Nanoprecipitation

The synthesis of nanoparticles through nanoprecipitation involves the preparation of two fluids: water-miscible organic solution (solute molecules in the organic phase) and anti-solvent. Nanoprecipitation involves mixing the organic solution with an anti-solvent (DI-water, salt, or surfactant solutions) [33-37]. At first, the solute molecules are dissolved in an organic solvent (acetone, tetrahydrofuran, ethanol), followed by the addition of anti-solvents (non-solvent for the solute molecules), as shown in **Figure 1**. The resulting

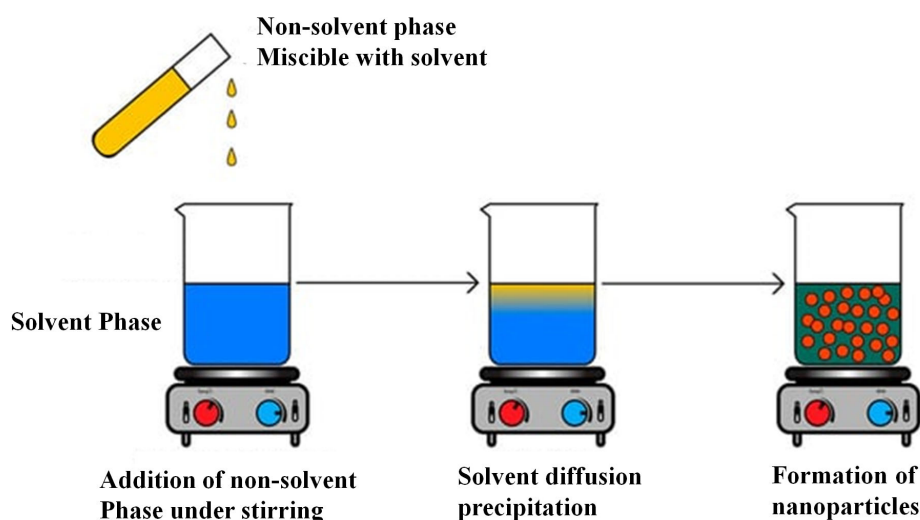


Figure 1. Schematic representation of the formation of nanoparticles in nanoprecipitation technique [38].

solutions become non-solvent for the solute molecules, which results in the formation of nanoparticles. During the mixing, supersaturating of the solute molecules takes place, resulting in the formation of particle sizes varying between a few nanometers and micrometers. Since this method of synthesizing the nanoparticle relies on reducing the quality of the organic phase by adding an aqueous anti-solvent phase, they are also known as solvent displacement or solvent shifting [11-13]. Once the particle has been grown, the solvents are removed through a different process, such as evaporation.

The growth of nanoparticles involves three processes: nucleation, growth, and self-assembly of the solute molecules, as shown in **Figure 2**. Mixing the organic and aqueous phases leads to rapid saturation of the solute molecules, which arises due to the immiscibility of the solute molecules in the anti-solvent. This process causes nucleation of solute molecules. After the nuclei form, they quickly grow because of a process that depends on diffusion. This increase in particle size is influenced by how long the fluids are mixed. If the mixing time is shorter than it takes for solute molecules to aggregate, the particle growth stops. However, if the mixing time is longer than the aggregation time of the solute molecules, the growth continues, resulting in larger particles.

Types of Mixing in Nanoprecipitation

Different nanoprecipitation techniques are followed to synthesize nanoparticles to load and release drug molecules. Some important and well-known nanoprecipitation techniques employed to synthesize nanoparticles are batch, flash, and microfluidics nanoprecipitation methods. In addition to this, other methods, such as electrohydrodynamic mixing, membrane, and electrospray, are also employed to synthesize nanoparticles, as shown in **Figure 3**. The details of these nanoprecipitation techniques are given below.

Batch nanoprecipitation

The most and simplest nanoprecipitation method is batch nanoprecipitation (BNP), also known as the traditional nanoprecipitation method, where the organic solutions and anti-solvents are mixed either rapidly using a pipette or controllably through drop-wise addition using a pump [39,40].

Flash nanoprecipitation

Flash nanoprecipitation (FNP) involves rapid mixing of the organic and aqueous phases in a jet-like arrangement of the

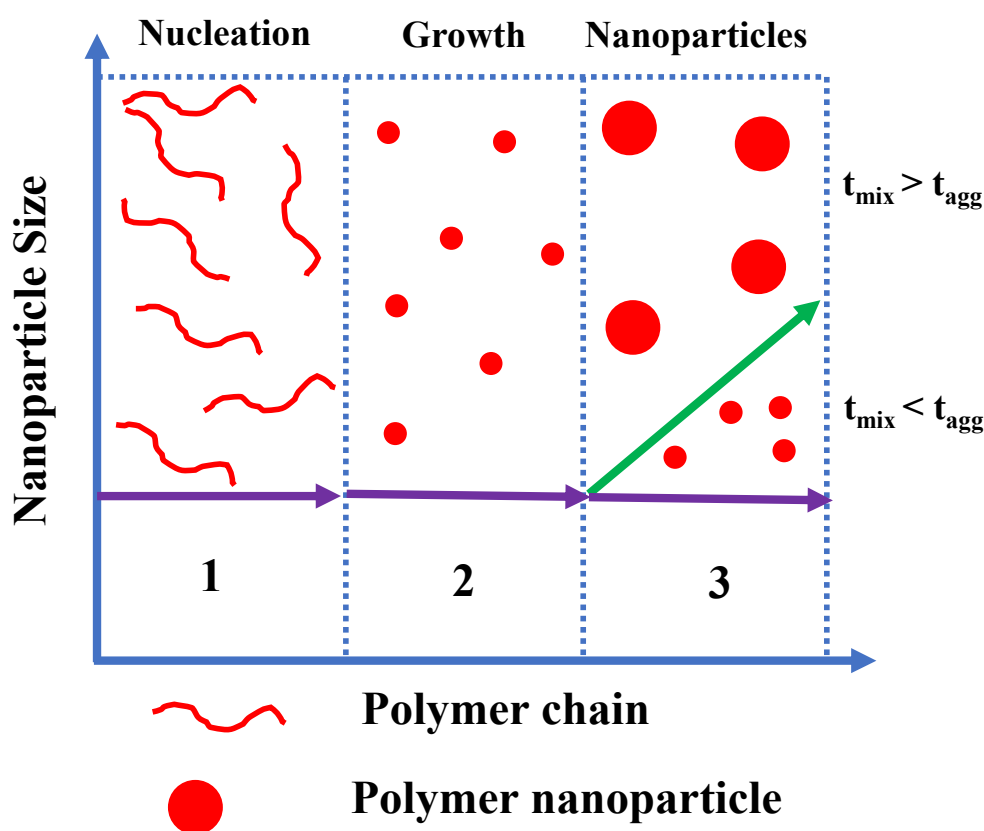


Figure 2. Schematic representation of the different stages of the growth of nanoparticles in nanoprecipitation.

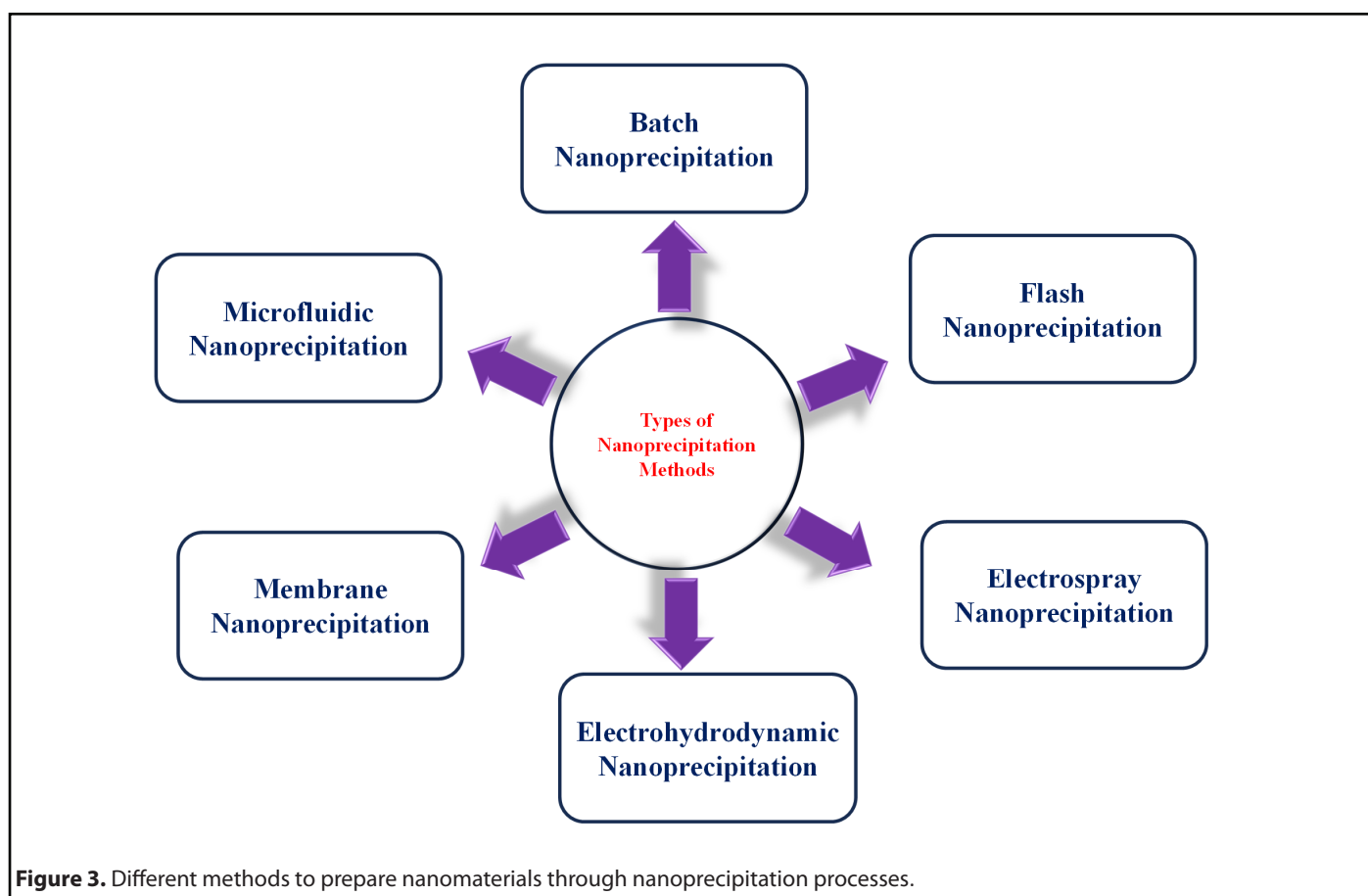


Figure 3. Different methods to prepare nanomaterials through nanoprecipitation processes.

confined space (to ensure effective mixing of the fluids) in a short period [41,42]. The period of mixing of the fluids is less than the nucleation time of the particle.

Micro-fluidic nanoprecipitation

It consists of multiple channels where very small volumes of fluids are used to ensure better control over the mixing of the liquids [43,44]. Parameters of the micro-fluidic setup, such as channel aspect ratio (length and width) and shape of the channel, determine the mixing of the fluids and, therefore, the particle size and morphology.

Membrane nanoprecipitation

This is one of the emerging membrane processes where the solvent and anti-solvents are mixed at the pore structure of the membrane [45]. In this method, the membrane acts as a supersaturation system that enhances the efficient mixing of the solvent and anti-solvent.

Electrospray nanoprecipitation

A high voltage is applied to the polymer solution through a nozzle that forms the droplets. The applied electric field-subjected droplets are mixed with the aqueous phase, which results in the formation of NPs [46].

Electrohydrodynamic nanoprecipitation

Here, the mixing of the solvent and anti-solvent follows the application of an external voltage to the solvent and the anti-solvent under turbulent mixing [47].

Basic Methodology in Preparing Drug-loaded Nanocarriers Using Nanoprecipitation Methods

Numerous conventional drug delivery systems have been developed to deliver the drug via oral, rectal, intravenous, intranasal, pulmonary, etc. Though conventional drug delivery systems have many advantages, they suffer many shortcomings that include instability of the drugs under gastrointestinal conditions, difficulty in consumption, low bioavailability, side effects, etc. This warrants the development of new drug delivery systems that overcome the drawbacks of conventional methods. The unique properties of the nanomaterials, such as enhanced surface-to-volume ratio, have been exploited to develop advanced drug delivery systems.

Though there are numerous ways to prepare nanoparticles, nanoprecipitation is used owing to its relative simplicity, less energy consumption, reproducibility, etc. The preparation of drug-loaded nanoparticles using nanoprecipitation methods

involves mixing two phases of liquids: an organic media containing a solute and drug molecules and an aqueous media, also known as anti-solvent (either DI-water or salt solution or surfactant solutions) [48]. When the organic phase containing solute molecules such as polymers and drug molecules mix rapidly with the anti-solvent (aqueous), precipitation of the solute molecules occurs. This occurs when the solubility barrier is crossed, which causes the solute molecules to phase-separate or nucleate in the continuous media. Once the nucleation occurs, further aggregation and growth leads to the formation of nanoparticles. The resultant size of the nanoparticle depends on numerous factors in each nanoprecipitation method.

The drug molecules are loaded on the surface of the nanomaterials and also encapsulated within the same. The nanomaterials used to carry the drugs and deliver them to the specific site in the body are known as nanocarriers. A wide range of nanocarriers have been produced using nanoprecipitation that has been exploited for loading clinically approved drugs [36,37,49-56]. Such encapsulation of drugs includes both hydrophobic as well as hydrophilic drugs [49,57]. The nanocarriers are broadly classified as inorganic and organic nanocarriers. Some well-known inorganic nanocarriers are silica and carbon-based nanostructures such as silica nanoparticles and single and multi-walled carbon nanotubes. In contrast, the organic nanocarriers include PNPs, liposomes, dendrimers, etc.

The efficiency of drug loading on various nanoparticle surfaces can be quantified using two important parameters, which are drug-loading (DL) and encapsulation efficiency (EE), and they are calculated as follows,

$$DL (\%) = \frac{W_{\text{drug in NP}}}{W_{\text{NP}}} * 100 \quad (1)$$

where $W_{\text{drug in NP}}$ and W_{NP} are the weight of the drug molecules loaded on the nanoparticles and the weight of the nanoparticles.

$$EE (\%) = \frac{W_{\text{drug in NP}}}{W_{\text{initial drug added}}} * 100 \quad (2)$$

where $W_{\text{drug in NP}}$ and $W_{\text{initial drug added}}$ are the weight of the drug molecules loaded on the nanoparticle surface and the weight of the initial drug molecules added into the system. DL gives information about the weight percentage of drugs loaded or entrapped on the nanoparticles. EE provides the percentage of drugs loaded or entrapped on the surface or inside the nanoparticles compared to the total drugs added.

Loading of Drug Molecules on the Nanomaterials and Interactions between Them

Drug molecules can be incorporated within nanoparticles through various methods depending on the type of nanoparticle, the nature of the drug, and the intended

application. The incorporation strategies aim to improve drug solubility, stability, controlled release, and targeted delivery. The drug is either adsorbed or attached to the surface of pre-formed nanoparticles, or it is enclosed within the core of the nanoparticle, offering protection from degradation and controlled release. In nanoprecipitation methods, the drug and polymer are dissolved in a solvent and added to a non-solvent. This leads to rapid precipitation of nanoparticles where the drug molecules are encapsulated inside the PNPs. The drug molecules are adsorbed or encapsulated within the nanomaterials either via electrostatic interactions, hydrophobic interaction [58], or a combination of both. In many cases, the drug molecule is chemically linked to the nanoparticle surface via covalent bonds. Here, the nanoparticles are functionalized with certain chemical groups that make very strong covalent bonds with the drug molecules. In addition to this, the chemical structure of the polymer and its amphiphilicity also play an important role in stabilizing the drug molecules [58].

Release of the Drug Molecules from the Nanomaterials

The release of drug molecules from the surfaces of nanomaterials or within the nanomaterials plays a pivotal role in nanomedicine, significantly influencing therapeutic efficacy, precision targeting, and the controlled delivery of treatments. This process is intricately linked to various factors, including the physicochemical characteristics of the nanomaterials, the drugs they carry, and the surrounding biological milieu. Drug release can occur through passive mechanisms such as diffusion and desorption or through active means driven by stimuli-responsive features, which enable a more dynamic interaction with physiological conditions. The drug molecules on the surface and core of the nanoparticles are released through two different stages: burst and prolonged release. The burst release occurs when the drug molecules are located on the surface of the nanoparticles. In contrast, the prolonged release occurs when the drugs are located in the core of the nanoparticles. The drug molecules encapsulated within nanoparticles are known as nanoencapsulation, which improves drug stability, solubility, and targeted delivery, leading to enhanced therapeutic efficacy and reduced side effects.

In nanoencapsulation, the drug diffuses from the nanoparticle matrix into the surrounding biological environment. The release of the drug molecules from encapsulated nanomaterials involves multiple mechanisms — diffusion, degradation, swelling, and stimuli-responsive behaviors. Through precise nanomaterial engineering, it is possible to tailor the release of kinetics for specific therapeutic needs, enhancing drug bioavailability, targeting, and patient outcomes. Several physicochemical and environmental factors influence the release of encapsulated drug molecules from nanoparticles produced via nanoprecipitation. Understanding these mechanisms is crucial for controlling

drug delivery kinetics, improving therapeutic efficacy, and minimizing side effects. The pH of the medium plays a crucial role in controlling the release of drugs from nanoparticles. This effect can vary depending on the type of nanoparticle and the chemical properties of the drug, etc. These diverse release strategies of the drug molecule from the nanomaterials are formidable tools in pursuing precision medicine. By delving into the underlying drug release mechanisms, researchers can design sophisticated, tailored drug delivery systems to maximize therapeutic outcomes while minimizing adverse side effects. Such understanding paves the way for more effective and personalized medical interventions.

The following discussion explains the preparation of drug and drug-loaded nanoparticles, the loading capacity and encapsulation efficiency, and its release kinetics at different physicochemical conditions using different nanoprecipitation methods.

Preparation of PNPs Based Nanocarriers through the BNP Method

The BNP method was employed to prepare the drug-loaded PNPs. PNPs are colloidal particles made of polymers prepared by mixing the organic solution of polymers with the anti-solvents. The drug molecules are added to the organic solvent encapsulated within the PNPs while precipitating the polymer molecules. The schematic representation of the preparation of drug-loaded nanoparticles using BNP technique [59,60] is shown in **Figure 4**. The following discussion concentrates on preparing various PNPs to encapsulate and deliver the drug molecules using the BNP method.

Block co-polymer NPs are widely used to encapsulate insulin owing to their biocompatibility and tailored surface properties. Chopra *et al.* [61] prepared the insulin-loaded PLGA-PEG NPs. Enhanced encapsulation of insulin (3.82 %) was observed when chelating ions such as zinc were used while maintaining the small size of the nanoparticles (<100 nm) where the conformation of insulin was not changed on the nanoparticle surface. *In vitro* release study showed the burst release of 80 % insulin in ~ 150 minutes, followed by prolonged release of 20% nanoprecipitation for 800 minutes. Related work on long peptides such as hydrophilic oxytocin and hydrophobic luteinizing hormone-releasing hormones (LHRH) on various PNPs such as PLGA, PLA, and PCL was carried out [62]. The *in vitro* drug release profile of the peptides at different pH conditions fulfills the requirements of nasal delivery with burst release of nearly 50% of the drug from the NPs within an hour. The entire drug was released within 35 hours when the pH was maintained at 2.2 and 5.5. With increasing the pH condition to 7.4, the release rate for oxytocin was slightly reduced. The release rate of LHRH was different from oxytocin, which was found to be low at all pH conditions.

PNPs with very high drug (Docetaxel) loading (66.5 weight %) and encapsulation efficiency (99.8%) were synthesized using salt-induced precipitation [63]. The loading efficiency was altered with a change in particle size that can be controlled by changing the salt concentrations in the PBS solution. The micro-size particle was obtained at a low salt concentration with very low encapsulation efficiency (46.7%). However, when the salt concentration was increased to 7 times the PBS concentrations, uniform PNP (size 50 nm) was produced, and encapsulation efficiency was estimated to be 98.2%.

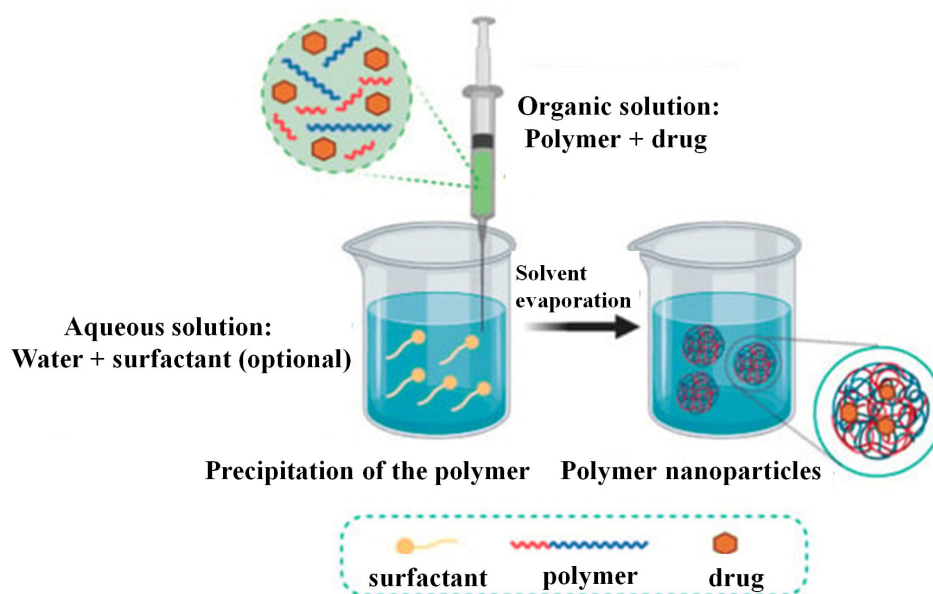


Figure 4. Preparation of drug-loaded nanoparticles in the batch nanoprecipitation method [59].

Curcumin (CUR) is a hydrophobic polyphenol that exhibits anti-inflammatory, anti-cancer, antioxidant, and anti-microbial properties. Such excellent properties of the CUR are inhibited due to its poor water solubility and sensitivity to high temperature, pH, and light. To overcome these limitations, ethyl cellulose (EC) stabilized CUR-loaded zein/ethyl cellulose colloidal dispersion was prepared using the BNP technique [64]. The release kinetics of CUR from pH 3 to 8 lies between 0.2 and 2.1 % of the total encapsulated CUR. No apparent changes were observed for ZN-CUR-EC nanoparticles in pHs from 3 to 8. Related work on loading various drugs on PNPs, including CUR, was demonstrated where high drug loading (up to 58.5 %) was achieved using a mixture of solvents instead of single solvents [52]. High CUR loading (58.5 %) and encapsulation efficiency (98.5 %) were achieved using core-shell (drug-polymer) nanoparticles by exploiting the co-precipitation of drug and polymer using a mixture of various solvents instead of one solvent to fine-tune their solubility [52]. The drug release kinetics study showed the burst release of CUR when single-layer NPs (PNP prepared using a single polymer) were employed and sustained release of drugs for 7 days when double-layer polymer NPs were used.

Astaxanthin is known to have strong antioxidant properties to fight against the excessive free radicals produced in our bodies. It is highly lipophilic, with lower oral bioavailability that hinders its absorption capabilities. Therefore, it is encapsulated with a non-toxic and biocompatible polymer to increase its absorption. Azaman *et al.* [65] conducted experiments in which astaxanthin drug was encapsulated with poly(lactic-co-glycolic acid) (PLGA) NPs. PLGA was used owing to its biocompatible and non-toxic characteristics. The stable and homogenous NPs were obtained with a mean particle size of 142.23 ± 0.961 nm. It represents a stable and homogeneous system.

The BNP method was employed to prepare chitosan nanoparticles, and the biological application of the prepared chitosan particles was tested using the model drug, Citral (3,7-dimethyl-2,6-octadienal) [53]. Chitosan was an excellent model biomaterial as a nanocarrier, and its good association and loading efficiency of the model drug molecule within it proved to be very high. With increasing the concentration of the model drug molecule (citral), the association efficiency of the drug molecule was found to be increased within the chitosan nanoparticle and reached a maximum of 88%. The loading efficiency of the citral was increased upto 38% within the chitosan particles.

Therefore, the polymeric nanocarriers synthesized through BNP offer advantages such as high encapsulation efficiency, biocompatibility, tunable release kinetics, etc. Furthermore, targeted and controlled drug delivery can be achieved by changing the nature of the polymer and its composition, such as incorporating stimuli-responsive elements. Despite its

advantages, challenges such as rapid drug burst release and limited scalability require further optimization and process standardization. Overall, BNP remains a promising method for preparing polymeric nanoparticles, offering a versatile platform for developing advanced drug delivery systems in nanomedicine.

Preparation of Drug-loaded Nanoparticles through the FNP Method

The FNP method was also employed to prepare the drug-loaded PNPs, which has numerous advantages over the BNP method. Here, the nanocarriers are prepared using a specialized instrument that is a jet-like arrangement of the confined space, as shown in the top-left portion of **Figure 5**. The following discussion concentrates on preparing various PNPs to encapsulate and deliver the drug molecules using the FNP method.

The FNP method was combined with the extrusion technique to synthesize lipid-stabilized solid drug NPs, Methotrexate (MTX) [66]. The drug nanoparticles (49.1 nm) were produced using FNP, and lipid stabilization was performed using membrane extrusion. This method of synthesizing particles allows the drug loading efficiency and payload to be 84.5% and 62.3%. The drug release rate of the bare and lipid-stabilized MTX drug NPs exhibited an initial burst release of the loaded drug molecules. However, sustained release of the drug for a day (24 hours) was noted only for the lipid-stabilized MTX NPs. The drug release rate depended on the solution pH condition, where enhanced drug release was noticed between the pH values of 5.5 and 7.4.

A confined impinging jets (CIJ) mixer of the FNP technique was employed to synthesize drug (cannabidiol-CBD) nanoparticles co-encapsulated with hydrophobic iron oxide nanoparticles with a low polydispersity [67]. During synthesis, the prepared hybrid CBD-iron oxide nanoparticle was stabilized with hydroxypropyl methylcellulose acetate succinate (HPMCAS) or lecithin. A comparative study of the *in vitro* release profile of CBD-HPMCAS- Fe_3O_4 , CBD-lecithin- Fe_3O_4 shows that the protein stabilized CBD- Fe_3O_4 exhibit better dissolution kinetics (six-fold increase) in the model intestinal media (FeSSIF). The drug release kinetics show that the lecithin-CBD- Fe_3O_4 releases the drug immediately, whereas HPMCAS-CBD- Fe_3O_4 shows an immediate release of 80% that was followed by gradual release kinetics over time owing to the thicker protective layer of HPMCAS over the hybrid nanoparticle system.

The FNP method was employed to prepare copolymer-nanoparticle (PEG-PPLA/zein) of smaller size and lower polydispersity to encapsulate the paclitaxel (PTX) drug [58]. The encapsulation efficiency of the drug in PEG-PLA/zein NPs was higher (51.17–78.14 %) as compared to PEG-PLA micelle

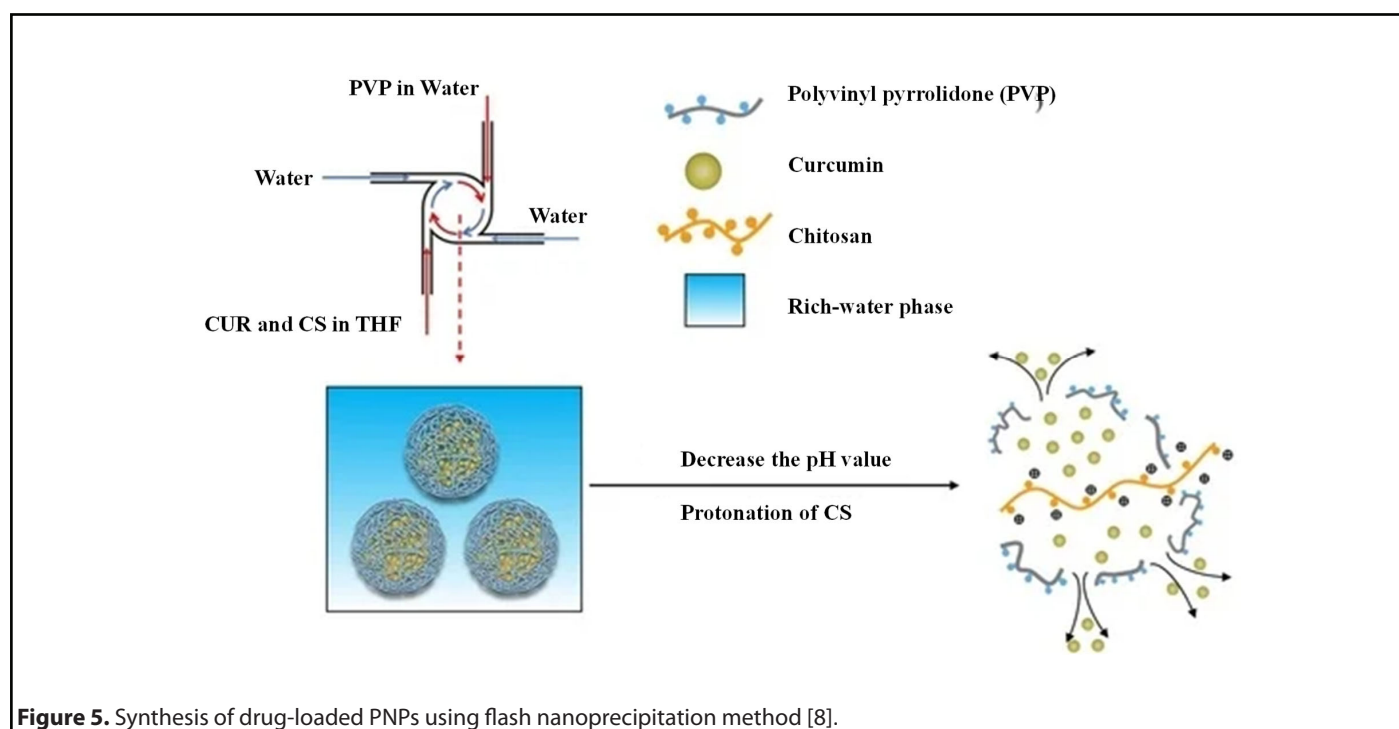


Figure 5. Synthesis of drug-loaded PNPs using flash nanoprecipitation method [8].

without zein. *In vitro* drug release behavior from PTX-micelles and PTX-NPs was assessed at pH 5.5 and 7.4. For PTX-micelles (without zein), the release of the drug was fast in the first 12 hours. In contrast, zein-loaded NPs showed a sustained release, suggesting that incorporating more zein in the NPs enabled stronger hydrophobic interaction between the drug and nanoparticles. Meanwhile, the drug was released more quickly from the carriers at pH 5.5 than 7.4, attributed to the increased hydrolysis of PLA and the enhanced aqueous solubility of the drug at acidic pH.

The FNP method was employed to synthesize the polymer-stabilized synthetic nanoparticle of the peroxide antimalarial drug, OZ439, for single-dose malaria treatment [68]. Two forms of OZ439 (mesylate and free base) were studied; the mesylate form could be formulated into a stable nanoparticle, whereas the free base form could not be made into dry powder via lyophilization. The OZ439 formulation was lyophilized by adding Methocel E3 Premium LV Hydroxypropyl Methylcellulose (HPMC E3). This process produces a powder that can be re-dispersed in water with narrow size distribution and without modifying the properties of the nanoparticles. The loading capacity of the drug was estimated to be 16%. Since the drug stabilized into an amorphous form, it exhibited higher dissolution kinetics. The *in vitro* study shows that the release rate of OZ439 was eleven times higher than the unencapsulated counterpart.

Qi *et al.* [69] prepared celastrol drug-loaded dextran-based amphiphilic copolymer nanoparticles using a multi-inlet vortex mixer (MIVM) setup using the FNP technique. The synthesized PNPs possess a size range between 80 and 160

nm with a narrow size distribution (PDI ~ 0.1). The prepared PNPs using the FNP technique were used for loading the drug effectively. With increasing the concentration of the drug molecules from 0 to 2 mg/mL, the size of the synthesized PNPs was reduced from 80 to 40 nm. The synthesized PNP exhibits high drug loading between 11 and 63 % and shows a tunable release. It also exhibits reduced cytotoxicity towards the liver cell, HL-7702, and inhibits the formation of lung cancer cells, A549.

All these studies show that the FNP method can be used to prepare PNPs of various morphologies. The FNP method allows a rapid, scalable, and efficient way of preparing the NPs. The prepared NPs using the FNP method can be capable of encapsulating a wide variety of drugs with high drug loading. Controllable release of the drugs can be achieved from the NPs synthesized via FNP. However, it suffers from certain disadvantages, such as the high cost of producing the drug loaded NPs. The process of FNP often requires specialized turbulent mixing devices, which can be expensive and complex to scale up.

Preparation of Drug-loaded Nanoparticles through the MNP Method

MNP is an advanced technique for synthesizing drug-loaded PNPs with precise control over nanoparticle size, uniformity, high reproducibility, scalability, precise morphology, and enhanced drug encapsulation efficiency. This method involves rapidly mixing a polymer-drug solution with an antisolvent in a microfluidic device, leading to the spontaneous formation of nanoparticles, as shown in **Figure 6**. However, it also suffers

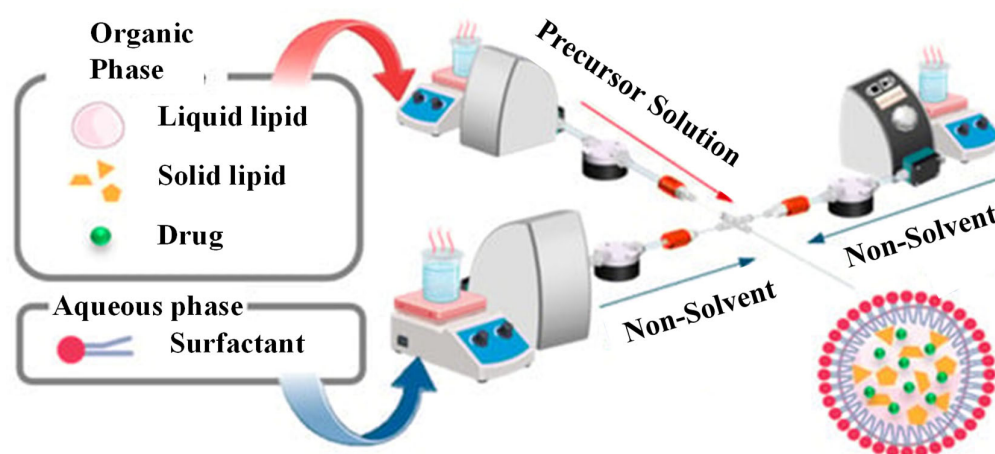


Figure 6. Synthesis of drug-loaded PNPs using microfluidic nanoprecipitation [73].

from some disadvantages, including the high cost of the equipment, limited consumption and compatibility of the polymers and solvents, and lower throughput compared to BNP. The MNP method has been employed to synthesize PNPs for various biomedical applications [70-72]. The presence of drug molecules while preparing the drug-loaded nanoparticles also influences the properties of the nanoparticles.

The MNP method was also employed to encapsulate the anticancer drug molecule SN-38 in the block copolymer poly(caprolactone)-block-poly(ethylene glycol) nanoparticles via curcumin [74]. By co-encapsulating CUR with SN-38 in PNPs, the drug encapsulation efficiency and control release were enhanced. The prepared PNP size increased slightly from 40 to 55 nm, but the PDI decreased significantly from 0.34 to 0.07, increasing the concentration of the drug-to-polymer ratio. However, the size and PDI of the PNPs decreased by increasing the concentration of the drug (CUR), making the synthesized PNPs highly monodispersed. With increased CUR concentration, the encapsulation percentage was found to be increased from 5 to 12%, and no further increase was noted with further increasing the drug concentration.

The MNP method was used to prepare the drug (CUR) loaded mPEG-PLGA NPs. The prepared mPEG-PLGA NPs size was found to vary between 47 and 74 nm with increasing the flow rate ratio of 0.03 to 0.3. For the experimental purpose, the authors chose the di-block copolymer (PEG-PLGA) NPs of size 60 nm also studied using the MNP method [72]. The drug loading and encapsulation efficiency were 2.6 and 77.3%, respectively, when the initial drug concentration was 3.3%. However, with an increase in drug concentration to 5%, the drug loading percent was slightly enhanced, whereas the encapsulation efficiency was decreased. This study shows that the polymer concentrations also decide the loading efficiency of the drug on the nanoparticles. Therefore, to enhance the drug loading

on the particle surface, the ideal condition is to precipitate the drug molecule before precipitating the polymers. This will allow the polymers to form a layer on the drug particle surface.

In another related study, Baby *et al.* [75] used MNP to synthesize pH-responsive PNPs (shellac) for drug (CUR) delivery applications using 3-D microfluidic tubing devices. In this method, the PNPs were prepared by using a mixture of multiple solvents instead of one solvent to obtain smaller-sized PNPs with improved stability. This method of preparing the PNPs allows for the tunable loading of the drug. The size of the prepared shellac NPs was between 40 and 71 nm. The prepared drug-loaded PNPs were stable for ten days under an acidic environment but released the drug at neutral pH conditions. Tuneable drug loading was achieved at a maximum of 50%. At neutral pH, around 28% of the drug was released in 4 hours, and almost 51% was released after 51 hours.

Therefore, MNP is an efficient and scalable method for producing drug-loaded PNPs with high precision. Designing tailored nanocarriers for controlled and targeted drug delivery applications is possible by optimizing flow rates, polymer composition, and solvent selection. This technique holds significant promise for advancing nanomedicine and improving therapeutic outcomes. Compared to bulk nanoprecipitation methods, MNP often has lower throughput, requiring additional process optimization or multiple microchannel for large-scale production. Moreover, the narrow micro channels are prone to clogging, especially when working with high-concentration solutions or nanoparticles with strong aggregation tendencies. Therefore, although there are many advantages of using MNP to prepare efficient nanocarriers, the drawbacks of the MNP method must be improved for better nanomaterial production to enhance drug-loading and controlled release at different physicochemical conditions.

All these studies clearly show that nanoprecipitation can be used to load various types of drugs on nanoparticle surfaces. The drug-loading and release kinetics can be tailored by suitably choosing the polymer and fine-tuning the physicochemical conditions. The following table shows the loading and release of various drug molecules on the PNPs synthesized through different nanoprecipitation methods.

Conclusions and Future Perspectives

This review discusses various advancements in achieving the desired properties of nanomaterials through different nanoprecipitation methods for drug loading and release

applications. This review also compares the efficiency of nanomaterials synthesized through different nanoprecipitation techniques. Nanoprecipitation is a straightforward, versatile, low-energy, and cost-effective approach to producing a range of nanomaterials. It allows for the preparation of polymeric nanoparticles (PNPs) with precise size and morphology, which can enhance drug-loading capacity and control release under varying physicochemical conditions. BNP is recognized as a promising method for preparing PNPs aimed at developing advanced drug delivery systems. It offers the advantage of simple preparation methods but faces certain drawbacks, such as non-reproducibility and the formation of larger particle sizes. These shortcomings are addressed by the use

Table 1. Preparation of various drug and drug-loaded PNPs using different nanoprecipitation methods.

Technique	Polymers/ Molecules	Drug Molecules	Organic phase	Aqueous phase	DL (%) *	EE (%) *	Size range (nm)	PDI*	Stability	Ref
BNP	PLGA	ATX	AC	F-127	---	84.3	142	0.146	---	[65]
BNP	Zein-Ethyl cellulose	CUR	EtOH	DI-Water	---	49-82	167-179	0.09- 0.11	6 months	[64]
BNP	PLGA, PLGA- PEG	CUR, PTX, IB and KT	DMSO, DMF and EtOH	DI-Water	40-58.5	70-90	100	0.2	15 months	[52]
BNP	Chitosan	CT	MeOH	NI-SAA	38	88	230-290	---	---	[53]
BNP	PLGA _{10K} - PEG _{5K}	Insulin	DMSO	DI-Water/ PBS	4	15	62 – 84	---	4 days	[61]
BNP	PLGA10k- PEG5k	DT	DMF	PBS	49.5	98.2	50 – 90	0.2	35 days	[63]
FNP	mPEG-b-PCL	-Carotene	THF	DI-water	---	86.3–93.6	89 – 205	0.12	15 days	[76]
FNP	PEO-PS, PEG- PCL	-Carotene	THF	DI-water	---	> 85	50 -500	---	---	[51]
FNP	Chitosan	CUR	THF	DI-Water	40	95	160 – 290	0.05 – 0.3	2 months	[50]
FNP	Lipid	MTX, DOX, CA	EtOH	DI-water	30.5 -62.3	39.2 -84.5	71	---	7 days	[66]
FNP	D-PLGA	CL	THF	PBS	11 - 63	80-90	80-160	0.2-0.3	2 weeks	[69]
FNP	PS-PEG, PCL- PEG	OZ439	THF, MeOH	DI-Water	16	---	50-400	0.15- 0.26	---	[68]
FNP	Zein	DOX	DMSO	DI-Water	9.2 to 16.3	40.9 to 77.3	190 – 1200	0.2 – 0.6	14 days	[77]
FNP	Chitosan	CUR	THF	DI-Water	40	95	160 – 290	0.05-0.3	2 months	[50]
MNP	PEG-PLGA	CUR	ACN	DI-Water	2.6	77.3	47-74	0.069- 0.13	---	[72]
MNP	PCL-PEG	SN-38 & CUR	DMF	DI-Water	0.5 – 1	5-12	40 – 50	0.1 -0.3	---	[74]
MNP	Shellac	CUR	EtOH, MeOH, DMF, DMSO	DI-Water	10-50	80	30-100	0.1-0.3	10 days	[75]

* BNP: Batch Nanoprecipitation; FNP: Flash Nanoprecipitation; MNP: Microfluidic Nanoprecipitation; DL: Drug Loading; EE: Encapsulation Efficiency; PDI: Polydispersity Index; Ref: Reference

of FNP and MNP methods, which provide precise control over nanoparticle size, uniformity, high reproducibility, scalability, and improved drug encapsulation efficiency. However, MNP does have its disadvantages, including the high cost of equipment, limited polymer and solvent compatibility, and reduced throughput compared to BNP. Moreover, nanoparticles synthesized through these nanoprecipitation methods often require additional purification steps, such as solvent removal and dialysis, which can complicate production and elevate costs. Scaling this method for large-scale production presents challenges as well, primarily due to the necessity for precise and reproducible mixing of solvents and anti-solvents containing the drug. Consequently, the choice of nanoprecipitation method may vary based on the specific needs of practical applications. Overall, this review enhances our understanding of drug encapsulation and targeted delivery by providing an updated perspective on the nanoprecipitation-based synthesis of nanomaterials.

In conclusion, the author would like to propose some interesting future directions for advancing nanoprecipitation techniques. One key area of focus should be the development of an efficient and rapid methodology for effectively removing residual organic solvents from nanoparticle dispersions. The presence of these solvents not only compromises the stability of the nanoparticles but also poses significant toxicity risks when introduced into biological systems. Secondly, most synthesized nanomaterials are made from hydrophobic ingredients, which facilitate the encapsulation of only hydrophobic drugs for pharmaceutical applications and are primarily unsuitable for water-soluble bio-macromolecules such as proteins and peptides [78]. Research is being conducted to develop formulations that include biological macromolecules based on hydrophobic ion-pair mechanisms [79-83]. Developing nanoprecipitation for hydrophilic ingredients may lead to even broader applications of the technology, including developing or encapsulating hydrophilic drugs. Thirdly, the proper selection of the polymer and solvents with better mixing conditions has to be determined to synthesize nanomaterials with enhanced drug-loading efficiency. So far, the maximum drug loading has been achieved to be close to 50%, which can be increased further. This remains one of the challenges in increasing drug loading efficiency. With regard to the testing of the prepared drug-loaded nanoparticles, *in vitro* testing and *in vivo* testing on animals have been studied significantly. However, the *in vivo* testing of the prepared drugs has to be performed in humans, which will help to implement the synthesized drug nanoparticles or drug-loaded nanoparticles for direct practical applications. Addressing these challenges is crucial for ensuring the safety and efficacy of nanoparticles in developing a better drug delivery system. By embracing these innovative approaches, it is possible to enhance the reliability of nanoprecipitation processes to open new avenues for developing next-generation drug delivery systems.

List of Abbreviations

ATX: Astaxanthin; AC: Acetone; BNP: Batch Nanoprecipitation; CL: Celastrol; CT: Citral; CUR: Curcumin; DCM: Dichloromethane; D-PLGA: Dextran-b-PLGA; DI-Water: De-ionized water; DOX: Doxorubicin hydrochloride; DLS: Dynamic Light Scattering; DMF: Dimethylformamide; EtOH: Ethanol; FNP: Flash Nanoprecipitation; IB: Ibuprofen; KT: Ketamine; LHRH: Luteinizing Hormone-Releasing Hormone; mPEG-b-PCL: Methoxy poly(ethylene glycol)-block-poly(caprolactone); MeOH: Methanol; MNP: Microfluidic Nanoprecipitation; MTX: Methotrexate; NI-SAA: Non-Ionic Surfactant; OZ439: Artefenomel (Peroxide antimalarial drug); PTX: Paclitaxel; PBS: Phosphate buffer solution; PDI: Polydispersive index; PNP: Polymer nanoparticle; PLGA: Poly(Lactic-co-Glycolic Acid); PVA: Poly(Vinyl Alcohol); SN-38: 7-Ethyl-10-hydroxycamptothecin; THF: Tetrahydrofuran; TRH: Thyrotropin-Releasing Hormone

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article.

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