Available online on 15.08.2024 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

Nanoparticles Preparation by Flash Nanoprecipitation

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A B S T R A C T

Flash nanoprecipitation (FNP) is a widely used technique for preparing particulate carriers based on various polymers that has been shown to be a promising technology for the industrial production of drug-loaded nanoparticles. The use of amphiphilic block copolymers as a stabilizer to protect the nanoparticles from aggregation makes flash nanoprecipitation (FNP) an ideal method for rapidly preparing nanosized drug particles with high drug-loading efficiency. Flash nanoprecipitation (FNP) is a controlled antisolvent precipitation process that has been shown to be effective for producing drug nanoparticles with a defined mean particle size and narrow particle size distribution. However, the physical instability of the generated nanoparticles remains a significant barrier to the use of this technology in pharmaceutical formulation. This review discusses the use of FNP to create poorly water-soluble drug nanoparticles using controllable mixing devices such as confined impinging jets mixers (CIJM), multi-inlet vortex mixers (MIVM), and a variety of other microfluidic mixer systems. The mechanisms and processes of drug nanoparticle formation by FNP are described in detail. Then, during the FNP process, the supersaturation level and mixing rate are controlled to tailor the ultrafine drug nanoparticles, as well as the influence of drugs, solvent, anti-solvent, and stabilizers. The control of supersaturation level and mixing rate during the FNP process to tailor ultrafine drug nanoparticles is discussed, as well as the influence of drugs, solvent, anti-solvent, stabilizers, and temperature on fabrication.

Keyword: Flash Nanoprecipitation, Multi-Inlet Vortex Mixers, Nanoparticles

A R T I C L E I N F O: Received 14 March 2024; Review Complete 26 July 2024; Accepted 05 August 2024; Available online 15 August 2024

Cite this article as:
Patil YB, Malpure PS, Talele GS, Deshmukh DH, Nanoparticles Preparation by Flash Nanoprecipitation, Asian Journal of Pharmaceutical Research and Development. 2024; 12(4):103-107, DOI: http://dx.doi.org/10.22270/ajprd.v12i4.1448

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INTRODUCTION:

Flash nanoprecipitation (FNP) is a powerful and scalable technology for producing solid drug nanoparticles with high payload by rapidly mixing drug-containing organic solvent and water in a microchamber. Nanoparticles are thought to be an effective method for delivering drugs that are insoluble in water. Flash nanoprecipitation (FNP) has been widely used to fabricate these drug nanoparticles, including pure drug nanocrystals, polymeric micelles, polymeric nanoparticles, solid lipid nanoparticles, and polyelectrolyte complexes, as a simple, rapid, and scalable method. This review discusses the use of FNP to create poorly water-soluble drug nanoparticles using controllable mixing devices such as the multi-inlet vortex mixer (MIVM). Many lipophilic active pharmaceutical ingredients (APIs) are generated during high throughput screening for drug discovery, necessitating formulation scientists to address their poor aqueous solubility and dissolution. More than 40% of drugs fall into the biopharmaceutics classification system (BCS) Classes II (low solubility-high permeability) and IV (low solubility-low permeability)[1].

These nanoparticle formulations offered several advantages for insoluble drug delivery, including:

A. The drug nanoparticles could improve the dissolution rate and solubility of poorly water-soluble drugs by increasing the surface area to volume ratio[2].BCS class II drugs

specific interactions with cells and tissues are improved, as is absorption and bioavailability[3].

B. The formulation of some drugs as nanodrugs will improve their chemical stability and control their release profile in the gastrointestinal tract.

C. The surface functionality of the drug nanoparticles could be tailored to achieve long circulation and targeted delivery[4].

Among the various nanoparticle production techniques, such as milling, high pressure homogenization, and the supercritical fluid process, flash nanoprecipitation (FNP) has the advantages of fast processing, simple equipment, smaller size, and narrower size distribution. The FNP also allows for the combination of several hydrophobic drugs as well as the incorporation of imaging agents. In the FNP technique, a highly hydrophobic drug is dissolved in a water miscible organic solvent with a block copolymer (BCP). This solution, along with water, is injected at high velocity into a small chamber. Because of the high velocity, turbulent mixing occurs, causing the hydrophobic drug and polymer to coprecipitate very quickly, forming nanoscaled particles. The amphiphilic block copolymer is composed of a hydrophilic poly (ethylene glycol) (PEG) block covalently bonded to a hydrophobic block. The hydrophobic block precipitates with the drug, halting particle growth, while the pendant PEG blocks prevent aggregation[5].

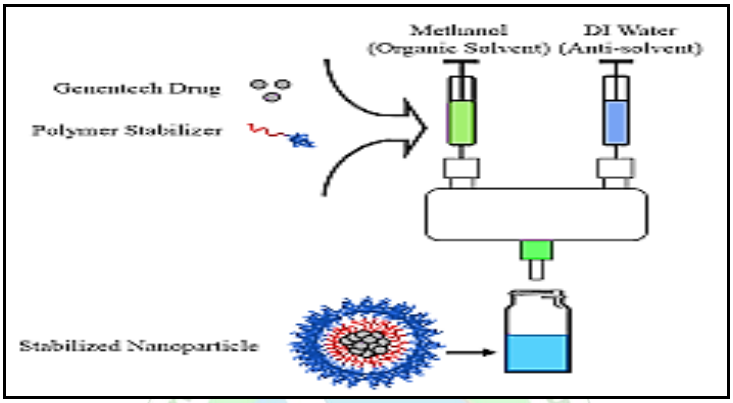

Figure 01: Nanoparticles prepared throughFlash NanoPrecipitation viaconfined impinging jet mixers

Principle of Flash Nanoprecipitation:

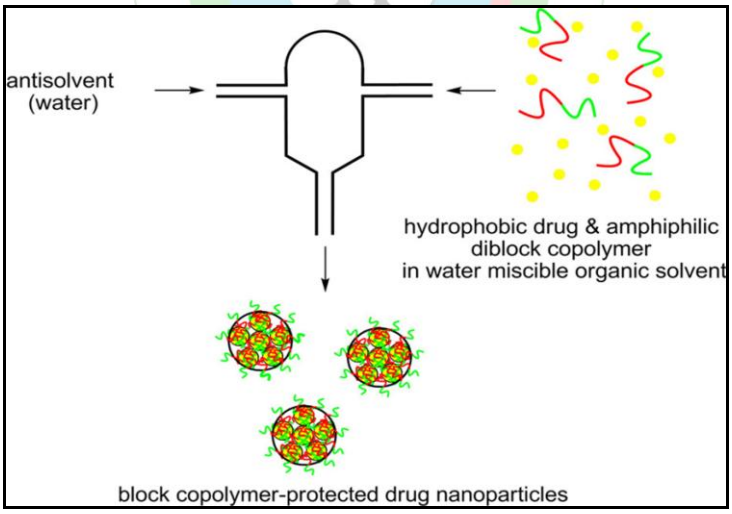

Figure 2: Schematic of impingement mixing to form block copolymer-protected nanoparticles

FNP is widely used in the bottom-up approach to tailor-made drug nanoparticles (i.e., aqueous nanosuspension of poorly water-soluble drugs). As with traditional crystallization, nanoparticles formed by FNP undergo an initial nucleation stage, after which newly formed nucleation seeds capture dissolved molecules to grow. The classical molecule crystallization theory is a useful model for understanding the mechanism of NP formation by FNP. It entails a thermodynamically favorable solid-liquid phase separation process. The reduction from the high free energy (G) of supersaturation to nanoparticle suspension, which has a low G and is thermodynamically stable, is the driving force behind such phase separation. According to this theory, nucleation mechanisms are classified as "homogenous nucleation," which occurs in the absence of a foreign substance, and "heterogeneous nucleation," which occurs in the presence of a foreign substance[6].

Overview of Flash Nanoprecipitation (FNP):

Fast mixing of a stream containing a molecularly dissolved solute and a stabilizing molecule with an opposing stream containing a miscible solvent, which acts as a non-solvent for

the solute and stabilizer, provides the local supersaturation required for particle nucleation. In the turbulent regime, mixing occurs in a confined volume, allowing for high energy dissipation rates and the supersaturation conditions required for simultaneous precipitation of the solute[7].

Mixing devices:

Confined Impingement Jets Mixer (CIJM)

The confined impinging jets (CIJM) have been widely used for the production of nanoparticles of water-insoluble drugs. The CIJM is made up of a syringe pump and a mixing chamber with two opposing liner jets. To reduce the scale of segregation between the micro-volume liquid streams in the mixing chamber, the two fluid streams in opposing liner jets were driven to collide at high velocity by a syringe pump. In fact, the first detailed evaluation of FNP was performed in 2003 using a CIJM. The process performance of a confined impinging jets mixer is affected by the different jet diameters, chamber size, geometry, and outlet configurations. They thoroughly investigated micro-mixing in impinging jets in order to predict mixing performance, reaction selectivity, and scale-up criteria[8].

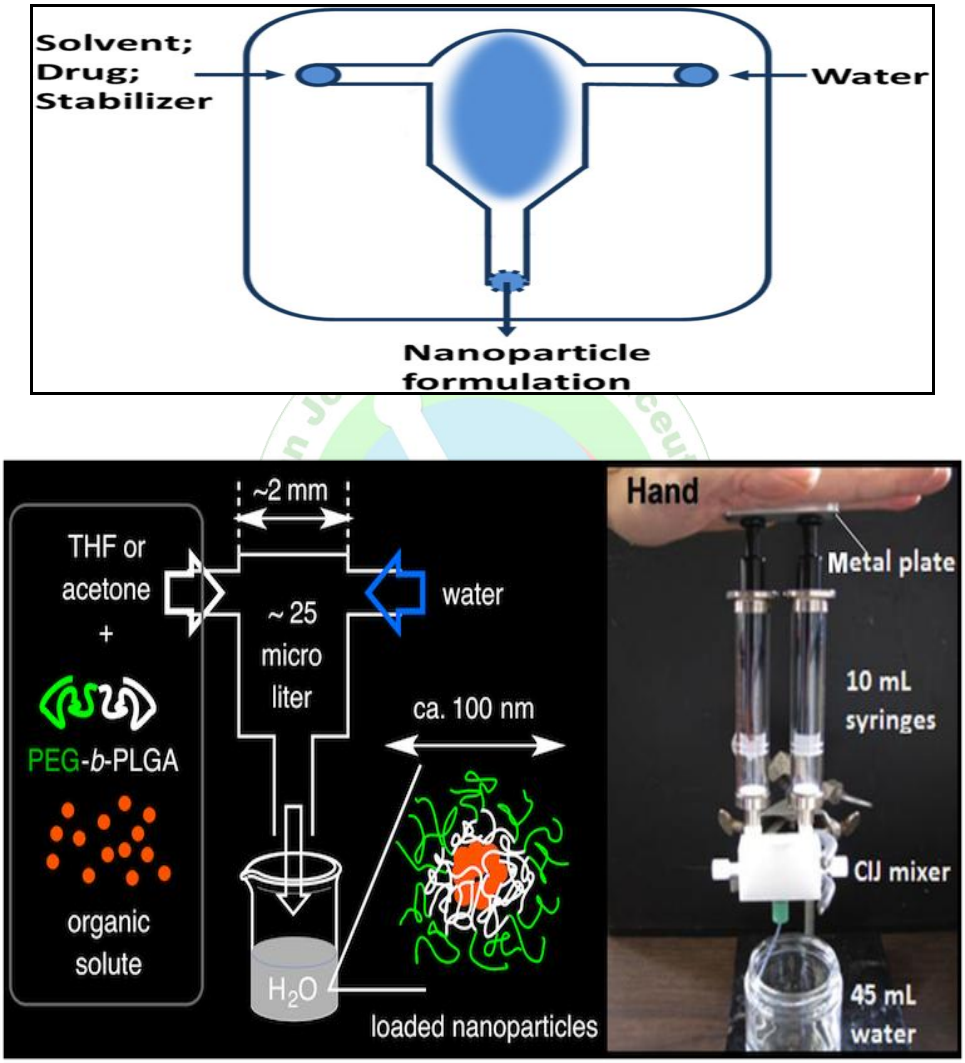

Figure 3: Simple Confined Impingement Jets Mixer

Flash nanoprecipitation (FNP) uses confined impingement jets (CIJ) to prepare nanoparticles loaded with hydrophobic compounds (e.g., drugs, inks, fragrances, or pheromones). The original CIJ design has been modified to allow hand operation, eliminating the need for a syringe pump, and a second antisolvent dilution stage has been added. Impingement mixing necessitates equal flow momentum from two opposing jets, one containing the drug in an organic solvent and the other an antisolvent, usually water. The new design's subsequent dilution step enables rapid quenching with high antisolvent concentration, which improves nanoparticle stability. This new CIJ with dilution (CIJD) mixer is a simple, low-cost, and effective tool for producing nanoparticles[9].

Multi-Inlet Vortex Mixer (MIVM):

MIVM, which is also commonly used for FNP, was developed to overcome the limitations of the CIJM while maintaining its ability of rapid mixing, scalability, and ease of operation. The mixing chamber in this device is connected to four inlets, and the liquid streams were driven to collide at an angle with high velocity by syringe pumps, resulting in vortex mixing. Because each stream independently contributes to the micro mixing process in the mixing chamber, the MIVM can

be applied to a wide range of solvent ratios and materials. It is possible to freely adjust the flow rate of solution and anti-solvent in the mixer to achieve various levels of supersaturation, thereby manipulating the nucleation and growth time scale. MIVM's high-efficiency and rapid mixing rates of solution and anti-solvent ensured that the mixing time was shorter than the time required for nanoparticle nucleation and growth. MIVM has a stronger function and a broader application than CIJM in the preparation of poorly water-soluble drug nanoparticles due to its flexibility in adjusting solvent ratios and materials by varying the content and flow velocity of incoming streams. MIVM was primarily used to create drug polymeric micelles, polymeric nanoparticles, polyelectrolyte complexes, nanocrystal drugs, and solid lipid nanoparticles[10].

We developed a multi-inlet vortex mixer (MIVM) to overcome the CIJ mixer's limitation while retaining its ability to provide rapid micro mixing, scalability, and ease of operation. The momentum from each stream contributes independently to drive micro mixing in the cell, according to the MIVM concept. As a result, it is possible to have one or more streams with a high volumetric flow rate and another with a lower flow rate while still achieving good micro mixing[11].

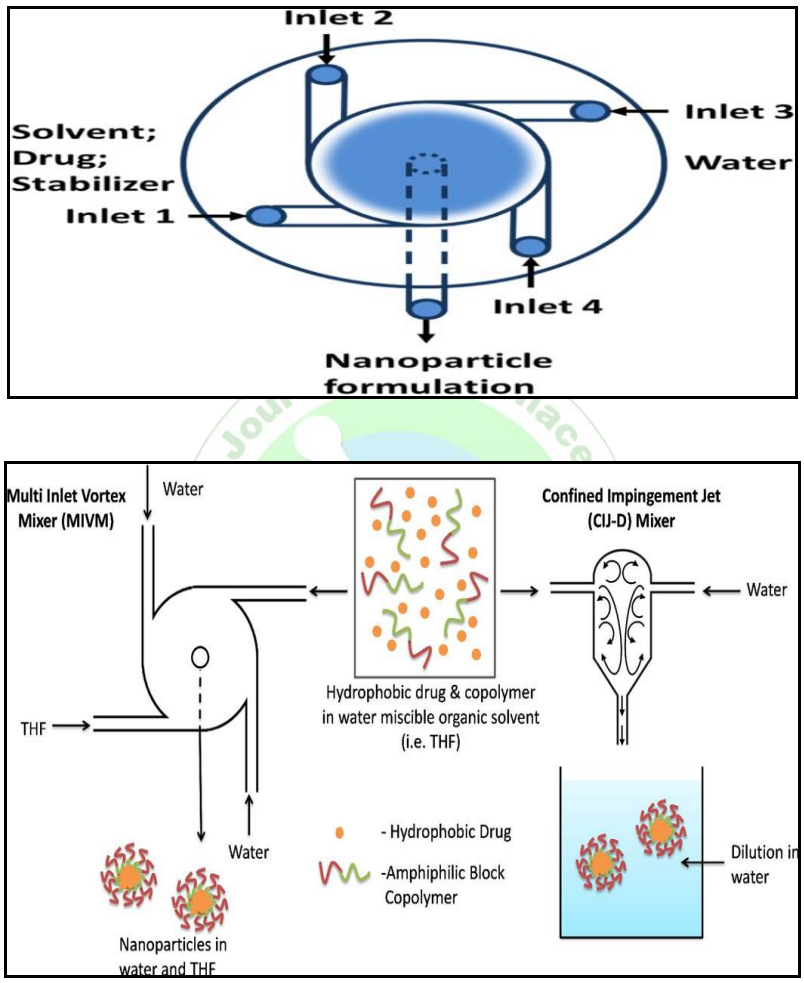

Figure 4: Multi inlet vortex mixer (MIVM) and Confined impingement jet (CIJ-D)

Summary and future perspectives:

- FNP devices have been used to prepare many different nanoparticle formulations of poorly water-soluble drugs using CIJM and MIVM, indicating that FNP devices are promising techniques for nanoparticle fabrication.
- These laboratory devices are extremely useful in optimizing conditions for nanoparticle production. The key to preparing ultrafine drug nanoparticles in FNP is to achieve rapid, uniform, and high solute supersaturation to drive high nucleation rates.
- Drug properties or parameters, solvent, anti-solvent, stabilizers, and temperature all have a significant impact on the formation of nanoparticles.
- Furthermore, the toxicity of the residual organic solvent may cause medication safety issues for patients. During storage, the drug nanoparticles produced by FNP were mostly amorphous and less stable than their crystalline counterpart. As a result, freeze drying or spray drying is preferable for removing the solvent and storing the nanoparticles in a solid state to improve their long-term stability.

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