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A Literature Review for Improving the Solubility of Poorly Water-Soluble Drug

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Abstract

Nanocrystal technology has showed significant potential for commercial applications and advancements as a novel pharmacological method to increasing the water solubility of certain poorly soluble medicines. Nanotechnology is the most effective method for solving the solubility issues with medications in BCS classes II and IV. This article is primarily concerned with the methods of preparing nanocrystals by means of Precipitation Lyophilization Homogenization (PLH) Technology. In particular, emphasised combinative technology could improve particle size reduction. Technology, equipment, and medication physicochemical qualities affect particle size reduction success. Precipitation, Lyophilization and homogenization have been used to develop and commercialize poorly soluble pharmaceuticals. Combination techniques, such as those discussed in this review article (Precipitating water-insoluble drug nanocrystals; Synthesis of Drug Nanoparticles Using Antisolvent Precipitation; Lyophilization Process; Nanoparticles Loaded with Proteins and Lyophilized); have led to significant advances in the field of drug delivery Microfluidizers, Piston Gap Homogenizer and Applications of PLH. Their potential therapeutic effectiveness in comparison to conventional medications could be potentially enhanced by future needs for PLH technology. Nanomedicine's long-term success will rely on pharmaceutically-informed, rationally designed PLH technology and tools.

Keywords: Precipitation; Lyophilization; Homogenization; Application

Introduction

Drug compounds poor solubility is a major problem in the drug business, and lowering particle size is an easy and effective solution. Currently, more APIs are poorly soluble, which is a problem in drug research and development [1]. They are difficult to find and produce because scientists don't fully understand the many chemical, physiological, and metabolic processes that occur between administration and absorption and how they impact bioavailability [2]. Poor-solubility drugs have increased during the last decade. 40% of drugs in development are insoluble [3]. The BCS categorizes medicines in Class II based on their low solubility and high penetration in the human body. Around 70% of BCS II medicines have low-solubility, high-permeability [4,5]. Advanced drug research is illuminated by nanocrystal formulation. The higher surface-volume ratio due to nano- or micro-meter diameters dramatically increases drug dissolving velocity and saturation solubility. Drug nanocrystals are an unique medication delivery strategy for certain illnesses due to their ease of manufacture and several administration routes. In the pharmaceutical field, nanoparticles are those smaller than a thousand nanometers (nm) (1 m), whereas microparticles are those between 1 and 10 nanometers (nm) [6,3]. Many techniques generate nanocrystals. Top-down and bottom-up technologies are the major types. Bottom-up technologies use an anti-solvent to precipitate molecules in the nano range from a solvent solution. Top-down technologies use wet milling disintegration methods. Drugs are dissolved in a solvent and then precipitated and mixed with the non-solvent. Nonionic polymer or surfactant can be used as a stabilizer. Disintegration usually involves high-pressure homogenization milling [7]. Nanomorph generates amorphous drug nanocrystals, which increase the speed and ease with which the drug dissolves in the body. Precipitation methods' primary benefit is that they need less complex and cheaper tools. With static blenders, scaling up is a simple process [8]. As compared to the high pressure homogenization technique, PLH's combination technology allowed for less homogenization cycles and faster development of nanosized crystals [9]. Novartis has the Hydrosol patent on the simple precipitation process, which may deter commercial interest [10]. Pharmaceutical and drug delivery systems increase poorly soluble drug solubility, bioavailability, and targeted distribution via nano crystals and lipid-based formulations. Nanocrystals Increased surface area improves bioavailability and dissolution.

Easy formulation with fewer excipients. Compatible with hydrophobic and hydrophilic medicines [11]. Lipid-Based formulations multipurpose method for lipophilic and hydrophilic pharmaceuticals. Lymphatic transport, bypassing first-pass metabolism, and medication absorption improve bioavailability. Protects medication degradation and metabolism [12]. For drug discovery and development, biomanufacturing, and material synthesis, High-Throughput Microfluidics is a new microfluidizer technology. By quickly screening compounds for pharmacological properties, solubility, stability, and formulation, high-throughput microfluidics helps speed up drug development. Microfluidic devices can precisely regulate reaction conditions and create biologically-inspired microenvironments. This method speeds drug candidate and formulation identification [13].

Precipitation

Precipitation techniques have been investigated for decades to make ultra-fine particles. A solution's solvent power may be lowered by adding an anti-solvent in the mix. Anti-solvents include water, organic solvents, and supercritical fluids [14]. In the last 20 years, several precipitation experiments have created nanoparticles of organic therapeutic substances. The addition of a liquid solvent and antisolvent, precipitation in a supercritical fluid, evaporation of the solvent, and high-energy processes are the four main areas studied [15]. Direct precipitation is easier and uses cheaper raw materials than homogenous precipitation [16].

Precipitating Water-Insoluble Drug Nanocrystals

Ultra-fine particle production by precipitation has been studied for many years. A solution's solvent power may be lowered by adding an anti-solvent that is not itself a solvent. Supercritical fluids, organic solvents, and water are all examples of anti-solvents. All the many methods of anti-solvent precipitation are discussed in this study, including mixing techniques, high-gravity, ultrasonic waves, supercritical fluids, and the like Basic mixing, impinging jet mixing, multi-inlet vortex mixing [17]. Methods of precipita-

tion using supercritical fluids, ultrasonic waves, and/or high gravity, restricted liquid jet mixing, and/or multiple inlets are all possible. Droplet evaporation techniques that rely on spraying include nanospray drying, the aerosol flow reactor method, spraying low-boiling point solvents in the ambient environment, and electrospraying electrically non-conductive solutions [18]. For this precipitation process to operate, the drug must be miscible with the antisolvent and soluble in at least one solvent. Precipitation cannot purify medications since they are insoluble in water and oil [19]. Precipitation improved the solubility and oral bioavailability of Danazol and Naproxen nanosuspensions. Naproxen's absorption increased by around four times as its size decreased [20].

Synthesis of Drug Nanoparticles Using Antisolvent Precipitation

Anti-solvent precipitation, also known as desolvation, drawing-out precipitation, or solvent displacement, removes the active component from a solvent by making it less soluble. Anti-solvent precipitation is produced by phase separation when a non-solvent is added to a solution. Nanoparticle synthesis solvents and anti-solvents must be miscible at the amounts utilized. An unfavorable ratio of molecular interactions between solute, solvent, and anti-solvent drives particle formation during anti-solvent precipitation. Precipitation occurs when solute solute interactions outweigh other interactions and the entropy of mixing effects for specific solvent/anti-solvent combinations [21]. The development of mixing systems and surfactant stabilizers for nanoparticles of poorly water-soluble pharmaceutical compounds with high dissolving rates is aided by particle size control in antisolvent precipitation [22]. Antilipidemic drug (Lovastatin) nanosuspension was made using the solvent-anti-solvent approach to improve solubility, dissolution, and oral bioavailability [23].

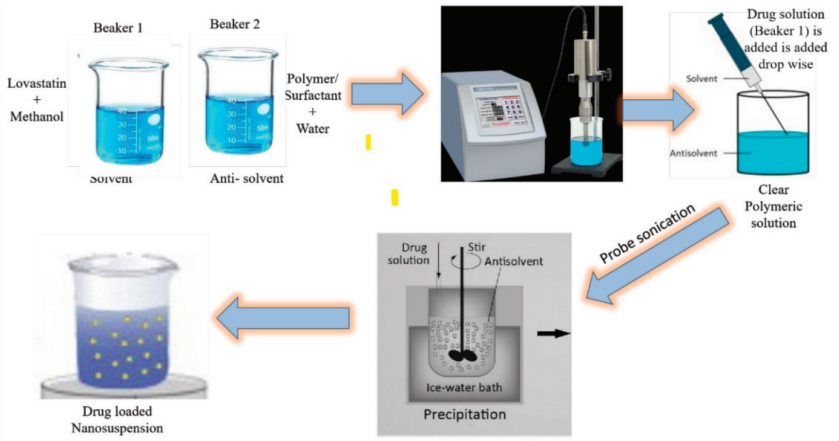

Figure 1: Antisolvent Precipitation Drug for the Nanoparticle Synthesis

Precipitation-Based Synthesis of Water-Insoluble Medicinal Nanocrystals

Ultra-fine particle precipitation has been extensively studied for decades. These methods precipitate solute by adding an anti-solvent, a solute-non-solvent. Water, organic solvents, or supercritical fluids are anti-solvents. anti-solvent precipitation via simple mixing, impinging jet mixing, multi-inlet vortex mixing, high-gravity, ultrasonic waves, and supercritical fluids. Based on crystallization theories, mixing during precipitation controls nucleation kinetics and particle development, resulting in stable nanocrystals [24]. Nanocrystals are produced using low-energy anti-solvent precipitation. Glyburide, ibuprofen, and artemisinin, all nearly insoluble in water, were produced as stable nanocrystals with uniform particle size. Crystal growth inhibitors/stabilizers were crucial and drug-specific [25]. Precipitation prepares amorphous drugs in nanoparticles, such as carotene nanoparticles in food (BASF). A carotenoid-surfactant solution in digestible oil is combined with an acceptable solvent at a certain temperature [26].

Lyophilization

Lyophilization, which freezes a substance in a vacuum to eliminate water, is filthy yet has numerous applications. Protein, collagen, peptide, oligonucleotide, chemical API, enzymes, and monoclonal antibodies (mAbs) are some medicinal products that are lyophilized [27]. Freeze-drying, spray drying, spray coating, vacuum drying, film drying, and supercritical fluid drying are used to

make granular medicinal medicines. Due of its many benefits, lyophilization—freeze-drying—is a popular drying procedure [28]. Preparing pharmaceuticals by lyophilization increases their stability for long-term storage [29]. Sugars also have a considerable impact on the optimization of the lyophilization cycle due to their effect on the glass transition temperature (Tg and Tg') of formulations. The redistribution of nanoparticles improves with both increased concentration of the cryoprotectant and a quicker freezing rate. Cryo- or lyoprotectant and freezing rate selection is not black-and-white, however, and may rely on formulation qualities and the lyophilization cycle [30].

Lyophilization Process

The first step in freeze drying is freezing. Pharmaceutical and food engineering freeze water. Water freezes to separate solutes. "Supercooling" occurs during this procedure. The freezing rate determines supercooling. Freezing usually takes a few hours [31]. The solution must be cooled to the point where ice nucleation occurs before the freezing process can begin. When a solution freezes, the crystals in it either develop to a crystalline or amorphous state, or they form a combination of the two [32]. Typically, secondary drying will occur once the product has been heated beyond its eutectic point. Now that the low-pressure environment needed by the succeeding solvents has been generated by the vacuum pump, the object may have a drier appearance [33]. The frozen ice is sublimed, resulting in a dry, structurally sound product. This takes the longest out of anything here. Product quality is maximized by controlling both the pressure within the chamber and the temperature on the shelves [34]. Bound moisture remains in the product after freeze drying and ice sublimes. Although dry, the product contains up to 8% moisture. It needs higher-temperature drying to reach acceptable levels. "Isothermal Desorption" removes bound water. Most items undergo secondary drying at a safe temperature above room temperature. Desorption drying is easier than primary drying, which uses low shelf temperature and moderate vacuum. It's crucial to keep the shelf temperature low during secondary drying to avoid protein polymerization or biodegradation [35]. Secondary drying normally takes 30–50% of main drying time. The shelf temperature and chamber pressure are raised and lowered to their lowest during freeze drying's secondary drying phase. Since there is no ice, "melt track" may be disregarded and higher temperatures can be applied without hurting the product. Secondary drying leaves firmly bound water that takes more energy to dissipate. Water desorption is optimized by lowering chamber pressure [36].

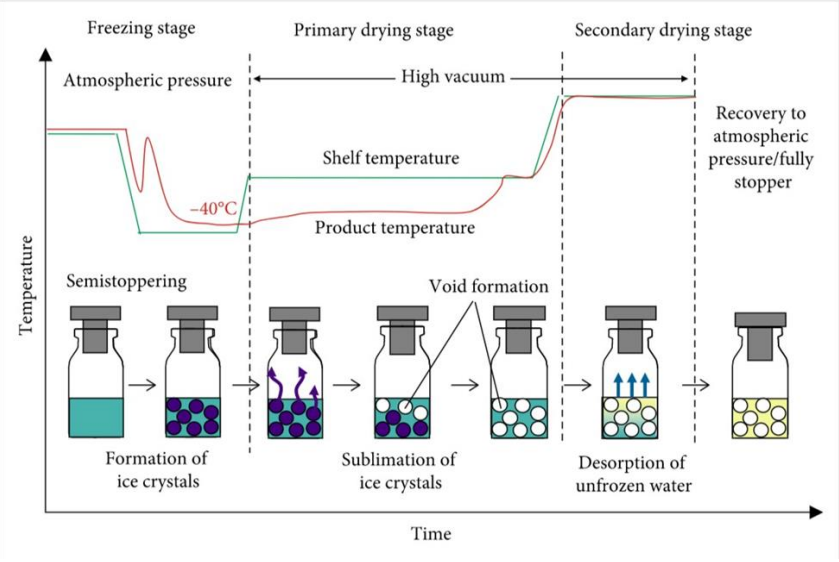

Figure 2: Steps of Lyophilization Process

Pharmaceutical Freeze-Drying Equipment

- Refrigeration subsystem
- Vacuum subsystem

- Control subsystem
- The carrying agent circulatory subsystem
- Hydraulic subsystem
- CIP subsystem (cleaning in place system or online cleaning system) [37].

Nanoparticles Loaded with Proteins and Lyophilized

Therapeutic proteins are often lyophilized for stability. Proteins are unstable and lose bioactivity due to lyophilization stressors, like nanoparticles. Protein denaturation and aggregation during freezing or drying have been linked to lyophilization. Stresses vary on protein type and lyophilization technique, according to several studies [38]. Sucrose, among the natural and synthetic lyoprotectants tested, was shown to be particularly efficient in reducing the size of freeze-dried nanoparticles on redispersion without significantly altering the nanoparticles' surface charge [39]. Strategies for the inhaled delivery of protein therapies to the heart for the treatment of heart disease are still in their developmental stages. Perfluorocarbons (PFCs) are non-reactive compounds that have lately found use in a wide variety of settings owing to their unusual physico-chemical characteristics and high level of biocompatibility [40].

Homogenization

Homogenization creates uniform particle size. Homogenization achieves micro- and nano-particle sizes, which affect formulation and biopharmaceutical properties. Particle size decrease affects medication absorption and dissolution. Reduced particle size improves medicine stability and efficacy. Homogenization technology ensures targeted, effective, clinically efficient, and low-side effect drug administration [41]. High-pressure homogenizers vary in valve design and geometry. The rapid restriction of flow by dynamic valves (radial diffuser, axial valves) results in pressure fluctuations and a more even distribution of particle sizes. Homogenizing at high pressure with a counter-jet valve results in USP-compliant injectable lipid emulsions below MPD and pFAT5 [42]. Microfluidizer (Nanojet) technology, piston gap homogenization in aqueous medium (Dissocubes) technology, and homogenization in water mixes or nonaqueous media are the three most important technologies in homogenization-based nanocrystal production. Incorporating Nano-Pure Methods [43].

Microfluidizer

Microfluidic technologies have the capability to imitate both the physiological and pathological circumstances that are found in vivo. As a result, these technologies are compatible with a range of different analytical methodologies for high throughput drug screening and assessments [44]. There are two microfluidization techniques used in nanodelivery systems. There are advantages and disadvantages to both single-step dual-channel and two-step single-channel microfluidization. Nanoemulsion-based delivery systems that need two separate channels for microfluidization to create the final product are inefficient and wasteful [45]. Microfluidization is a high-energy technique that uses microchannel dynamics. Turbulence and momentum help the lipid carrier break through. The compressed air pump mixes the lipids and active chemicals at extremely high velocities in the designated microchannels, generating stable nano-sized delivery systems [46]. In a recent research, microfluidized solid lipid nanoparticles (SLNs) had a particle size of 36–136 nm and increased stability [47]. Several drug-based nanosuspensions improved medication bioavailability in chronic illness therapies. Budesonide nanosuspension with 122 nm particles was generated recently utilizing microfluidization. The lung delivered and distributed the medicine better than normal-sized particles. Another microfluidized medicine, ritonavir suspension, has a consistent particle size and 3.5-fold better effectiveness [48].

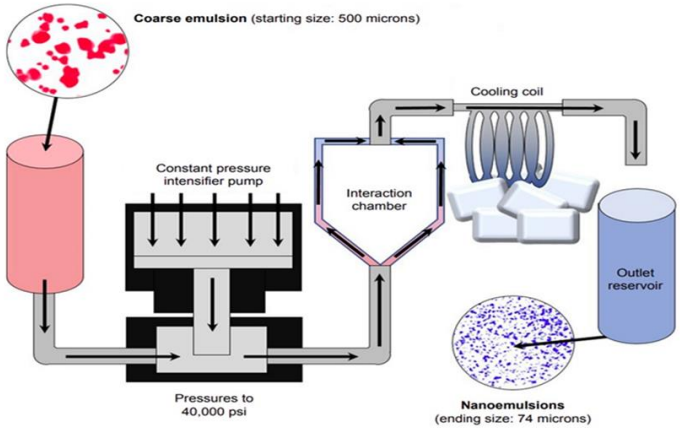

Figure 3: Preparing Nanodelivery Systems Through a Microfluidization Method

High-Pressure Homogenization

Pharmaceutical solids and nanoparticles are comminuted, mixed, and stabilized using high-pressure homogenization (HPH). HPH is one of the most versatile and scalable methods for preparing vesicular and non-vesicular lipid-based nanosystems like nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanocrystals, and polymeric nanoparticles [49]. High-pressure homogenization breaks cells by rapidly shearing cellular jets against solid surfaces. Compression chambers pressurize cell suspension. A small nozzle or valve accelerates the compressed cell suspension to a low-pressure chamber. The cell suspension is depressurized when the accelerating cellular jet hits the valve surface. Processed cells are damaged by hard surfaces and pressured-drop shear stress [50].

Piston Gap Homogenizer

A piston forces the drug solution through a very small homogenization gap at high pressure. The drug is suspended in an aqueous surfactant solution [51]. In piston-gap HPH, particles are broken down by cavitation, shear forces, and collisions. Because of the separation, the diameter of the suspension is reduced from 5 cm to 25 m. The huge diameter change increases dynamic pressure and decreases static pressure, according to Bernoulli's law. The homogenization gap boils liquid because static pressure is smaller than vapor pressure. Cavitation happens when empty gas bubbles rupture. Shear forces and particle collisions result from high pressures (up to 1500 bar). APV, Gaulin, and Avestin make piston-gap homogenizers [52].

Application of PLH

PLH method only required five cycles to effectively and swiftly decrease the particle size of nanocrystals of clarithromycin to 460 ± 10 nm with homogeneity size distribution [53]. Nanosuspensions of vitexin with an MPS of 80.5 nm were produced using a combination of antisolvent precipitation and high pressure homogenization, and then lyophilized [54]. Docetaxel, a cancer medication, has been nanosized. Sodium deoxycholate (SDC) and hydroxypropyl methylcellulose (HPMC, E5) were utilized in varying amounts to stabilize the DOX-loaded nanoparticles that were prepared using a solvent precipitation approach. The smallest measured particle size was 83.97 nm [55]. Drug Nanoparticles of Itraconazole Produced by Antisolvent Precipitation. Under a broad variety of energy dissipation rates, aqueous solutions may precipitate sub-300 nm particles, even with drug loadings as high as 86% itraconazole weight/total weight [56]. Nanoparticles loaded with methotrexate and an amphiphilic codendrimer PGD derived from polyamidoamine and oligothylene glycol dendrons were synthesized by antisolvent precipitation coupled with ultrasonication. This extraordinary material stood out due to its round form, nanoscale particle size (about 182.4 nm), and narrow particle size dispersion [57]. The solvent precipitation method was used to create docetaxel nanosuspensions, and it is a bottom-up approach. Using sodium deoxycholate as a stabilizer resulted in the smallest particles (83.97 nm) [58]. Amphotericin B nanosuspensions were made using high-pressure homogenization, and the resulting particles had a PCS diameter of 528 nm [59].

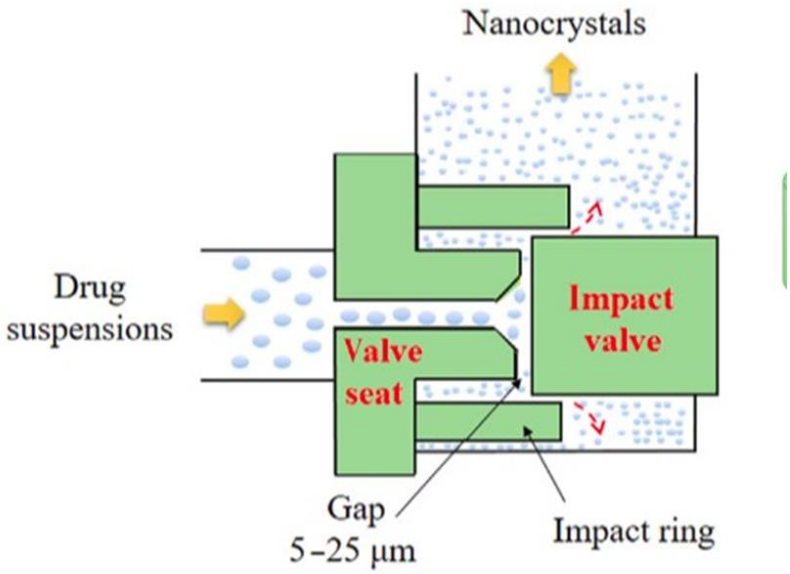

Figure 4: Piston Gap Homogenizer

Precipitation-Lyophilization-Homogenization (PLH) Processes

Precipitation, lyophilization, and homogenization are combined in this invention. Precipitation shrank drug particles. Dilution in an organic solvent and addition to an aqueous phase precipitated compact, friable crystals. Organic solvent was carefully removed from nanosuspensions to reduce cosolvent-induced particle growth. The second lyophilization step changed the substance and eliminated the organic solvent from precipitation. High-pressure homogenization reduced crumbly particles to nanometers in the last step [60]. Using poloxamer 407 and sodium dodecyl sulfate (SDS) as co-stabilizers, nanocrystals of clarithromycin were successfully produced by this approach. Nanocrystals of clarithromycin were developed; they were crystalline or partly amorphous cube-shaped particles with a size of around 400 nm. It had exceptional solubility and permeability [9].

Conclusion

The review article presents an in-depth analysis of Nano crystals as a promising approach for formulating poorly water-soluble medicines. Nano crystals have shown significant potential in resolving solubility and bioavailability issues, especially for drugs with narrow therapeutic windows. Poorly water-soluble medicines are best formulated with nanocrystals. This method can solve solubility and bioavailability issues for poorly water-soluble medicines. When a medicine has a small therapeutic window for absorption, solubility improvement becomes even more significant. Increased solubility and dissolution velocity improve bioavailability in these circumstances. Drug nanocrystals may attain moderate blood levels with lower doses, reducing adverse effects. Granulation fluid for tablet manufacture, multilayer dispersion in fluidized bed process, solid/liquid PEG, spray drying, and lyophilization are all examples of nanosuspension preparation methods. Applying PLH technology allows for the creation of finished dosage forms with enhanced drug loading capacity, redispersibility at the site of action, and targeting.

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